

## LECTURES ON THE SYMPATHETIC NERVOUS SYSTEM.<sup>1</sup>

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The term *sympathetic nervous system* is applied to a series of ganglia, united by intervening nerves, found on either side of the vertebral column, and extending from its cephalic to its caudal end. These ganglia with their uniting nerves form the two *great gangliated cords* or *chains*, and as such are found among all vertebrate classes, with the possible exception of some of the lowest fishes. For purposes of description, these cords are divided into a cervical, dorsal, lumbar and sacral portion, the number of ganglia in each division corresponding in the main with the number of vertebræ found in each of the above named regions; with this proviso that in the cervical region the number of ganglia is often found reduced to three. The sympathetic system includes further a number of so-called *cranial ganglia*, namely the sphenopalatine, the otic, ciliary, sublingual and submaxillary, all of which are paired, and three unpaired ganglia or aggregations of ganglia, found in the median line, in front of the spinal column. Of these, the *cardiac* is found in the thorax, the *semilunar* in the abdomen and the *hypogastric* in the pelvis. The sympathetic system comprises, further, myriads of smaller ganglia, the greater number of which are not to be seen with the naked eye. These are found in the coats of the intestine, the walls of the trachea and bronchi, in the heart and probably in or near all the larger glands of the body. From all these widely distributed ganglia, smaller or larger nerves, composed of a varying number of so-called sympathetic nerve fibers, have their origin.

Characteristic of this system is, that these nerves are

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united into intricate plexuses, from which arise numerous smaller branches, destined to innervate all involuntary muscle, heart muscle, the viscera and the glands.

The great majority of all the sympathetic ganglia, those of the gangliated cords, the prevertebral and perhaps also the terminal ganglia, are connected with the cerebro-spinal system through medullated nerve fibers, which leave the medulla or cord through its anterior or motor roots, and end in the ganglia. These medullated nerves constitute the so-called *white rami communicantes* of the sympathetic ganglia. Many of the sympathetic ganglia, notably those of the gangliated cords, are further connected with the spinal nerves, by means of *grey rami communicantes*. The grey rami are composed of fibers that have their origin in the ganglia, which they leave to join said spinal nerves.

This portion of the nervous system has been variously named by authors. "The older anatomists described it under the name of the *great intercostal nerve*. The fact of its being chiefly distributed to the viscera belonging to the circulatory, the digestive and generative systems led Chaussier to give it the term *tri-splanchnic nerve*, and under the supposition that it alone influenced the organic processes it was termed by Bichat the *nervous system of organic life*. The term sympathetic system, or great sympathetic, was given it by Winslow from its being believed to be the channel through which are affected the different sympathies sometimes found to exist between distant organs when in morbid condition". [7]\*. And this term, although not so well chosen is now almost universally used.

A subject of frequent debate among earlier writers was, whether the sympathetic system was to be looked upon as an independent nervous system or as dependent on the cerebro-spinal system. Bichat(2), Reil, Bidder and Volkmann maintained it was functionally and structurally distinct, while Valentine and his followers denied its independence and described it as a modified cerebro-spinal nerve. The many questions involved in these discussions could however receive no definite answers

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\*The numbers enclosed in brackets refer to the literary references at the end of article.

until more was known concerning the structural elements constituting this system. The fact that the sympathetic is made up of nerve cells and nerve fibers, as is the brain and cord, was known to these earlier writers. That its nerves seemed structurally different was also known. Yet their views concerning the relation of sympathetic nerve fibers to the sympathetic cells, the endings of these fibers in the tissues to which they had been traced, and the relation of sympathetic cells and fibers to the cerebro-spinal system, were based on opinions obtained only in part by observation, speculation often playing an important rôle. This of course is not at all surprising when we consider the imperfect histological methods known to these pioneer investigators, for it must be remembered that it is only a little more than three decades since Gerlach discovered that solutions of carmine would stain effectively animal tissues.

Our knowledge of the ultimate structure of the nervous system taken as a whole has in the last twenty years been greatly extended by the results obtained through the application of new and improved methods of microscopical technique. It is however not my purpose to mention even briefly all the neurological methods which have thus materially aided in the furtherance of our knowledge. I deem it profitable however to draw your attention to two methods, consequent upon the application of which, more than upon all other methods, has the elucidation of the difficult problem here involved been possible. One of these methods was suggested by Golgi (3) in 1875, who found that nerve tissues prefixed in a solution of bichromate of potash and after-treated with silver nitrate, would take a most delicate stain, the nerve cells with all their branches, even to their finest details being most clearly portrayed. This method has become especially valuable since Ramon y Cajal has demonstrated that it is especially applicable to embryonic tissues, even in the very early stages of the developing embryo, where the structural appearances are often somewhat simpler and more amenable to a correct interpretation. The other method, of more recent origin, was suggested by Ehrlich (4) in 1886. Ehrlich found that by injecting a solution of methylen-

blue, prepared with normal salt solution, into the circulation of a living animal, many of the nerve cells and nerve fibers would be colored blue in a most satisfactory manner. The great drawback to this method as introduced by Ehrlich was that tissues so stained could be examined only in their fresh state, and even then would soon fade.

This method was however soon improved by Smirnow (5) and Dogiel (6) who showed that the tissues so stained might be fixed in a saturated watery solution of ammonium picrate, and it was further modified by Bethe (7) who found that ammonium molybdate would convert the very unstable methylen-blue stain into one practically insoluble in water and alcohol. So that tissues stained *intra vitam*, with a methylen-blue solution, may now be embedded and sectioned and even double stained without losing much of their original blue color. By way of parenthesis I may here say that, while both of these methods are applicable to the study of the entire nervous system, the Golgi method has been most useful in the study of the central nervous system, while the methylen-blue method is now more generally used in the study of peripheral ganglia, peripheral nerves and their endings.

The results obtained by these methods are so convincing that we are not surprised to find that all parts of the nervous system have been subjected to repeated investigations, since their introduction. Some of the more important results which these investigations have brought to light, are, on account of their bearing on the subject under discussion, worthy of brief mention in these introductory remarks.

As a result of these investigations we know that the entire nervous system, peripheral as well as central, is like all other tissues of the body built up of anatomical units, which, though they vary greatly in shape and size, are nevertheless to be regarded as highly differentiated cells.

Such nerve units consist of a cell body and nucleus and one or several processes. These processes are of two kinds. The one kind essential to each cell, usually becomes the axis-cylinder of a nerve fiber, and as such may attain great length,

giving off only a few branches (*collateral branches*) in its course, and terminating in a complex of end branches,—the *end-brush*. Such branches are described as axis-cylinder processes or *neur-axes*. The other kind of processes, not so essential, as many cells do not possess them, are the protoplasmic branches or *dendrites*. The dendrites may be said to be of two distinct types,—in the one, belonging to cells of sensory ganglia, the single dendrite present may also attain great length, become the axis-cylinder of a nerve fiber, and also terminate in an end-brush; in the other type, the dendrite or the dendrites break up near the cell body into secondary and tertiary branches and so on, also ending free. To such nerve units, consisting of cell body and nucleus, of neuraxis and its end-brush, and of dendrites, if present, the term *neuron* has been applied by Waldeyer. Every neuron therefore is a distinct anatomical unit, a distinct structural element, as much so as an epithelial cell, or any other cell. This *neuron-conception* of the structure of the nervous system is applicable to all its parts, to the brain and cord and all peripheral ganglia; and has been a most potent factor in the development of our knowledge of the finer anatomy of the nervous system.

Recent investigations have further shown that while a neuron is a distinct anatomical unit, it is always found associated with other neurons. Nowhere in the body of a vertebrate does one find a neuron completely disconnected from other neurons, or as Donaldson (8) has expressed it: "A group of nerve cells completely disconnected from other nerve tissues of the body, as muscle or glands are disconnected, would be without physiological significance." This association of one neuron with another is brought about by the close contiguity always existing between the *end-brush* of the neuraxis (or the end-brush of one of its collateral branches) of one neuron, and the *cell body* or *dendrite* of one or several other neurons. Investigations with Golgi and methylen-blue methods have shown that the neuraxis of one neuron may, with its end-brush, surround the cell body of another neuron by the formation of what is known as an *end-basket*; or the end ramifications of the neu-

raxis of a neuron may come in very close proximity to the end branches of the dendrites of one or several other neurons. By this contiguity of end-brush and cell body or end-brush and dendrites, neurons, while not losing their identity, are linked into chains, so that a physiological continuity exists between them. Such *nerve-chains*, or *neuron-chains*, as we may call them, vary greatly in complexity, and in the number of neurons which enter into their construction. They may be very simple, consisting of only two neurons, or very complex indeed, embracing a large number of them.

The entire nervous system may therefore be said to be made up of such neuron chains, and the tracing of them is a problem, which, perhaps more than any other, engages the attention of the neurologist at the present time. For it is only as the respective positions of the several links in such chains or paths become established, that the results of the many investigations become of practical value.

It may be seen from what has been said, that the cells of the peripheral ganglia, the various sympathetic ganglia included, the peripheral nerves, as well as the neurons in the central nervous system, form each in its respective place, a link or a portion of a link in such a chain. These neuron-chains are paths along which nerve impulses travel from the periphery to the nerve centers; from one nerve center to another; and from the centers to the peripheral tissues, such as muscles, glands, etc. The anatomical mechanism which probably underlies a volitional muscular contraction, and a simple reflex may here be briefly described, as illustrations of neuron-chains. If we take first the example of a volitional muscular contraction we will find that a chain consisting of two neurons is involved. The cell body and dendrites of one of these is situated in the motor, cortical center of the brain, its neuraxis passes through the internal capsule, the crura and one of the pyramidal tracts of the medulla and spinal cord. Somewhere in the cord it ends in the grey matter of the anterior horn, terminating in an end-brush which is in close proximity to the cell body or the dendrites of a neuron, which forms the second link in the chain. The neur-

axis of this second neuron (the motor anterior horn cells) leaves the cord through the anterior root, enters a nerve trunk and ends in an end-brush in a voluntary muscle fiber.

In the other example chosen, the path involved in a simple reflex, the chain is also made up of two neurons. In this instance the impulse originates in the end-brush of the dendrite of a spinal ganglion neuron, is conveyed along the dendrite to the cell body of the neuron in question, thence along its neuraxis, which on entering the dorsal portion of the spinal cord divides into an ascending and descending branch, from which a number of secondary branches are given off (collateral branches); some of these secondary branches terminate in an end-brush in the anterior horn of the grey matter in adjunction with the cell body or dendrite of a motor neuron, which forms the second link in the chain. The impulses pass out along the neuraxis of this cell to a voluntary muscle fiber. The two examples chosen may serve to illustrate the more modern conception of the structure of the nervous system.

If then the entire nervous system may be looked upon as a complex of neurons, and if these are all united into nerve-chains as I have tried to show you, the most logical way of considering the sympathetic system is to treat of it as a portion of the entire nervous system, this being looked upon as a unit. This I hope to do in these lectures.

The results I wish to bring before you are in a large measure consequent upon the application of these improved methods—the Golgi and the *intra vitam* methylen-blue method—which in the hands of many investigators have in this portion of the nervous system, as well as in others, greatly extended our knowledge.

These results will be taken up under the following heads:

1. The development of the sympathetic ganglia and nerves.
2. The shape and structure of a sympathetic neuron,
  - (a) cell body and dendrite;
  - (b) neuraxis;
  - (c) the endings of the neuraxis.

3. The relation of the sympathetic neurons to—
  - (a) the cerebro-spinal system ;
  - (b) to other sympathetic neurons.
4. Sensory fibers of the sympathetic system.
5. Reflexes in the sympathetic system.

*Development of the sympathetic system.*—The entire nervous system, peripheral as well as central, has its *anlage* in a band or plate of ectodermal cells, known as the *medullary plate*, and from the ectoderm in the immediate vicinity of this plate. During the further development of embryonic *anlagen*, the edges of this plate become elevated to form the *medullary groove*, and the edges of the groove fuse to form the medullary canal, which ultimately becomes completely separated from the remaining ectoderm. The ectoderm of the medullary plate, the groove and the earlier stages of the canal, consist of a single layer of cells. At a very early stage in the development of the nervous system, indeed before the groove has been converted into a canal, a differentiation is noticed in these cells, two distinct forms being recognized. The one form, tall columnar cells, which extend from one surface of the ectoderm to the other, so-called *spongioblasts*, which develop, as has been clearly shown, into the sustentacular tissue of the central nervous system, forming the ependym and neuroglia cells: and the other form, large oval or round cells with prominent nuclei, found between the spongioblasts; these develop into nerve cells and are known as *germ cells*.

His (9) has shown that the germ cells proliferate very actively by means of karyokinetic cell division and migrate from a position near the inner wall of the medullary canal toward the outer wall. While they are thus wandering, the round or oval cell becomes pear-shaped and from the attenuated end there begins to bud a process which is the *anlage* of a neuraxis. The cells are now known as *neuroblasts*.

The processes of many of these neuroblasts grow through the ventral portion of the developing cord or brain and from the *anlagen* of motor roots.

Many of the germ cells are therefore the *anlagen* for the



motor neurons, the dendrites present in the fully developed motor neurons budding from the cell bodies at a later stage in their development. The other germ cells, that is those not developing into motor neurons, form intra-medullary neurons.

While these developmental changes are going on in the neural canal, similar changes are seen in that portion of the ectoderm just outside of the canal. In this region, even before the medullary groove has become a canal, germinal cells, like those found in the sides of the groove, wander out into the angular space between the ectoderm and closing neural canal, to form the neural crests. These neural crests, composed of germinal cells, segment, a group forming opposite each mesoblastic somite. The cells in these segments wander to a position between the neural canal and the respective somites, and form the *anlagen* for the spinal ganglia. The cells have become bipolar and are known as gangioblasts (Lenhossék), one of the processes growing into the dorsal portion of the developing neural canal, forming the posterior or sensory root, the other toward the periphery, joining the developing anterior root and forming the sensory fibers of peripheral nerves. The bipolar cells become unipolar, with "T-shaped" processes as found in the fully developed spinal ganglia, either by a fusion of a short portion of the two processes or, as Lenhossék has suggested, by drawing away of the cell body from the two processes, the extended and attenuated portion of the cell-body forming the vertical arm of the "T."

I have in this very brief account thus hastily traced the development of motor, sensory and intra-medullary neurons, and a moment's reflection will show that only the sympathetic system, and some of the special sense organs are still to be accounted for.

The development of the sympathetic system begins somewhat later than does the cerebro-spinal system.

His (10) states that, in the human embryo of 7 mm., there is as yet no evidence of the sympathetic system, while the medullary canal is completely closed, and the ganglia of all the spinal nerves as well as the anterior roots are to be seen. In a

human embryo 10 mm. in length, its *anlage* may be observed ; its development falls therefore into the second month. His further states that its development begins with the development of the white rami communicantes. In a human embryo about 7 mm. in length, he describes short visceral branches, which leave the *anlage* of the spinal nerves, a short distance beyond the junction of the anterior and posterior roots, and at a point where the spinal nerves reach the dorsal cœlom border. These branches grow in toward the aorta, and at this stage there are as yet no cells in or on these rami. In tracing the development of the sympathetic cells I shall follow the account given by His, Jr. (11). The description given has reference chiefly to observations made by him on chick embryos of the fourth day. In cross sections of such embryos passing through a spinal ganglion, small clusters of cells, the clusters numbering 2-4-10 cells respectively, are seen in the mesoblastic tissue between the point of junction of the anterior and posterior roots and the aorta. The cells in these clusters differ in structure and in their affinity to staining reagents from the surrounding mesoblastic cells.

