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THE GANGLIA, PLEXUSES, AND NERVE-TERMINATIONS OF THE MAMMALIAN LUNG AND PLEURA PULMONALIS

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NINETEEN FIGURES

CONTENTS

Introduction.......... 97
Literature.......... 98
Material and methods.......... 104
Descriptive.......... 105
A. Intrapulmonary plexuses and ganglia.......... 105
Bronchial plexuses and ganglia.......... 106
Sensory nerve-terminations in smooth muscle.......... 116
Innervation of blood-vessels, glands, and lymphatics of the lung... 119
B. Innervation of the pleura pulmonalis.......... 121
Summary.......... 129
Literature cited.......... 131

INTRODUCTION

In a recent contribution the writer ('21) has described several types of sensory nerve-terminations in the mammalian lung, including their distribution with reference to the bronchial tree. Motor fibers to the bronchial musculature, and nerve-endings of motor type in the smooth muscle of the pulmonary blood-vessels, including the arterioles, were described and figured. In another article (Larsell and Mason, '21) the relation of the vagus nerve to the sensory endings, and to the intrapulmonary ganglia was demonstrated by experimental degeneration of the vagus, followed by staining the lungs and their remaining nerve fibers by the intra-vitam methylene-blue method.

In the present article it is the writer's purpose to describe the distribution and arrangement of the ganglia and nerve plexuses within the lung and on the pulmonary pleura. Nerve-terminations in the pulmonary pleura, and an apparently hitherto undescribed type of sensory nerve-ending in smooth muscle (the bronchial muscle bands) will also be included.

The anatomical literature on the innervation of the lung is so widely scattered that a summary of the principal contributions with reference to the nerves of the mammalian lung, appears justified as an introduction to the present paper.

LITERATURE

The physiological literature on the pulmonary afferent system has recently been reviewed by Ranson ('21), and Wiggers ('21) has given a résumé of the contributions relating to the nervous control of the pulmonary circulation. These two reviews cover most of the physiological work which has an anatomical bearing, and only casual reference will be made in the present article to the various contributions of this group.

Without attempting an exhaustive survey, the principal steps in arriving at our present anatomical knowledge of the innervation of the mammalian lung may be briefly outlined.

It has long been known that the lungs receive their nerves from the anterior and posterior pulmonary plexuses. Also the fact that these plexuses are formed by a mingling of fibers from the two sympathetic trunks with branches from the vagi, and that they contain ganglia, was observed by the early anatomists.

Remak ('44) appears to have been the first to study the ganglia within the lungs themselves. He figures numerous small ganglia on the bronchi, from which are given off nerve branches. These nerve branches penetrate into the walls of the bronchi. Remak's description is based on the lung of the ox.

According to Kandarazki ('81), Arnold ('63) describes ganglia within the lungs. He states that the nerve cells are bell-shaped, with two processes. Kandarazki also cites the observations of Reitz ('67), who described ganglion cells in the connective tissue between the (bronchial?) glands; and Verson ('68) who found no ganglia in the mucosa, but saw them 'behind' the muscles. Verson concluded that the nerve cells serve to innervate the smooth muscle of the bronchi. Frankenhauser ('79) found ganglia on the membranous part of the trachea and bronchi, and a nerve plexus between the glands.

The papers of Arnold, Reitz, Verson and Frankenhauser have not been accessible to me, and are cited from the article by Kandarazki. The observations were based chiefly on the dog, cat, several rodents, and some on the human.

Kandarazki ('81) extended the observations above cited to a number of other animals, including the frog, dog, cat, sheep, rabbit, and human. He found that the myelinated fibers which enter the bronchial ganglia may either pass between the cells, directly through the ganglia, or may form loops within the cell clusters. No terminations in relation to the cells were apparent to him. According to Kandarazki, Verson is incorrect in denying the presence of ganglionic clusters in the mucosa of the respiratory passages. He further states that the distribution of the ganglia with respect to the bronchial tree is primarily at the division points of the bronchi of the first to the third orders. These ganglia are connected by a plexus of nerve fibers.

Ismajloff ('73) attacked the problem with the aid of the gold-chloride method of staining, using various domestic animals. He describes three plexuses of nerve fibers in the submucosal tissue, namely: 1) an outer large-meshed network parallel to the axis of the air-passages; 2) a second network in the mucosa which has its origin by anastomosis of branches of the first, and is of finer mesh; and 3) a subepithelial network of very fine branches, which are lost, in part, in the subepithelial layer, and in part, pass directly to the upper surface of the epithelium. Ismajloff was not able to demonstrate the individual terminations of these fibers. He saw a network of black fibers which penetrate the epithelium, and also saw certain bodies within the latter from which processes extended to the mucosa. He was uncertain if these bodies were nerve terminations.

