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VII. *Development of the Sympathetic Nervous System in Mammals.*

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[Plates 22–30].

I. Introduction.

The Mammalian sympathetic nervous system presented apparently insurmountable obstacles to both anatomists and physiologists till the publication of Gaskell's Monograph in 1885 (1). Our knowledge of its structure and functions is now, however, placed on a much firmer basis; and it is possible to enter seriously into a consideration of its morphology and development.

A. *Physiology.*

The *cells* composing the ganglia in the main sympathetic chain are shown by Gaskell to be trophic only. They are neither automatic nor reflex in their action, but merely nourish the fibres which pass from them centrally or peripherally. The gray *Rami communicantes* spring from the ganglia and are distributed as trophic fibres to the roots and trunk of each spinal nerve and their *meninges*, and the bodies of the vertebræ. In some cases (*e.g.* fore and hind limbs) the vasomotor fibres reach their destination through these Rami. The white *Rami communicantes* are only found in two regions. In the Dog between the tenth and twenty-fifth spinal nerves (second dorsal—second lumbar), and in the Rami of the second and third sacral nerves. This corresponds fairly accurately with their distribution in the human subject (2). In both regions they consist of very small medullated fibres (1·8μ to 2·7μ). In the anterior region the white Rami pass from the spinal nerves to the ganglia, and there separate into two groups; one set forms *vasomotor* fibres, which join the ganglia, become connected with the ganglion-cells, and are distributed peripherally as gray fibres, greatly increased in numbers. The other set does not join the ganglia, but, passing over them, forms the nerves distributed in the Splanchnics to the abdominal viscera as *viscero-inhibitory* fibres. In the posterior region

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white Rami arise from the second and third (and in man fourth (2)) sacral nerves which pass over without joining the ganglia; becoming connected with the hypogastric plexus, they are distributed as the *Nervi erigentes* (*vaso-inhibitory* fibres). They are possibly also *viscero-inhibitory.*

The only spinal nerves which come into direct communication with the sympathetic ganglia are the vasomotor fibres. In fact, so convinced is GASKELL of this that he maintains that "this chain might, therefore, be most appropriately called the chain of vasomotor ganglia, instead of the present meaningless title of main sympathetic chain." GASKELL shows, moreover, that these vasomotor fibres are conducted along the sympathetic chain from their source to their distribution. In the anterior thoracic region they pass forwards along the chain to be distributed to the carotid and vertebral arteries, to the arm, and to the heart. In the posterior part of the thorax they pass backwards to the aorta, abdominal vessels, and lower limbs.

The functions of the gangliated cord of the sympathetic thus appear to be:—1. To nourish the vasomotor fibres after converting them into non-medullated fibres; and 2. To act as "a guiding rod" to direct the course of the stream of vasomotor fibres emerging from the cerebro-spinal axis.

B. *Morphology.*

The prevailing notion among anatomists regarding the morphology of the gangliated cord of the sympathetic is one which springs from the analogy which it bears to the bilaterally gangliated chain in Invertebrates, and which has been elaborated by BALFOUR chiefly among embryologists (3). It is generally spoken of as being *segmental,* and the attempt is made to harmonise the arrangement of the ganglia with that of the vertebral somites. Instead, however, of presenting a distinctly metameric arrangement, there is anything but a correspondence with the segmentation of the body, as illustrated in the case of the spinal nerves or vertebræ. In the human subject, for example, in the neck there are only two, sometimes three, ganglia in the sympathetic cord. The first is elongated, connected with four spinal nerves, and sometimes irregularly constricted, and so "is favourable to the view that it may be regarded as consisting of several ganglia which have coalesced." (4). The last cervical ganglion is frequently fused with the first thoracic. In the gangliated cord in the other regions the same irregularity is seen. Of the thoracic ganglia there are usually twelve, but variations are formed occasionally by the "coalescence" of adjacent ganglia. In the loins there are generally four ganglia, but the number is often diminished. They are sometimes even fused into a single ganglion, much elongated, passing over several vertebræ, and connected at intervals with the lumbar nerves. "The sacral ganglia are usually four in number, but the variation both in number and size is more marked than in the thoracic or lumbar ganglia" (4).

The assertion of GASKELL (1), which I shall venture in the sequel to uphold from embryological considerations, that the superior cervical ganglion is to be looked upon neither morphologically nor physiologically as a fundamental portion of the gangliated cord, but rather as a distal or collateral ganglion, makes it still more difficult to regard the gangliation of the chain as indicative of its metameric constitution.

It is noteworthy that the central connexions of the main chain form the only evidence of segmentation, which is not discredited by exceptional characters. These connexions are obviously truly segmental, being intimately related to the spinal nerves; and the segmental hypothesis of the formation of the sympathetic is founded essentially on these anatomical relations. Hereafter I shall endeavour to demonstrate that the sympathetic is primarily unsegmented, and shall attempt to show adequate cause for the appearance of segmentation in the cord.

C. *Embryology.*

The recent memoirs bearing on the development of the sympathetic are comparatively few, and the excellent account given of the literature of the subject in Onodi's monograph (15), makes it unnecessary to repeat it here at length. Various steps in the process have been traced by previous observers; but there is absolute divergence in their views regarding the most vital points. In the first place it cannot be said to be definitely proved from which of the embryonic layers the gangliated cord arises. On the one hand we have the weighty authority and historical researches of Remak (5, 6), supported by Bidder and Kupffer (7), Kölliker (8), Hensen (9), His ? (10), Götte (11), and Schwalbe (12), in defence of its origin from mesoblast. On the other hand Balfour's work on the development of Elasmobranchs (13), the memoir of Schenck and Birdsell (14), and the elaborate monograph of Onodi support the idea of its origin from epiblast. There is a third hypothesis to the effect that the sympathetic is originally derived from hypoblast. As far as I am aware, this theory has never been seriously supported by any observer, and, as it will not bear investigation, it is not necessary to discuss it further.

Those who, like Remak and his followers, uphold the mesodermal origin of the sympathetic, maintain that it springs from isolated segmental ganglia arising from the mesoblast in the neighbourhood of the protovertebræ, which ganglia obtain connexions with the periphery, with the spinal nerves, and antero-posteriorly with the contiguous ganglia.

Balfour (13) was the first to suggest the ectodermal origin of the sympathetic, in order to harmonise it with the rest of the nervous system. In his monograph on the development of Elasmobranchs, he makes some observations on the development of the ganglia. He says: "There may be seen short branches from the spinal nerves, which take a course towards the median line of the body, and terminate in small irregular cellular masses immediately dorsal to the cardinal veins. These form the first traces that have come under my notice of the sympathetic nervous system. In the youngest of my embryos, in which I have detected these, it has not been possible for me either definitely to determine the antero-posterior limits of the system, or to make certain whether the terminal masses of cells which form the ganglia are connected by a longitudinal commissure." There is here only one positive observation, namely the connexion of the ganglia with the spinal nerves, which might be obtained from an examination of the adult, and BALFOUR himself, while inferring that the ganglia spring from the spinal nerves, and therefore from ectoderm, admits that his investigations, "though they may naturally be interpreted in this way, do not definitely exclude a completely different method of development for the sympathetic system." In his 'Comparative Embryology' he states that "the sympathetic ganglia (in Elasmobranchs) are at first simply swellings on the main branches of the spinal nerves, some way below the ganglia. . . . I have been unable to find a longitudinal commissure connecting them in their early stages, and I presume they are at first independent, and become subsequently united into a continuous cord on each side." He also derives the suprarenal bodies of Elasmobranchs from the sympathetic. Other observers, BRUNN (16), KÖLLIKER (17) and BRAUN (18), have shown that the medullary parts of the suprarenals are derived from the sympathetic, the cortical parts from undifferentiated mesoderm.

SCHENCK and BIRDSELL (14), working with Chick, Dog, and Human embryos, came to the conclusion that the ganglia are derivatives of the central nervous system, and are pushed out from the spinal ganglia. Their paper is not, however, convincing; the illustrations do not clearly express the meaning of the text; and the facts adduced do not appear to justify the generalisations at which they arrive.

ONODI (15) has given the most complete account of the development of the sympathetic. His researches cover all the classes of vertebrates. In fishes he studied the question in *Scyllium canicula*, *Mustelus lævis*, *Scymnus*, and *Torpedo*. In the first only he describes the earliest appearance of the sympathetic ganglia as thickenings on the ventral ends of the spinal *ganglia*. These thickenings are composed of large cells, which stain deeply, are arranged in rows, and are sharply marked off from the pale mesoderm cells. By the further growth of this bulbous expansion the sympathetic ganglion is formed, remaining in connexion with the spinal nerve by a double row of cells. In the other examples, the commencement of the gangliated cord was not discovered; in the youngest specimens examined the ganglia were fully formed, and connected to the spinal nerves (as BALFOUR described) by *Rami communicantes*. These *rami* ONODI describes as being first cellular, afterwards becoming fibrous. The main conclusion of his researches in Fishes agrees with that of BALFOUR, that the ganglia are segmental and ectodermal in origin. They disagree, however, in regard to the process of formation. BALFOUR regards the sympathetic ganglia as buds from the spinal nerves, the connecting stalk being gradually elongated into the *ramus communicans* as the ganglion grows. ONODI, on the other hand, asserts that ganglia and rami are direct proliferations from the spinal ganglia. Nor in either case is the evidence clear regarding the fusion of the ganglia to form the connected chain.

In Birds and Mammals, ONODI did not see the earliest stages in the development of the sympathetic. In the Chick at 3 and 5 days the gangliated cord was present, and connected by rami to the spinal nerves. In the Rabbit (10 mm.) and Human embryos (18 mm.) the same conditions were found—ganglia already formed, with their rami communicantes. These observations do not differ markedly from those of other investigators—HIS, SCHENCK and BIRDSELL, BRAUN, &c. Yet, although in no case were the ganglia *seen* to spring from the spinal ganglia, ONODI expresses himself as convinced (from the appearance he describes in *Scyllium*) that that is the source from which they originally start.

Summarising the conclusions of previous observers discussed above,—the sympathetic gangliated cord in Mammals consists of vasomotor ganglia, trophic in their functions, and pseudo-metameric in their morphological arrangement. Two opposite views exist amongst embryologists regarding its development. In both views the segmental formation of the cord is upheld. According to one view it is mesodermal, and is formed *in situ*. According to the other view, it is ectodermal. But the observers who assert this view disagree as to its fundamental source. BALFOUR regards each ganglion as an offshoot from the spinal nerve; ONODI and SCHENCK and BIRDSELL consider it as a direct proliferation from the spinal ganglion.

In the succeeding pages the attempt will be made to find the source of the sympathetic system in Mammals, by tracing its development from its first appearance to the date at which it can be fairly compared with the adult condition; and thereafter, by a study of its morphology at different ages, and in different animals, to harmonise the conflicting views of anatomists and physiologists.

II. THE DEVELOPMENT OF THE SYMPATHETIC SYSTEM.*

The following researches were begun some years ago, during an investigation into the development of the spinal nervous system. It was then noted that the first apparent connexion between the sympathetic ganglia and the spinal nerves arose in the formation of the splanchnic or visceral branch of the latter, which passed into the splanchnic area and seemed to join the gangliated cord. Beginning at this point, and continuing the investigation into earlier and later stages, it has been possible to arrive at conclusions regarding the main features in the formation of the gangliated

* Dealing exclusively with Mammals, in the following pages, it is necessary to explain the method used in determining the ages of the embryos employed. It is not possible, in my opinion, to be certain as to exact ages, as the time of impregnation after connexion varies in different cases; and two embryos from the same uterus often differ in size and extent of development. From a comparison of a large series, however, it is possible to determine *approximately* the age of a given embryo. In the following description the probable age of the embryo is given, and when possible, its axial length also.

cord, its connexion with the spinal nerves, its terminations, cephalic and caudal, and its relations to the suprarenal bodies, and collateral ganglia. In the succeeding account the order followed will be that of development, as far as the subject under consideration allows, and as far as possible drawings from the actual specimens will be utilised to demonstrate the facts adduced.

1. *Formation of the Main Sympathetic Cord: Early Stages.*

The examination of very young Mammalian embryos leads only to negative conclusions regarding the origin of the sympathetic cord.

In Rat embryos about 5–6 days old, cut *in utero*, hardened in spirit and stained with aniline blue-black (Bevan-Lewis), the spinal cord is incompletely closed, the brain consists of its three primary vesicles, and the optic vesicles are in process of formation. In transverse sections through the thoracic region (Plate 22, fig. 1), the notochord (*No.*) is large and distinct, is surrounded by a sheath, and is in close contact with the spinal cord (*Sp.C.*). Below is the alimentary canal (*Al.*), in the ventral wall of which the first steps in the formation of the pulmonary passages are to be seen. On each side are the separate aortæ (*Ao.*) and muscle plates (*M.P.*), the inner layers of which are undergoing proliferation. The dorsal ganglia (*D.R.*) are beginning to form, as indistinct buds of fusiform cells (stained like those of the spinal cord more deeply than the surrounding mesoblast), springing from a hardly perceptible neural ridge on the summit of the spinal cord. There is no sign, as yet, of the ventral roots of the spinal nerves, or of the sympathetic cord. Between the muscle plate and aorta laterally, and the spinal cord, notochord, and alimentary canal in the middle line, is a clear space containing only some scattered embryonic cells with branching processes.

In Rabbit embryos aged about 7 days (axial length 5 mm.), hardened in picric acid, and stained with borax-carmine, the dorsal aortæ were fused into a single trunk, having a cardinal vein on each side; the lungs had begun to form, and the limbs were represented as rudimentary rounded buds. The spinal cord was almost entirely cellular, a very narrow belt of fibres being found only in the neighbourhood of the dorsal and ventral roots. The development of the spinal nerves was further advanced. In transverse sections through the thoracic region (Plate 22, fig. 2), the dorsal ganglion (*D.G.*) is distinctly seen: fusiform in shape, it is connected to the spinal cord (*Sp.C.*) by a bundle of fibres, among which are cells possessing large nuclei and fine tapering processes at either end. At its distal end, a bundle of fibres can be traced to join the ventral root. The latter is also distinct: it leaves the spinal cord as a number of separate fine fibres which combine with the dorsal root to form the nerve (*Sp.n.*). This can be traced outwards almost as far as the cardinal vein (*C.V.*), and to the level of the somato-splanchnic angle (α); or in the regions where the limbs are sprouting as far as the roots of the limbs, where in certain sections the fibres can be seen to separate out slightly before their termination. The nerves consist for the most part of fibres: the cellular elements are plainly mesoblastic, and help in forming the nerve-sheaths.

There is no sign as yet of the formation of the superior primary division, or splanchnic branch of the nerve. The ventral root passes out entirely below the dorsal ganglion, which is easily defined. The interval before mentioned between the aorta, cardinal vein, spinal nerve, and spinal cord, is now filled up by a mass of mesoblastic cells (intermediate cell-mass) in process of vertebra formation. The cells are large, often with several nuclei, and are in an active state of division. They all stain equally with borax-carmine, except the nuclei of blood corpuscles, which stain more deeply.

Sagittal sections of embryos from the same uterus show the spinal nerves in transverse section; but there is no evidence of the existence of the sympathetic cord or ganglia.

In Mouse embryos of about 8 days, and in Rat embryos of a similar age (the axial length of the latter being 7 mm.), the first indication of the formation of the sympathetic cord has been found. The general condition of development in both these animals corresponds with that of the Chick at the end of the third and beginning of the fourth day. The spinal cord is cellular, a narrow belt of fibres being present on each side in the neighbourhood of and between the nerve-roots. The spinal nerve has extended almost as far as the somato-splanchnic angle, and to the cardinal vein in places where the latter is present; and in some sections the superior primary division is apparent. The pulmonary diverticulum from the alimentary canal has become divided into the two main bronchi. The Wolffian duct and Wolffian body are distinct.

The Mouse embryos (Plate 22, fig. 3) were hardened in picric acid and stained with borax-carmine. A change is now apparent among the cells of the mesoblast surrounding the aorta (*Ao.*). In the interval between the latter and the cardinal vein (*C.V.*), instead of a uniformity in the cells composing the intermediate cell-mass, an irregular group of cells is seen among them (*Sy.*), lying on the ventral side of the intercostal arteries, and in close proximity to the aorta. On close examination, this mass of cells is strikingly different from the surrounding mesoblast. The cells stain more deeply; the nuclei are larger, and often possess a considerable number of nucleoli; and the cells form a rounded clump closely massed together, only in some sections clearly demarcated from the cells in which they are imbedded. This mass is bilaterally symmetrical, and is evident in continuous series of sections from the level of the cephalic border of the fore-limb anteriorly, where it ends abruptly, to the middle of the trunk—the region of the stomach—posteriorly. It is comparatively large anteriorly, and gradually tapers off and becomes indistinct posteriorly. The mass in front is double the thickness of that seen further back. There is no connexion, fibrous or cellular, with the spinal nerves or ganglia.