They are of round, oval or polygonal shape, and have large nuclei and nucleoli. They stain well in hæmatoxylin and eosin, so that even under low power they may be differentiated from the surrounding mesoblastic cells. The evidence seems in favor of the supposition that these cells, which, as we will see, are the germ cells of the sympathetic ganglia, do not develop *in loco*, that is from the surrounding mesoblastic cells as was formerly believed and has quite recently been asserted by Paterson (12), but that they wander out from the spinal ganglia as germ cells possessing this motile power. The origin of these cells from the spinal ganglia was first suggested by Balfour (13) in his monograph on Elasmobranch fishes. Schenk (14) and Birdsell arrived at the same results for birds and mammals. Onody (15) has more recently, in a very comprehensive paper, in which he gives the results of his observations on the development of these structures, in the various classes of vertebrates, reached a similar conclusion.

His, Jr. (16) and Romberg were, I believe, the first to draw attention to the fact that these cells were not simply split off from the spinal ganglia, nor were they pushed out of the ganglionic *anlage* as a result of a rapid proliferation of the cells in these *anlagen*, as was held by the earlier investigators, but that they migrated from the spinal ganglia into the surrounding tissue. His, Jr. (11) describes these cells as wandering in swarms, indistinctly bounded, toward the ventral portion of the embryo. In the cervical and upper dorsal region, these migrating cells collect in larger groups on the dorsal side of the carotids, in the abdominal region, by the side of the aorta, thus forming, with the developing rami communicantes, above noted, the *anlagen* for the great sympathetic cords or chains.

At this early stage in the development of the sympathetic system the great majority of the cells are as yet apolar, and many show karyokinetic figures. From the groups of cells, forming the *anlagen* of the ganglia of the chain, germinal cells wander to a position below the aorta, to form the cœlic and the other ganglia found here. This wandering of the germ cells of sympathetic ganglia from the *anlagen* of the spinal ganglia or the larger ganglia of the chain to peripheral organs has been most clearly shown for the ganglia found in the heart. His, Jr. (11) has given us a very complete account of the way in which the germ cells reach this organ. He has studied the development of the heart nerves in fishes, amphibia and birds, also in the human embryo. It would encroach too much on the time I have set for this portion of my subject, to give a detailed account of the results obtained by him; I will therefore simply give the following conclusions reached: "That the ganglia of the heart are developed from germ cells which wander to this organ from the spinal ganglia and the sympathetic ganglia. This migration takes place by one of two paths:—in fishes and batrachians along the veins, and in birds and mammals along the arteries."

That the sympathetic ganglia which are found in connection with some of the cranial nerves are developed in the same way as are the ganglia of the great chains may be gathered from observations made by Remak (17) on chicks, of the third day of

incubation, and by Kölliker (18) on rabbit embryos 16 days old they having shown that the ciliary, the spheno-palatine and otic ganglia have their *anlage* in cells which "bud out" from the Gasserian ganglia.

In this brief sketch I have endeavored to show that the evidence is in favor of the supposition that the sympathetic ganglia of the great chains and those found on the cranial nerves, are developed from germ cells which wander out from the *anlagen* of the spinal ganglia and from the *anlagen* of the sensory ganglia on the cranial nerves. These cells are at first apolar and proliferate by karyokinetic cell division. The clusters of cells which form the beginning of the ganglionic chains are centers from whence germ cells wander to organs and tissues to form the *anlagen* of the sympathetic ganglia there found. As development proceeds, the apolar germ cells develop into sympathetic neurons by a budding out of the neuraxes and of the dendrites, this differentiation or further development being essentially the same as that described for the germ cells or neuroblasts found in the developing neural canal, which, as I have above stated, develop into the motor and intra-medullary neurons.

*Shape and structure of neurons of the sympathetic system.*—The neurons of the sympathetic system are usually found in larger or smaller groups, forming the so-called sympathetic ganglia. These ganglia vary greatly in size. Many attain dimensions great enough to make their recognition very easy, as for instance, the superior cervical ganglion, which in man is about 20 mm. long and 4 to 6 mm. broad (Quain). From ganglia of such size, every gradation in size is met with until the microscopic ganglia—the terminal ganglia—found in the various organs are reached. All sympathetic ganglia, large and small, are invested with a connective tissue capsule, which is continuous with the perineural sheath of the nerves entering and leaving the ganglion. In a general way it may be stated that the thickness of the capsule is proportionate to the size of the ganglion. From the capsule, connective tissue trabeculæ,

bands or septæ, pass into the substance of the ganglion, forming a framework.

Consequent upon results obtained by the Golgi and methylen-blue methods, we now possess very definite information concerning the shape and to some extent also the structure of the nerve cells constituting the sympathetic ganglia. Kölliker (19) as early as 1889 drew attention to the fact that the sympathetic nerve cells might be stained with the Golgi method and showed that in the mammalia these cells were multipolar. Ramon y Cajal (20) soon corroborated these results and extended them in so far as his researches also included birds, he finding that here also the sympathetic nerve cells were multipolar. Cajal further made the important discovery that, while the cells were multipolar, they possessed only one neuraxis, the other branches being dendrites.

These observations were soon confirmed by van Gehuchten (21), Retzius (22), Sala (23), v. Lenhossék (24), they also using the chrom-silver method in their several researches, and by Dogiel (25) who has studied these structures with the methylen-blue method.

My own observations confirm the results above briefly sketched, and further show that the sympathetic nerve cells of fishes and of reptilia are also multipolar. The statement that the neurons of the sympathetic system of fishes, reptilia, birds and mammalia are multipolar, needs to be qualified to this extent—that only the great majority of these cells belong to this type, a few unipolar and bipolar cells being also found. These, as Dogiel (25) has correctly stated, are usually in the peripheral portion of the ganglia, and more often near one of the poles.

My own observations on the structure of the sympathetic ganglia of vertebrates were made both with the Golgi and methylen-blue methods; the former method was however soon discarded, as in my hands the *intra vitam* methylen-blue method gave much more definite results.

These observations pertain to preparations made of sympathetic<sup>1</sup> ganglia of the following vertebrates:—

Fishes,—black and rock bass and perch, (*Micropterus dolomieu* [Raf.], *Ambloplites rupestris* [Raf.], *Perca flavescens* [Mitch.]).

Amphibia,—frog, (*Rana catesbiana* and *Rana halecurea*).

Reptilia,—tortoise, (*Chrysemys picta*, *Chelhydra serpentina*, *Emys melegaris*).

Birds,—chicken, *Gallus domesticus*.

Mammalia,—Guinea pig, rabbit, cat and dog.

*Structure of the cell bodies of neurons of the sympathetic system.*—The structure of the cell body of nerve cells of the sympathetic system does not differ in any essential from that of motor or sensory neurons.

In sympathetic ganglia stained in methylen-blue, fixed in ammonia molybdate and sectioned, only a few of the cells in any one section are as a rule stained; some deeply, others with varying degrees of intensity, while many of the cells are entirely unstained. This enables the observer to study the development of the staining in the ganglion cells. Under high power it may readily be seen that the staining of the cell bodies is due to the fact that certain granules—*chromophile granules*—which show an especial affinity for the stain, give them their color. Chromophile granules in the cell bodies of neurons were first described by Nissl, who has further shown that in pathological conditions involving nerve cells, these granules are markedly affected. In the motor cells of the cord these granules are relatively large, giving the cell a mottled appearance. In sensory cells (spinal ganglia) they are often quite small (Lenhossék). In sympathetic nerve cells, where faintly stained, only a few very small chromophile granules are to be seen scattered more or less evenly through the protoplasm; while in more deeply stained cells the granules are more closely packed, are usually somewhat larger, and have often an angular shape. Between the

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<sup>1</sup> The results here briefly referred to will appear in a much fuller account accompanying colored plates, now in preparation.

granules an almost colorless and apparently structureless ground substance may be seen. These observations confirm very closely results obtained by Dogiel (25) with this method.

Dehler (26) has described a centrosome in the sympathetic ganglion cells of the frog. This is, as far as I am aware, the only observation of this structure in sympathetic nerve cells, although Lenhossék (27) had previously drawn attention to its existence in the spinal ganglia of the frog, and Miss Margaret Lewis (28) has quite recently found it in some large nerve cells, which she describes as giant cells, in an annelid belonging to the *Maldaniæ* family; and Schaffer (29) in the head-ganglia of *Petromyzon*.

The nuclei of sympathetic neurons are as a rule only imperfectly stained in methylen-blue. They are relatively large and often have an eccentric position, nearer the pole, opposite the one from which the neuraxis arises. Nucleoli may or may not be observed.

I wish here briefly to refer to the curious fact that in some of the rodents—rabbit, hare and Guinea pig—a large number of the sympathetic neurons possess two or even three nuclei. Attention was drawn to this fact, many years ago, by Schwalbe (30), and has quite recently been the subject of a special communication by Apolant (31). Schwalbe showed that in the ganglia of the sympathetic chain of young rabbits, mono-nuclear ganglion cells and ganglion cells with two nuclei were to be found; and that the number of the mono-nuclear cells decreased with the age of the animal. He states that in old animals the mono-nuclear ganglion cells of the sympathetic are bipolar, while those with two nuclei are multipolar.

That these are not simply degenerated cells, Apolant (31) argues may be shown by the fact the multinuclear sympathetic nerve cells are to be found in embryo rabbits of the third week. They develop, he states, by an amitotic division of the nuclei of the mono-nuclear cells. Apolant discusses the question, whether the cells with two nuclei might have two neuraxes, as suggested by Guys. His results with the methylen-blue method seem to have been unsatisfactory, and as this question

could alone be approached by a study of preparations obtained with this method, he leaves the question unanswered.

In methylen-blue preparations of sympathetic ganglia of half grown rabbits and of full grown Guinea pigs, fixed in ammonia molybdate and sectioned, I find that, in the semilunar ganglion, sympathetic cells with two nuclei are numerous, although mono-nuclear cells may easily be found. I find no fixed relation between the number of nuclei in a given cell and its shape, as has been stated by Schwalbe, i. e., bipolar cells being mono-nuclear and multi-polar cells being multi-nuclear. Multi-polar cells with one nucleus were found, as well as bipolar cells with two nuclei. In such multi-nucleated neurons in which it was possible to designate the neuraxis, only one was found. The sympathetic ganglia of rabbits and Guinea pigs, in which neurons with two nuclei were observed, are in all other respects similar in structure to the sympathetic ganglia of vertebrates having only mononuclear neurons, as will be shown later.

Apolant (31) suggests that "The development of two nuclei, in the cells in question, is in close inter-relation with the growth of the cells, and in this way—the nucleus of a mono-nuclear cell attains a relatively large size (as he has shown by measurement), it then divides amitotically, this reacts on the cell body and causes it to grow proportionately. The process is therefore not a functional one, but a biological one." Apolant does however not explain why this should take place only in certain ganglia of the rabbit and not in others; in the ciliary ganglion, for instance, only mono-nuclear cells are found; and why in certain rodents and not in others, he himself having shown that in the sympathetic system of the rat, mouse and squirrel only mono-nuclear cells are to be found. This curious fact, it seems to me, still awaits explanation.

*Capsule.*—The cell body of a sympathetic neuron is surrounded by a nucleated capsule, which consists of cells resembling endothelial cells. In multi-polar cells, the dendrites pierce this capsule. Whether the capsule extends out on to the dendrites for any distance, I am unable to say positively, although the evidence points against such a view. It is generally stated



that the capsule and the neurilemma of the neuraxis are continuous; my own observations do not allow me to formulate any definite opinion on this point.

*Dendrites.*—The number and the arrangement of the dendrites of sympathetic neurons vary greatly, even in the same ganglion. As already stated, some few cells are unipolar; this is especially so in the larger ganglia. The single process present, is of course the neuraxis. In amphibia cells of this character are the general rule for all ganglia, excepting those found in the coats of the intestine.

In sympathetic cells possessing dendrites, their number may vary from one—bipolar cells—to ten or perhaps even more. These dendrites may have their origin from any portion of the cell body, as is the general rule, or several dendrites may arise from one large process, from which springs also the neuraxis. Cells of this character are prevalent in the larger ganglia of the sympathetic system of the reptilia.

The dendrites usually break up near the cell body into secondary and tertiary branches, and undergo further and repeated divisions until exceedingly fine terminal branches are reached. In well stained sections the dendrites form a very complicated network, which is found between the ganglion cells. This dendritic plexus is especially dense toward the periphery of the ganglion, as has been shown by Dogiel (25) and described by him as the "general peripheral plexus." The plexus formed by the branching dendrite is always extra-capsular, as may easily be seen in methylen-blue preparations double stained in alum carmine. In preparations well stained the cell bodies of the neurons are surrounded by a densely woven, basket-like plexus, in which the dendrites of several neurons may take part.

Ramon y Cajal (20) has described such basket-like plexuses as pericellular nests, and supposed this arrangement to be of physiological importance, believing that the sympathetic neurons were by means of it associated in their function. Dogiel (25) has, however, and I think very justly, discredited this conclusion, and, while he describes and pictures such pericellular

nests, he thinks their presence is due to an accidental arrangement of the dendrites. The fact that these pericellular nests are always extra-capsular, and that therefore the several dendritic processes which participate in their formation are not in contiguity with the cell bodies of the neurons which they surround argues very strongly against Cajal's hypothesis.

The statement has just been made that the dendrites break up into branches which terminate in the respective ganglia. Dogiel (25) has however shown that a few of the dendrites of some of the neurons in a ganglion pass beyond the bounds of said ganglion, enter a nerve trunk coming to, or leaving the ganglion and thus reach a neighboring ganglion, where, after undergoing division, they terminate. Such branches, he states, resemble very closely non-medullated nerve fibers, and only when they can be traced to the cell from which they spring, and when it can be made out that from the same cell there arises an axis-cylinder, can the true nature of these protoplasmic branches be ascertained.

*Neuraxes of sympathetic neurons.*—Sympathetic neurons are no exception to the very general rule, that a neuron has only one neuraxis. The neuraxis may spring directly from the cell body, as is commonly the case, or from one of the dendrites. In the former case the neuraxis has its beginning in a cone-shaped extension of the cell body. In the latter case it may arise from any portion of a dendrite. In some cases, as for instance in the larger cells of the sympathetic ganglia of reptilia, all processes—neuraxis and dendrites—have their origin in a single large process, which in turn arises from the depth of a depression seen on one side of the cell body. Even in such cells the neuraxis may arise from a dendrite, at a variable distance from the cell body. The fact that a neuraxis may be given off from a dendrite, is only another proof of the opinion now very prevalent, that the dendrites are only extensions of the cell protoplasm, and will therefore receive no further discussion.

In describing the structure of the neuraxes of sympathetic neurons I shall follow very closely a summary by Kölliker (32),

touching on this point. After discussing the literature and reviewing his own work, he reaches the following conclusions :

1. The neuraxes of sympathetic neurons become invested in many cases with a thin medullary sheath, thus forming very fine medullated fibers, which on account of their small size can be differentiated from the smallest cerebro-spinal fibers.