Retzius ('93) described the innervation of the lungs in a 15-cm. human foetus, using the Golgi technique. He found fibers which follow the bronchi and bronchioli as far as the 'necks of the alveoli.' No mention is made of ganglion cells.

In the same year, Berkley ('93) published an account of the distribution of the nerves in the lung of the rat, also based on a modified Golgi technique. He described the main nerve trunk as accompanying the bronchial artery. From this trunk fibers pass to the mucous membrane and to the bronchial muscles. Berkley also described nerve fibers and bundles in the septa of the lung between the alveoli. Nerve-terminations were found, but none near the air-sacs. The blood-vessels are described as possessing a nervous plexus, that about the bronchial artery being more pronounced than those surrounding the pulmonary artery or vein.

A study of the ganglia of the lungs was published by Budde ('04), which was based in part on wax reconstructions. He concluded that sympathetic ganglia are present in the bronchial tree in mammals and in the human. Their number, size, and form vary in different species. He describes 'peribronchial' and 'submucous' ganglia. In the mouse, guinea-pig, and dog there are present only peribronchial ganglia, while in the rabbit, hedge-hog, and the human foetus, both peribronchial and submucous ganglia are to be found. According to Budde, ganglia are never present in the mucous membrane proper or in the lung tissue itself. He states that the peripheral distribution of the peribronchial ganglia on the bronchial tree is totally different in various species of animals. The submucous ganglia never reach as far peripherally as do the peribronchial, and are also smaller than these.

'Predilectionsstellen' for the presence of the peribronchial ganglia, especially those of larger size, are the division points of the bronchi, and the points of contiguity between the bronchi and the pulmonary vessels. The nerves leading to these ganglia belong to the bronchus itself, rather than to the pulmonary artery or vein. Budde suggests by a question that the ganglia are perhaps related to the finer reactions of the bronchial musculature to various stimuli.

The source of the pulmonary fibers and their relation to other parts of the nervous system has been studied experimentally by a number of workers.

Ikegami and Jagita ('07), after extirpation of the inferior lobe of the right lung of the dog, observed chromatolysis in some of the cells of the ganglion nodosum of the corresponding side. They concluded that about 12 to 13.3 per cent of the total number of cells of the right nodose ganglion are in connection with nerve fibers terminating within the lung. With reference to motor fibers, they state:

Die motorischen Vagusfasern versorgen, wenigstens in direkter Weise, die Lunge nicht, weil erstens, nach dem Extirpation des Basislappen der Lunge keine nennenswerte Veränderung sowohl im dorsalen als auch im ventralen Vaguskerne zu sehen ist und weil zweitens die Durchschneidung des Vagus oberhalb des Plexus nodosus keinen Markscheidenzerfall an den dazugehörigen Lungenasten zur Folge hat. Freilich ist dabei die Möglichkeit nicht ausgeschlossen dass der motorische Vagus indirekt auf die Bronchien wirken kann.

Molhant ('10), on the other hand, after obtaining similar results in the rabbit, so far as chromatolysis is concerned, following extirpation of the lung, concluded that the smooth muscle of the bronchi and lungs receives its innervation through the vagus nerve from the dorsal X nucleus. He accounts for the small effect on the cells of this nucleus of severing the pulmonary branches of the vagus nerve by two hypotheses, namely: either the fibers below the bulb terminate in the numerous ganglia located in the neighborhood of the hilum, so that the method of operation employed by Molhant did not sever the preganglionic fibers; or the injury to the peripheral ends of the fibers was not of sufficient severity to produce chromatolysis of the cells connected with them. Molhant removed the lobes of the lung individually, by applying ligatures to them at their bases, near the hilum, and then severing the tissues distally to the point of ligation. Of the two possible explanations which he suggests of the slight effect on the ganglion cells of this procedure, Molhant himself favors the first. As will be shown below, it is likely that both are needed. He adds:

Nous sommes heureux de constater que nos résultats concordent avec ceux de Kosaka, Jagita et Ikegami, qui, après ablation du lobe inférieur pulmonaire chez le chien, n'ont pas plus que nous constaté de réaction cellulaire dans les noyaux moteurs bulbaires. Notre opinion est cependant différente de la leur, en ce sens que ces auteurs, ayant méconnu la dégénérescence spéciale aux petites fibres myéliniques destinées au poumon, semblant exclure toute action bulbaire du vague sur cet organe.