The Rat embryos of the same age were hardened in spirit, and stained with aniline blue-black. They were in the same condition of development as the Mouse embryos. The spinal nerves (*Sp.N.*, Plate 22, fig. 4) were distinctly fibrous, terminating in a thickened brush-like ending in the neighbourhood of the cardinal or jugular vein (*V.*). The dorsal ganglia (*D.G.*) were well defined, and consisted of fusiform cells with large ovoid nuclei, and with long and fine processes directed towards the spinal cord and nerve. In transverse sections a more or less rounded mass of cells (*Sy.*) is seen lying between the aorta (*Art.*) or carotid artery, and the cardinal or jugular vein (*V.*). It is formed of a mass of cells closely packed together and sharply marked off from the ordinary mesoblast by a capsule composed of a single layer of flattened cells, which, like the blastema-cells in which the mass is imbedded, stain less deeply than the mass itself. The cells forming this group, besides being evident from their deeper staining, possess nuclei, which have a striking appearance in transverse sections. Some are large and prominent, with several nucleoli; others are very small; while some cells appear to be without nuclei. In transverse sections they are round or angular. These appearances are due to the fact that the cells are fusiform, and so are cut at different levels in transverse sections. The mass, as a whole, is in close proximity to the aorta or carotid artery. It is distinct and separate from the spinal nerves. It is traceable in transverse sections from a point slightly anterior to the root of the fore-limb to the middle of the trunk, being thickest in front, and gradually becoming attenuated and indistinct behind.

In longitudinal (sagittal) sections of embryos from the same uterus, prepared in the same way, one can make out by means of continuous series of sections that this apparently rounded mass is distinctly evident on either side of the middle line as a long rod or column of fusiform cells (*Sy.*, Plate 26, fig. 11), possessing large, deeply stained, ovoid nuclei, and fine thread-like processes. All the cells are directed antero-posteriorly, and bear a marked resemblance to the cells of the dorsal ganglia at this date (*D.G.*). The column lies in close proximity to the aorta and carotid vessels (*Art.*), and can be traced forwards as far as the level of the mouth (*Mo.*) and first vertebral segment (1*st V.S.*), where it ends abruptly in a pointed brush-like process composed of the filiform processes of the cells, and not apparently due to any admixture of fibres. It is marked off from the surrounding tissues by a narrow but distinctly evident interval. Behind the level of the lungs the column of cells becomes less distinct; it can, however, be followed to the anterior end of the kidneys (Wolffian bodies), where it becomes connected with a mass of mesodermal cells, which form one portion of the suprarenal bodies. Above and behind the kidneys the character of the column changes. It can be followed to the level of the hind limbs, but is more indefinite; its cells, while retaining their fusiform character and columnar arrangement, are less closely packed together, are less regularly arranged, and are less deeply stained than in the anterior part of the column. Traced backwards, it becomes more and more indistinct, and is finally lost in the region of the hind limbs. In its entire length I failed to find any connexion between this cellular column and the spinal nerves. It is slightly thicker in front than behind, but is of almost uniform width throughout. It presents no evidence whatever of segmentation.

I have not the slightest hesitation in asserting that the cellular column above described is the precursor of the main sympathetic chain. It occupies the position of that chain; and there is no other structure to be found in the vicinity, in the form of isolated ganglia or otherwise, which might lead one to doubt its significance. It is mesodermal in origin; it is formed *in situ;* and it is unsegmented and unconnected with the spinal nerves. The next step in the investigation is to discover how this connexion takes place.

2. *Connexion of the Sympathetic Cord and Spinal Nerves: Formation of the* Rami communicantes.

In Rat embryos, aged between 8 and 9 days, axial length 8·5 mm., hardened in spirit, and stained with aniline blue-black, the above-mentioned cellular cord (*Sy.*, Plate 23, fig. 5) is slightly larger than before. In transverse sections it has the same close connexion with the aortic wall (*Ao.*); and in certain places can be traced into continuity with small bundles of similar cells, which form groups lying against the sides of the vessel, and tapering off in a ventral direction. These cells form the first sign of peripheral distribution from the cord. At this date the cord itself presents no sign of constriction or segmentation, and has the same antero-posterior limits as before.

It is in the spinal nerve that the most significant change is now seen. In previous sections the inferior primary division was traced as far as the cardinal vein, above the somato-splanchnic angle. It is now seen (*Sp.N.*) to divide at that spot (α) into two unequal parts, a larger external (*So.*) and a smaller internal branch (*Spl.*), both of which are very short and end abruptly in a fringe of nerve fibres lying between and against scattered mesoblastic cells. These two short branches form the first appearance of the somatic and splanchnic branches of the nerve. The former is directed towards the body wall, the latter inwards, behind the cardinal vein (*C.V.*) towards the median line.

In Mouse embryos of about 9 days, hardened in picric acid, and stained with borax-carmine, development has perceptibly advanced. Transverse sections (Plate 23, fig. 6) show the spinal cord (*Sp.C.*) with its cells arranged in two groups; a broad band of deeply stained cells surrounds the neural canal, while more externally a mass of paler and more scattered cells is found, the precursor of the proper gray matter of the cord. Outside the cells the belt of peripheral fibres has become distinctly thicker. The cellular cord (*Sy.*) presents the same characters as before; it is thick anteriorly, gradually tapering off posteriorly; and it possesses the same bundles of cells in connexion with it, passing ventrally, and embracing the sides of the aorta. In the spinal nerve the condition of development is advanced. The superior primary division is plainly seen; the somatic branch (*So.*) of the inferior primary division (*I.D.*) is longer and larger, and in the regions of the limbs has entered their substance and has divided into dorsal and ventral branches. The splanchnic branch (*Spl.*) can now be traced to a point midway between the cellular sympathetic cord (*Sy.*) and the origin of the branch from the spinal nerve. It is most evident in the thoracic region. In the neighbourhood of the origin of the trachea and anterior to that, it could not be found. There the cellular cord was very distinct; the superior primary division and somatic branch were visible, but so far as I could discover, no splanchnic branch was present.

In transverse sections of Rat embryos at about 10 days, hardened in spirit and stained with aniline blue-black (Plate 23, fig. 7), the cellular cord of the sympathetic (*Sy.*) has much the same characters as in the last case. It still presents in continuous sections a uniform thickness. Cellular outgrowths from it (*Br.*) can be traced ventrally round the aorta, especially in the region of the kidney, and in front of it, to form the collateral ganglia, and to join the suprarenal bodies. Behind that point the cord becomes attenuated. The spinal nerve shews an advanced condition of development. The superior primary division (*S.D.*), though well formed, is not yet differentiated into its separate roots. The somatic part (*So.*) of the inferior primary division (*I.D.*) is seen divided into its dorsal and ventral branches (1.2.). The splanchnic part (*Spl.*) is very evident in the region in front of the kidney. Each branch is thick, and directed inwards above the cardinal vein (*C.V.*); and reaches almost, but not quite, up to the sympathetic cord. The interval between the two varied slightly in different nerves, but in no single case was the junction perfectly evident. Round the end of the splanchnic branch are large fusiform cells which obscure the ends of the nerve fibres, probably mesodermal cells, which are proceeding to form the sheaths of the nerves, possibly cells derived from the sympathetic cord and pursuing a central direction. The nerve fibres throughout the spinal nerves are larger than before, and appear in the form of wavy bands.

In transverse sections of Mouse embryos at about 11 days (Plate 24, fig. 8), hardened in picric acid, and stained with borax-carmine, development is further advanced. The spinal cord is more fibrous; the anterior commissure is thicker, and the decussation of fibres within it more evident. The superior primary division of the spinal nerve (*S.D.*) is now traceable to two independent roots, one dorsal, the other ventral. The splanchnic branch (*Spl.*) has now joined the sympathetic cord (*Sy.*). The fibres on entering the mass present, in transverse sections, cut ends, and cannot be traced into direct communication with the cells. Surrounding the junction of the nerve with the cellular cord are groups of cells, some of them in continuity with, and apparently forming part of, the sympathetic cord, others resembling the blastema cells surrounding the splanchnic branch. Some of the cells of the sympathetic cord are ovoid, or occasionally stellate in transverse section, with one long process directed towards the nerve, and others radiating in different directions, chiefly towards the aorta. These processes can be seen joining others from neighbouring cells of the mass, in the midst of which the fibres of the splanchnic branch can be seen coursing downwards and inwards. The splanchnic branch was not traced beyond the sympathetic cord. The latter was lost in the region of the neck in front, and in the region of the hind limb behind.

In transverse sections of Rat embryos, at about 12 days, hardened in picric acid, and stained with borax-carmine, general development has advanced a stage (Plate 24, fig. 9). The cells of the intermediate cell mass have grouped themselves closely round the notochord (*No.*), in process of vertebra formation. The cells of the spinal cord (*Sp.C.*) are more distinctly separated into two groups, and the fibrous belt is thicker, especially near the origins of the spinal nerve-roots. The ventral root-fibres are seen to be in direct continuity with the cells of the spinal cord; the dorsal ganglion has its cells more regularly arranged in vertical rows. The divisions of the spinal nerves have increased in length, and are more distinctly differentiated. The splanchnic branch (*Spl.*) can, in transverse sections, be traced into the sympathetic cord, with which it is directly connected. In the thoracic region its fibres can be traced proximally through the spinal nerve and into continuity with both dorsal and ventral roots. Distally, its fibres can be traced into direct connexion with the cells of the sympathetic cord. In some cases the fibres are traced into the mass, and their cut ends appear in transverse sections. In the anterior part of the thorax, the fibres cannot be traced beyond the sympathetic cord. In the region of the neck, and in front of the origin of the vertebral artery, no splanchnic branch at all could be found joining the sympathetic. In some situations—especially in the region of the stomach —the splanchnic branch is divisible into two bundles of fine wavy nerves, one of which joins the sympathetic, and either communicates by its fibres with the cells, or is directed forwards or backwards in the cellular column; the other bundle passes round the sympathetic cord, and can be followed in a ventral direction for some distance, in the interval between the aorta and cardinal vein. Here the wavy fibres are surrounded by large blastema cells, which lie pressed against their side; among them, also, are seen other cells, directly continuous by their processes with the cells of the sympathetic cord. In other places, even more distinct cellular branches proceed peripherally from the latter, round the aorta, to form plexuses, collateral ganglia, &c. The sympathetic itself has much the same constitution as before, the noteworthy points in its structure being found at the ends. Posteriorly it narrows, and finally disappears at the point of bifurcation of the aorta. Traced forwards, it becomes thicker, attaining its greatest size near the origin of the vertebral artery. It here gives off a slender fibro-cellular cord which accompanies that vessel, and itself suddenly narrows and becomes decidedly fibrous. It soon swells out again, and resumes its cellular characters, and in this form is traceable to the level of the top of the pharynx, along the common and internal carotid arteries. Lying near the ganglion of the vagus, it becomes gradually narrower, and can be followed only as a thin fibrous cord along the carotid artery, as it courses beneath the auditory capsule, where it finally disappears.

In Rat embryos, at about 13 days, hardened in spirit, and stained with aniline blue-black, the sympathetic cord can be followed backwards as far as the middle sacral artery, and slightly behind the bifurcation of the aorta. In coronal sections in the thoracic region, it shows no constriction whatever; it is composed of fusiform cells arranged longitudinally, with nerve fibres coursing forwards and backwards among them, derived from the splanchnic branches of the spinal nerves, which can be seen to enter the cord obliquely, the fibres diverging and being traceable for some distance. The cellular branches from the sympathetic cord have now extended still further in a ventral direction, and the formation of the collateral ganglia and suprarenal bodies is more advanced. The splanchnic branches first become evident and join the sympathetic cord at the point where the dorsal aorta becomes single and median. In front of that point there was no evidence of a splanchnic branch joining the sympathetic cord. Again, behind the bifurcation of the aorta no splanchnic branches could be found. Between these points they were distinct and evident. In the region of the stomach and kidney the splanchnic branch was most clearly divisible into two parts, one joining the sympathetic, and the other passing round the outer side of it accompanied by a cellular branch from the cord, to join the semi-lunar ganglia, or solar plexus.

In Rat embryos about 14 days, stained with borax-carmine or aniline blue-black, the mesoderm has begun to show signs of cartilage formation. At this date the sympathetic cord still presents no sign of constriction, except at the anterior end. At the point of origin of the vertebral artery—the point to which it could originally be traced—it becomes narrow, its tenuity being due to the presence of nerve-fibres, and largely to the absence of cells. Having given off a large fibro-cellular cord, which accompanies the vertebral artery, it again swells out to form the "superior" cervical ganglion. This lies close to the ganglion of the vagus, with which it appears to communicate. It can be traced, as before, along the internal carotid artery to the auditory capsule, beneath which it becomes first fibrous, and then, gradually attenuating, finally disappears. The vertebral artery at its origin is completely surrounded by the cellular cord. There is no change at the caudal end.

The splanchnic branches in the thoracic and lumbar regions can now be traced proximally to the roots of the spinal nerves, and are found to receive fibres from both, especially the ventral roots. In the neck, in front of the origin of the vertebral artery, there is no sign of splanchnic branches joining the sympathetic. Branches, however, are seen springing from the ventral roots of the cervical nerves, which course horizontally inwards round the under surface of the vertebral artery, and become lost in the protovertebral mass around the notochord. These branches are situated at some distance from the sympathetic, on its dorsal aspect. As they are traced backwards successively towards the origin of the vertebral artery, they approach nearer to the cord, and finally, behind the origin of the vessel, the splanchnic branches proper appear, and partly join, partly pass over, the cord.

This latter arrangement is most obvious, however, in the posterior dorsal and lumbar regions. Here the splanchnic branch (*spl.*, Plate 26, fig. 13) is distinctly formed of two parts. Each consists of fine nerve-fibres, among and around which are long fusiform mesodermal cells, forming a sheath for them. Reaching their extremities, the fibres of each portion separate into bundles of fine, wavy fibrils. These fibrils, in the case of that portion (α) which joins the sympathetic (*Sy.*), join the cells or separate out among them. The portion (β) which passes beyond the sympathetic cord, is accompanied by a cellular branch (γ) derived from the latter, and the two proceed in a ventral direction round the aorta. Around the cœliac axis, the cellular branches from both sides, coursing round the aorta, are now seen to unite together to complete the solar plexus. Both splanchnic branch and cellular branch from the sympathetic are larger and longer than before.

In transverse sections of a Human embryo about the end of the first month, hardened in spirit and stained with aniline blue-black, the sympathetic cord has very much the characters just described. The cord itself is large and uniform in width, widening out anteriorly to form the inferior cervical ganglion; beyond this it narrows, encloses the subclavian artery, and forms a fibrous cord; this again becomes cellular, and widens out into the "superior" cervical ganglion. No splanchnic branches join the cord in front of the level of the inferior cervical ganglion. In the thorax (Plate 28, fig. 16) the splanchnic branches are seen (*spl.*) arising from both roots of the spinal nerve (*I.D.*), and, as in the figure, terminating wholly in the sympathetic cord (*sy.*). Sometimes a small portion of a splanchnic branch can be traced round the ventral side of the cord, accompanied by a cellular branch from it. In the hinder thoracic region, a small part only of the splanchnic branch joins the cord, the greater part, along with cellular outgrowths from the sympathetic, passing onwards to form the solar plexus and semi-lunar ganglia, which are seen in process of formation on the ventral aspect of the aorta. A similar fibro-cellular bundle passes to join the suprarenal body. In the lumbar region the splanchnic branch can be seen for a considerable distance almost entirely unconnected with the sympathetic cord, and separated by an interval from it. The cord gradually narrows as it is followed backwards, and, becoming attenuated, disappears at the point of bifurcation of the aorta.

In Rat embryos at about 15 days, stained with borax-carmine or aniline blue-black, there is not much further change. The sympathetic cord has much the same extent as before (Plate 27, figs. 14 and 14A, *Sy.*); is uniform in width for the most part (except that it is considerably thickened in the situation where the fibro-cellular bundle arises to join the solar plexus, semilunar ganglion, and suprarenal body); and consists of cells which, especially anteriorly, are long, narrow, and fusiform, with deeply stained round or oval nuclei, and terminal filiform processes. In some cases the cells seem almost converted into fibres. Near the posterior end the cells are wider and shorter. The cell processes are seen to join the splanchnic branches directly. Careful examination of the anterior nerves strengthens my confidence that the first splanchnic branch which joins the sympathetic does so just behind the origin of the vertebral artery.

In older embryos the sympathetic cord presents similar characters, modified by the collateral development of other parts and organs. In Mouse embryos of 17–18 days (Plate 25, fig. 10, and Plate 28, fig. 15), in which the cartilages have become evident, the cord is still uniform and unsegmented. The cervical part of the cord is unaltered; the "superior" cervical ganglion terminates as before, in front and behind. The cervical splanchnic branches do not join the sympathetic cord. The "inferior" cervical ganglion is joined by fine splanchnic branches, along which cellular branches can be seen coursing towards the ventral roots of the spinal nerves. In the thorax the cord is uniform, diminishing in diameter from before backwards. In transverse sections it is oval at the points where the intercostal arteries cross it, round in intermediate situations. The splanchnic branches arise from both spinal nerve roots, and in the anterior part of the thorax appear to join the sympathetic cord entirely; in the hinder part of the thorax they partly join, and partly pass, the cord. Cellular branches can be traced ventrally from the sympathetic, as well as others, which pass centrally along the splanchnic branches of the nerves. The whole thoracic portion appears much more minute than in younger embryos, on account of the great strides which other parts have taken in development. It narrows gradually to the level of the diaphragm, and as it passes through this it becomes very minute. Behind the diaphragm, and in relation to the liver, the cord is greatly increased in thickness, and gives off considerable bundles, partly fibrous, partly cellular, to form the solar plexus, suprarenal body, &c., and derived partly from the splanchnic branches directly, partly from the sympathetic cord. Behind that the cord again gradually narrows; the splanchnic branches in some sections wholly (as in fig. 10) join the cord; in others can be seen passing alongside it towards the mesentery, accompanied by a cellular stream from the sympathetic. In the lumbar region the splanchnic branches are very long and fine; they arise from both spinal nerve roots. They cease behind at the bifurcation of the aorta. None were found behind that point. Behind that level the cord gradually tapered off and lay in relation to the middle sacral artery, behind which, near its termination, a junction seemed to be effected between the cords of the two sides.