2. In some cases this thin sheath of myelin accompanies the respective neuraxis to near its termination. Such fibers, he states, are found in the ciliary branches of the ophthalmic ganglion ; in the nerves innervating the muscles of the hair papillæ (cat); and many of the fibers of the sympathetic chain.

3. In many of the sympathetic nerve fibers the medullary sheath is sooner or later lost, the neuraxis continuing as a non-medullated fiber; as for instance in the intestine, the liver, and in some of the nerves going to the spleen.

4. And finally the sympathetic system contains a large number of fibers—neuraxes of sympathetic neurons—that are non-medullated throughout their whole course. The great majority of the neuraxes of the neurons in the peripheral ganglia, in the intestine, in glands and in the heart are fibers of this nature.

As regards the structure of the neuraxes of sympathetic neurons the following observations have been made—

1. Dogiel (25) has shown that they consist of very fine ultimate fibrillæ, between which there is found a very small amount of inter-fibrillar substance—the neuroplasma.

2. Dogiel (25) further states that these neuraxes have as a rule a very regular and smooth contour, and only now and then small spindle-shaped enlargements, which resemble varicose enlargements, are to be seen. My own observations would lead me to modify this statement to this extent,—that only the larger neuraxes of sympathetic neurons, such, I have reason to believe, as are invested with a sheath of myelin, show this smooth contour; while a great many of the neuraxes (such as remain non-medullated) show the typical varicose enlargements; it is true more often near their termination. The structure and importance of such varicose enlargements is a point concerning

which opinions differ. Without attempting to discuss this point here, I may say that I have regarded them simply as accumulations of the neuroplasma, and the fine thread uniting the globules, as the ultimate fibrillæ of the respective fiber. The observations which have suggested this hypothesis are briefly these: In fresh methylen-blue preparations in which the sympathetic nerves were well stained, examined as soon as the tissue was removed from the body, I have often noticed that the varicose enlargements, both on sympathetic fibers and ultimate branches of the cerebro-spinal nerves, are far less numerous than when the preparations are exposed to the air sometime before they are studied or when such examination is deferred until the tissues are fixed. The method of their development I have explained to myself to be the following,—when the nerve fiber begins to break down, the semi-fluid neuroplasma collects in small globules, which usually stain quite deeply; the more resistant ultimate fibrillæ unite the small globules, and give us the appearance commonly described as a varicosity of the fibers.

Very characteristic for non-medullated sympathetic fibers, that is neuraxes of sympathetic neurons not invested with myelin, is the presence of a large number of sheath-nuclei; nuclei of the sheath of Schwann.

These are much more numerous than in a medullated nerve fiber, where, as is well known, usually only one nucleus is found in an inter-nodal segment. These nuclei are often relatively large and when stained with methylen-blue, as they sometimes are, they may simulate a ganglion cell. In thin sections, however, and by double staining, their true nature may be revealed. The neuraxes of the neurons of a given sympathetic ganglion wind their way between the ganglion cells, toward the periphery of the ganglion, and enter one of the nerve trunks leaving the ganglion.

Lenhossék (24) and Dogiel (25) have observed that now and then such neuraxes give off one or several collateral branches, while yet within the ganglion, which, as Dogiel states, may branch between the ganglion cells into further branches; their mode of ending is however not known.

As already stated, sympathetic cells have only one neuraxis; the apparent exception to this rule, ganglion cells in the peripheral ganglia of the intestinal canal, as first described by Ramon y Cajal(33), has been shown to rest on faulty observation. Cajal believed that all the processes of these cells were to be looked upon as neuraxes. Kölliker(34), as he himself states, was at first inclined to accept Cajal's interpretation of these structures. Dogiel(35) has however quite recently shown that the cells in these ganglia are in structure like similar cells in other ganglia—possessing only one neuraxis, the other branches being dendrites. These observations I can fully confirm, and that on a large number of methylen-blue preparations of the intestinal wall of fishes, of amphibia, reptilia and mammalia, in which the ganglion cells of Auerbach's plexus were well stained. In every instance in which it was possible to make out clearly the shape of these ganglion cells, and trace their respective processes, only one neuraxis was made out.

The neuraxes of the sympathetic neurons thus far described carry efferent impulses. Their mode of termination may be one of the following,—

1. In involuntary muscle tissue;
2. In heart muscle tissue;
3. In glands;
4. In spinal ganglia;
5. In other sympathetic ganglia.

1. *Ending in involuntary muscle tissue.*—It is now generally believed that all non-striated muscular tissue, namely that of the intestinal canal and the gland ducts in connection with it, the smooth muscle of the urogenital system, the smooth muscle found in the skin, the eye and all vessels, receives its nerve supply from sympathetic neurons. However, only in recent years has this view received its full morphological demonstration; by which is meant, that the staining of a sympathetic neuron in its entirety has only in recent years been accomplished. The only existing figure, with which I am familiar, showing a whole neuron and its ending in involuntary muscle, is found in an article

published by Arnstein (36), on the nerve supply of the respiratory organs. Arnstein in this illustration, a portion of which is reproduced in Fig. 1, shows a sympathetic neuron, the cell body and dendrites of which are situated in a small sympathetic ganglion found in the posterior wall of the trachea, where he was able to trace the neuraxis of said neuron into the muscular tissue of the tracheal wall. Non-medulated nerve fibers—the neuraxes of sympathetic neurons—can without difficulty be stained in involuntary muscle tissue, but such fibers are usually woven into intricate plexuses, so that the tracing of a single fiber with its branches, especially when of some length, becomes a matter of extreme difficulty. I have some few times succeeded in doing this for neurons situated in Auerbach's plexus. In fishes and reptilia the sympathetic cells of this plexus are often quite isolated; this is especially true of fishes, where also the neuraxes are relatively short, so that in methylen-blue preparations the neuraxis could be traced from the cell body to its ending in the involuntary muscle cells. The neuraxes and dendrites of the neurons destined to innervate the involuntary muscle are united into an intricate plexus, at the nodes of which the cell bodies of the neurons are grouped into small ganglia. From this plexus, smaller or larger bundles of nerve fibers are given off, which form a plexus around the fasciculi of the muscle. This plexus is very well shown in the bladder of the frog, where the fasciculi form an interlacing network. From the plexus around the fasciculi, fibers or small bundles of fibers are given off, which can often be traced for longer or shorter distances between the muscle cells as they course along in the intercellular cement, and where they run parallel to the long axis of the muscle cells.

The ultimate ending of these fibers in or on the muscle cells has been a point much disputed; two very distinct views being held until quite recently, Arnold (37), Frankenhäuser (38), Lustig (39) and Obregia (40) believing that the nerve fibers terminate in the nuclei of the involuntary muscle cells, often passing through the nucleus of one cell, again entering the intermuscular plexus, and entering another cell before terminating.

Other writers, among whom may be mentioned Kölliker (41), Löwit (42), Gescheiden (43), Retzius (44), Müller (56) and Dogiel (45), state that the ultimate fibrillæ terminate on the muscle cells. To throw, if possible, some new light on this question, I have made sections, 5  $\mu$  in thickness, of the muscular coat of the intestine of fishes, amphibia, reptilia and mammals, previously stained in methylen-blue and then double stained in alum carmine. In such preparations, when well stained in methylen-blue, only the nerve fibers show a blue color, while the muscle cells are colored in the carmine. In such sections, one may see the terminal branches of the sympathetic neurons, in the inter-cellular cement between the muscle cells; and it may be observed that all along, in their course, they give off short and exceedingly fine branches, or side twigs, which end on the muscle cells often near the nucleus, in small terminal swellings of round, oval or pear-shaped form. The terminal branches are always very varicose, and after giving off a number of "side twigs" also end on the muscle cells in the manner above described. This description corresponds very closely to those given by Erik Müller (56) and by Retzius (44), the latter having described an especially well stained, Golgi preparation made from the bladder of a rabbit 9 days old; the results obtained by the two methods being thus corroborative. In Fig. 2, may be seen the ultimate ending of the neuraxis of a sympathetic neuron on an involuntary muscle cell.

A question of some importance in this connection is the following—Do all of the muscle cells in involuntary muscle have a distinct and separate nerve supply?

Retzius (44) gives no definite answer to this question, although he inclines to the view that they do not. The answer is difficult in so far as it is impossible to determine whether all of the nerve fibers in a given preparation are stained. In preparations in which this would seem to be the case, not nearly all the muscle cells have a separate nerve ending. In the smooth muscle of the intestine the varicose, intra-fascicular branches, above referred to, have a more or less parallel course, and in my most successful preparations, three to four rows of the

spindle shaped muscle cells are usually found between two such fibers. It is of course impossible to say whether, in the preceding or succeeding sections, terminal fibers which held a very close relation to the muscle cells found between two parallel fibers, might not exist. In thicker sections, there always seem to be some muscle cells that are not touched by a nerve fiber or an ending of such fibers. I am inclined to think therefore that not all the cells in involuntary muscle have a nerve fibril ending on them.

The innervation of the involuntary muscle of vessels is best studied in relatively small vessels. In such vessels, sympathetic nerve fibers, often very varicose, form a plexus in or outside of the adventitia. Such a plexus is well shown in Fig. 3, which shows a portion of a small vessel from the pharynx of a frog, injected with methylen-blue. From this peri-vascular plexus, terminal fibers or small bundles of fibers enter the muscular media, where in thicker vessels they form an intra-muscular plexus; from the intra-muscular fibers, terminal branches arise which end on the muscle cells.

The account here given is very similar to one given by Retzius (44), who has described the innervation of the vessels in the choroid of white rabbits, also vessels of the frog's pharynx, and corroborates observations made by Dogiel (45) on the nerve supply of the vessels of the human eye-lid, to some extent also the accounts given by His and Kölliker of an earlier date.

2. *Ending of sympathetic neurons in heart muscle.*—It is not my purpose to give here the older literature bearing on this portion of my subject; for this the reader is referred to articles by Retzius (44), Berkley (46) and Jacques (47). The first communication dealing with the innervation of heart muscle, giving observations obtained either with the Golgi or methylen-blue method, we have from Arnstein (48), who describes a loose plexus around the bundles of the heart muscle cells. From it small varicose branches are given off, which may often be traced for long distances. These end on the cells without forming bulbar enlargements. In the account given by Retzius



(44) we learn that Cajal succeeded in staining the heart nerves in reptilia, batrachians and mammalia, with the rapid Golgi method (personal letter to Retzius). The nerves are described as non-medullated, forming plexuses around the heart muscle fibers, and ending in varicose fibers which terminate on the heart muscle cells in small end bulbs. Retzius' (44) description corresponds very closely to that given by Cajal and need therefore receive no further mention. Heymans (49), who cut the frog's heart stained after the Golgi method, into serial sections, reaches the conclusion, based on the richness of the nerve supply, that each heart muscle cell is directly innervated.

Berkley (46) has studied the ending of heart nerves in the white rat, the frog, sparrow and the dog, using a modified Golgi method (tissues were prefixed in picric acid). Berkley describes two kinds of fibers in the inter-muscular plexus—varicose fibers, of a brownish black color, and fibers rarely showing any knotty thickenings and giving off few branches and often showing a rounded or elongated bulb near their termination. Two kinds of endings are described :

(a) "The end-apparatus of the varicose network is usually very simple, being represented almost without exception by a minute ball-like enlargement at the terminal point of the end-branches."

(b) The second type of fiber presents an end-apparatus more complex ; "an end-termination of considerable size, lying upon the sarcous substance of a single muscular fiber may be seen." The end-apparatus of the second type is found on the fibers presenting the nodular enlargements above referred to, and Berkley looks upon these nodular enlargements as bipolar cells, situated in the path of the fiber, and suggests as a hypothesis that we may here have sensory fibers, either of the sympathetic or cerebro-spinal system.

Jacques (47) has made observations on the intrinsic heart nerves in the frog and mammals, both with the Golgi and methylen-blue method. As regards the ultimate ending of the motor nerves he has this to say in his summary :

"The nerve trunks anastomose with each other after their

entrance into the myocardium to form a fundamental myocardial plexus from which the system of intermuscular fibers originates. It is from the latter that the terminal fibers arise which penetrate between the cells of the muscle bundles and enter into communication with them by the medium of lateral and terminal branches of varied form and size, comparable for the most part to the terminations described in striped muscle of different invertebrates."

My own observations on the innervation of cardiac muscle, were made largely on the auricle of the cat's heart. The tissue was stained in methylen-blue, fixed in ammonia molybdate, sectioned and counter-stained in alum carmine. In such preparations, the plexus of non-medullated fibers around the bundles of heart muscle cells, described by other investigators, may easily be seen. In the auricular wall, numerous small ganglia, composed of sympathetic cells, are found. From such ganglia one may often trace small bundles, made up largely of non-medullated fibers (no doubt the neuraxes of the sympathetic neurons constituting the ganglia, although, owing to the fact that as a rule the cell bodies of the neurons are not stained with the methylen-blue, the tracing of the neuraxes to their respective nerve cells often becomes a matter of extreme difficulty) into the above mentioned plexus.

From such plexuses, single varicose fibers, or small bundles composed of two, three or four such fibers, can be traced between the heart muscle cells and can often be followed for some distance, giving off in their course short side branches which terminate on the heart muscle cells. The terminal endings of the side branches and the endings of the fibers differ in complexity, as may be seen from Fig. 4. In (*a*) of this figure is shown a very simple ending, the fine fiber terminating *on* the muscle cell ending in two small end bulbs. In (*b*) and (*c*) of the same figure are shown more complicated endings, the small end-branch terminating in several secondary branches which end in nodular end-swellings.

That these endings are on the heart muscle cell may be

clearly seen in double stained preparations, only the nerve fiber staining blue, the muscle cell red. This is especially well shown where a heart muscle cell and ending are cut transversely; in such a case it may be seen that the ending rests on the cell and does not in the least enter it. The more complex endings described correspond, I think, to the end-apparatus of the second type mentioned by Berkley (46). In preparations made of the auricles of a cat's heart, I find no appearances which might lead me to think that nerves having a distinctive structure are associated with characteristic endings as Berkley (46) has stated in the admirable account from which the quotations above given were taken. In the cat, nerve fibers going to the more simple and the more complex endings are distinctly varicosed, and furthermore the endings seen by me vary so in complexity, from a single small end bulb, to one with two, three, four or more nodular enlargements, that a division into two types would be a purely artificial one. In my preparations I have found no bulbous enlargements, which might be interpreted as bipolar cells, such as Berkley (46) has described. I have however often found large sheath-nuclei on the non-medullated fibers, plainly made out in double stained preparations, which, if stained with the nerve fiber after the Golgi method, might, I believe, give an appearance similar to the bulbous enlargement described by Berkley. While not denying the existence of bipolar cells in the heart, it would seem that further confirmatory observation is necessary, before their presence is assured, and that with methods by means of which the structure of these nodules may be ascertained.

To summarize this portion of my subject, I may say that the neuraxis of sympathetic neurons (most probably those in the heart ganglia) terminate on the heart muscle cells either by a very simple ending, one that resembles those found in involuntary smooth muscle, or by a more complicated ending, resembling slightly the ending in striated muscle. The question may here be asked—do all heart muscle cells have a direct innervation? As already stated, Heymans (49) suggests this for the frog's heart. In well stained preparations of the auricle of a cat's heart it would appear from the number of nerve fibers

present in some fields, that this number was sufficient to innervate every cell. Sometimes two, three and in some few instances four successive cells in a given heart muscle fiber, show a nerve ending, yet when adjacent fibers were observed no endings were seen. This might of course be due to imperfect staining. Such heart muscle fibers are often touched by varicose nerve fibers, but the presence of an ending is missed. This question needs therefore further study.