In a subsequent article which had reference primarily to sensory fibers, the same author (Molhant, '13) reports chromatolysis of ganglion cells in the external portions of the median and inferior segments of the ganglion nodosum. This reaction followed extirpation of the superior and median lobes of the right lung in the rabbit, and Molhant deduced from it the presence of sensory fibers within the lung.

The most comprehensive work of which the writer is aware on the sources of the pulmonary nerves, has been reported by Möllgaard ('12). This author employed the method of von Gudden on young kittens and puppies, and the method of Nissl on older animals of the same species.

On the basis of his experiments, he draws up a scheme of lung innervation under two principal divisions, namely: 1) the spinal sympathetic system and, 2) the vagus system. Each contains afferent and efferent fibers. The efferent fibers of the spinal-sympathetic system Möllgaard finds to pass from the processus lateralis of the cord, via the rami communicantes albae to the ganglion stellatum. From this ganglion the fibers pass to the ansa subclavia, and then via the vagus nerve to the lungs of the same and of the opposite side. According to Möllgaard's interpretation, these fibers function as vasomotors.

The afferent fibers of the spinal-sympathetic group are derived from both the homolateral and the contralateral lungs. They pass via the vagus and the ansa subclavia to the ganglion stellatum, thence via the rami communicantes to the second and third thoracic spinal ganglia. Central processes from nerve cells in these ganglia pass to the dorsal horn of the cord.

In the vagus system the efferent fibers arise in the dorsal nuclei of the vagus nerve in the medulla oblongata, pass via the vagus nerve to the nodose ganglion, thence via the vagus to the lung of the same side, with some possible crossing of fibers to the opposite side. Möllgaard divides these nerve fibers into two groups, the 'bronchomotors' and the 'secretory' nerves. The 'bronchomotors' he subdivides into 'constrictors' and 'dilatators.' The 'constrictors' he states arise from multipolar cells, but the 'dilatators' he believes have their origin in unipolar cells which are located in the ganglion nodosum.

The vagus afferent fibers, according to Möllgaard, come from both the homolateral and the contralateral lungs and pass via the vagus nerve to the nodose ganglion. Central processes pass from the nerve cells within this ganglion to the dorsal X nucleus of the bulb and to the uppermost part of the tractus solitarius.

Miller ('18) has briefly described the nerves and ganglia of the human lung in a case of pulmonary tuberculosis.

Turning attention to the pleura pulmonalis, it is stated in many of the larger works on anatomy that its innervation is from the vagus and the sympathetic trunks, through the pulmonary plexuses. Rauber-Kopsch ('20) ascribe to Kölliker the discovery of the pleural nerves and the statement that they show ganglion cells here and there in the course of their ramifications. Miller ('16) refers to the nerves of the visceral pleura, but makes no mention of ganglion cells.

The nerve terminations within the lung have been studied by Berkley ('93) and by Retzius ('93), using the Golgi method, as already noted, and by the writer ('21) with the methylene-blue technique. The latter method revealed terminations of sensory type in the epithelium of the main-stem bronchus and at the division points of the bronchi of the various orders, and most distally, in the walls of the atria. Retzius found a few fibers of apparently sensory type extending this far. In addition, nerve endings of motor type were revealed by the methylene-blue method in the smooth-muscle cells of the bronchial musculature, as far distally as the openings of the alveolar ducts into the atria. In the pulmonary vessels, particularly the arteries and arterioles, nerve-terminations of motor type are present in the muscle cells of the tunica media.

It was also shown that the intrapulmonary ganglion cells are surrounded by the pericellular network of terminal fibers which are characteristic of the visceral ganglia in general.

In a subsequent publication (Larsell and Mason, '21) it was demonstrated by experimental degeneration that most of the sensory endings within the lung are terminations of vagus fibers, and that the ganglion cells have the typical relation to vagus fibers of postganglionic neurones to preganglionic fibers. It was further shown, in agreement with Möllgaard, that there is a crossing over of vagus fibers in the pulmonary plexuses.

MATERIAL AND METHODS

In the course of the present investigation various methods of technique were employed. To demonstrate myelinated fibers and the general distribution of the larger nerve trunks and plexuses, which are fairly rich in myelinated fibers, the lungs were injected through the trachea with one-third of 1 per cent osmium tetroxide. They were then imbedded in parlodion and sectioned serially. Sections 50μ to 108μ were cut, both parallel with the longitudinal axis of the main-stem bronchus, and in other lobes of the lung, transversely to this axis.

Serial sections through the entire pulmonary lobe, both transverse and longitudinal, were also stained with haematoxylin and orange G. Vom Rath's fluid was employed to good advantage on lungs which had been previously hardened in 10 per cent formalin.