The connexions of the spinal nerves and sympathetic cord have now been sufficiently described. First a cellular, unsegmented column, the sympathetic, appears on each side of the middle line in the neighbourhood of the aorta. This is, secondarily, joined by branches from the inferior primary divisions of certain spinal nerves, which have a definite origin and distribution. They are fundamentally spinal nerves, deriving their origin from both dorsal and ventral roots, and being formed by the division of the inferior primary division into two branches, onesomatic, the other (the nerve in question) splanchnic. Coursing downwards and inwards, they reach the sympathetic cord. Here the splanchnic branch terminates in one of two ways. It may end entirely in the sympathetic cord, as seems to occur in the anterior part of the thoracic region. [This mode of ending is not absolutely certain. It may be only apparent from the manner of section of the nerve trunks.] On the other hand, in the hinder dorsal and lumbar regions, the splanchnic branch on reaching the cord divides into two parts, one of which joins, the other passes beyond the cord. In either case the splanchnic fibres which join the cord become directly connected with the component cells. The connexion between the spinal nerves and sympathetic cord is, therefore, to be regarded as quite a secondary connexion.

In certain regions no such connexions can be made out. Behind the kidney and bifurcation of the aorta (*i.e.*, behind the lumbar region) the splanchnic branches cease. In front of the fore limbs and the origin of the vertebral arteries (*i.e.*, in the cervical region) the splanchnic branches do not join the sympathetic. In comparatively advanced embryos distinct nerves, analogous to the splanchnics, course inwards round the vertebral artery to the tissues lying round the growing vertebræ and beneath the spinal cord, but occupying a position altogether dorsal to the sympathetic cord and unconnected with it.

The regions, in short, where the sympathetic cord is joined by the splanchnic branches are those in which it lies in relation to the main vascular trunks—in the line of the embryonic aorta.

3. *Formation of the Sympathetic Ganglia.*

Up to the time of the formation of the cartilaginous vertebral *centra* there is no gangliation or constriction of the main sympathetic cord. Sagittal sections of embryos prior to this date have already been referred to and their characters noted. These are exemplified in Rat embryos of 8 days (Plate 26, fig. 11), of 10 days (fig. 12), of 15 days (Plate 27, figs. 14 and 14A), &c.

In sagittal sections of Mouse embryos of 17–18 days (Plate 28, fig. 15) the vertebral *centra* (*V.S.*) are distinctly cartilaginous, connected together by dense masses of cells, and plainly demarcated from the surrounding tissues. The segmentation of the body is also indicated by the intercostal vessels (*Int.*) lying opposite to the vertebral *centra*. Along the sympathetic cord there are seen at places, in successive series of sections and in relation to these segments, occasional bulgings. These are rare, however; sections through a considerable length of the cord at its thickest part show it as an unconstricted column (*Sy.*, fig. 15), composed of large fusiform cells with terminal processes, and with large, deeply-stained nuclei.

Sagittal sections of a Human embryo, about $\frac{3}{4}$ in. in length, hardened in spirit, and stained with aniline blue-black, show a slightly later condition (Plate 30, fig. 19). They are very instructive, as indicating the manner in which the gangliation of the sympathetic cord occurs. The several parts of the vertebræ are already moulded in cartilage, the intervals between the *centra* being filled up as before with embryonic cellular tissue. When serial sections of this embryo are examined, the first indication of the presence of the sympathetic cord is found in isolated, segmentally-arranged masses, which in successive sagittal sections grow larger and larger, gradually fuse together, and give rise to a continuous fibro-cellular cord. The condition of the cord (*Sy.*), cut through in its thickest part, is indicated in fig. 12. It is mainly cellular, uniform in width except at certain points, and with a considerable admixture of nerve fibres on its ventral aspect. It is joined, dorsally, in the intervals between the vertebræ, by the splanchnic branches of the spinal nerves (*Spl.*), and at these "nodes" the cord has a greater width than in the intervals between them.

In this condition is seen the first commencement of gangliation or nodulation of the sympathetic cord. Two causes produce it: (1) the union of the splanchnic branches. This causes the cord at a given spot to attain a larger size, by the accession of a bundle of nerve fibres, some of which join the cells of the cord, and so insure their permanent occupation of that spot, as the cells of the ganglia; and (2) the position of the cord in relation to the vertebral column. By the growth of the latter the cord is stretched, and the part lying against the vertebral somites is elongated and narrowed, and is indented by the growing vertebræ and intercostal vessels, the result being the formation of a longitudinal fibro-cellular commissure connecting the nodes or ganglia together. The ganglia themselves are permitted to increase in size, by their position, and by their connexion with the splanchnic branches of the spinal nerves. The commissures, at first cellular, become fibro-cellular, and afterwards fibrous, owing to the admixture of spinal fibres, and apparently also to the conversion into fibres of the original cells of the cord. By the formation and gradual constriction of the commissures the ganglia are made still more definite.

This process of ganglion formation, due primarily to these two causes, can be followed in older embryos; but as the parts gradually attain their adult form the regularity of alternate swelling and constriction is not so evident. As the ganglia become defined in form, their position tends to become irregular. While one may lie in the interval between two vertebræ, the next may be seen opposite the vertebra itself. Again, two ganglia may be co-terminous, not by fusion, but from the fact that separation is incomplete. This arrangement is shown in Plate 29, fig. 18, taken from a sagittal section of a Rat embryo at about 22 days. The sympathetic cord (*Sy.*) is figured in the region of the diaphragm (*Di.*), just beyond the point at which the stream of cells arises for the formation of the semilunar ganglion (*S.G.*) and solar plexus (*Sol.*). The cord is constricted at intervals, so as to form ganglia and commissures, both of which are irregular, and bear, as may be seen, no definite relation to the vertebral segments (*V.S.*) or intercostal vessels (*Int.*). The commissures are, for the most part, fibro-cellular; in some instances they are mainly fibrous; in others there are groups of cells enclosed among the fibres: while in others again there are comparatively few fibres, so that the ganglia are practically fused together. The cord is here represented in its greatest thickness; in sections on either side the irregularity of the ganglia (into which splanchnic branches can be traced) is much more marked.

From this point the gangliation of the cord gradually proceeds until the condition found in the adult is produced.

The truth of these observations has been tested by another method. Fig. 21 (Plate 30) shows life-size drawings taken from dissections of Human embryos at various ages. In the dissections made, individual variations were found in the two sides of the same body—differences in the state of gangliation of the cord, as well in the arrangement as of the spinal communications.

In an embryo in the third month (fig. 21, *A.*) the connecting branches from the spinal nerves were too fine to be seen with sufficient distinctness to warrant their being drawn. In the upper half of the thoracic region, the sympathetic cord formed a wavy band which swelled out above and below. Above, it joined the inferior cervical ganglion (*I.G.*), which was again connected by a narrower strip to the long, oval, superior cervical ganglion (*S.G.*), which occupied nearly the whole length of the neck. The vertebral (*V.P.*) and carotid plexuses (*C.P.*) were seen. The lower swelling of the dorsal band marked the origin of the first root of the great Splanchnic nerve (*G.Spl.*). In the lower dorsal region were two swellings, distinct, and connected to one another and the neighbouring parts of the cord, by short longitudinal commissures. Below these ganglia were two long oval masses separated by a slight constriction; and below these, again, were two distinct ganglia joined by commissures. The last lay free and unattached (to spinal fibres), on the cartilage representing the second sacral vertebra. It is noteworthy that the diaphragm was complete in this embryo.

In an embryo of the fourth month (fig. 21, *B.*) the cord again forms a uniform band in the thoracic region, joined by the upper nine thoracic nerves. Angular projections (ganglia ?) are seen at the junctions of the spinal branches, and also where the roots of the Splanchnic nerves arise, especially in the case of the great Splanchnic (*G.Spl.*). The thoracic band swells out above into the inferior cervical ganglion (*I.G.*), which is joined by branches from the eighth cervical and first dorsal nerves. After giving off the vertebral plexus (*V.P.*) this forms a narrow commissure on which is a minute swelling, the middle cervical ganglion (*M.G.*), and finally broadens out into the superior cervical ganglion (*S.G.*), which ends above in the carotid plexus (*C.P.*). In the lower thoracic region two constrictions separate off a small mass, which is joined by branches from the tenth, eleventh, and twelfth thoracic nerves. Below the second constriction the cord forms a broad oval band, joined by the twelfth thoracic and all the lumbar nerves. Lastly, a sacral portion is constricted off, which consists of three fairly definite ganglia and a terminal filament, the ganglia being joined by the first three sacral nerves. I was not able to trace the existence of a connecting loop between the lower ends of the two cords.

In an embryo of the sixth month (fig. 21, *D.*) a very similar condition of things was found, so that it will be sufficient to note the differences from the last example. The inferior cervical ganglion (*I.G.*) was much larger: was joined by branches from the seventh, as well as the eighth cervical, and first dorsal nerves: and the commissure connecting it with the middle cervical ganglion was double. The lumbar portion of the cord showed a faint indication of separation into four ganglia: was not joined by the last dorsal nerve: and was connected to the sacral portion by a double commissure. The existence of a fourth sacral ganglion was noted as doubtful.

In an embryo of the fifth month (fig. 21, *C.*) the condition of the sympathetic cord, in some respects, more resembled the adult state than did the cord at the sixth month. The inferior cervical ganglion (*I.G.*), after having given off the vertebral plexus and branches *to* the eighth cervical and first thoracic nerves, was continued up into the neck in the form of two incompletely separated swellings, which were joined respectively by the seventh and sixth spinal nerves. The same ganglion was continued down into the thorax as far as the junction of the second thoracic nerve—receiving roots also from the eighth cervical and first thoracic nerves,—where it gave rise to a commissure connected below with an elongated mass, joined by the three succeeding nerves. Below this were a series of co-terminous ganglia, joined on the one hand by the lower thoracic nerves, and on the other giving off the roots of the Splanchnic nerves. The disposition of the cord in this portion of its extent appears to indicate the mode in which the individuality of the ganglia arises. The eleventh thoracic nerve was connected with two small ganglia; the twelfth was joined by three branches to two other ganglia. In the loin a single oval mass was found, joined by long, fine branches from the lumbar nerves. This was joined by a delicate commissure to the sacral ganglia, which were three in number, the first connected with two, the other two each with one sacral nerve.

These dissections could not, alone, be taken as proof of the original absence of segmentation of the sympathetic cord. When, however, they are compared with one another, and with the disposition of the adult cord, and are considered also in the light of the foregoing investigations, they lend support to the view that at an early date gangliation of the cord has not occurred, but that it is due to later collateral changes in the cord itself, and in the surrounding parts.

The only observation I am acquainted with dealing with this question from the point of view of comparative anatomy is one by SWAN. He figures the cord in the Snake as being imperfectly gangliated; and he describes it as resembling a band rather than a chain of ganglia. This observation I have had opportunities of repeating, with the result that I have found the cord precisely as he figures it.

4. *Cephalic and Caudal Terminations of the Sympathetic Cord.*

a. Cephalic termination; superior cervical ganglion; vertebral and carotid plexuses.

The embryonic cord when first formed can, in transverse sections, be traced forwards as far as the cephalic border of the fore-limb: in sagittal sections to the level of the mouth, or first vertebral segment (Rat, 8 days, Plate 26, fig. 11). As growth continues and the large vessels are better developed, the cervical part of the cord lies in distinct relationship to the large arteries. It very plainly divides into two parts at the point of origin of the vertebral artery. One fibro-cellular cord accompanies that vessel, having arisen from the main cord at the point where the artery crosses it. Growth still proceeding, this part of the cord becomes more and more fibrous, until at length it assumes a condition characteristic of the adult vertebral plexus, and is gradually lost on the anterior part of the vessel.

The other division, or main part of the sympathetic cord, accompanies the common and internal carotid arteries, at first only to the level of the mouth, where it forms a pointed extremity composed of cells, or a brushlike ending of cell processes. Growing larger along with the growth of the neck, this part of the cord becomes more and more constricted off from the part of the cord lying behind the level of the vertebral artery, by the formation of a fibrous commissure. A fibro-cellular mass is thus formed, which represents the "superior" cervical ganglion. The commissure connecting it posteriorly to the main cord is formed, partly by direct conversion of the cellular elements into fibres: partly by the passage into it of fibres derived from the anterior thoracic splanchnic branches. In this way the presence of a middle cervical ganglion may be explained, as representing a mass of cells derived from the elementary sympathetic cord which have been included among the fibres of the growing commissure.

From the anterior end of the growing mass of the superior ganglion, a narrow bundle of fibres arises, which is closely applied to the internal carotid artery in its course beneath the auditory capsule. This bundle can be followed for a considerable distance, and is gradually lost upon the vessel, forming the carotid plexus. In fig. 17 (Plate 29), the anterior end of the cervical ganglion (*Sy.*) is shown in a sagittal section of a Mouse embryo of 17–18 days, along with this fibrous bundle accompanying the internal carotid artery (*Art.*) beneath the Eustachian tube (*Eust.*). In this embryo the stream of fibres forming the vertebral plexus has much the same appearance as that shown in the figure.

These parts—the vertebral and carotid plexuses, and superior cervical ganglion—I regard as pertaining to the collateral portion of the sympathetic system, for the following reasons:—(1), they are out-growths from the main cord (the ganglion, fundamentally a part of the original cord, undergoes extensive growth, and becomes soon constricted off from the main cord); and (2), no splanchnic branches enter this part of the cord. This agrees with GASKELL's conclusion regarding the ganglion, which from morphological considerations he regards as belonging "to the distal rather than to the proximal group of ganglia."

b. Caudal Termination.

In the youngest embryos in which the sympathetic cord was found (Rat, 8 days,

p. 166), behind the point at which the mass of cells arises for the formation of the suprarenal body, the cord is irregular in form, and composed of cells less closely packed together than in anterior regions. At a slightly later period it has extended further backwards (Rat, 12 days, Plate 27, fig. 14A), and becoming attenuated is lost at the point of bifurcation of the aorta. In still older embryos it passes further backwards on each side of the middle sacral artery, and on the dorsal aspect of the rectum, from which it is separated by cellular tissue.

In Rat embryos of 22 days the cord (*Sy.*, Plate 30, fig. 20) can be traced backwards in successive transverse sections for a considerable distance, lying in the interval between the middle sacral artery (*m.s.*) and its accompanying veins (*v.v.*). The cords of the two sides approach one another as they pass backwards. Cellular branches (*Br.*) arise from them at intervals, and are directed downwards between the vessels. The cords themselves are more irregular in form than anteriorly, and are not joined by splanchnic branches. Near their posterior terminations, having approached very close to one another, they become connected here and there by transverse cellular commissures (*Co.*) of which one is represented in fig. 20. These are not in direct continuity with one another, but are separated by intervals, and beyond them the two cords taper off, and finally are lost in the undifferentiated mesoblast above the middle sacral artery. These commissures, which lie close together, and are formed by the fusion of outgrowths from the two cords, apparently give rise to the fibres connecting the adult coccygeal ganglia together, which form the loop containing the coccygeal ganglion, or *ganglion impar*. It is only in an advanced condition of development that the fusion of the two cords can be made out; until they have reached their ultimate limits the fusion does not take place.

The posterior, like the anterior end of the sympathetic cord, may be regarded as an outgrowth from the original cord. It is formed by an extension of the cord backwards along the main vascular trunks, and it likewise receives no splanchnic branches from the spinal nerves.

5. *Collateral Distribution.*

(*a.*) The development of the superior cervical ganglia, the carotid and vertebral plexuses, has already been traced, and the opinion has been expressed that these structures properly belong to the collateral distribution of the sympathetic cord.

(*b.*) Regarding the formation of the peripheral branches, and collateral ganglia of the sympathetic, my investigations in the main support the conclusions arrived at by REMAK (5, 6). As already noted, cellular buds or branches arise from the sympathetic cord (figs. 7 and 13, Plates 23 and 26), and accompany the parts of the splanchnic branches of the spinal nerves which pass beyond it. These cellular outgrowths gradually increase in length and thickness. They consist of cells which resemble in every way those of the sympathetic cord itself. They communicate by their processes with one another and with the cells of the cord; and, especially in the hinder part of the thoracic region, form considerable masses traceable along the main vessels. In older embryos (Plate 29, fig. 18, Rat, 22 days) they form ganglia and nerves, in the way already described for the main cord; and, in the region referred to, give rise to the Splanchnic nerves, semilunar ganglia, &c. These branches appear to follow in their development the same line of growth as the splanchnic branches of the spinal nerves; although they are equally evident in places where the latter are not seen.

(*c*.) The mode of development of the gray *Rami communicantes* I have not made out with perfect satisfaction. They appear to take their origin from the sympathetic cord as cellular outgrowths, which in some cases are traceable along the splanchnic branches of the spinal nerves towards their roots; but on this question I must withhold a definite opinion until supported by more conclusive evidence. I have not been able to satisfy myself about their formation in places where the splanchnic branches are absent, or are unconnected with the sympathetic cord.