3. *Ending of sympathetic nerves in gland tissues.* The problem here involved is one concerning which much has been written, yet it is only since investigators have used the Golgi and methylen-blue methods for its elucidation that anything like a definite answer could be given. As early as 1888 Retzius(50) presented to the Biological Association of Stockholm a short paper, in which the results obtained by staining the nerves of the small salivary glands, found near the papilla foliata of the rabbit, were discussed. In this account Retzius speaks of a plexus of fine varicose fibers surrounding the alveoli of the glands. He was however unable to determine what was the ultimate ending of the fibrils of this plexus or their relation to the gland cells. Ramon y Cajal(51) shortly after published results obtained by a chrome-silver impregnation of the submaxillary glands of the rat and rabbit. He here describes the non-medullated nerve fibers as entering the gland with the blood-vessels. These fibers form plexuses around the alveoli, from which fibrillæ are given off which end on the membrana propria or on the outer surface of the cells. Fusari and Panasci(52) studied the ending of nerves in the small glands of the tongue, also with the Golgi method. They state that the non-medullated fibers not only form a plexus around the alveoli but also the gland cells. Marinesco (53), who has published results obtained by staining the glands of the tongue with methylen-blue, states that both medullated and non-medullated nerves take part in the formation of the peri-alveolar plexus. From this plexus, which is external to the membrana propria, fibers pass through the membrana and end between the gland cells.

Korolkow (54), who gives in a preliminary notice results

obtained with methylen-blue staining of the salivary glands of mammalia, also finds medullated and non-medullated nerves in the glands, and was able to trace these nerve fibers through the membrana propria, and between the gland cells. In another paper Cajal (55) treats of the ending of the nerves in the pancreas. In this tissue when stained with the Golgi method, he was able to trace the ultimate branches of the nerves between the gland cells. Müller (56) corroborates in the main Cajal's results on the ending of nerves in the pancreas. He also finds that non-medullated nerves form a plexus around the alveoli—  
“Ein Flechtwerk von feinen Fäden, welche unmittelbar den Zellenkörpern anliegen und mit freien Endzweigen schliessen.” Müller was not able to trace the ultimate fibrillæ between the gland cells. Further observations were recorded by Retzius (57) on the submaxillary glands of rabbits and dogs, in which he gives no definite account of the ultimate ending of the nerves, but mentions the existence of sympathetic ganglion cells, by the side of the ducts and blood-vessels of this gland, but states that he was not able to ascertain the distribution of the axis cylinders belonging to these cells. In another communication on the ending of nerves in the parotid of the salamander (*Salamandra maculata*) and the sublingual of lizards (*Lacerta agilis*), Retzius (58) describes inter-epithelial endings. Both of these investigations were made with the Golgi method. Dogiel (59) has studied the ending of nerves in the lachrymal glands of rabbits and Guinea pigs with the methylen-blue method. In this very admirable paper he gives the following account of the nerve endings. The nerves entering these glands are almost exclusively non-medullated. They follow the gland ducts and blood-vessels. The branches of these nerves form plexuses about the alveoli, external to the membrana propria. From these plexuses fibers are given off which pierce the membrana propria and form a second plexus between it and the gland cells, and from this second plexus, nerve fibrils pass between the gland cells, which branch, anastomose and form an intercellular network, in the meshes of which are found the gland cells. Dogiel finds no free ending on the cells; when such an

ending seemed indicated, it was interpreted as showing imperfect staining.

Berkley's (60) results on the innervation of the submaxillary gland of the rat stained with his modified Golgi method, confirm in the main results obtained by preceding investigators. On the ultimate ending of the nerves he has this to say,—two kinds of terminal endings exist: supracellular, here the ending lies on the extreme outer edge of the cell, the fibril ending in a small bulb, which rests in a pit-like depression of the surface of the cell; and inter-epithelial, of less frequent occurrence, the nerve fibril ending in the cement substance between the cells.

I wish finally to refer to a communication from Arnstein (61), "On the Morphology of the secretory nerve-apparatus." In this article Arnstein gives a summary of results obtained by himself and several of his pupils on the ultimate ending of nerves in the following glands,—mammary gland by Dmitrewsk; skin glands by Ostrowmow; prostate by Timofiew, and the pancreas, salivary glands and Harder's gland by Arnstein. Their results are summarized as follows,—the gland nerves form around the secreting tubuli or alveoli, a plexus—epilamellar plexus—which rests on the membrana propria; from this fine fibers are given off, which pierce the membrana, and as peri-cellular fibers, without forming a network, and with or without further branching, end on the gland cells in small varicose endings, the configuration and complexity of which varies for different cells, even in the same gland. These results were obtained largely on macerated and teased preparations made from glands stained in methylen-blue. In such preparations it was often possible to obtain isolated cells, showing the terminal nerve apparatus in connection with short segments of the pericellular nerves. And, if the account of Arnstein is to be trusted at all, he has given us the most complete description of the terminal ending of nerve fibers in glands. The nature of these endings may be seen in Fig. 5, taken from Arnstein's article.

I have thus reviewed the literature touching on the subject in question, partly on account of its importance, also to show

that nearly all glands have been studied either with the Golgi or the methylen-blue method and further to show that in the branched tubular or racemose glands studied a unanimity exists in the results obtained; certainly so far as pertains to grosser distribution of the nerve fibers. It may be seen that bundles of nerve fibers, largely composed of non-medullated fibers, or in other words of the neuraxes of sympathetic neurons, enter the gland with the gland ducts and with the vessels. On entering the glands they form a plexus around the branches of the ducts and vessels, from which fibers or small bundles of fibers are given off which surround the secreting alveoli or tubuli to form the epilamellar plexus. Concerning the mode of the terminal ending, opinions differ as yet. The greater portion of the evidence points however to an ending on the gland cells, either in a free ending or in a small end-bulb or, as the work of Arnstein and his pupils would show, in a more complicated end-apparatus, resting on the cells. That the non-medullated nerve fibers found in the glands are the neuraxes of sympathetic neurons, may be seen in sublingual or submaxillary glands; where, especially in the latter, large numbers of small ganglia are found in the gland itself. The writer (62), in an article in which he discusses the innervation of the sublingual and the submaxillary glands in the dog, has shown that these ganglia, which are situated in the connective tissue surrounding the gland ducts, are composed of sympathetic nerve cells. In tissue impregnated after the Golgi method and cut so that the plane of section is more or less parallel with the gland ducts, the neuraxes of the sympathetic neurons may often be followed for long distances by the side of the gland ducts, their branches forming the plexus surrounding the ducts above referred to. In a few instances a neuraxis coming from a sympathetic nerve cell, which was observed following a duct, could be followed as it left a duct and approached a group of alveoli; and in one instance of a section of a chorda-lingual triangle, which contained a portion of a sublingual gland, two sympathetic cells deeply stained were seen, the axis cylinder of one of which could be followed for quite a distance by the side of an inter-

lobular duct, and after a very short interruption a fiber of the same size and appearance, and which seemed to be a direct continuation of the axis cylinder just mentioned, could be traced into a peri-alveolar—epilamellar—plexus.

The medullated fibers which enter the glands, do not, I am inclined to think, enter into the formation of the epilamellar plexuses, as Fusari and Panasci, and Korolkow have suggested. Medullated nerve fibers, of cerebro-spinal origin are undoubtedly found in glands, and have I believe two distinct modes of termination. Some of these fibers are no doubt sensory, ending in free endings between the columnar cells lining the gland ducts. The free endings described by Arnstein (61) and myself, (62) belong I believe to fibers of this nature. Other medullated fibers end in baskets around the sympathetic cells, as pointed out by the writer. These fibers will be given no further consideration now, but will receive due consideration in one of the following lectures. From what has been said, and especially if we extend our consideration to glands which in their fully developed condition are not classed as tubular or alveolar glands; (we may refer here to work done by Berkley (63) on the intrinsic nerves of the liver, who states that such nerves are non-medullated; and the thyroid, where Anderson (64) and Berkley (65) have shown that non-medullated nerve fibers enter this gland with the blood-vessels, there to form peri-follicular meshworks, the terminal branches of which end on the gland cells (Berkley); and the supra-renal, worked on quite recently by Dogiel (66) where he has shown that the intrinsic nerves are non-medullated, in part neuraxes of sympathetic nerve cells found in this gland) we may see that the general statement, that gland cells are innervated by the terminal branches of the neuraxes of sympathetic neurons, is based on abundant observation, even though we must say with Arnstein (61), "That many an eye will tire before the secretory nerve-endings will in their true nature be fully understood."

4. *The ending of the neuraxes of sympathetic neurons in the spinal ganglia.*—The existence of sympathetic nerves in the spinal ganglia is a point concerning which there exists as yet



some doubt. The facts we possess, pointing to such fibers are the following. In Ehrlich's (4) first publication, on the reaction of methylen-blue on living nerve tissues, he describes a very delicate network enclosing the cell bodies of some of the spinal ganglion cells of the frog. The nature of this network could however not be ascertained. Aronson (67), in a dissertation which followed Ehrlich's paper, briefly mentions similar pericellular networks, or baskets, found in the spinal ganglia of the rabbit. Such pericellular baskets were then described by Ramon y Cajal (68), seen (presumably) in the spinal ganglia of the rat, as the figure he gives in his summary of the histological structure of the central nervous system was made from a Golgi preparation of a young rat. Cajal here suggests that these baskets may represent the endings of sympathetic nerve fibers, which he was able to trace through the rami communicantes into sympathetic ganglia. These sympathetic fibers, divided in the spinal ganglia into two or three branches, which could be traced into the substance of the ganglion, where he suggests they may end in the pericellular baskets.

Dogiel (69) in a recent publication on the structure of the spinal ganglia of mammalia (dogs, cats, rabbits and Guinea pigs having been investigated) gives the following description of these structures.

"It may now and then be seen, that through an anterior branch of one of the spinal nerves a few small, medullated, sympathetic fibers enter a spinal ganglion. These at a node of Ranvier give off one or two small medullated or non-medullated branches."

These branches, medullated and non-medullated, the medullated fibers soon losing their myelin, approach a spinal ganglion cell, and, after making a few twists about its nerve-process, break up into an extra-capsular plexus, from which fibers proceed, which pierce the capsule to form a pericellular basket. Dogiel is inclined to believe that the cell bodies around which these sympathetic fibers form pericellular baskets belong to peculiar neurons found in the spinal ganglia, and first described by him. To these he has given the name, "*spinal*

*ganglion cells of the second type.*" The type two cells have the following peculiarity.—The neuraxis of such a cell, breaks up within the ganglion into a large number of branches, which, like the neuraxis, are myelated. These branches soon lose their myelin and terminate in peri-cellular baskets, enclosing the cell bodies of the spinal neurons of *type one*, the cells commonly known as spinal ganglion cells. So that, as may be seen, although relatively few sympathetic fibers enter a spinal ganglion, yet through the cells of type two, they may exert an influence over a large number of the typical spinal ganglion cells.

I may add that Dogiel looks on the sympathetic nerve fibers ending in the spinal ganglia as the neuraxes of *sensory sympathetic cells*, a type of sympathetic cells which he has described. These will be further discussed in the next section.

Finally, I may briefly mention some observations made by the writer (70) and recorded in a short paper on the spinal ganglia of amphibia.

In a number of methylen-blue preparations of the spinal ganglia of the large bull-frog, I have observed fine nerve fibers, which are sometimes wound spirally about an axis-cylinder or have a very tortuous course and break up into a network of finer branches, which terminate within the capsule of ganglion cells, from the axis-cylinders of which short processes, which end in disc-like expansions, are given off. I suggest, as an hypothesis, that this network represents the ending of sympathetic fibers found in the spinal ganglia of frogs. In some few instances I was able to trace such non-medullated fibers some distance from the cells on which they end, toward a bundle of sympathetic nerve fibers, which seemed to come from the distal portion of the spinal ganglion. Peri-cellular baskets have further been found in the vagus ganglia of the frog, also in the spinal ganglia of *chrysemys picta*, a small tortoise examined by me. Such baskets could not however be connected with nerve fibers.

5. *Ending of the neuraxes of sympathetic neurons in other sympathetic ganglia.*—Before discussing this mode of termina-

tion of neuraxes of sympathetic neurons, I wish to refer to some observations recently published by Dogiel (71), wherein he states that in sympathetic ganglia two types of sympathetic nerve cells are found. The cells belonging to the first type have been the subject of discussion thus far, and are, according to the ending of their neuraxes, either motor, ending in involuntary or heart muscle; vaso-motor ending in blood-vessels; and what we may term secretory nerve fibers, ending on gland cells. The dendrites of such neurons usually end within the respective ganglion in a manner previously described.

The cells of the second type are described by Dogiel as follows:—The cell body of such cells is as a rule somewhat larger than that of the cells of the first type (motor cell etc.). The number of their dendrites varies from five to sixteen or even more. These dendrites are much longer than the dendrites of the cells of the first type, undergo less branching and may often be traced as fine varicose branches beyond the bounds of the ganglion. In preparations of the ganglion cells of Auerbach's plexus, the dendrites of the cells of the second type were now and then traced into the submucosa of the intestine, and in such instances they resemble very closely axis-cylinders. Dogiel thinks that the cells of this structure are sensory sympathetic cells and suggests the possibility of their forming sensory endings in the epithelium. The neuraxes of these cells may arise either from the cell body directly or from one of the protoplasmic branches. They leave the ganglion through one of its nerve roots, in which they may become invested with a thin layer of myelin. They could now and then be traced into another ganglion, where one, two or three branches were given off. These branches, which may or may not be myelinated, break up into secondary branches, which take part in the formation of the inter-cellular plexus of the ganglion. The axis-cylinder may pass on and terminate in another ganglion. Dogiel states it quite probable that the sympathetic fibers which end in pericellular baskets about the cell bodies of the spinal ganglion cells

of type two as above mentioned, are the neuraxes of sensory sympathetic cells.

The relation of the sensory sympathetic cells to other structures is well shown in Fig. 6 copied from Dogiel's paper. The importance of these observations, in case they receive corroboration, can not be over-estimated. The existence of sensory sympathetic cells would explain certain phenomena which have been observed in connection with the sympathetic system. I may mention, for instance, peripheral reflexes and peristaltic movements of the intestine, etc. These points will however receive fuller discussion at another time.

It is not my purpose to discuss fully at this time, the question of the ending of the neuraxes of sympathetic neurons in sympathetic ganglia. In order to do that it would be necessary for me to mention certain important structures found in sympathetic ganglia, to which I have not as yet alluded, and which are more fittingly discussed in the next division of my subject; and also to refer to some very important physiological work, in connection with the sympathetic system, which has been done by Langley and some of his pupils, the discussion of which I desire to defer until the above mentioned structures have received due attention. Mention may however be made of the fact that Lenhossék (24) has observed, in Golgi preparations made of embryo chicks of the 14th day, sympathetic fibers that enter a sympathetic ganglion from the periphery, there to terminate in free endings, endings which he describes as "simple end-brushes," the fibrillæ of such end-brushes often terminating on cells in small end-bulbs.