The methylene-blue method, as previously described by the writer ('21) was employed for the finer details. Some of the most instructive preparations were made by dissecting away the lung parenchyma from the bronchial walls, to the farthest point where this was possible without tearing off the branches of the bronchial tree itself. The bronchi and their branches were then split longitudinally and spread on a slide. After clearing in xylol, the preparations were mounted in balsam with a cover-glass. This method was employed on material which had been previously stained with methylene-blue and fixed with ammonium molybdate or ammonium picrate. The ammonium molybdate gave the clearest mounts. Similar mounts were also made of material fixed and stained with osmium tetroxide. Serial sections of lungs stained by the methylene-blue process were also employed for many details of structure.

In studying the nerves of the pleura pulmonalis, the method of stripping off portions of the pleura from lungs previously stained with methylene-blue, was found invaluable. The pieces of pleura thus obtained were cleared in xylol and mounted in balsam.

The lungs of dogs and rabbits were utilized in the investigation. Some human material was available, but was only obtainable so long after death as to be useless for the methylene-blue method. It also gave inferior results by other methods. The general plan of arrangement of the pulmonary plexuses appears to be similar in the three forms, although there are many differences of detail. Except, however, when stated specifically to the contrary, the description following will apply primarily to the lung of the rabbit.

DESCRIPTIVE

A. Intrapulmonary plexuses and ganglia

Shortly after entering the lung at the hilum of the organ, the nerve trunks which have constituted the pulmonary plexuses, become segregated into two groups. One of these groups forms a plexus about the main-stem bronchus and its branches (figs. 1 and 2), the other follows the pulmonary vessels (fig. 13).

Near the hilum, where the vessels and bronchi are not widely separated from one another by lung parenchyma, these groups cannot be distinguished. Within the lung, however, two principal features, aside from their position, serve to differentiate them. One is the presence of ganglion cells in the plexuses about the bronchial tree (fig. 2); the other is the greater size of the nerve bundles, their larger number, and the more numerous myelinated fibers, which are present around the bronchial tubes (figs. 2 and 3). In contrast to these features not even the periarterial plexus (fig. 13), which is more pronounced than that about the other vessels, has ever been observed in the writer's preparations, to contain ganglion cells. The nerve trunks of the pulmonary vessels are of smaller size, relatively, than on corresponding bronchi, with little, if any anastomosis. Moreover, the myelinated fibers are smaller, and are apparently, confined to the larger roots of the arteries.

In the region of the hilum, ganglionic clusters of cells are frequently located in the connective-tissue septa which separate the main-stem bronchus from the roots of the pulmonary vessels. In such positions it is not possible to determine with certainty by location alone whether they should be ascribed to the bronchial tree or to the blood-vessels.

Bronchial plexuses and ganglia. Two plexuses of nerve trunks surround the larger elements of the bronchial tree. The larger of these lies external to the cartilaginous plates of the bronchi, in the connective tissue between the cartilage and the lung parenchyma (figs. 1, 2, and 3). The second plexus lies between the cartilage plates and the muscular layer, and in part, upon and within the latter (figs. 4, 5 and 8). Budde ('04) has called the ganglia which lie in these two plexuses the 'peribronchial' and the 'submucosal,' respectively. For reasons which will become more apparent as the description proceeds (p. 115), the writer prefers to designate the external plexus of fibers, with its ganglia, as the extrachondrial plexus; the inner one, with reference to the center of the bronchus, will be called the subchondrial plexus.

A third stratum of nerve fibers may be recognized between the muscle and the epithelium, but these fibers represent terminal

ABBREVIATIONS

alv., alveolus
art., artery
art.br., bronchial artery
art.pul., pulmonary artery
bl.v., blood-vessel
br., bronchus, general designation
br.II, secondary bronchus
br.mu., bronchial muscle (muscle of Reisseisen)
ca.pl., cartilage plate
c.t., connective-tissue layer
du., duct of bronchial gland
epith., epithelium
ex.ch.pl., extra-chondrial plexus
gn., ganglion
int.lo.se., interlobar septum
m.fi., smooth-muscle fiber
mu.bd., smooth-muscle band
mu.sp., smooth-muscle nerve spindle
my.fi., myelinated nerve fiber
n.ter., sensory nerve termination in bronchial epithelium
n.tr., nerve trunk
par., parenchyma
r.br.II, branch of nerve trunk to secondary bronchus
s.fi., sensory nerve fiber
su.ch.pl., subchondrial plexus
t.fi., terminal motor fiber to smooth muscle cells
vn., vein