(*d*.) The relation of the sympathetic cord to the development of the suprarenal bodies is very evident in younger embryos. A considerable column of cells (Plate 27, fig. 14A) can be traced in sagittal sections from the ventral aspect of the main cord, downwards and backwards, to join a mass of mesoblastic cells situated at the anterior end of the embryonic kidney (*K*.). Entering this mass the cellular column spreads out, so as to constitute the central portion or medulla of the suprarenal body (*Sr.C.*), while the tissue around forms the cortex. This agrees, in general terms, with the mode of development of the suprarenal bodies described by previous observers (13, 16, 17, 18). It must be borne in mind that according to this view the *whole* of the Mammalian suprarenal capsule is mesoblastic. The connecting stalk becomes converted into nerve fibres connecting the suprarenal body to the sympathetic cord.

III. Conclusions.

A. *The Development of the Sympathetic System.*

The following are the principal conclusions derived from the preceding investigations:—

1. The formation of the main sympathetic cord is the first event. It is developed as a cellular rod or column, uniform in outline, and without ganglia or constrictions. It is formed in, and derived from the mesoblastic tissue on either side of the embryonic aorta, and in front of the growing vertebral column. The cord appears after the formation of the roots and ganglia of the spinal nerves, and is entirely independent of them at first.

2. The connexion of the spinal nerves with the main sympathetic cord occurs secondarily. The inferior primary division of a (typical) spinal nerve divides, on reaching the junction of body wall and splanchnopleure, into a somatic and a splanchnic

branch. The splanchnic branch grows gradually in a mesial and ventral direction, towards the sympathetic cord, with which it finally becomes connected. It generally divides into two parts, of which one joins, the other passes beyond, the sympathetic cord. The fibres which join the cord are traceable into direct continuity with its cells, or can be followed forwards or backwards in its substance. The part of the splanchnic branch which does not join the sympathetic, can be traced beyond it into the splanchnic area.

This arrangement obtains for the spinal nerves in the posterior thoracic and lumbar regions. In the anterior part of the thorax the whole of the splanchnic branch appears to be joined to the sympathetic cord. Behind the level of the bifurcation of the aorta no splanchnic branches were found. In the neck, above the point of origin of the vertebral artery, they are unconnected with the sympathetic cord. Instead, they proceed from their origin in a ventral and mesial direction external to the vertebral artery, and round that vessel, to be distributed to the tissues of the neck lying on the dorsal aspect of the sympathetic cord.

These splanchnic branches correspond to the white *Rami communicantes.* Tracing them back to their origin they are found to be derived from both the dorsal and the ventral root of the spinal nerve, of which the latter usually contributes the greater number of fibres.

The gray *Rami communicantes* appear to arise from the sympathetic cord as cellular outgrowths, which find their way along the splanchnic branches towards their central connexions. They thus may be regarded as belonging to the group of collateral branches from the cord.

3. The formation of the ganglia on the main cord of the sympathetic is a subsequent event, and is subordinate to the connexion of the splanchnic branches of the spinal nerves with the cord. The causes leading to the formation of the ganglia are: mainly, the junction of the splanchnic branches, and the accession of a large number of nerve fibres at the point of entrance; the consequent persistence of the cells of the cord, which are joined by these nerves, as ganglion cells; and to a less extent, the anatomical relations of the cord to the bony segments, &c., over which it passes, which, in their growth, cause indentation of the cord at certain points.

This view is supported by the condition of affairs found in dissections of Human embryos at various periods of development (3–6 months), where the cord has the form of a band or strip, rather than a regularly nodulated chain: and by the evidence derived from the normal adult structure, where the "segmentation" of the cord is apparent, rather than real.

4. Cephalic termination. The parts derived from the sympathetic cord in the neck in front of the "inferior" cervical ganglion, may be regarded as belonging to the peripheral or collateral distribution of the nerve. A fibro-cellular bundle springs from the cord and accompanies the vertebral artery; beyond this the original cord, which is, at first, limited anteriorly at the level of the mouth, becomes constricted by

the formation of a fibro-cellular commissure, separating off the "superior" cervical ganglion. This ends anteriorly in a fibrous bundle, which accompanies and is lost upon the internal carotid artery, beneath the auditory capsule. The "middle" cervical ganglion, when present, is to be regarded as formed of a group of cells which have been included in the commissure connecting the superior ganglion with the main cord, and which have persisted. The connexions of the sympathetic cord with the cranial nerves have not been thoroughly investigated, and reference to them has been purposely omitted, as they bear no direct relation to the development of the main cord.

The reasons for placing the parts named in the category of peripheral branches are that (1) they are essentially out-growths from the main sympathetic cord, and (2) no splanchnic branches join them from the spinal nerves.

5. Caudal termination. The sympathetic cord is at first ill-defined behind the region of the kidneys; it gradually extends further back, alongside the aorta and middle sacral artery, where the two cords become closely approximated. They become gradually more and more attenuated, and finally disappear. Near their termination they are joined together on the dorsal aspect of the middle sacral artery by cellular commissures, from which the connecting loop and *ganglion impar* are developed. No fusion of the two cords can be seen until they have reached their permanent posterior limit. The sympathetic cord behind the lumbar region may be regarded as belonging to the peripheral distribution of the cord for the same reasons as the cervical portion.

6. The peripheral branches from the sympathetic cord, including the collateral ganglia, as well as the medullary portions of the suprarenal bodies, the superior cervical ganglia, &c., are formed by out-growths from the cord, which are at first cellular. These give rise to ganglia, nerves and plexuses, and are accompanied by the parts of the splanchnic branches of the spinal nerves which do not join the ganglia. In this category are placed doubtfully the gray *Rami communicantes.*

B. *The Morphology of the Sympathetic System.*

1. *The Secondary Segmentation of the Sympathetic Cord.*

It has been shown that the main cord of the Mammalian sympathetic is primarily unsegmented, that in comparatively old Human embryos the differentiation of ganglia and longitudinal commissures is not definite, and that in the adult sympathetic cord there is no certain indication of true segmentation, except in the obviously metameric splanchnic nerves, which are connected with it. Now, in this respect, the sympathetic cord does not differ from, but agrees with, not only the other elements of the nervous system, both in vertebrates and invertebrates, but also with all other longitudinally placed structures in the body. It agrees, firstly, with the medullary tube, forming the cerebro-spinal axis, which, so far as present evidence goes, is formed without any sign of segmentation, the spinal nerves being secondary and subordinate formations.

Again, the gangliated cords of invertebrates, which are formed from epiblast, are at first developed as solid, uniform, and unconstricted columns, which only secondarily become constricted and gangliated. A second reason in support of the view here propounded is that we possess, in the gangliated cords of the sympathetic, bilaterally symmetrical structures, placed along the bony axis of the trunk, in relation to the main vascular and alimentary tubes. On the one hand, there is no evidence of strict segmentation in the branches distributed peripherally from these cords; and, on the other hand, the parts over which they preside—the heart, blood-vessels, lungs, intestinal tract, &c.—are all morphologically unsegmented, like other parts and organs in the Mammalian trunk which are longitudinally placed. The cerebro-spinal axis, the notochord, heart, vascular system, alimentary canal and diverticula, ureters, &c., present no signs of being developed in a segmental manner. In fact, it might be formulated as a morphological law, to which the sympathetic cord is no exception—*that longitudinally-placed structures, whether single and median, or laterally placed, are primarily and uniformly unsegmented.**

2. From the morphological point of view, however, the most important conclusions derived from the investigations recorded above are undoubtedly the following:—

a. The independent origin of the sympathetic system, and its secondary connexion with the cerebro-spinal system.

b. Its development from the mesoblast.

Both these points are of interest, more particularly because, on the one hand, the sympathetic system has previously been regarded as a specialised portion of the general nervous system; and, on the other hand, there is no fact in embryology more firmly established than this, that whenever a nervous system is present, it is developed from the epiblast.

As the foregoing observations are confined to Mammals—a highly specialised group of vertebrates—it may be objected that, until other and more primitive groups are investigated, it is unwise to draw conclusions of so general a nature. On the other hand, I would venture to urge the following considerations:—

(1) In maintaining the independent and mesoblastic origin of the sympathetic, one is supported by the investigations of a considerable number of embryologists (p. 161), including REMAK, who studied the subject in the Chick, the main difference between REMAK's view of the development of the Avian sympathetic system and the observations made in Mammals being in regard to the primary or secondary segmentation of the main sympathetic cord.

* The longitudinal muscles of the trunk form an apparent exception to this rule, but an exception which in reality may be said to prove the rule. Formed from the muscle plates, and strictly segmental in origin, they retain this character in their fully-formed condition, being, as regards their deeper layers, closely related to the various body segments, in relation to which they are formed. With regard to the fusion of the segmental masses in their superficial parts to form elongated longitudinal muscles passing over several segments (and joints), they follow the same laws as are found to govern the development and evolution of muscles in other parts of the body.

(2) My own investigations reveal definitely the earliest appearance, and the complete history of the formation of the sympathetic system in Rodents (a comparatively primitive group of Mammals); and distinctly indicate the existence of a considerable period during which the sympathetic cord is entirely independent of the cerebro-spinal system.

(3) Investigators who have assigned an epiblastic origin to the sympathetic system differ materially as to the actual mode of development. As already stated (p. 162), BALFOUR regards the sympathetic ganglia (in Elasmobranchs) as outgrowths from the spinal nerves; while ONODI (working at the same group) maintains that they are direct proliferations from the spinal ganglia. Moreover, these authors have left the history of the development of the system in an incomplete state. The earliest steps in the process have not been described for Mammals; and the ultimate and peripheral branches and ganglia have not been traced back to the epiblast. The fragmentary nature of the observations, and the divergence of opinion regarding them, show that further investigations are necessary before the origin of the sympathetic system as an outgrowth from the cerebro-spinal system can be accepted as proved even for any group of vertebrates, still less for all.

(4) Besides the embryological facts recorded in the preceding pages, it may be further pointed out that there are strong grounds, histological and physiological, for drawing a sharp distinction between the sympathetic and the cerebro-spinal nervous systems.

The cells comprising the sympathetic ganglia differ from those of the spinal ganglia in histological character, the latter being rounded, the former angular. In birds, RAMAGE (25) describes the difference as being very evident, "que les cellules des ganglions sympathiques étaient nettement multipolaires, et qu'il était facile de les distinguer de celles du ganglion spinal, qui sont sphériques et unipolaires." The fibres of the sympathetic system are essentially different from those of the cerebro-spinal system, being non-medullated branching fibres.

Physiologically also, the sympathetic is clearly distinct from the cerebro-spinal system. Its functions appear to be to direct and regulate the distribution of certain nerves which emanate from the cerebro-spinal axis. The ganglia are not stated by physiologists to be either automatic or reflex, but only trophic, from which we may infer that they have a "vital influence" over the parts within their jurisdiction. The ganglia apparently neither augment, diminish, nor alter the character of the nerve impulses which permeate them.

From these considerations it may be regarded as very possible that under the term "sympathetic nervous system" are included two structures, entirely independent in nature, origin, and function, the *sympathetic* system, and the *nervous* system proper. Such a view would be in entire harmony with the mode of development described above, and would render more intelligible than has hitherto been possible certain developmental peculiarities, such as the conversion of part of the sympathetic system into the suprarenal bodies.

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Explanation of Plates 22–30.

The figures of embryonic sections are in some cases compiled from several successive sections, as, for example, when a nerve had to be followed for some distance.

PLATE 22.

Fig. 1. Transverse section of Rat embryo (5–6 days) in thoracic region. *Sp.C.*, spinal cord; *No.*, notochord; *M.P.*, muscle plate; *D.R.*, dorsal root of nerve; *Al.*, alimentary canal; *Ao.*, aorta.

Fig. 2. Transverse section of Rabbit embryo (7 days) in thoracic region. *D.G.*, dorsal ganglion and root; *Sp.N.*, spinal nerve; *C.V.*, cardinal vein; *Co.*, cœlom; *L.*, lung; *A.V.*, allantoic vein; *α*, somato-splanchnic angle. Other letters as before.

Fig. 3. Transverse section of Mouse embryo (8 days) in lower thoracic region. *Sp.N.*, *S.D.*, *I.D.*, superior and inferior primary divisions of spinal nerve; *H.*, heart; *W.D.*, Wolffian duct; *W.B.*, Wolffian body; *Sy.*, sympathetic cord.

Fig. 4. Transverse section of Rat embryo (8 days) in upper thoracic region. *L.*, trachea; *Art.*, carotid artery; *V.*, jugular vein; *Sy.*, sympathetic cord.

PLATE 23.

Fig. 5. Transverse section of Rat embryo (8–9 days) in lumbar region. *Sp.N.*, spinal nerve, dividing at somato-splanchnic angle (*α*) into somatic (*So.*) and splanchnic (*Spl.*) branches; *Me.*, mesentery.

Fig. 6. Transverse section of Mouse embryo (about 9 days) in lower thoracic region.

Fig. 7. Transverse section of Rat embryo (about 10 days) in lumbar region. *I.D.*, inferior primary division of nerve, dividing into somatic (*So.*) and splanchnic (*Spl.*) branches, somatic branch subdividing into dorsal or lateral (1) and ventral or inferior (2) branches; *Sy.*, sympathetic cord, showing growth of cellular peripheral branch (*Br.*).

PLATE 24.

Fig. 8. Transverse section of Mouse embryo in region of fore-limb. *S.D.*, superior primary division, arising by two roots; *Spl.*, splanchnic branch of spinal nerve joined to sympathetic cord (*Sy.*); *P.*, pleural cavity; *L.*, lung; *F.L.*, fore-limb.

Fig. 9. Transverse section of Rat embryo (12 days) in thoracic region.

PLATE 25.

Fig. 10. Transverse section of Mouse embryo (about 17–18 days) in lumbar region. *Sp.art.*, spinal artery; *V.*, vertebra (cartilaginous); *Panc.*, pancreas; *mes.*, mesentery; *K.*, kidney; *Spl.*, splanchnic branch, arising from two roots.

PLATE 26.

Fig. 11. Sagittal section of Rat embryo (about 8 days). *Sy.*, sympathetic cord; *Mo.*, mouth; *To.*, tongue; *Hy.*, hypoglossal nerve; *B. W.*, body-wall; *H.*, heart; *Per.C.*, pericardial cavity; *L.*, lung; *Pl.C.*, pleural cavity; *Art.*, carotid artery; *V.*, vein; *Va.*, vagus; *V.S.*, vertebral somites; *D.G.*, dorsal ganglia; *Br.*, brain.

Fig. 12. Sagittal section of Rat embryo (about 10 days).

Fig. 13. Transverse section of sympathetic cord (*Sy.*) in Rat embryo (about 14 days) in thoracic region. *Ao.*, aorta; *Spl.*, splanchnic branch of nerve, dividing into (α) a branch joining the cord, and (β) a branch passing beyond it—γ, a cellular branch arising from the cord, and accompanying (β).

PLATE 27.

Fig. 14. Sagittal section of Rat embryo (about 15 days), showing the anterior termination of the sympathetic (*Sy.*). *Sp.C.*, spinal cord; *Eust.*, Eustachian tube.

Fig. 14A. Sagittal section of same embryo (15 days), showing posterior termination of sympathetic (*Sy.*). *Sr.C.*, suprarenal body; *K.*, kidney; *Sto.*, stomach.

PLATE 28.

Fig. 15. Sagittal section of Mouse embryo (about 17–18 days). *V.S.*, vertebral somites (cartilaginous); *Int.*, intercostal vessels (*Cf.* fig. 10).

Fig. 16. Transverse section of Human embryo, aged about one month, in thoracic region.

PLATE 29.

Fig. 17. Sagittal section of Mouse embryo (about 17–18 days), showing anterior termination of superior cervical ganglion (*Sy.*). *Art.*, internal carotid artery.

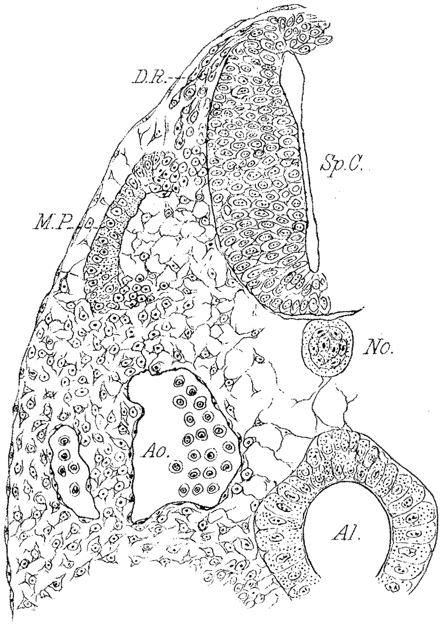
Fig. 18. Sagittal section of Rat embryo (about 22 days) in lower thoracic and lumbar regions. *Lu.*, lung; *Di.*, diaphragm; *Li.*, liver; *Pl.C.*, pleural cavity; *Perit.C.*, peritoneal cavity; *S.G.*, semilunar ganglion; *Sol.*, solar plexus; *Sy.*, sympathetic cord.

PLATE 30.