In methylen-blue preparations of the ganglia of the chain taken from mammalia and birds, I have often observed a free ending of branches of non-medullated nerve fibers in sympathetic ganglia; not however on the cell bodies of the sympathetic neurons as Lenhossék would have us believe, but on the dendrites of sympathetic neurons. Fig. 7 shows such an ending, sketched from a moderately thin section of a sympathetic ganglion of a cat, stained in methylen-blue. As may be seen from

the figure, the end-branch of the non-medulated fiber terminates in several very small nodular enlargements.

The fiber thus ending did not seem to enter the ganglion from the periphery, or, to state it in an other form, did not seem to be the termination of a neuraxis, a part of a sympathetic neuron, situated distal to the ganglion in which said ending was found. I am free to admit, that in sections such orientation becomes a matter of extreme difficulty. Yet, in larger ganglia, studied as a whole, even when cleared in glycerine, and especially if the ganglion is at all well stained, the tracing of nerve fibers and the recognizing of their mode of ending is to me a task more beset with difficulties and more open to misinterpretation. Hence the reason for studying the larger ganglia in sections. I may say that the observation here presented is not unique, but has been met with many times. Whether the free ending on the dendrites of sympathetic cells, is to be looked upon as the ending of neuraxes of sensory sympathetic neurons, in the sense suggested by Dogiel, I am unable to say. I would suggest, however, as an hypothesis, the possibility of a similar ending for the neuraxes of sympathetic neurons, situated central to the ganglion in which they end, neurons not sensory in their nature. This point will, however, as above stated, be taken up again.

*Ending of cerebro-spinal nerve fibers in the sympathetic ganglia.*

—In methylen-blue stained sympathetic ganglia there are always found a varying number of medullated nerve fibers. Some of these medullated fibers pass through the sympathetic ganglia, without in any way making connection with the sympathetic nerve cells contained therein; these are in all probability sensory, cerebro-spinal fibers, and will be discussed at a future time. Other medullated fibers terminate in the sympathetic ganglia, by ending in peri-cellular baskets, which surround the cell bodies of the sympathetic neurons. These fibers will now be more fully considered.

Ehrlich (4) in his first communication on the reaction of methylen-blue on living nerve tissues, described a plexus of fine fibrillæ about the cell bodies of the sympathetic nerve cells

of the frog, which was in connection with the spiral process of these cells. Ehrlich's observations were soon confirmed by Retzius (72), Smirnow (73) and Arnstein. About the same time Aronson (67) described and pictured peri-cellular plexuses in methylen-blue stained ganglia of the rabbit—superior cervical, cœliac and cardiac. They were then described by Sala (23), Van Gehuchten (21) and Lenhossék (24) in Golgi preparations of the sympathetic ganglia of mammalia, and in more recent years by Dogiel (25) and Kölliker (34) and a number of other investigators. The peri-cellular plexuses or baskets have thus been found in the various ganglia of the chain, in the prevertebral and terminal ganglia.

They are, as will be shown, always intra-capsular, in direct contact with the cell bodies of the sympathetic neurons, within the capsule of which they are found; and are therefore not to be confused with the *peri-cellular nests* described by Cajal, which, as will be remembered, are extra-capsular.

In giving a fuller description of these structures as found in the various vertebrates, I shall take up first the mammalia, then birds, reptiles, amphibia and fishes in the order named.

(a) *Mammalia*. The peri-cellular baskets, about the sympathetic cells of mammalia, vary greatly in complexity, even in the same ganglion. A typical one may be described as follows, a section of a sympathetic ganglion of a cat or dog, stained in methylen-blue and counter-stained in alum carmine serving for purpose of description. In such preparations the cell bodies of the sympathetic neurons are stained a pale red, the axis-cylinders and baskets are alone stained blue. In such preparations it may be seen that one, two, three or even more, small varicose nerve fibers approach a ganglion cell and before or after piercing the capsule, they break up into a number of smaller branches, which in turn may or may not undergo further division and then anastomose or interlace to form a plexus around the cell body of the ganglion cell in question. It seems to me that the complexity and the arrangement of the fibrillæ in the network constituting the so-called peri-cellular baskets are largely accidental and not to be looked upon as showing

essential structural differences. The fibrillæ of the peri-cellular baskets are as a rule very varicose, and often present quite large nodular enlargements. In *a*, of Fig. 8, a cell body of a sympathetic ganglion cell with peri-cellular baskets, from a sympathetic ganglion of a dog, is reproduced.

It would seem that now and then a large number of fibers take part in the formation of such baskets. Sala (23) describes small bundles of nerve fibers, which in their course give off one or several fine branches, which take part in the formation of such baskets. This condition has not been met with by me. Aronson (67) states that the nerve fibers are often wound spirally about the neuraxis of the ganglion cell, before breaking up into the baskets. I have seen this only a very few times in mammalia, and believe it not to be as common as Aronson's account would lead one to infer. In all mammalia studied these peri-cellular baskets have essentially the same structure and, as already stated, have been found in nearly all sympathetic ganglia. In the ganglia of the chain they have been repeatedly described. They were seen by Kölliker and Michel (74) in the ciliary ganglion of the cat; by Lenhossék (24) in the sphenopalatine ganglion of the mouse; by me (62) in the sublingual and the submaxillary ganglion of the dog; by Aronson (67) in the cardiac ganglia of the rabbit; by Arnstein (36) in the sympathetic ganglia of the trachea and bronchi; by Dogiel (35) in the ganglia of the intestinal canal; by Timofiew (75) in the sympathetic ganglia of the epididymis. They have further been seen by me in the sympathetic ganglia of the bladder and prostate of the cat, and in those of the œsophagus of the cat and rabbit. It would therefore seem safe to assume, that these structures are found in all the sympathetic ganglia of the mammalia.

That these peri-cellular baskets are the mode of ending of many of the medullated fibers in the sympathetic ganglia there can be no doubt, the medullated fibers losing their sheath of myelin at a variable distance from the baskets, the neuraxes continuing as varicose non-medullated fibers. Van Gehuchten (21), Dogiel (25) and Kölliker (34) have shown that many of

the medullated fibers in the sympathetic ganglia divide into branches, from which collateral branches (as a rule non-medullated) are given off, so that, as Dogiel (25) has pointed out, a single medullated fiber may end, according to the number of collateral branches present, in a number of peri-cellular baskets.

(b). *Birds.* In birds (chicken) the peri-cellular baskets in the sympathetic ganglia have essentially the same structure as those found in mammalia, and are also the endings of medullated fibers in the ganglia. The fibrillæ of the network forming the peri-cellular baskets in birds are on an average somewhat finer and not so numerous as in mammalia, so that as a whole the baskets are somewhat simpler. They are always intra-capsular. In Fig. 8, *b*, are shown two ganglion cells from one of the dorsal sympathetic ganglia of a chicken, where a small varicose fiber breaks up into two branches, each of which ends in a peri-cellular basket.

(c) *Reptilia.* In the tortoise the structures in question vary greatly in complexity. Many of the peri-cellular baskets resemble in structure those found in sympathetic ganglia of mammalia and birds; this is more especially the case in the smaller ganglia—the cardiac ganglia and the smaller ganglia of the chain. The cells enclosed in such baskets are usually multipolar, resembling in shape those found in mammalia and birds. But, as previously stated, many of the sympathetic neurons of reptilia (and this is more especially true of the larger ganglia) are relatively large and of peculiar form. The cell body of such neurons may be round or oval, and from it springs one large process, which may be straight or twisted around the cell body or upon itself. In either case, it breaks up at a variable distance from the cell body into several large branches one of which becomes a neuraxis, the others being dendrites. The peri-cellular baskets found enclosing such cells are usually much more complicated than those found about the multipolar cells, above described. The medullated fiber ending in these more complex baskets is often wound spirally around the neuraxis of the sympathetic cell, and about the large process from which the neuraxis springs, before breaking up into the fibrillæ form-



ing the network of the baskets. The number of the turns of such a spiral may vary from two to fifteen or even twenty. Several medullated fibers may take part in the formation of such a spiral. The neuraxes of the nerve fibers of such spirals break up into nerve fibrillæ, which may also be given off from some loop of the spiral, and these are woven into a complex network to form the basket. The fibrillæ of the complex baskets are usually very varicose. The spirals and end-baskets are intra-capsular. Such baskets have often been found in the inferior cervical and the stellate ganglia. In the smaller ganglia of the chain—dorsal, lumbar and caudal—there is, as a rule, found only here and there one of the more complex baskets. In *C*, of Fig. 8, are shown two sympathetic cells, from a sympathetic ganglion of a reptile, the one surrounded by a pericellular basket of the simpler type, the other more complex with a spiral fiber.

(d) *Amphibia.* The cells of the sympathetic system of the frog have, since they were first described by Arnold and Beale, been the subject of numerous contributions. These cells were described among the older writers as bipolar, with straight and spiral processes. Ehrlich, as has been shown, discovered that the spiral process terminated in a peri-cellular network. Ehrlich (4) regarded the spiral fiber as of cerebro-spinal origin, largely because it was invested with a layer of myelin. Retzius (72) corroborated Ehrlich's observations and further showed that the spiral fiber often branched "T"-shaped, at a variable distance from the cell on which it ends in a basket. Retzius also believes the spiral of cerebro-spinal origin. In a communication published by Arnstein (73) giving the results of an investigation by himself and Smirnow, of the sympathetic ganglia of the frog, when stained with methylen-blue, and in a further publication by Smirnow (76), very different conclusions are reached. They describe the spiral fiber as going to the periphery, and according to Smirnow ending according to the location of the ganglion in various peripheral tissues.

Smirnow further states that the spiral serves form anastomosis between ganglion cells, the spiral dividing, one branch

going to the periphery, the other going to another ganglion cell.

In *d* of Fig. 8 is shown a ganglion cell of the sympathetic of a frog. This was sketched from a section of a sympathetic ganglion, stained in methylen-blue and counter-stained in alum carmine. As may be seen in the figure, the peri-cellular plexus (basket) is intra-capsular, as described by Retzius, and encloses the cell body, as stated by Ehrlich (4), Retzius (72), Arnstein (73), and Smirnow (76); and does not, as for instance Feist (77) suggests, form a portion of the cell body. Double stained preparations leave no doubt concerning this question. The figure further shows that this basket is formed by branches of the spiral fiber, as first accurately described by Ehrlich (4). We have I believe, very strong evidence, that these spiral fibers do not go to the periphery, but are the terminal branches of medullated fibers ending in baskets. In ganglia partially stained in methylen-blue, fixed in picrate of ammonia and cleared in glycerine, medullated nerve fibers can often be traced for long distances, and their mode of ending clearly made out. In Fig. 9 is reproduced a sketch of such a fiber drawn under the 1-12 oil immersion with the aid of a camera lucida and then reduced to two-fifteenths. At the top of the figure is seen a medullated nerve fiber, a fiber which entered a ganglion through a white ramus. The course and branchings of the fiber are shown in the figure. As may be seen, a number of the non-medullated branches were traced into end baskets.

The "T" division described by Retzius (72), and the anastomosis between ganglion cells suggested by Smirnow (76) may I believe be explained on the supposition of incomplete staining of a medullated fiber the branches of which end in end-baskets.

I should thus regard the sympathetic neurons of the frog as unipolar cells, the straight process being the neuraxis of such cells, the spiral fibers the ending of another neuron, as Kölliker (34) has previously stated.

(e.) *Fishes.* In fishes the peri-cellular baskets are as a rule somewhat simpler than in other vertebrates, simpler in so

far that the terminal fibrillæ of the nerve fibers ending in these structures are not always woven into a network.

In *E*, of Fig. 8, is shown a nerve cell from a sympathetic ganglion of a black bass. It may be seen that the nerve fibers ending on the cell, (intra-capsular ending), break up into a number of varicose fibrillæ which only partly surround the cell. The endings are often more complex, but the cell shown in the figure may serve as an illustration. In fishes, as in other vertebrates, the end basket, or the intra-capsular end-brush, as it may be more correctly termed, represents the termination of a medullated nerve fiber found in the sympathetic ganglia.

From this review of the structure of the peri-cellular end-baskets in the sympathetic ganglia of vertebrates, we may deduce the following facts:

1. These structures are found in the various classes of vertebrates.

2. In all vertebrates they are intra-capsular, and have essentially the same structure. The fact that in some vertebrates—amphibia and reptilia—the nerve fiber terminating in the end-basket is wound spirally about the neuraxis of the ganglion cell, does not modify this statement.

3. In all vertebrates these peri-cellular baskets are the mode of ending of medullated nerve fibers found in the sympathetic ganglion, medullated fibers which often divide and give off collateral branches, which in their turn end in the baskets.

These questions may now be asked. Where do these medullated fibers come from; are they neuraxes or dendrites of neurons; are the cell bodies of such neurons found within or outside of the ganglion; and if outside of the ganglion, in some portion of the cerebro-spinal axis?

In answering these questions, I may at the outstart state that all the evidence we possess—experimental and histological—goes to show that these medullated fibers enter the sympathetic ganglia through the white rami communicantes. This evidence is in brief as follows:

In the first place let me draw your attention to the fact that “all effects which can be produced by stimulating the sym-

pathetic in any region, can be produced by stimulating the spinal nerves in the vertebral canal, or by stimulating the cord itself." I infer from Langley's (78) account (from whom this statement was taken) that Budge and Waller were the first to discover this fact; it has however since been repeatedly shown by other investigators.

Attention has already been drawn to the fact that the sympathetic ganglia of the chain and the pre-vertebral ganglia are connected with the spinal nerves by nerves known as the white and grey rami communicantes. The efferent impulse excited, on stimulating the cord or a spinal nerve within the vertebral canal, must therefore reach the sympathetic, through one of these communicating branches. On making sections of the white and grey rami it may be seen that the white rami consist almost entirely of medullated fibers, while the grey rami contain a great many non-medullated fibers. Gaskell (79) has shown that the majority of the medullated nerves of the white rami are unusually small, varying in size from  $1.8 \mu$  to  $2.7 \mu$ . He has further shown that in some of the anterior spinal roots nerves of the same size and structure are to be found. To state this in another form and to quote again from Gaskell, sections of the several anterior spinal roots reveal these facts:—In sections of the anterior roots of the cervical nerves, hardened in osmic acid, the great majority of the nerve fibers are large medullated fibers, varying in size from  $14.4 \mu$  to  $19 \mu$ , a few smaller fibers, not less than  $3.6 \mu$  in diameter, are also found. The first thoracic anterior root has essentially the same structure. Beginning with the second thoracic nerve, all the anterior roots to the third lumbar contain the small medullated fibers above referred to, fibers of  $1.8 \mu$  to  $2.7 \mu$  in thickness, and these can be traced into the white rami. It follows, then, that only these spinal nerves have white rami. Langley (78) who has examined the dog, cat and rabbit with reference to this point, states that the uppermost white ramus is given off from the first thoracic nerve, the lowermost probably from the fourth lumbar.

All the spinal nerves have grey rami, which, as above stated, consist largely of non-medullated fibers. Since no non-medullated nerves leave the cerebro-spinal axis through either its anterior or posterior root (Gaskell, 79) and since "the first thoracic spinal nerve, the uppermost nerve which has a white ramus, is the uppermost nerve which on stimulation produces sympathetic effect" (Langley, 78) and since, further, the white rami can be traced into the sympathetic ganglia of the chain and the pre-vertebral ganglia, it follows that a stimulus applied to a spinal nerve in the vertebral canal or to the cord itself, producing a sympathetic effect, excites an impulse which travels along nerve fibers contained in the anterior roots and thence passes through the white rami to the sympathetic ganglia.