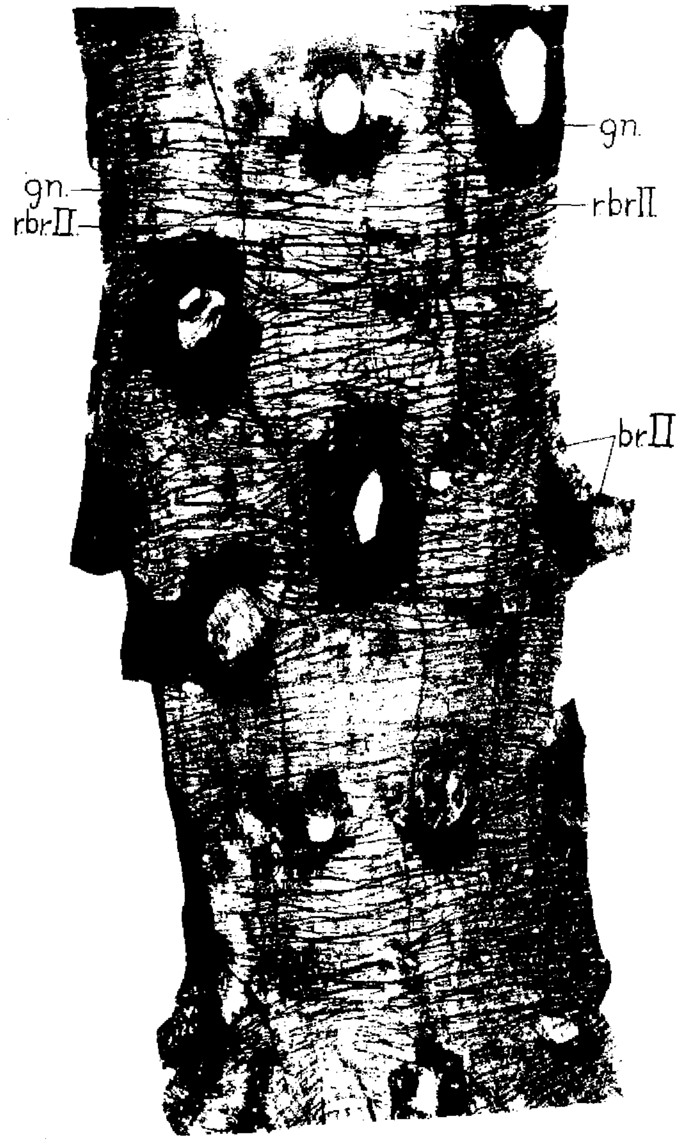
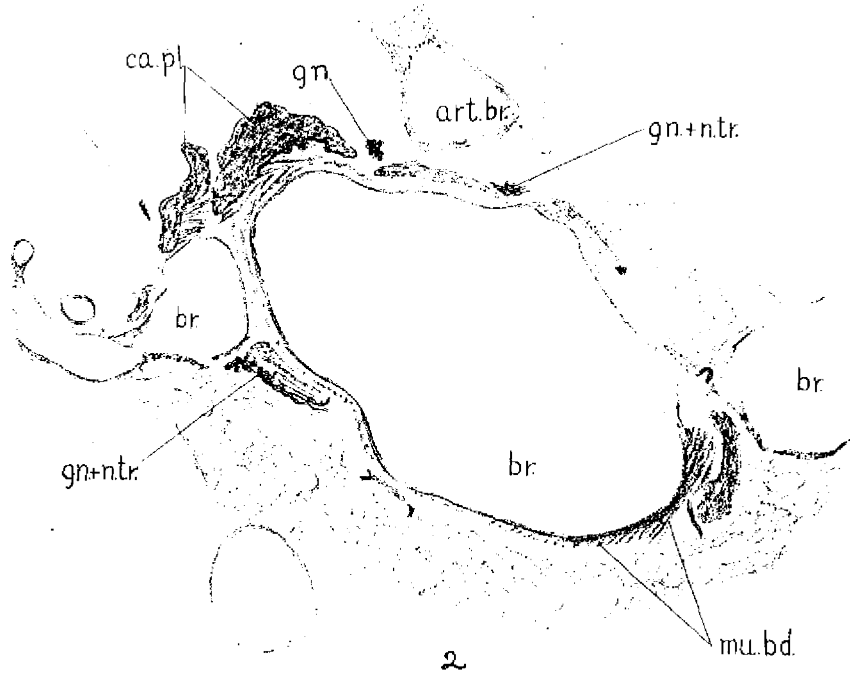


Fig. 1 Photomicrograph of a portion of the main-stem bronchus of the rabbit, which had been split open and mounted flat, after fixation and staining with osmium tetroxide. Reduced to × 11.