Fig. 19. Sagittal section of Human embryo, about $\frac{3}{4}$ inch long. *Sy.*, sympathetic cord, joined by splanchnic branches (*Spl.*).

Fig. 20. Transverse section through sympathetic cords (*Sy.*), middle sacral artery *M.S.A.*), and veins (*V. V.*), with peripheral branches (*Br.*, *Br.*), and a connecting commissure (*Co.*). Rat embryo (about 22 days).

Fig. 21. The sympathetic cord, from dissections of Human embryos in the (*A.*) third, (*B.*) fourth, (*C.*) fifth, and (*D.*) sixth month. *S.G.*, *M.G.*, *I.G.*, superior, middle, and inferior cervical ganglia; *C.P.*, *V.P.*, carotid and vertebral plexuses; *G.Spl.*, great splanchnic nerve, with ganglion (*X.*). Connexions with various spinal nerves, numbered in order: *C.*, cervical, 1, 2, 3, 4, &c.; *D.*, thoracic; *L.*, lumbar; *S.*, sacral.



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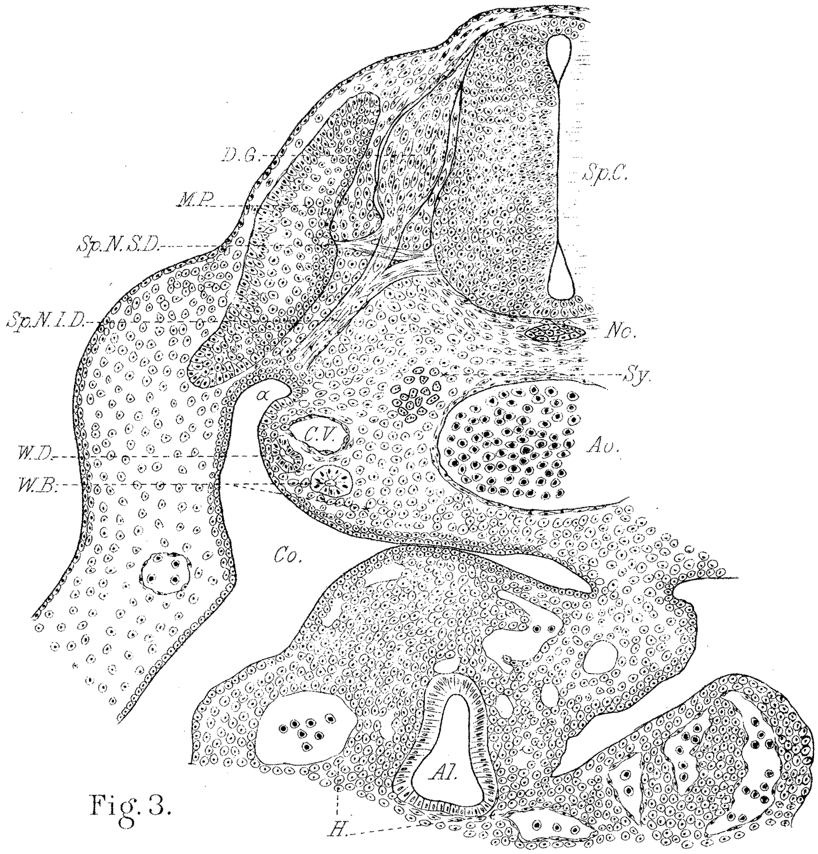

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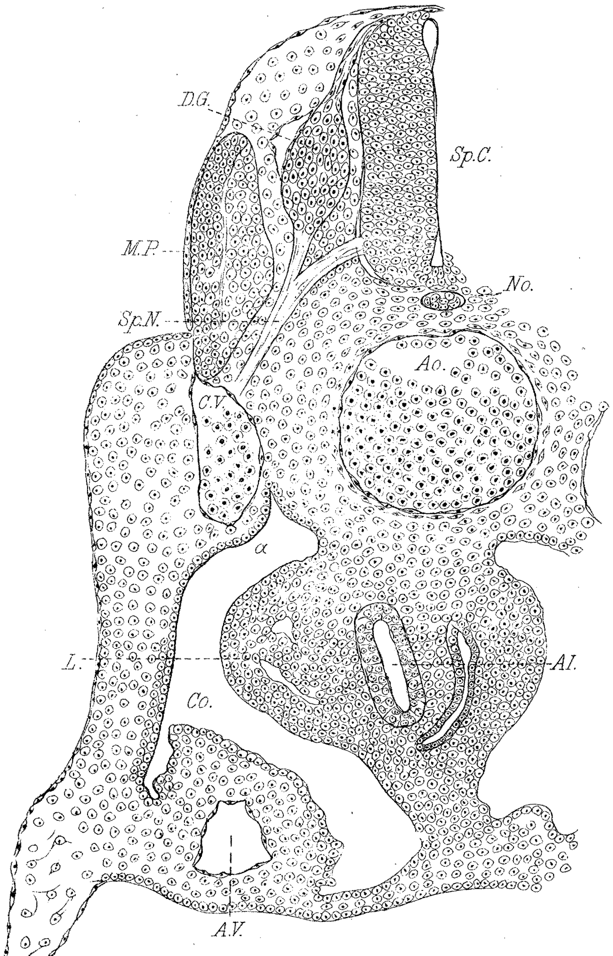

Fig 2

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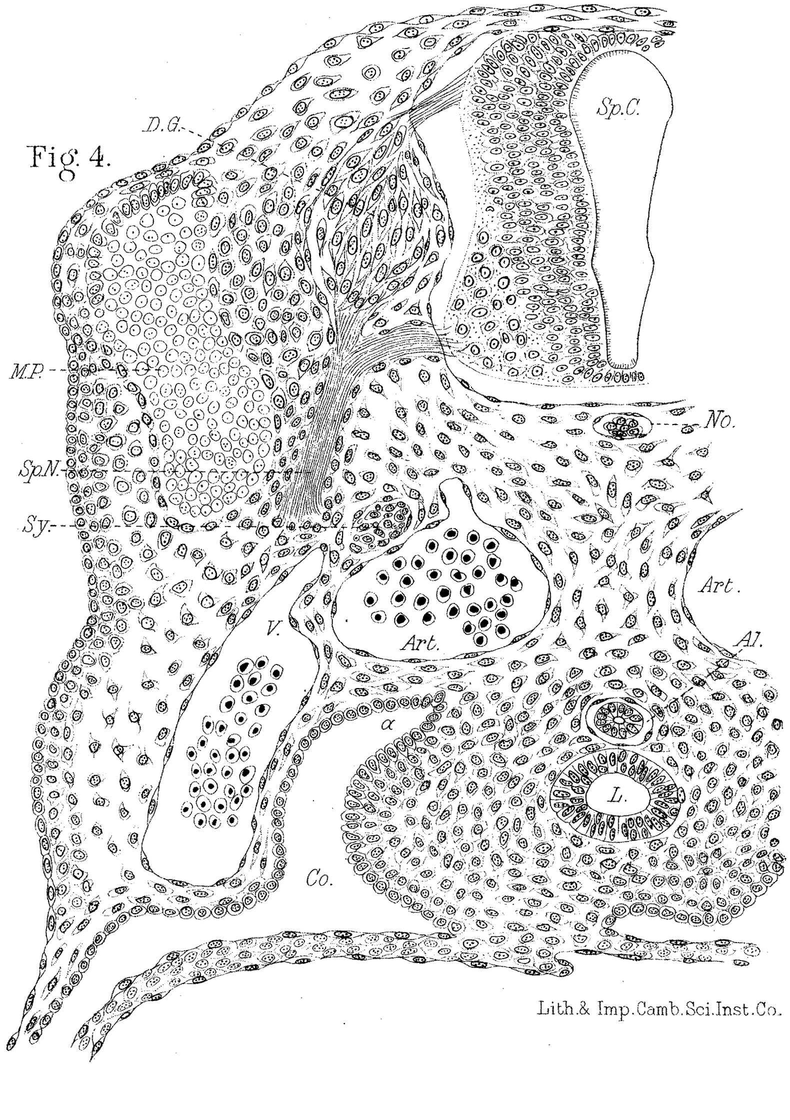

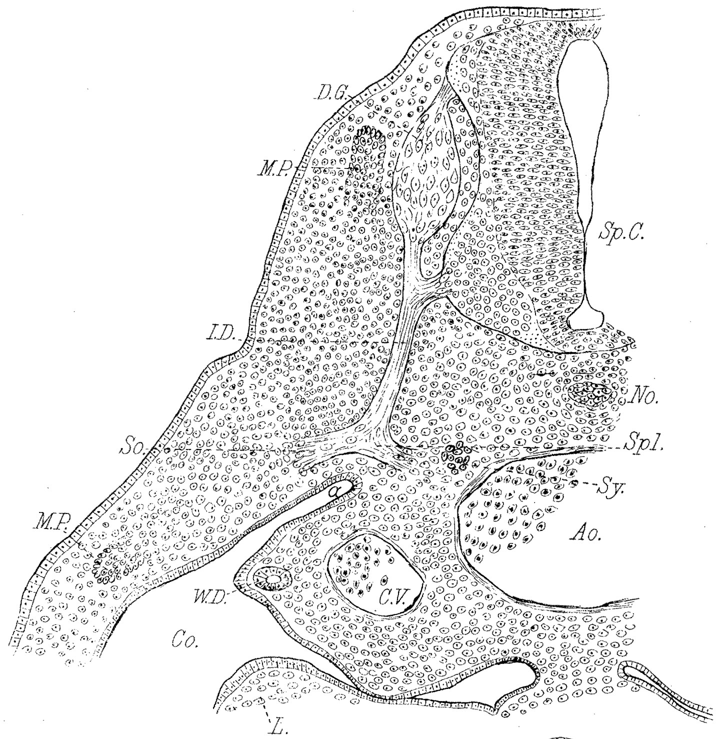

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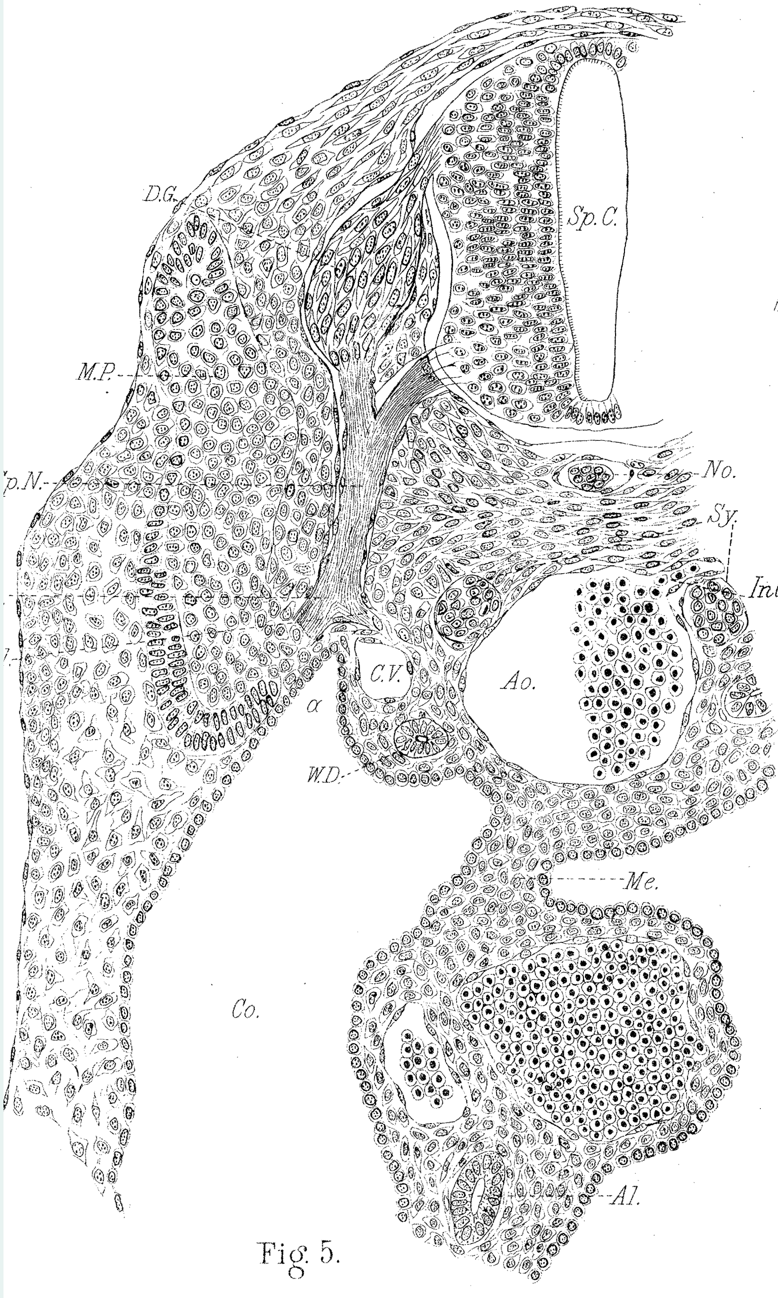

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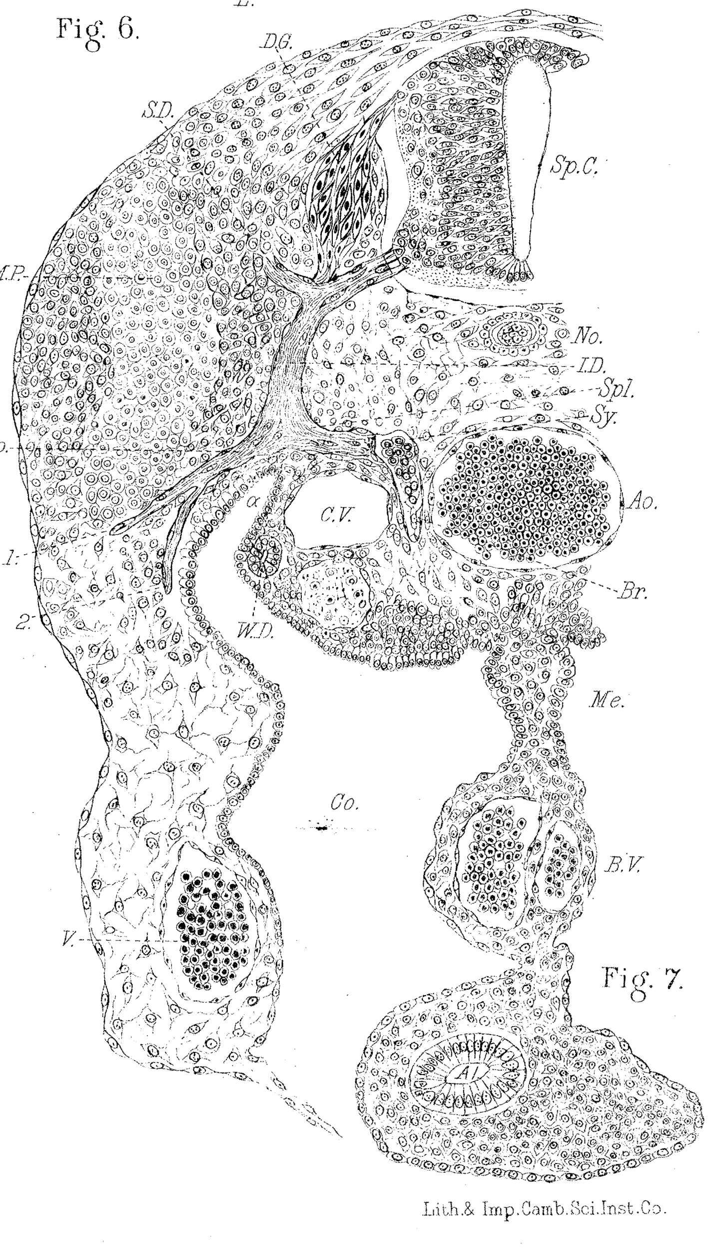

Fig. 7.


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I.D.
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Fig. 8.

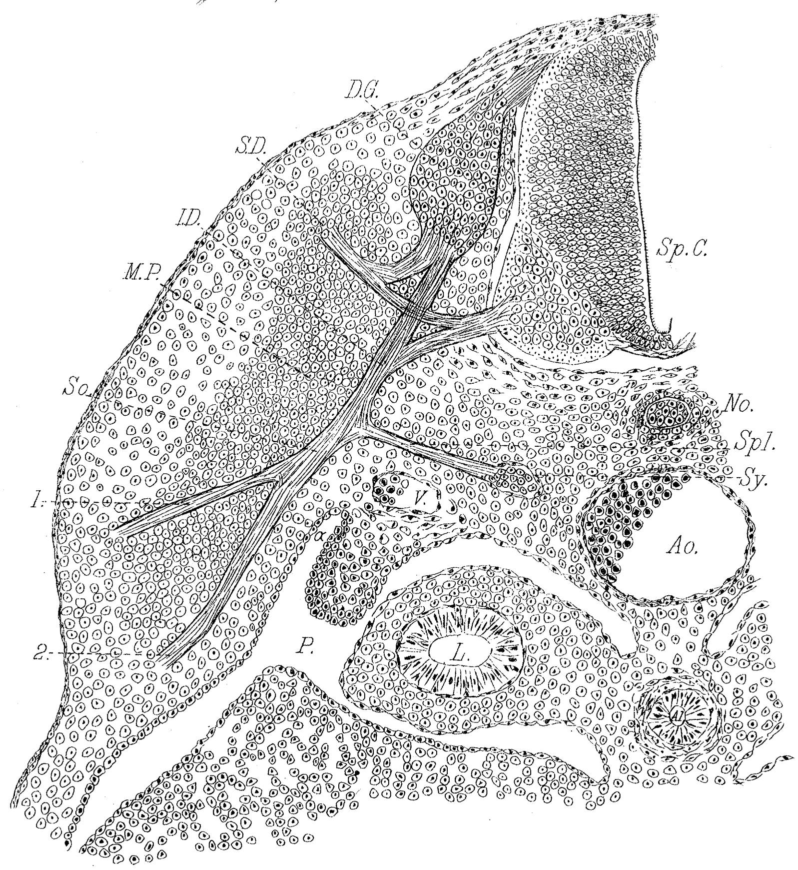
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Fig 9.