Gaskell (79) expresses this thought in the following language:—

"The white rami communicantes are formed by an out-flow of medullated fibers from both anterior and posterior roots of the spinal nerves between the second thoracic and second lumbar inclusive (the fibers from the posterior root are probably sensory as will be explained later), which medullated nerves pass not only into their metameric sympathetic (lateral) ganglia, but also form three main streams, upwards into the cervical ganglia, downwards into the lumbar and sacral ganglia, and outwards into the collateral (pre-vertebral) ganglia."

"The white rami communicantes alone constitute the rami viscerales of the morphologist. The out flow of visceral nerves from the central nervous system into the so-called sympathetic system takes place by their means alone."

To bring these points more closely before you, I may describe briefly some of the physiological effects observed in stimulating the cervical sympathetic. It is well known that by stimulating the cervical sympathetic of the dog, cat or rabbit the pupil becomes dilated, there is an increase in the secretion from the submaxillary gland and a constriction of the small vessels of the ear, conjunctiva and other parts of the head. These same changes may be observed on stimulating the superior cervical ganglion directly, or on stimulating some of the nerves given

off from this ganglion. It has further been shown (Langley and others), that the same physiological effects may be produced on stimulating the upper thoracic nerves in the vertebral canal. To be more explicit and to follow Langley's (78) account, we find that "the pupil receives dilator fibers from the Ist, IInd, IIIrd thoracic nerves. The relative effect of these nerves varies somewhat in different animals of the same species, and varies considerably in animals of different species." "In the dog and cat the Ist, IInd, IIIrd, IVth and sometimes also the Vth thoracic nerves, contain vaso-motor fibers for the head, while in the rabbit the IInd to the VIIth thoracic nerves carry such fibers." In the dog and cat Langley found that "the second thoracic nerve carried the greatest number of the fibers which on stimulation cause a secretion of the submaxillary gland; although the IIIrd, IVth and Vth (the latter in the cat) carried such fibers." From these results we learn that an impulse, which leaves the spinal cord through the upper thoracic nerves, is carried along nerve fibers in the cervical sympathetic to the superior cervical ganglion, and from there to the head (vaso-motor); to the eye (pupil dilators); and to the submaxillary gland (secretory).

This question may now be asked. What relation do the small medullated fibers which leave the spinal cord through the anterior roots and pass through the white rami to the sympathetic ganglia and which, as has been shown, on stimulation cause physiological effects similar to those obtained when the ganglia or their nervous branches are directly stimulated hold to the sympathetic nerve cells of the ganglia? Do they pass through the ganglia, or do they end therein?

The physiologists have aided very materially in the solution of this problem, and of their number, especial credit must be given to Professor Langley, who through his untiring search and wonderfully exact work has done so much to give us a better understanding of the physiology of the sympathetic system.

The work to which I wish especially to refer at this point is the following:

Langley and Dickinson (80-81) have shown that "after

the injection of a certain dose of nicotin, stimulation of the cervical sympathetic, below the superior cervical ganglion, does not produce dilation of the pupil or constriction of the vessels of the ear, while stimulation of the sympathetic nerve fibers above the ganglion produces these changes in the normal manner." This, as they suggest, might be due to the fact that the medullated fibers below the ganglion are paralyzed and not the non-medullated fibers above the ganglion. That the medullated fibers as such are not paralyzed is shown by the fact that, at a time when stimulation of the cervical sympathetic does not cause dilation of the pupil, stimulation of the sciatic causes a normal contraction of the muscles supplied by this nerve. They have, however, offered a much better proof in the following experiment :

The cervical sympathetic was exposed and painted with a 1 % solution of nicotin. The nerve was then stimulated at intervals of about two minutes, central to the area over which nicotin had been painted. Such stimulation always produced a normal effect. However, on painting, the superior cervical ganglion with a similar solution, stimulation of the cervical sympathetic had no effect, while stimulation of the nerve filaments above the ganglion produced a normal effect. They conclude therefore that "Nicotin paralyzes the cells of the superior cervical ganglion," and further that "the dilator fibers for the pupil, the vaso-constrictor fibers for the ear (probably also those for the head generally) and the secretory fibers for the glands end in cells of the superior cervical ganglion."

As a result of these and other observations with nicotin the following conclusion is reached by them,— "That by stimulating a nerve fiber running to and those running from any peripheral ganglion, before and after the application of nicotin to it, the class of nerve fibers which end in the nerve cells of the ganglion can be distinguished from those which run through the ganglion without being connected with the nerve cells."

Langley, Anderson and Dickinson and Sherrington have shown, in a series of important contributions, which have ap-

peared since the publication of the article from which the above quotations were taken, that these conclusions, as first enunciated, are correct.

We see therefore that an impulse, set up in a nerve fiber coming from the spinal cord through the anterior root and through a white ramus to a sympathetic ganglion, passes through a nerve cell before reaching its destination. Langley (82) has suggested the term pre-ganglionic (pre-cellular) fiber, to designate the efferent medullated sympathetic fibers before they have traversed the nerve cell, and post-ganglionic (post-cellular) fiber, for the sympathetic fibers after they have traversed the nerve cell. He states "that these terms involve the view that each sympathetic nerve fiber has a nerve cell on its course in one ganglion and in one ganglion only." And further,— "In saying that a nerve fiber 'traverses a nerve cell' or 'has a nerve cell on its course,' or 'becomes connected with a nerve cell,' I mean that a nervous impulse set up in a fiber on issuing from the spinal cord passes through a nerve cell before it reaches the periphery; I express no opinion as to the histological connection of the nerve cell with the incoming or with the outgoing nerve fiber. And I express no opinion as to whether there is any branching of pre-ganglionic nerve fibers, but that if such branching occurs, then each branch must have a nerve cell on its course."

It seems to me that we have every fact in favor of the supposition that the pre-ganglionic fibers of Langley, which enter the ganglia through the rami, are the medullated fibers which in Golgi and methylen-blue preparations can be traced into the ganglia, and which as previously stated end in intra-capsular, peri-cellular baskets, these baskets forming the histological connection between the pre-ganglionic fibers and the nerve cells of the ganglia. That the pre-ganglionic fibers branch, a possibility mentioned by Langley (82), has been shown by a number of investigators, and may be seen in Fig. 9. The branches probably all have end-baskets, although it is a difficult task to demonstrate that fact. Fig. 9 shows that many certainly do.



The pre-ganglionic nerve fibers with their terminal baskets are the neuraxes and end-brushes of cerebro-spinal neurons which leave the cord through the anterior root. The exact location of the cell bodies of these neurons is not as yet known. Gaskell (78) has attempted to place them in Clarke's columns of the cord. It is now, however, well known that the neurons, the cell bodies of which constitute Clarke's columns, are intra-medullary neurons, the neuraxes of which form the direct cerebellar tracts.

I question the advisability of speaking of the pre-ganglionic fibers as sympathetic fibers, as Langley does in his articles. It is true they end in the sympathetic ganglia. Yet the cell bodies of these neurons are undoubtedly in the cerebro-spinal axis. They develop very much as do the motor neurons, and are, as His (10) has shown, to be seen in the human embryo before the *anlagen* for the sympathetic ganglion can be made out. They are cerebro-spinal fibers, forming a portion of a link in a neuron chain, the terminal link of which is formed by a sympathetic neuron. Neither can I consider the term "visceral nerves" used by Gaskell and others as consistent, as all of these nerves do not end in the viscera.

Some term expressing their central or cerebro-spinal origin, would seem to me more appropriate, and for want of a better term they may be spoken of as *central fibers*.

The post-ganglionic, or post-cellular fibers of Langley (82) are the neuraxes of the sympathetic neurons of the ganglion, a part of the sympathetic cell, and therefore not post-cellular. These fibers are the sympathetic nerves, neuraxes of sympathetic neurons, which as has previously been shown, end in involuntary muscle, in heart muscle and in the glands.

In Langley's writings, the statement that nicotin paralyzes the ganglion cells of the sympathetic ganglia repeatedly occurs. His reason for such a statement is, of course, based on the fact that the effects which are produced when stimulating the central (pre-ganglionic) fibers of a ganglion, can not be obtained when the ganglion, in which said central fibers end, is painted with a dilute solution of nicotin, but are obtained when the

neuraxes of the sympathetic neurons of the ganglion (post-ganglionic fibers) are stimulated directly. In discussing this point with Prof. Cushney, and taking into consideration, what is now well known concerning the minute anatomy of the sympathetic ganglia, with especial reference to the histological connection between the central, the cerebro-spinal fibers, and the sympathetic cells, we have reached the conclusion that nicotine does not paralyze primarily the sympathetic cells, but rather the intra-capsular, peri-cellular baskets of the central fibers. This conclusion is based largely on the analogy which exists between the physiological action of certain drugs—curare, spartan and others—and nicotine.

For example, it is well known that curare paralyzes the motor endings in striated muscle. That the ending, and not the muscle or the cell body of the neuron terminating in said muscle is paralyzed can easily be shown by well known physiological experiments, which it will not be necessary to mention at this place. Langley and Anderson (83) have shown that curare in large doses paralyzes also "the *cells* of the ciliary ganglion." That is, when large doses of curare are injected, stimulation of the IIIrd cranial nerve does not cause constriction or closure of the pupil.

Langley and Anderson (83) have also shown "that ten milligrams of nicotine is sufficient to paralyze the nerve-ending of the extrinsic muscles (striated muscles) of the eye. But this amount of nicotine is not sufficient in the rabbit and rarely in the cat, to paralyze the nerve endings in other muscles of the body." Nicotine, of course, also paralyzes the ciliary ganglion, it being a sympathetic ganglion, as was first shown by Retzius. (It is of interest to note in this connection that a smaller dose of curare is required to paralyze the motor endings in the extrinsic eye muscles, than in other muscles of the body.) Langley and Dickinson (84) found that "the motor nerve-endings are paralyzed in the cat by 10 to 15 m. g. of nicotine, that rather more is required in the rabbit, and considerably more in the dog." The analogy between the action of nicotine and curare is therefore worthy of notice. They both

paralyze the motor nerve-ending in skeletal muscle and both (according to Langley) paralyze the sympathetic cells. They differ in their action in so far that nicotin paralyzes the sympathetic cells more readily than does curare, while curare paralyzes the motor nerve-ending more readily than does nicotin. (Other minor differences need not here be mentioned.) Taking these facts into consideration, it would seem to us more reasonable to say that since curare and nicotin paralyze the *ending* of a motor fiber in skeletal muscle, they paralyze also (reasoning from analogy) the ending of the central, cerebro-spinal fibers in the ganglia, i. e., the end-baskets and not sympathetic nerve cells.

In other words, nicotin and curare paralyze in both instances the end-brush of the cerebro-spinal fiber, which in striated muscle ends under the sarcolemma; in the sympathetic ganglia this end-brush is woven into a basket-like structure, the intra-capsular, peri-cellular basket. Ehrlich (4), in his first communication on the action of methylen-blue on living nerve tissues, draws attention to the similarity in structure between the end-baskets and the ending in voluntary muscle, and adds: "I think these phenomena (resemblance in structure and the fact they both stain readily in methylen-blue) may be of importance to physiology and pharmacology, as it is very probable that the end basket may localize poisons, other than methylen-blue, and may therefore be locally paralyzed like the ending in striated muscle."

By way of summary, I shall reproduce briefly the arguments, which seem to indicate that the central fibers are of cerebro-spinal origin and end in sympathetic ganglia. I shall for this purpose select the ciliary ganglion and the nerves in connection with it.

It is well known that the ciliary ganglion receives fibers from the IIIrd and Vth cranial nerves and probably also sympathetic fibers, and from it the short ciliary nerves, 6 to 10 in number, pass to the ciliary body and iris. Stimulation of the third nerve causes, among other things, closure of the pupil

and contraction of the ciliary body. Direct stimulation of the ganglion and the short ciliary nerves give the same results.

When the ciliary ganglion is stained with the Golgi method, as has been done by Retzius (85), Kölliker (33) and Michel (74), it may be seen that its cells are multipolar, therefore sympathetic neurons, the neuraxes of which extend into the short ciliary nerve, and no doubt innervate the involuntary muscle of the ciliary body and iris. Kölliker (32) and Michel (74) have shown that the cell bodies of these sympathetic neurons are surrounded by peri-cellular baskets. In methylen-blue preparations, I find that these peri-cellular baskets are intracapsular and are the endings of small medullated nerves entering the ganglion.

Langley and Anderson (85) have shown that after the injection of 10 m. g. of nicotin into the vein of a rabbit or cat, stimulation of the third cranial nerve has no effect of any kind, the non-contraction of the extrinsic eye muscle innervated by this nerve, being due to a paralysis of the motor endings, the non-closure of the pupil, to paralysis of the ganglion cells of the ciliary ganglion, or, if our interpretation of the action of nicotin is correct, to a paralysis of the end-baskets of the third nerve in this ganglion. Stimulation of the short ciliary nerves causes closure of the pupil after injection of nicotine which of course would not be the case if the third nerve passed through the ganglion without ending therein. Further proof of the ending of the third nerve in the ciliary ganglion is furnished by Apolant in the following experiments. Apolant divided the third nerve, on one side, in cats, just before it enters the orbital cavity. At the end of two weeks, the contents of the orbit, on the operated and unoperated side were removed and hardened in Müller's fluid. After proper hardening the ciliary ganglia with the third and the branch from the fifth nerve were dissected out and pinned out on elder pith—this to bring the ganglion and its roots into a plane. The preparation was then stained after Marchi's method, embedded and cut into serial sections. Apolant states that on the operated side, the third nerve and its branches were in every instance degener-

ated. The degenerated fibers could be traced to the periphery of the ciliary ganglion but not beyond the ganglion cells, while the short ciliary nerves were never found degenerated. These experiments show very conclusively that these medullated fibers ending in the ciliary ganglion, are the neuraxes of neurons situated central to the point of section. The non-degeneration of the short ciliary branches can only be explained by the fact that they are neuraxes of neurons, the trophic center of which—the cell body and nucleus of the neuron—are situated peripheral to the point of section, namely in the ciliary ganglion. Sections of the ganglion and nerves of the normal side containing no degenerated fibers show however that the fibers entering the ganglion from the third nerve are very small medullated fibers, which can be likened to the central fibers ending in other sympathetic ganglia.

The fibers from the Vth nerve and those from the sympathetic, forming the sensory and sympathetic roots do not end in the ganglion, as may be seen from Langley and Anderson's (83) and from Apolant's (86) work.

Thus far my discussion has been largely concerned with the larger ganglia of the chain and the cranial ganglia, into which the small medullated nerves—central fibers—can be traced without much difficulty.