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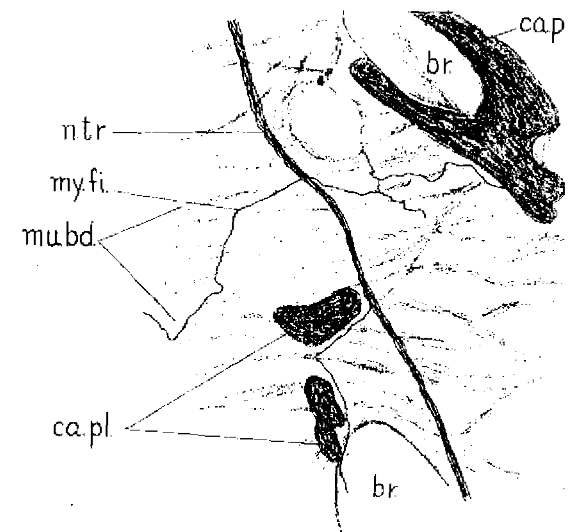

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Fig. 2 Transverse section of the main bronchus of one of the pulmonary lobes of the rabbit, showing the arrangement about it of the nerve trunks and ganglia. Osmium tetroxide. Section 108μ. Edinger-Leitz projection apparatus. Reduced to × 12.5.

Fig. 3 Portion of a secondary bronchus of the rabbit, spread out and mounted entire, to show the distribution of the myelinated fibers. Osmium tetroxide. Camera lucida. Reduced to × 35.

branches of sensory fibers from the two plexuses just noted. They do not appear to the writer to warrant a designation as a

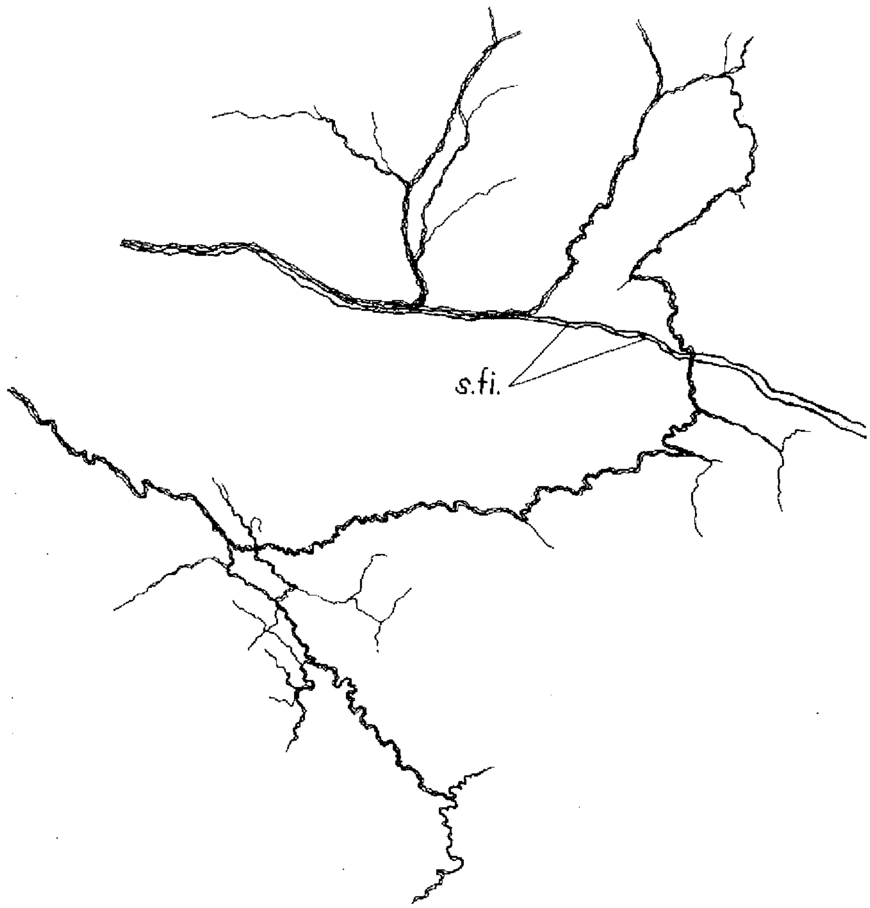


Fig. 4 Portion of the subchondrial plexus from a secondary bronchus of the rabbit, mounted entire, after it had been split open and spread out. Methylene blue. Camera lucida. Reduced to × 95.