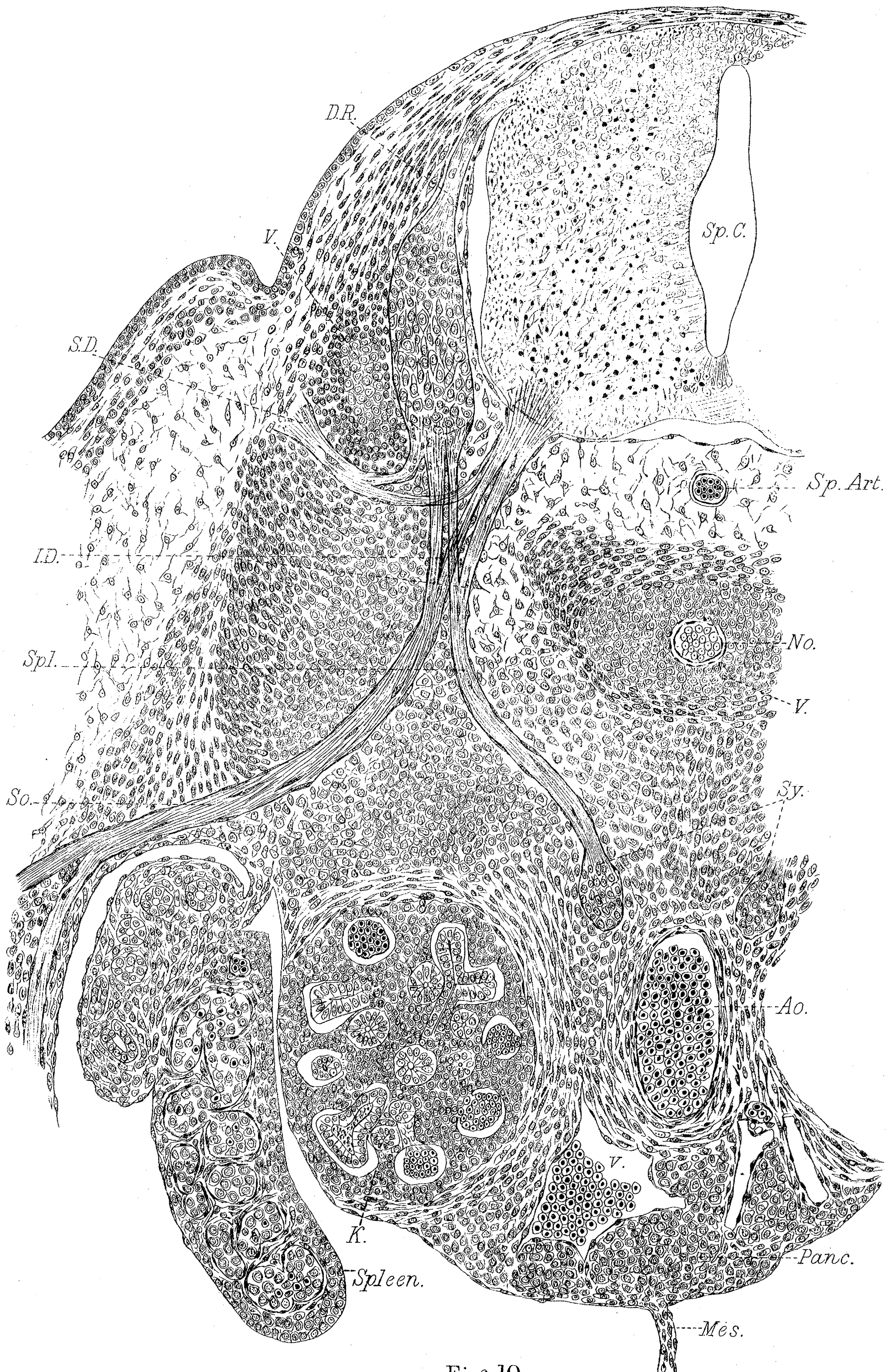

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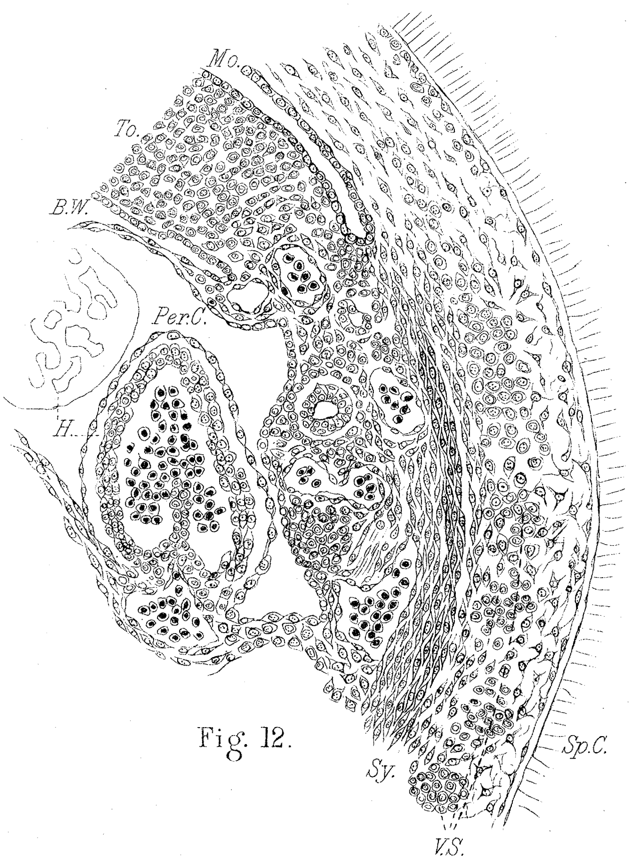
Fig. 11.



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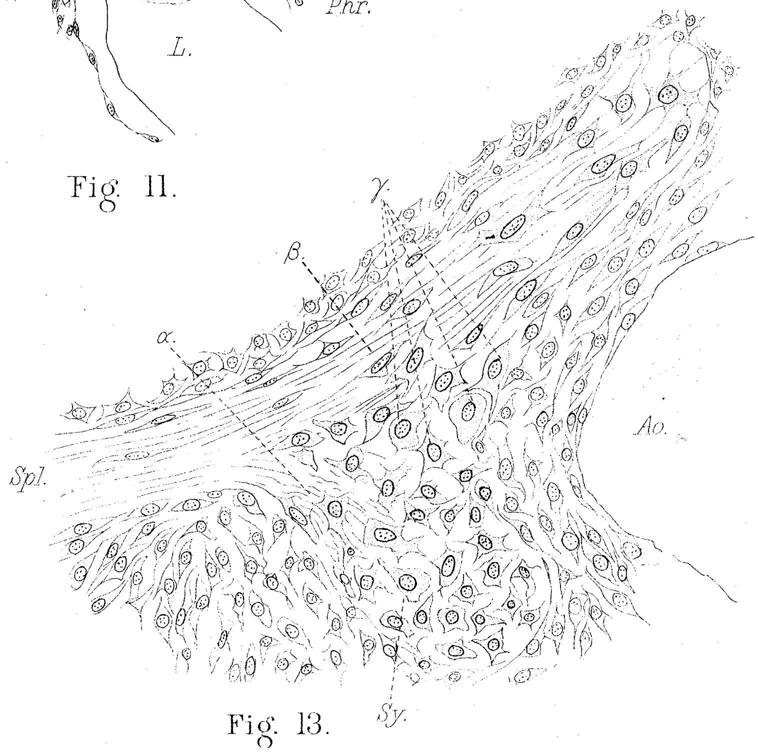

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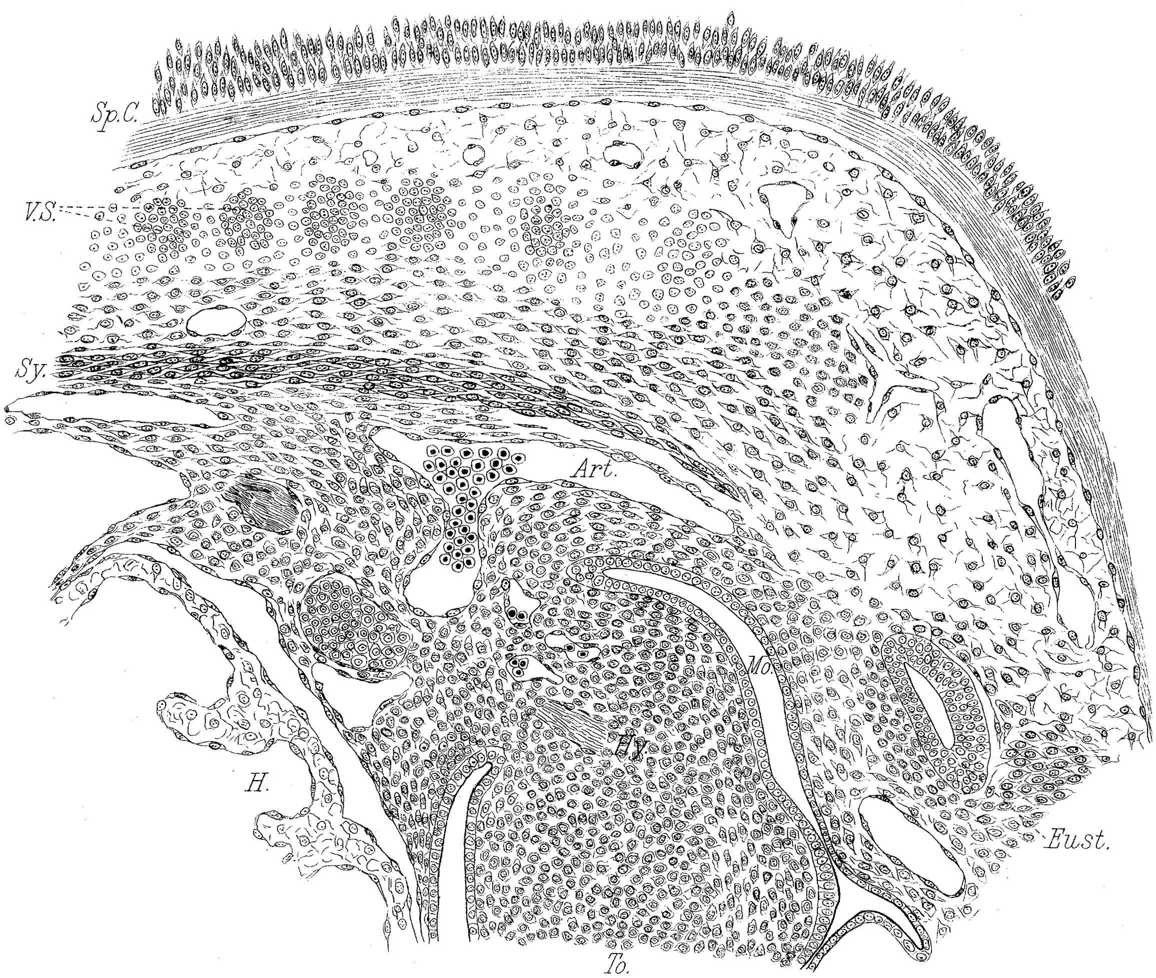

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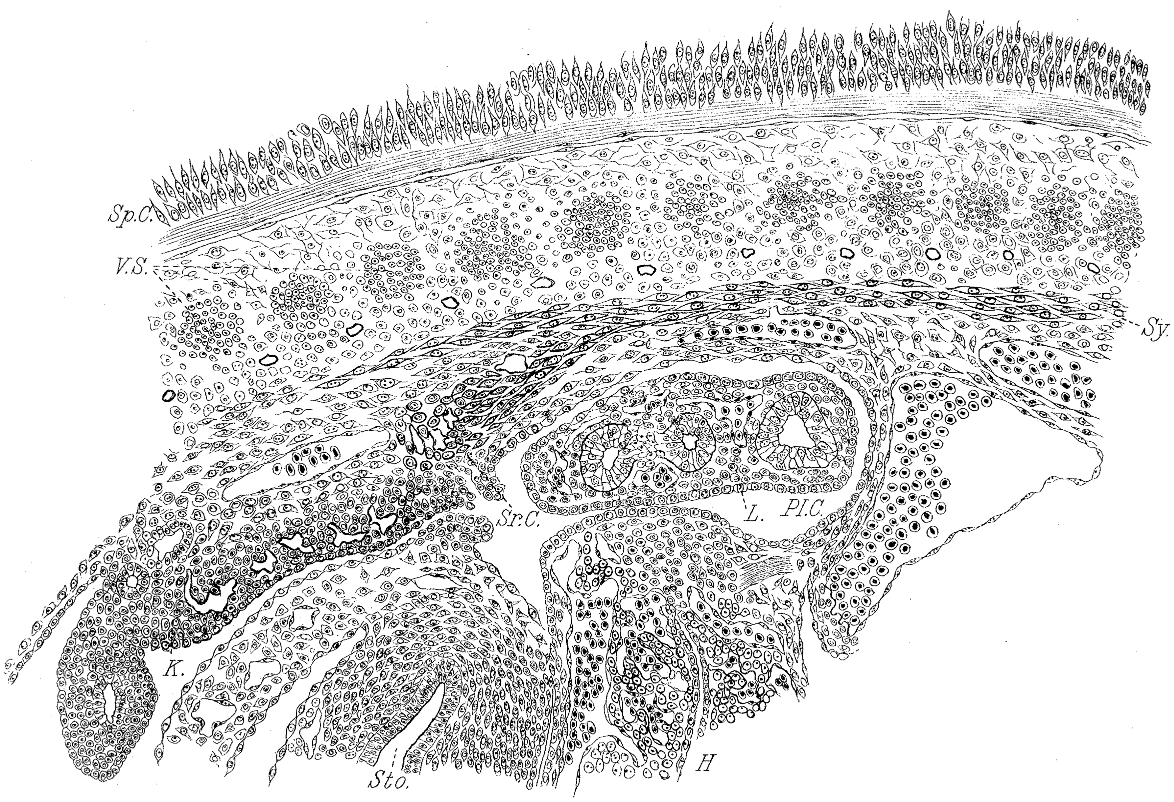

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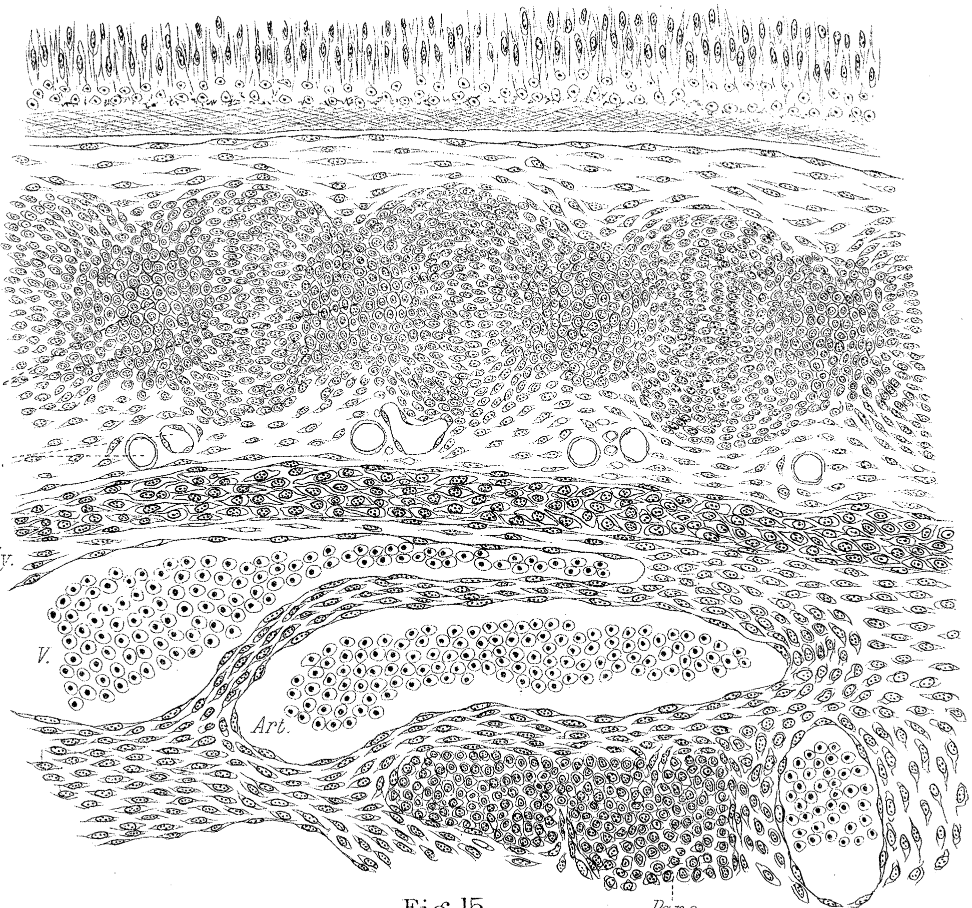