It must not however be supposed that such nerves end only in these larger ganglia. All evidence we possess goes to show that similar nerves end in all the sympathetic ganglia, even the small terminal ganglia. Attention has already been drawn to the fact that intra-capsular, peri-cellular baskets—the endings of the small medullated, the central or pre-ganglionic fibers—are to be found in even the smallest peripheral or terminal ganglia. This alone would justify the assumption that pre-ganglionic fibers end in the peripheral ganglia. It is however not difficult to show, (and especially in methylene-blue preparations) that small medullated fibers, larger than the medullated fibers of the sympathetic system, enter the small peripheral ganglia and terminate in end-baskets. We must assume then that many of the nerve fibers of the white rami pass

through the ganglia of the chain to the peripheral ganglia, or, at most, give off only collateral branches in the chain-ganglia, the fiber itself going to the periphery, and ending in some ganglion situated at a variable distance from the chain.

Such medullated fibers constitute the white rami of the peripheral ganglia. The central or pre-ganglionic fibers forming such white rami differ only in length, not in structure, from the central or pre-ganglionic fibers ending the ganglia of the chain.

There is reason to believe that a central fiber may end in peri-cellular baskets in more than one ganglion, as Langley (87) has shown and represents in several diagrammatic figures, and as may be seen from Fig. (10) combined and slightly altered from Langley's figures.

In methylen-blue preparations of the sympathetic of the frog, in which only a few fibers ending in baskets were stained, I have several times observed that a medullated fiber—central fiber—giving off one or two side branches, terminating in a spiral and end basket, could be traced beyond the ganglion in which these side branches were given off, into a neighboring ganglion. These observations corroborate to some extent Langley's conclusions arrived at in experiments with nicotine. I have thus far not succeeded in finding spiral fibers and end-baskets on the same medullated fiber in two ganglia, but would think that in suitable preparations such a fiber might be found.

We are prepared, it seems to me, to formulate the following conclusions. The sympathetic neurons, the cell bodies and dendrites of which are grouped to form the sympathetic ganglia, form the terminal link of a nerve or neuron chain, of which the second link is formed by a neuron, the cell body of which is situated in the cerebro-spinal axis and the neuraxis of which leaves the spinal cord or medulla through the anterior or motor root as small medullated fibers, which fibers end in intra-capsular, peri-cellular baskets, enclosing the cell bodies of the terminal—sympathetic—neuron. An impulse issuing from the cord or medulla along the central or pre-ganglionic fibers is transferred to the cell body of a sympathetic neuron and thence along its

neuraxis to some peripheral tissue. Whether all sympathetic neurons are thus connected with the cerebro-spinal system can at present not be positively stated. The evidence is, however, in favor of the supposition that by far the greater majority form the terminal link in such a neuron chain.

The question has no doubt suggested itself to you, whether the neuraxes of sympathetic neurons ever terminate in other sympathetic ganglia, there to stimulate other neurons, or do they always form terminal links in a neuron chain? Langley, in several of his communications, denies the possibility of such an ending. In his (88) short account of the sympathetic system the following statement occurs,—“The ganglia of the sympathetic trunk send no fibers to one another.” This conclusion, if I understand Langley correctly, is based largely on observations made after the injection of nicotin. In certain ganglia, as for instance the superior cervical, local application of nicotin stops all the effects produced by stimulating the cervical sympathetic. In Auerbach's and Meissner's ganglia however, Langley and Anderson (89) have shown that “Large doses of nicotin do not paralyze any of the effects which can be obtained by stimulating the fibers given off by the inferior mesenteric ganglion of the pelvic plexus.” They add: “It is true that in most cases motor effects on the intestine were diminished to a greater extent than inhibitory or vaso-constrictor effects, this difference was however not constant.” They conclude that the connection which exists between the nerves coming to the intestine and the cells of Auerbach's and Meissner's plexus is of a different nature from that which exists between the pre-ganglionic fibers and sympathetic nerve cells in other parts of the sympathetic; and, “That the nerve cells of the plexuses of Auerbach and Meissner do not belong to the cells of the sympathetic but are cells of a different nature.”

Kölliker (34) has already drawn attention to the erroneous-ness of this last conclusion, and Dogiel (55) has shown that in mammalia the cells of Auerbach's and Meissner's plexuses are in shape and structure like the ganglion cells in other sympathetic ganglia. Dogiel (55) has further shown that medullated

fibers, which end in peri-cellular baskets, can be traced, into these ganglia. These observations I can corroborate for the cat and rabbit and also for the reptilia (*Chelydra serpentina*). I have also found peri-cellular baskets; the number has however been relatively small. I should infer that not all the sympathetic neurons of Auerbach's plexus are in connection with medullated fibers through peri-cellular baskets. In frogs and fishes the nerve cells of Auerbach's plexus have often been stained, but so far no peri-cellular baskets have been observed.

The diminution in the motor effect, observed after the injection of nicotin and subsequent stimulation of the fibers given off from the inferior mesenteric ganglia and those of the pelvic plexus, may be due to a paralysis of peri-cellular baskets in Auerbach's and Meissner's plexus. The fact that not all the effects were lost after the injection of nicotin may be explained in one of two ways—(1) Some of the nerve fibers in Auerbach's and Meissner's plexuses may not be connected with nerve cells beyond the inferior mesenteric ganglia, in which case nicotin would not paralyze their action. (2) Some of the neuraxes of the neurons in the inferior mesenteric ganglia may terminate in the peripheral ganglia of Auerbach's and Meissner's plexuses.

I have previously stated that evidence of the ending of neuraxes of sympathetic neurons on the protoplasmic branches of other sympathetic neurons was to be had from a study of thin sections of methylen-blue stained sympathetic ganglia, and that such neuraxes seemed to come from neurons in more centrally located ganglia. The fact that nicotin experiments lead to a contrary conclusion, seems to me to be insufficient evidence on which to base such a conclusion. If we assume that nicotin paralyzes the end baskets, and not the ganglion cells of sympathetic ganglia, it may readily be seen, that, owing to this selective action of nicotin, the endings of the neuraxes of sympathetic neurons on the dendrites of other sympathetic neurons may escape paralysis by nicotin, as the terminations of the neuraxes of sympathetic cells in non-striated or heart muscle or in gland tissue escape paralysis. It would seem



therefore that experiments with nicotin are not suitable for the solution of the question under discussion. It may be said that the evidence seems against the assumption that nicotin paralyzes the endings of the neuraxes of sympathetic neurons, as it does the endings (peri-cellular, intra-capsular baskets) of the central fibers in the sympathetic ganglia. This hypothesis is offered, as a suggestion, to explain certain sympathetic effects which nicotin does not interrupt.

*The grey rami communicantes.*—In a general way it may be stated that each spinal nerve has a grey ramus. Langley (82) states that in the cat the superior cervical ganglion gives off dorsally, from its posterior surface, fibers to the first three spinal nerves; the stellate ganglion sends branches from the IIIrd cervical to the IIIrd or IVth dorsal nerve inclusive. From the Vth dorsal to the first coccygeal, there is usually a sympathetic ganglion and grey ramus corresponding to each spinal nerve.

As has already been shown, structurally a grey ramus consists largely of non-medullated nerve fibers, which, as Gaskell (78) states, are intimately connected with the corresponding lateral ganglion, its nerve fibers being in direct connection with the nerve cells of that ganglion.

Langley (82), Langley and Sherrington (90) have made some very interesting observations on the distribution of the grey rami in two communications dealing with the pilo-motor nerves of the cat and monkey. In their joint publication, they point out that, in the monkey, stimulation of the cervical, and in the cat, stimulation of the lumbar sympathetic causes a contraction of the erectores pilorum in certain definite areas of the skin, thus causing an erection of the hairs in these areas. The nerve fibers going to these muscles are spoken of as pilo-motor nerves.

Langley (82) has found that the pilo-motor fibers run from the spinal cord in the anterior roots of the spinal nerves. And further finds that, "Nicotin annuls the pilo-motor effect of stimulating the roots of the spinal nerves (as it does all the visceral effects), but does not effect the the pilo-motor effect of

stimulating the peripheral nerves. The pilo-motor nerves then (like all visceral nerves) are connected at some point of their course with nerve cells. \* \* \* The pilo-motor nerves in the various rami of the superior cervical ganglion are typically all connected with the nerve cells in this ganglion. The cervical rami of the ganglion stellatum, and the grey rami of the first three thoracic nerves are connected with the nerve cells in the ganglion stellatum. From the Vth thoracic to the VIth lumbar grey ramus inclusive, all the fibers of the grey ramus are, as a rule, connected with the nerve cells in the corresponding ganglion.

It will not be necessary to describe in detail the experiments which have led to the above conclusions, nor to do more than to state that experiments with nicotine show conclusively that the grey rami consist largely of the neuraxes of the sympathetic neurons of the respective ganglia. As to the further course of the pilo-motor nerves in the spinal nerves, Langley has shown: "That so far as the skin is concerned, the distribution of all the sympathetic fibers which run to the spinal nerve (grey rami) is the same as that of the sensory fibers of the nerve, and that the distribution of the sympathetic fibers of a spinal nerve can in the main be determined by dissecting the nerve in its course." The white and gray rami differ therefore in structure and function. The former consist of the small medullated fibers, the neuraxes of neurons of the cerebro-spinal axes, ending in baskets; the latter of the neuraxes of the sympathetic neurons in the ganglia, which become associated with the spinal nerves. They form the terminal link of a neuron chain of which the white rami form a portion of the second link. In the grey rami are found a variable number of medullated fibers, as has been shown by Gaskell, Langley and others. Langley (91) states that their diameter varies from  $2\ \mu$  to  $4\ \mu$  and some fibers above this size 6 to  $12\ \mu$ . Some of the smallest are medullated sympathetic fibers (Kölliker (32) states that the pilo-motor fibers—"Haarbalgmuskeln-Nerven"—of the cat are medullated sympathetic fibers); a few, chiefly the medium sized and larger, come from the posterior

root ganglia ; and sometimes a few efferent medullated fibers, passing to the sympathetic ganglia by the white rami, leave the sympathetic ganglia by the grey rami. They are destined to terminate on the aberrant sympathetic cells, lying in the grey rami before they reach the spinal nerves.

*Sensory nerve fibers in the sympathetic.* There seems to be no doubt that sensory nerve fibers—cerebro-spinal fibers—exist in the sympathetic system. Lenhossék (28) has shown that fibers from the sensory roots enter the sympathetic ganglia, also that the spheno-palatine ganglion (sympathetic, Lenhossék) receives a bundle of nerves from the Gasserian ganglion, and further that some of the peripheral fibers of the geniculate ganglion (this ganglion contains "T"-shaped cells like the spinal ganglia, Lenhossék (92)) enter the chorda tympani. Lenhossék inclines to the view that these sensory fibers end in the sympathetic ganglia, presumably in peri-cellular baskets, possibly in free endings. From what has been said concerning the white rami and their endings in the ganglia, it may be seen that the central fibers leave the cord through the anterior root. It would seem therefore that these sensory fibers do not end in the ganglia, which they reach probably through the white rami, but pass through the ganglia of the chain and become associated with the efferent sympathetic nerves. They may in this way pass through a number of sympathetic ganglia before reaching their destination. Such medullated fibers, which are larger than the central or pre-ganglionic fibers, have been traced by me through two and through three of the small ganglia found in the frog's bladder ; and in no instance were they seen to give off any branches before terminating. Kölliker and Langley state that these medullated fibers are of variable size. No doubt many of the medium sized and larger medullated fibers found in sympathetic nerves are sensory. As to their mode of ending we have as yet very little positive evidence. Some no doubt end in the Pacinian bodies found in the mesentery and occasionally in the pancreas. The medullated fibers ending in the Pacinian bodies are, judging from the size of their axis-cylinders as seen in methylen-blue

stained preparations, quite large. Other sensory fibers of the sympathetic terminate in free endings. In a number of methylen-blue preparations of the frog's bladder in my possession, such an ending is most clearly shown. In some of the most successful preparations, large medullated fibers can be traced in small nerve trunks, from a point at which such nerve trunks reach the base of the bladder, through several sympathetic ganglia, to their ending. From place to place one or the other of the large medullated fibers, or several such fibers, leave the main trunk and, after traversing a longer or shorter distance, break up into two or three short medullated branches, each consisting of two, three or four short internodal segments. From these short medullated branches, varicose, non-medullated side branches are given off at the nodes of Ranvier, which break up into a large number of finer branches, ending in small bulbous enlargements between the cells of the bladder epithelium. The medullated branches after losing their myelin terminate in the same way. I estimate that a sensory fiber ending in the bladder of the frog supplies an area of about .2-.3 sq. mm. In Fig. 11 is reproduced the ending of a sensory fiber in this organ.

Smirnow (93) has described sensory endings in the heart of amphibia and mammalia; in the latter both in the endocardium and the exo-cardium. The endings are found in the connective tissue of the heart and are the terminal branches of large medullated nerves, which, after giving off side branches, lose their myelin and terminate in an end-brush with terminal bulbar enlargements.

Smirnow has endeavored to ascertain, by degeneration, whether the sensory endings belong to the depressor nerve of the heart. The two experiments, one on the cat and one on the rabbit, in which such degeneration was attempted, gave results which were interpreted as showing that the sensory endings in the heart belonged to this nerve.

I may at this point draw attention to the fact that in our text-books of anatomy it is customary to speak of a sympathetic ganglion as having three roots, a motor, a sensory and a

sympathetic root. I refer here more especially to the sympathetic ganglia in connection with some of the cranial nerves. If we take for instance the ciliary ganglion, to which your attention has previously been drawn, we find it generally stated, that it receives its motor root from the 3rd cranial nerve, its sensory root from the nasal branch of the ophthalmic and its sympathetic root from the cavernous plexus of the sympathetic. I have tried to show you that the motor root, consisting of small medullated fibers, ends in the ganglion in peri-cellular baskets. The sensory root, when viewed in the light of our more modern ideas of the structure of the nervous system has no connection, by that of course is meant no histological connection, with the ganglion. It is doubtful whether the sympathetic root really forms any connection with the ganglion; some of its fibers may end free on the dendrites of the sympathetic neurons constituting the ganglion. Or if we take the so-called sub-maxillary ganglion, Quain states: "The posterior connecting branch from the lingual nerve, often broken up into two or three filaments, conveys to the ganglion fibers from the chorda tympani and inferior maxillary nerves and thus represents the motor and sensory roots of the ganglion. The sympathetic root is formed by slender twigs from the plexus on the facial artery." Langley (94) has shown (by his nicotin method) that some of the chorda tympani fibers end in this ganglion, and I have endeavored to show that such fibers end in peri-cellular baskets. The sensory fibers no doubt pass through the ganglion to end in some of the larger gland ducts. I infer this from the fact that some of the larger medullated fibers pass through the ganglia without ending therein; similar medullated fibers are found by the side of the larger gland ducts. They are no doubt sensory fibers, as some of them end free in the epithelium of the ducts. It may also be stated that Langley finds medullated fibers, 7 to 10  $\mu$  in diameter in the plexus surrounding the sub-maxillary duct. These fibers were seen branching. On general grounds he thinks they are sensory fibers. We have no reason to assume that the fibers of the sympathetic root

end in the sub-maxillary ganglion. They may do this in the manner above described for the ciliary ganglion.

The point I wish to emphasize in the two examples selected for analysis, is this. The motor root *ends in the ganglion*, no doubt in peri-cellular end-baskets. This root constitutes the *white ramus of the ganglion*. The sensory root forms no histological connection with the ganglion, accompanying the efferent sympathetic nerves to the tissues. Whether the sympathetic root ends in the ganglion is questionable, if so, its nerves end on the dendrites of the sympathetic cells and are not paralyzed by the nicotin.