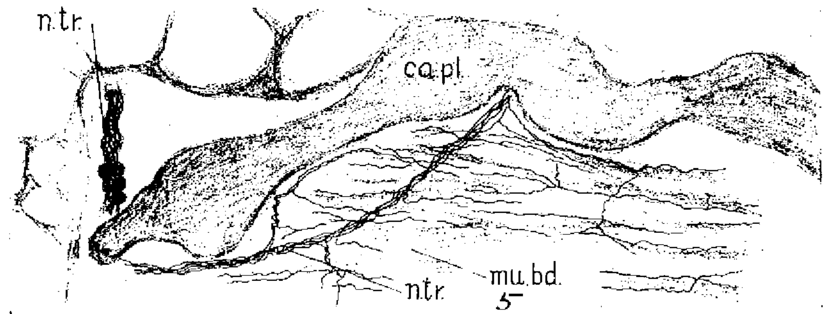
separate plexus, particularly as there is no anastomosis of nerve bundles or trunks in this zone. Ismajloff ('73), further subdivides the nerves of the submucosal tissue into three layers. This appears to me unnecessary.

The extrachondrial plexus about the larger bronchi consists, as a rule, of two to six main trunks (figs. 1 and 2) which subdivide into smaller bundles. The smaller bundles may rejoin the parent trunk or they may anastomose with others, large or small. They thus form a plexus with elongated meshes. As a rule, however, the smaller bundles pass to the secondary bronchi (fig. 1) to form smaller plexuses about these air-passages. As shown in figure 2, the main trunks are distributed about the periphery of the larger bronchi at fairly uniform distances one from the other. A trunk of somewhat larger size than the rest is usually to be found near the bronchial artery (figs. 2 and 14).

The extrachondrial plexus contains many myelinated fibers, as is shown by osmium-tetroxide staining (figs, 1, 2, 3 and 8), but the methylene-blue and other methods reveal also even more numerous fibers without medullary sheaths. Some of the myelinated fibers are of considerable size and represent the sensory fibers which lead to nerve terminations in the mucosa and in the muscle bands, as described below. Others are of medium or small size, with thin sheaths of myelin. The small ones, for the most part, probably represent the preganglionic fibers which terminate in relation to the ganglionic cells.

Scattered through this plexus, particularly at the points of intersection of the nerve trunks, and at the division points of the bronchi, are clusters of ganglionic cells (figs. 1, 2, 5, 6, 7). As already noted, both Kandarazki ('81) and Budde ('04) have called attention to these characteristic situations of the ganglia. Near the hilum of the lung and in the larger bronchi these clusters are quite numerous. They consist, in the rabbit, of five or six to approximately twenty cells. Distally they become more scattered and are composed of fewer cells. They are rarely encountered beyond the points of origin of the bronchi of the third order.

Methylene-blue preparations reveal rich pericellular networks about the ganglion cells (figs. 6 and 7). As has been shown in a recent article already cited (Larsell and Mason, '21), these pericellular networks disappear on degeneration of the vagus. This indicates that they represent the terminations of pregan-



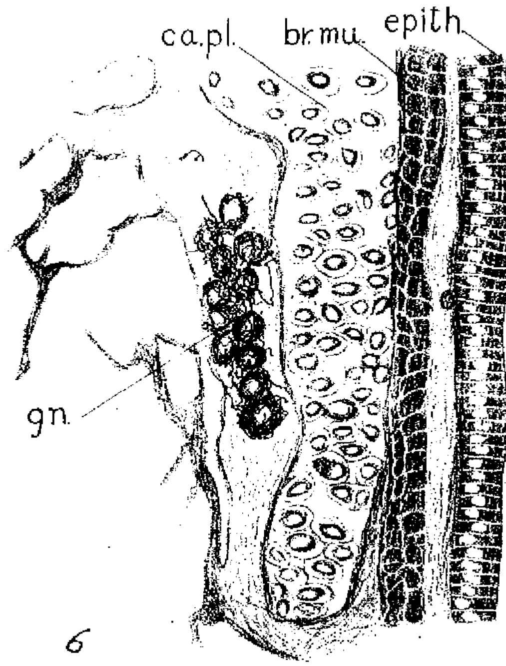


Fig. 5 Portion of the subchondrial plexus from the rabbit's lung. This figure shows the relation of the subchondrial plexus to the bronchial muscle bands. A little of the extrachondrial plexus and a cluster of ganglion cells are also shown in the left-hand side of the figure. Methylene blue. Section 72μ. Camera lucida. Reduced to × 84.