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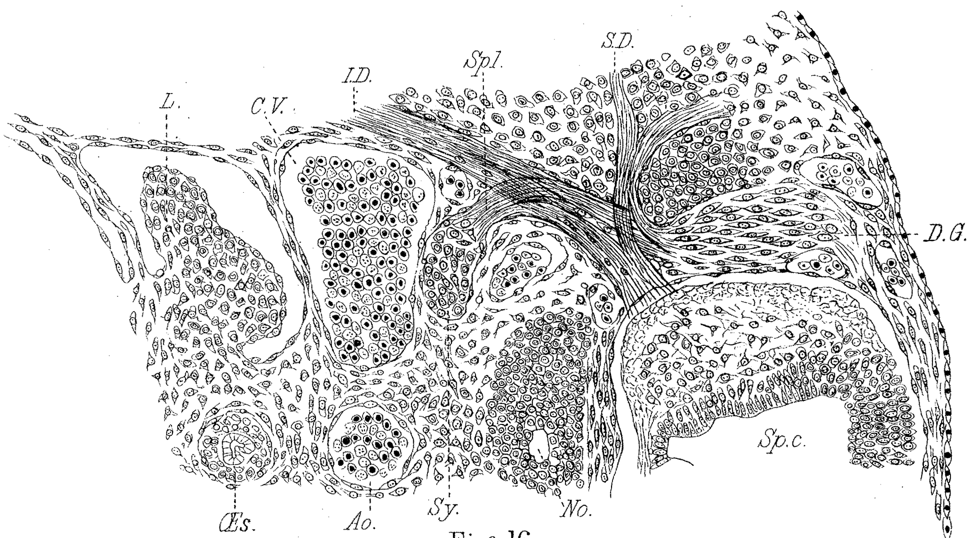

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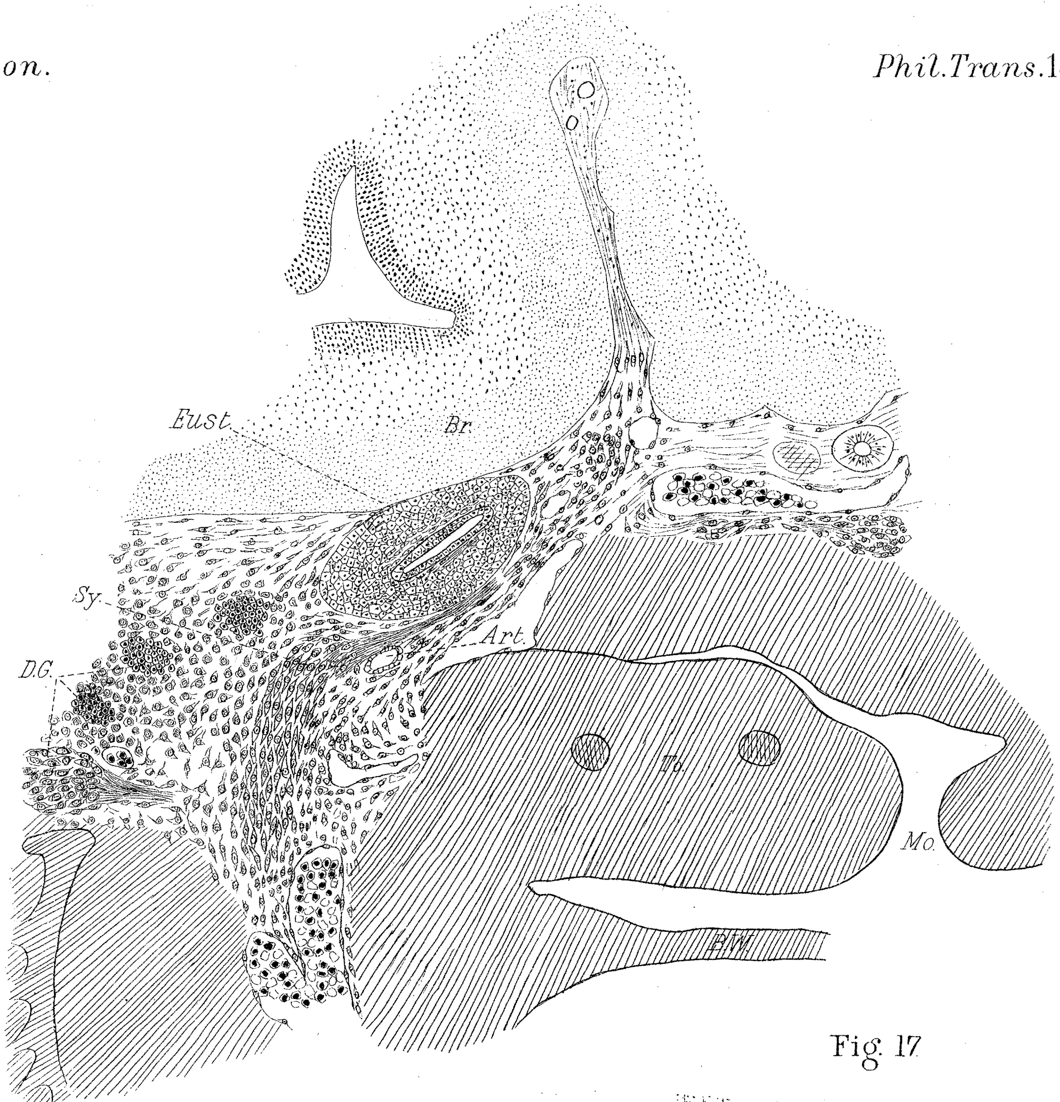

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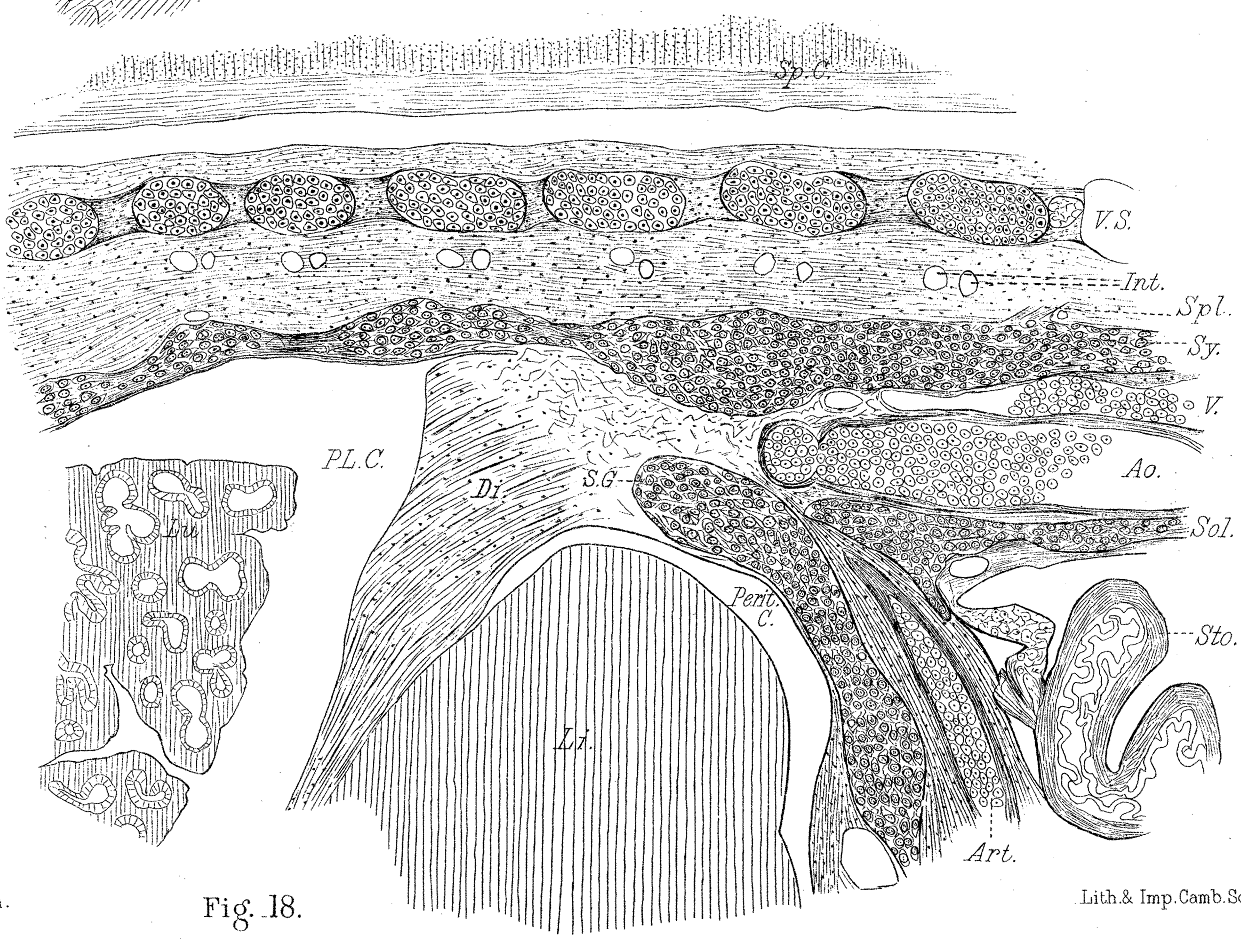

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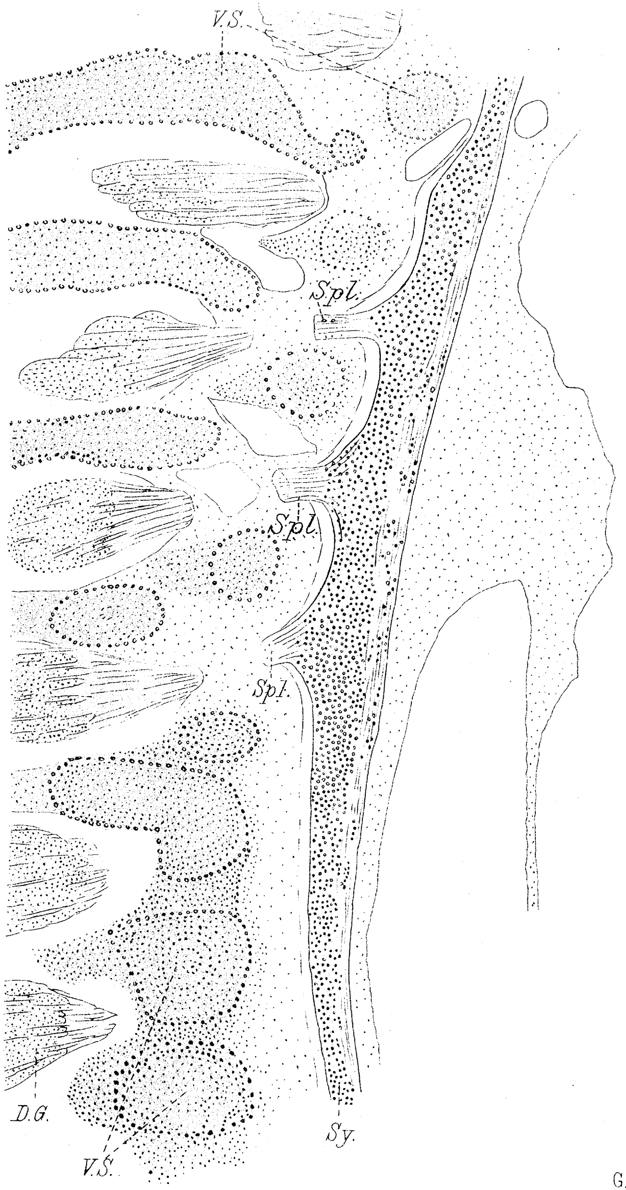

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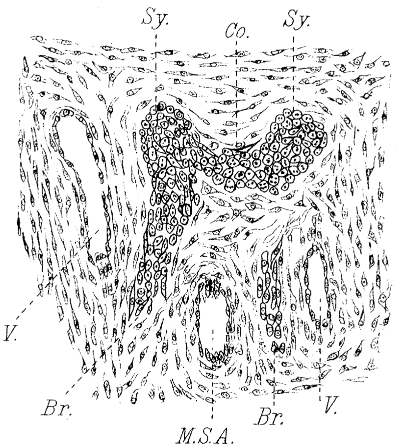

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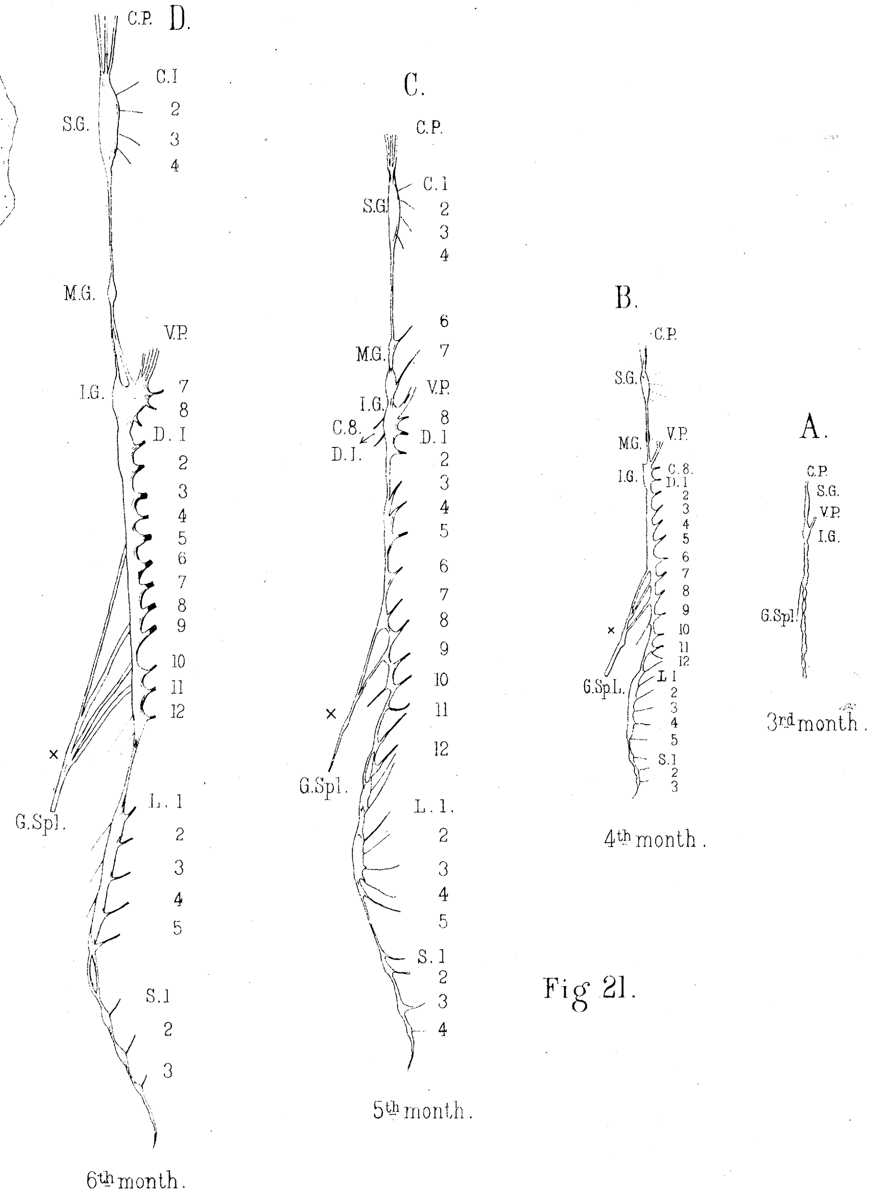

Fig 21.