*Reflexes in sympathetic ganglia.*—Attention has previously been called to the possibility of peripheral reflexes, i. e. reflexes in sympathetic ganglia, in speaking of the sensory sympathetic cells described by Dogiel (71). This type of cell, it will be remembered, has long dendrites, which, as Dogiel suggests, may reach to the free surface; the neuraxis ending free in other sympathetic ganglia. A sensory sympathetic neuron, stimulated through its dendrite, might excite through its neuraxis a motor sympathetic neuron, the impulse not going to the cerebro-spinal axis. Langley and Anderson (95) state that two cases of reflex action occurring in peripheral ganglia have been brought forward—reflex from the submaxillary ganglion of the dog (Claude Bernard) and reflex from the inferior mesenteric ganglion of the cat (Sokownin). The apparent existence of recurrent fibers in the lingual nerve makes it difficult to determine with any degree of accuracy the existence of a peripheral reflex in the submaxillary ganglion. For the inferior mesenteric ganglion the existence of a peripheral reflex seems quite clearly established by Langley and Anderson. It would be beyond the scope of these lectures, to reproduce fully the observations, which lead to this conclusion. I may however add that they show: "That the effects which follow the stimulation of the central end of the hypogastric nerves (all nerves going or coming from the inferior mesenteric ganglion, except the hypogastrics having previously been cut) are not due to recurrent fibers, but to fibers, the trophic centers of which are in the

spinal cord." They further conclude that such reflexes are due to motor nerves.

The view which they tentatively express is the following. They suppose that on stimulating a peripheral nerve, the impulse may travel up this peripheral nerve until it reaches a collateral branch (in this case in the inferior mesenteric ganglion), then down the collateral branch, and that this impulse may set up other impulses in the sympathetic nerve cells. The following diagram (Fig. 12), which is slightly modified from one given by Langley (88) in his short account of the sympathetic system, *Physiological Congress, Berne, 1895*, may serve to illustrate the point in question.

*A* and *A'*, a central (pre-ganglionic) fiber; *B*, a collateral branch; *C* and *D* sympathetic neurons with neuraxes (*a*) ending in the bladder, *Bl.* The central fiber is stimulated at *A'*, the arrows indicate the course the impulse would travel in a peripheral reflex. I am not prepared to make comment on this hypothesis, as suggested by Langley. It would seem well, however, to regard it as tentative until further work, both physiological and histological, corroborates or disproves its accuracy. Possibly the existence of sensory sympathetic cells, the cell bodies of which are located in the inferior mesenteric ganglion, the dendrites of which extend into one of the hypogastric nerves, may be found, in which case a peripheral reflex in this ganglion might take place through such sensory cells.

In closing these lectures, I desire to draw your attention to two diagrams, by means of which I hope to summarize in a graphical way many of the points I have emphasized in these lectures.

These diagrams may serve to show,—(1) the probable arrangement of the spinal nerves in a metameric segment, and their connection with the sympathetic ganglia of the chain, the pre-vertebral ganglia and peripheral ganglia; (2) the probable connection of the nerves concerned in the innervation of the sub-lingual and submaxillary glands.

Fig. 13. Showing the probable arrangement of the neu

rons in a metameric segment. In the construction of this diagram I have been greatly aided by Fig. 840 of Vol. II, Part II, of Kölliker's *Gewebelehre* and also several figures in Vol. III, Part II, of Quain's *Anatomy*.

In the figure *S. C.* represents one half of the spinal cord; *A. R.*, the anterior root; *P. R.*, the posterior root with the spinal ganglion; *P. S. B.*, the posterior branch of the spinal nerve; *L. S. B.*, the lateral or mesial branch of the spinal nerve; *W. R.*, the white ramus; *G. R.*, the grey ramus; *I-II-III C. G.*, three sympathetic ganglia of the chain united by intervening nerves; *Pr. V. G.*, a pre-vertebral ganglion; *Periph. G.*, a peripheral ganglion.

In Fig. 13, the following colors have been used to designate neurons of different orders, and in the following way:—A *black line (m. n.)* designates a motor neuron of the spinal cord, with the cell body in the anterior horn, the end-brush in striated muscle. A *black line crossed by short black dashes (s. n.)*, a sensory spinal neuron of a somatic nerve, ending in the epidermis or in some special sense organ. The cell body of such a neuron is in the posterior root ganglion. An *interrupted black line* denotes a sensory, spinal nerve, accompanying efferent sympathetic fibers to the viscera (*s. s. f.*). Such fibers, it is assumed, come from cells in the posterior root ganglion, pass to the sympathetic ganglia through the white rami, and through the several sympathetic ganglia until they reach the periphery, there to end either in a free ending (*s. s. f. (1)*), or in a Pacinian corpuscle (*s. s. f. (2)*). The neurons *colored blue*, are the pre-ganglionic fibers of Langley or the 'central fibers'. I have followed Fig. 240, of Quain's *Anatomy*, Vol. III, Pt. II, in placing the cell bodies of such neurons in the lateral portion of the anterior horn of the spinal cord. The neuraxes of such cells leave the spinal cord through the anterior horn, and reach the sympathetic ganglia through the white rami (*W. R.*), where they terminate in peri-cellular baskets, enclosing the cell bodies of the sympathetic neurons (red in the figure).

The pre-ganglionic fibers leaving the anterior root and the



white ramus of a segment may terminate in one of the following ways.

In the figure, *a* shows a pre-ganglionic fiber which passes through the chain ganglion of the segment (I C. G.), to terminate in the next higher chain ganglion (III C. G.); *b*, a pre-ganglionic fiber passing through the chain ganglion of the segment to terminate in the next lower chain ganglion (II C. G.); *c*, two pre-ganglionic fibers ending in the chain ganglion of the segment; *d*, a pre-ganglionic fiber passing through the chain ganglion and ending in a pre-vertebral ganglion (*Pr. V. G.*) (this fiber may represent one of the fibers of a splanchnic nerve); *e*, a pre-ganglionic fiber passing through the ganglion of the chain, through a pre-vertebral ganglion to end in a peripheral ganglion; *f*, a pre-ganglionic fiber, which gives a collateral branch in one ganglion (terminating in a peri-cellular basket), and passes on to terminate in some more peripheral ganglion. The ganglion of each segment, probably receives pre-ganglionic fibers from the adjacent higher and lower ganglion, designated by the letters *g* and *h* in the figure.

The sympathetic neurons are colored red in the figure. The cell bodies of such neurons are enclosed in peri-cellular baskets (see figure). The neuraxes of the sympathetic neurons may terminate, either in blood-vessels—vaso-motor—*i*, of the figure; in the involuntary muscle of the viscera—motor—*j*, of the figure; in heart muscle, not shown in the figure; in glands—secretory fibers—*k*, of the figure, or in the sympathetic ganglion (?), *l*, of the figure.

The diagram shows, further, two sensory neurons (Dogiel) one in a peripheral ganglion, *o*; the other in the chain ganglion, *p*, its neuraxis ending in the spinal ganglion in a peri-cellular basket, enclosing the cell body of a 'type two' spinal ganglion cell (Dogiel), *q*, in the figure. Fig. 14 shows the nerve supply of the sub-lingual and sub-maxillary glands. In this figure the several colors used in Fig. 13, and there described, are again made use of. *Sub. max.*, a portion of the sub-maxillary gland with its duct. *Sub. ling.*, a portion of the sub-lingual gland with its duct. *Ch. T.*, the chorda tympani. *Ling.*, the lingual

nerve. *Gen. G.*, a cell of the geniculate ganglion. *Ch. L. T.*, the chorda-lingual triangle (Langley), formed by the chorda tympani, the lingual nerve and the sub-maxillary duct. This triangle contains the sub-lingual ganglion (*Sub. l. G.*). *Sub. m. G.*, the sub-maxillary ganglion in the hilum of the sub-maxillary gland. *Sup. c. G.*, superior cervical ganglion; *Cerv. S.*, cervical sympathetic; *Inf. c. G.*, inferior cervical ganglion; *An. V.*, Annulus of Vieussens; *St. G.*, the stellate ganglion; *Symp. c.*, a portion of the sympathetic chain, *sp. c.*, a portion of the dorsal spinal cord with II, III, IV; *Dr. n.*, the second, third and fourth spinal nerves; *W. R.*, the white rami coming from these spinal nerves.

The nerve fibers of the lingual nerve (*ling.*) are diagramed in black. The figures show its neurons to be sensory. The cells of the geniculate ganglion are also sensory (Lenhossék). The nerve fibers coming from these cells join the chorda (*ch. T.*) and terminate in a free ending on the ducts of the sub-maxillary gland (probably also in the sub-lingual gland).

The fibers in the chorda tympani (*ch. T.*) colored blue in the figure, are comparable to the fibers of the white rami. Some end in peri-cellular baskets in the sublingual ganglion (*sub. l. G.*), others accompany the sub-maxillary duct to the hilum of the gland, where they end in peri-cellular baskets.

The sympathetic neurons of the sub-lingual ganglion (*sub. l. G.*) and of the sub-maxillary ganglion (*sub. m. G.*) are colored red. The neuraxes of the sympathetic neurons of the sub-lingual ganglion accompany the ducts of the gland and end on the secreting cells. The neuraxes of the sympathetic cells of the sub-maxillary ganglion (*sub. m. G.*) accompany the sub-maxillary gland ducts and end on its secreting cells.

The secretory fibers from the spinal cord leave the cord through the anterior roots of the II, III, IV dorsal nerves; through their white rami (*W. R.*) they reach the stellate ganglion, (*St. G.*). They pass through this ganglion, through the annulus (*An. V.*), through the inferior cervical ganglion (*Inf. c. G.*), and by way of the cervical sympathetic they reach the superior cervical ganglion, (*Sup. c. G.*), and end in peri-cellular

baskets enclosing the cell-bodies of sympathetic neurons, (colored red in figure), the neuraxes of which (*symp. n. g.*) follow the blood-vessels to the sub-maxillary, and probably also to the sub-lingual gland. Their mode of ending is not known.

Finally, in closing these lectures, may I again emphasize the fact that at least the great majority of the sympathetic neurons form terminal links in a neuron chain, of which the second link is formed by the fibers constituting the white rami. I trust therefore that the statement that the entire nervous system is a unit, of which the sympathetic system is of necessity only a part, may have become to you a demonstrated fact, and that in your future work you will regard it as such.

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## DESCRIPTION OF PLATES.

## PLATE VIII.

*Fig. 1.* Small sympathetic ganglion in the wall of the trachea, stained in methylen-blue. (Arnstein (36) Fig. 8)

*A*, sympathetic cell; *a*, neuraxis; *b*, dendrites; *c*, involuntary muscle tissue. *Pr. G. F.*, preganglionic fiber; *Pr. B.*, pericellular baskets.

*Fig. 2.* Ending of non-medullated nerve fiber, neuraxis of sympathetic neuron, in involuntary muscle cell of the intestine of a cat. 1-12 in. oil immersion obj., Leitz, and No. 1 eye piece. From section of  $5\mu$  thickness, double stained in methylen-blue and alum carmine; *a*, neuraxis of sympathetic neuron, ending on cell *b*, at *a'*; *c*, nucleus of cell.

*Fig. 3.* Showing vaso-motor nerves of a small vessel in pharynx of frog, stained in methylen-blue. Leitz 1-12 in. oil im., No. 1 eye-piece. A few of the non-striated muscle cells of the vessel wall were stained, as shown in the figure.

*Fig. 4.* Ending of the neuraxes of sympathetic neurons on the heart-muscle cells of a cat's auricle; from sections double stained in methylen-blue and alum carmine. The figure shows endings of varying complexity: *a*, a very simple ending; *b* and *c*, more complex endings. Leitz 1-12 oil im., No. 1 eye piece.

*Fig. 5.* Ending of sympathetic nerves on gland cells. Copied from Arnstein (61):—

*a*, isolated gland cell from the parotid gland of a rabbit;

*b*, isolated gland cells from the mammary gland of a pregnant cat;

*c*, isolated gland cell from a sweat gland;

*d*, a portion of a teased sweat gland, showing a number of cells with nerve endings.

*Fig. 6.* Scheme of reflex in the sympathetic ganglia in the intestinal plexus. Copied from Dogiel (71).

*a*, motor sympathetic neurons; *b*, a sensory sympathetic neuron; *pr*, dendrites or protoplasmic branches; *ax*, axis-cylinder branches or neuraxes.

1, tunica propria; 2, muscularis mucosa; 3, submucosa; 4, muscular coat with four sympathetic ganglia.

*Fig. 7.* From section of sympathetic ganglion (semilunar) of a cat, stained in methylen-blue. Leitz 1-12 in. im. No. 1 eye piece, reduced to two-thirds.

*a*, cell body of sympathetic neuron; *c*, dendrite; *d*, neuraxis; *b*, neuraxis of another sympathetic neuron ending on dendrite at *b'*.

*Fig. 8.* Sympathetic cells and pericellular baskets from sympathetic ganglia of vertebrates:—

*A*, mammal, (dog); *B*, bird, (chicken); *C* and *C'*, reptilia, (*Chelhydra serpentina*); *D*, frog, (*Rana Catesbiana*); *E*, fish, (*Micropterus dolomieu Raf*).



*a*, neuraxis of a pre-ganglionic fiber, a cerebro-spinal fiber ending in a pericellular basket enclosing the cell body of a sympathetic neuron (*b*); *c*, capsule of sympathetic cells.

Sketches made from ganglia stained in methylen-blue and alum carmine. Camera lucida drawings under 1-12 in. oil im., No. 1 eye-piece, Leitz.

*Fig. 9.* Sketch of the course of a pre-ganglionic, a cerebro-spinal fiber in sympathetic ganglia of a frog. Camera lucida drawing, 1-12 in. oil im., No. 1, eye-piece, reduced to two-fifteenths.

*A*, a medullated cerebro-spinal fiber, which entered the ganglion through a white ramus. An *x* in the course of the fibers indicates a node of Ranvier; the fibers become non-medullated at *y*; *a*, pericellular baskets and spirals.

*Fig. 10.* Showing the ending of a pre-ganglionic fiber in more than one ganglion. Copied and slightly altered from two of Langley's (87) figures.

*Sp. c.*, cell in spinal-cord; *Ch. G.*, chain ganglion; *S. G.*, solar ganglion; *Pr. G.*, peripheral ganglion.

*A, A', A''*, pre-ganglionic fiber with branches; *a*, neuraxis of sympathetic neurons.

*Fig. 11.* See Plate IX.

*Fig. 12.* Scheme to show how a reflex may occur in the sympathetic system, taken from Langley's (88) account. For description see the text.

#### PLATE IX.

*Fig. 11.* Ending of a sensory neuron in the bladder of a frog. Methylen-blue stained preparation. Camera lucida drawing, 1-12 in. oil im., No. 1 eye-piece. Drawing reduced three times.

*A*, medullated nerve fiber. An *x* indicates a node of Ranvier; *y*, a non-medullated collateral or terminal branch ending in an end-brush.

#### PLATE X.

*Fig. 13.* Diagrammatic representation of the distribution of the spinal and sympathetic neurons in a metameric segment of the cord.

For description see the text.

#### PLATE XI.

*Fig. 14.* Diagram to show the course and connection of the neurons innervating the sublingual and submaxillary glands.

For the description see text.