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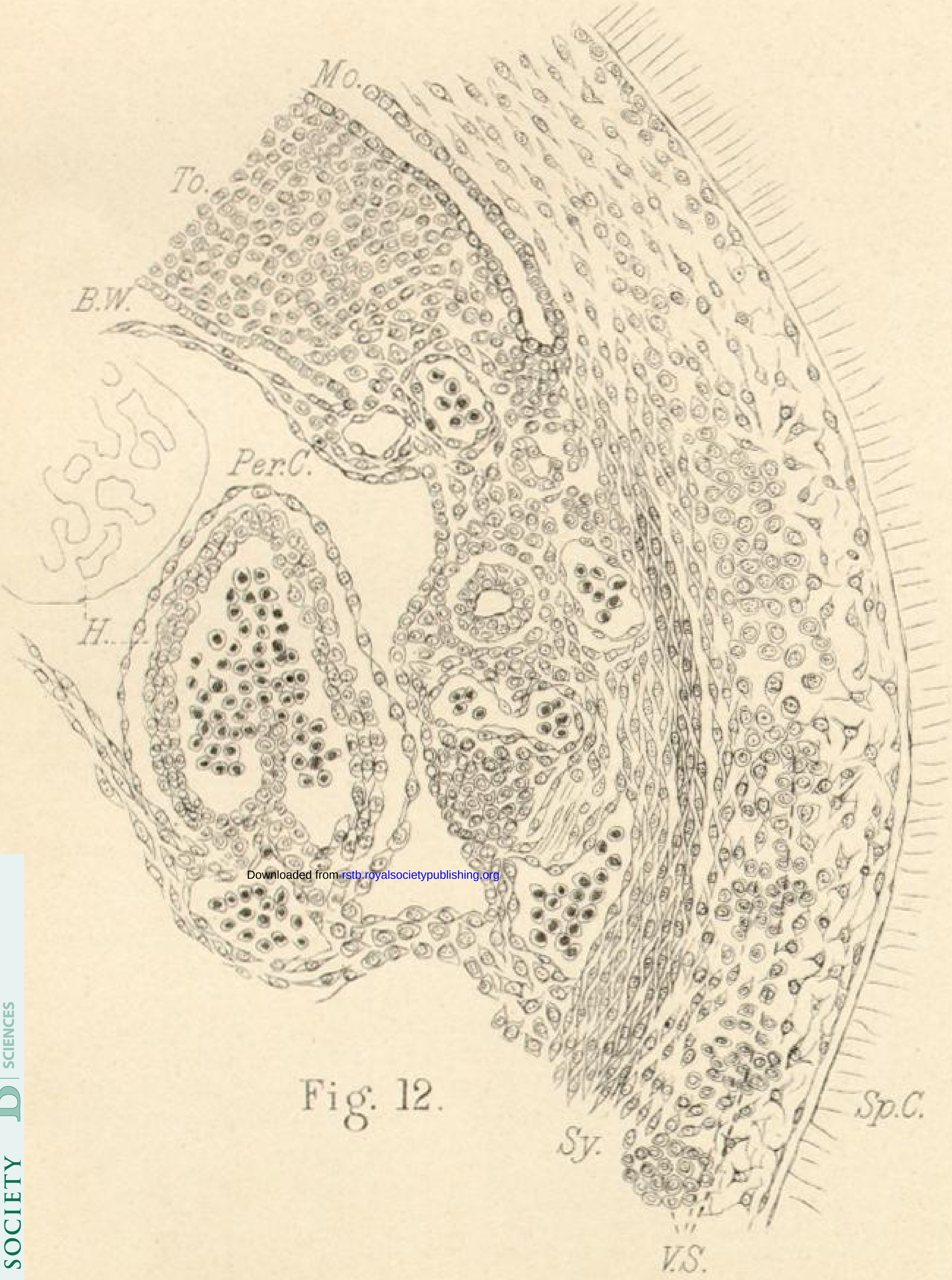
Fig. 11.



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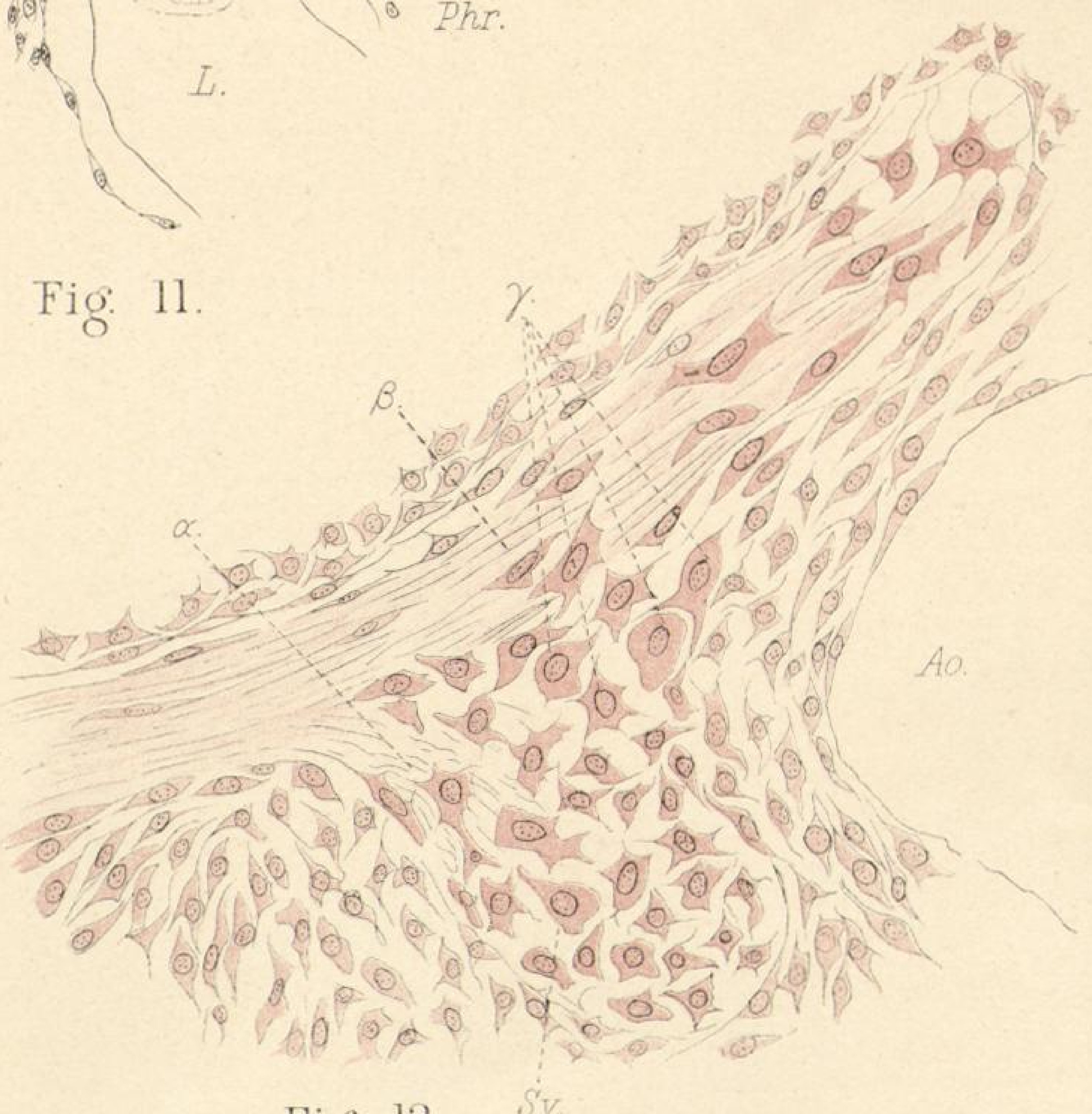

Fig. 13.

PLATE 26.

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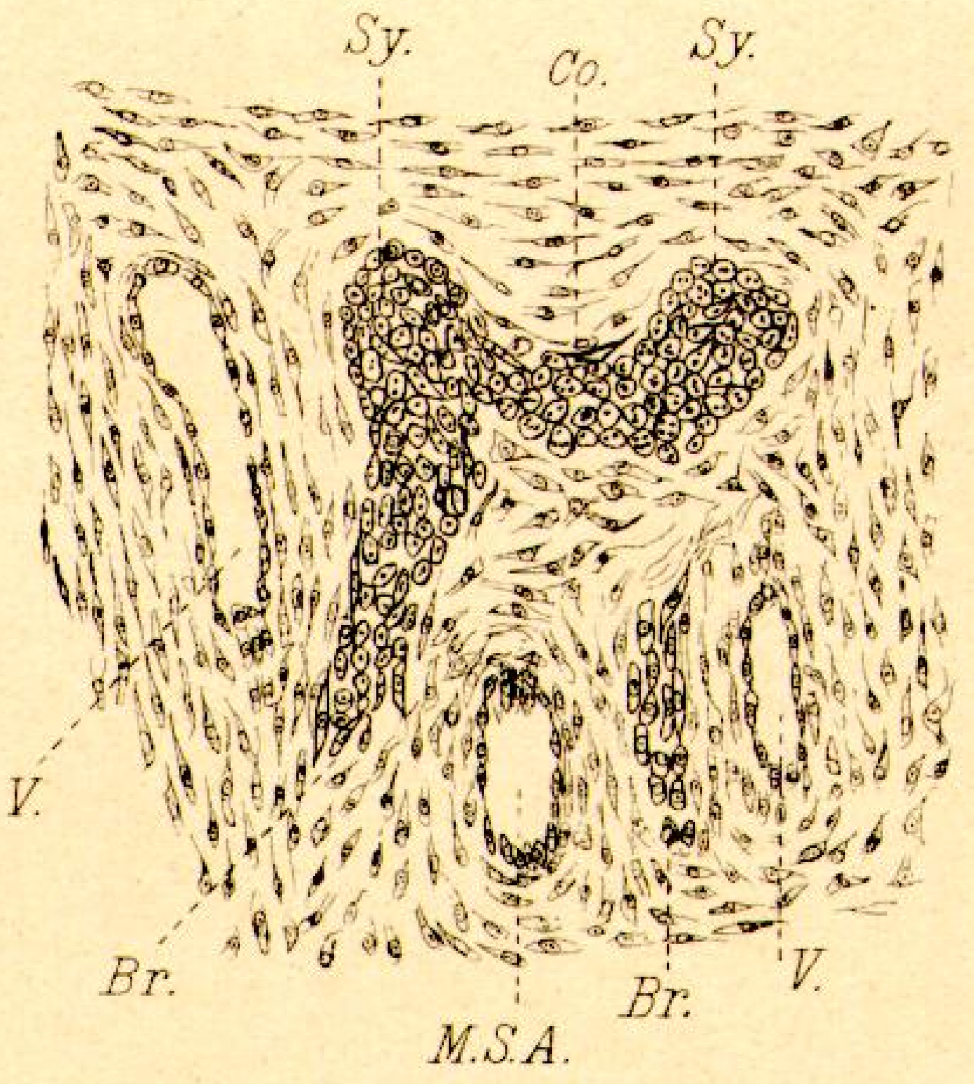

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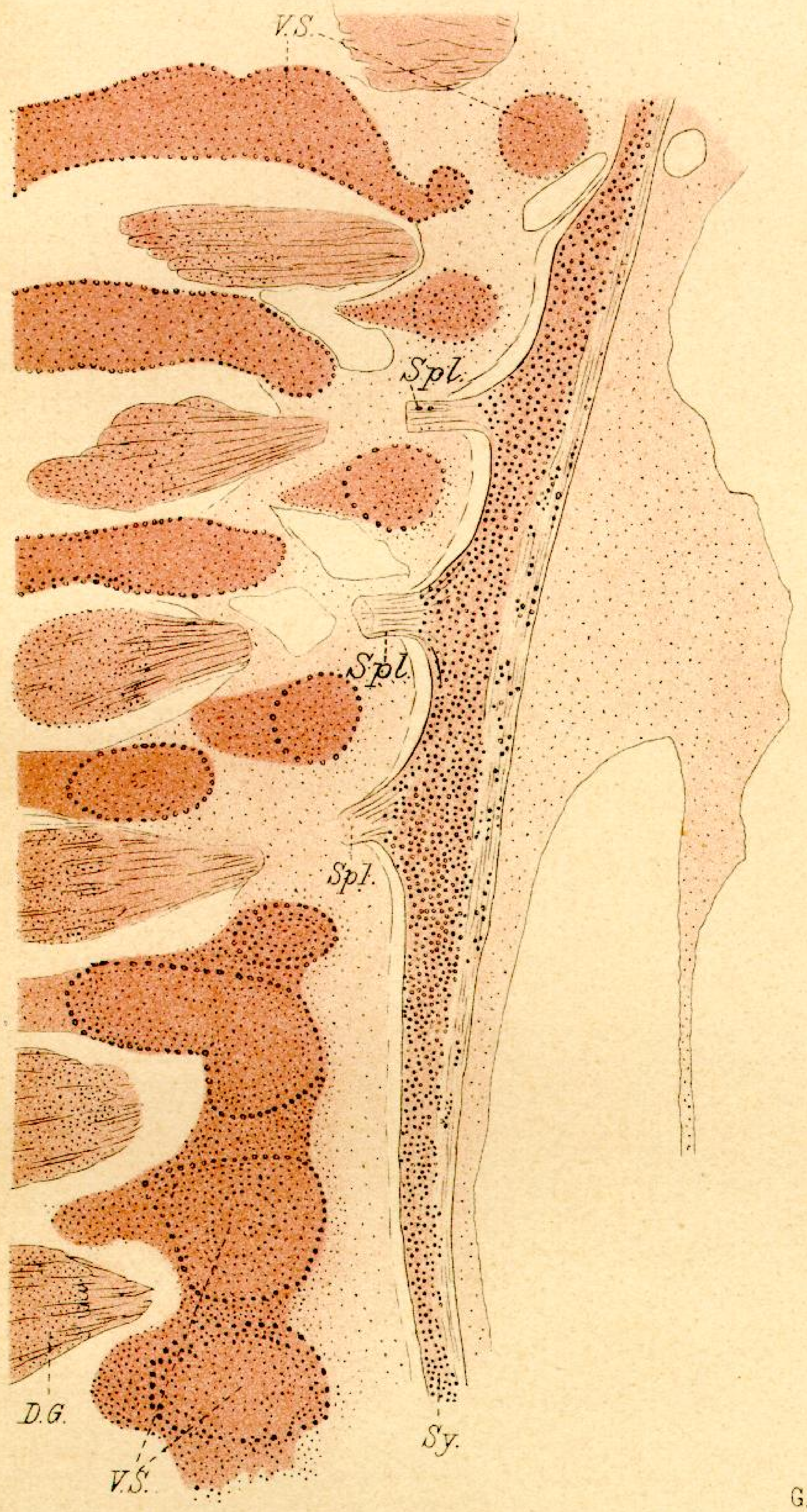

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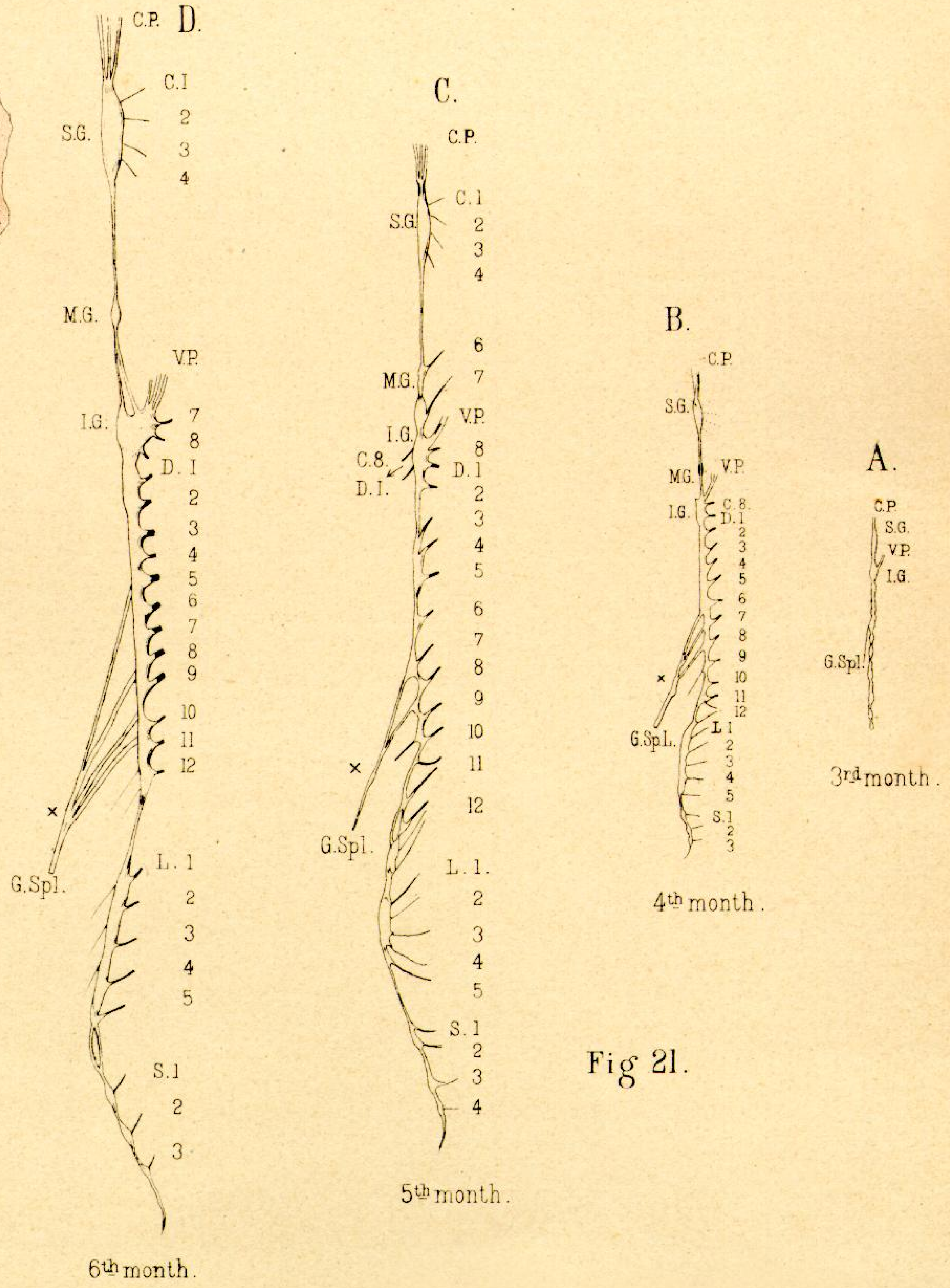

Fig 21.

PLATE 30.

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