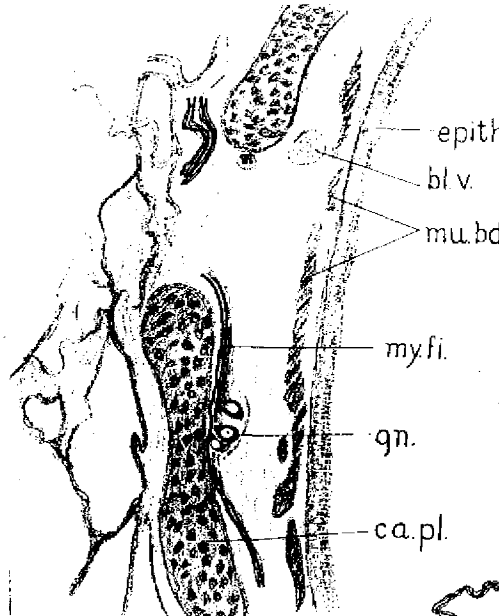
Fig. 6 Ganglion, with pericellular baskets, from the extrachondrial plexus of the main-stem bronchus of the rabbit. Methylene blue and aurantia. Section 62μ. Camera lucida. Reduced to × 270.

glionic fibers about the cells. The cells of the intrapulmonary ganglia must, accordingly, represent the perikaryons of post-ganglionic neurones. They give off fine unmyelinated fibers which unite to form nerve trunks, as shown in figure 7. The trunks thus formed pass between the cartilage plates to form, by anastomosis with similar trunks from other ganglia and with other trunks composed of both myelinated and unmyelinated fibers, the subchondrial plexus, to which reference has already been made.

Undoubtedly many, if not the greater number, of the post-ganglionic fibers which pass to the bronchial musculature have their origin from cells of the pulmonary plexuses external to the lung. The number of intrapulmonary ganglion cells, particularly in the dog, does not appear great enough to account for the rich innervation of the smooth-muscle bands. This fact, together with the fact that most of the intrapulmonary ganglion cells are located near the hilum of the lung, thus requiring only a short stretch of the nerve fibers to reach the cells from the hilum, justify both of Molhant's suggested reasons for the slight amount of chromatolysis in the dorsal X nucleus already mentioned (p. 101). It will be recalled that Molhant extirpated the lobes of the lung by first applying ligatures to them individually near the hilum. He then severed the tissues distally to the point of ligation. By this method the extrapulmonary ganglia were undoubtedly entirely unaffected, and possibly many of the intrapulmonary cells also escaped removal. The result, therefore, would be a relatively slight injury to those preganglionic fibers which enter the lung lobes.

The subchondrial plexus (figs. 4, 5, 7 and 8) is composed of a preponderating number of unmyelinated fibers and a smaller number of the myelinated variety. A small number of ganglionic clusters are encountered. These consist, as a rule, of only a few cells (fig. 8). Occasionally isolated cells are found. No subchondrial ganglia have been observed by the writer in the dog's lung. This is in agreement with the statements of Budde ('04).

With the exception of processes from such subchondrial ganglion cells, this plexus consists of fibers which have their course



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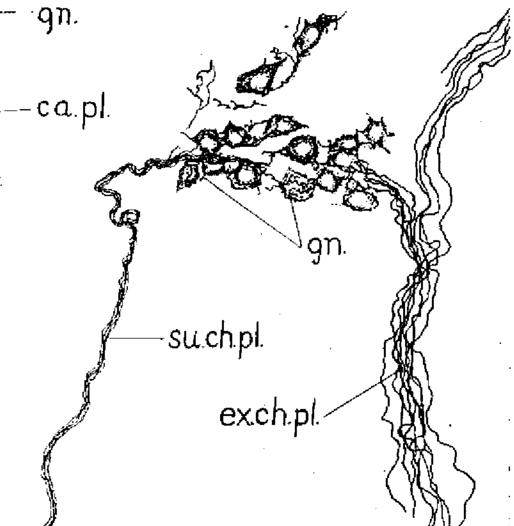

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Fig. 7 Ganglion of the extrachondrial plexus, showing the relation of the ganglia to the two plexuses. Fibers from the extrachondrial trunk terminate as pericellular baskets about the ganglionic cells. Axonic processes from the cells unite to form the bundle of the subchondrial plexus. Rabbit. Methylene blue. Section 72μ. Camera lucida. Reduced to × 270.

Fig. 8 A subchondrial ganglion near the point of branching of a secondary bronchus into one of the third order. Rabbit. Osmium tetroxide. Section 108μ. Camera lucida. Reduced to × 133.

for a greater or less distance in the extrachondrial plexus. The fibers of the myelinated variety are of medium to large size. They undoubtedly represent sensory fibers which pass through the subchondrial plexus to terminate as sensory endings, either in the mucosa (cf. figs. 1 to 6; Larsell, '21), or in the smooth-

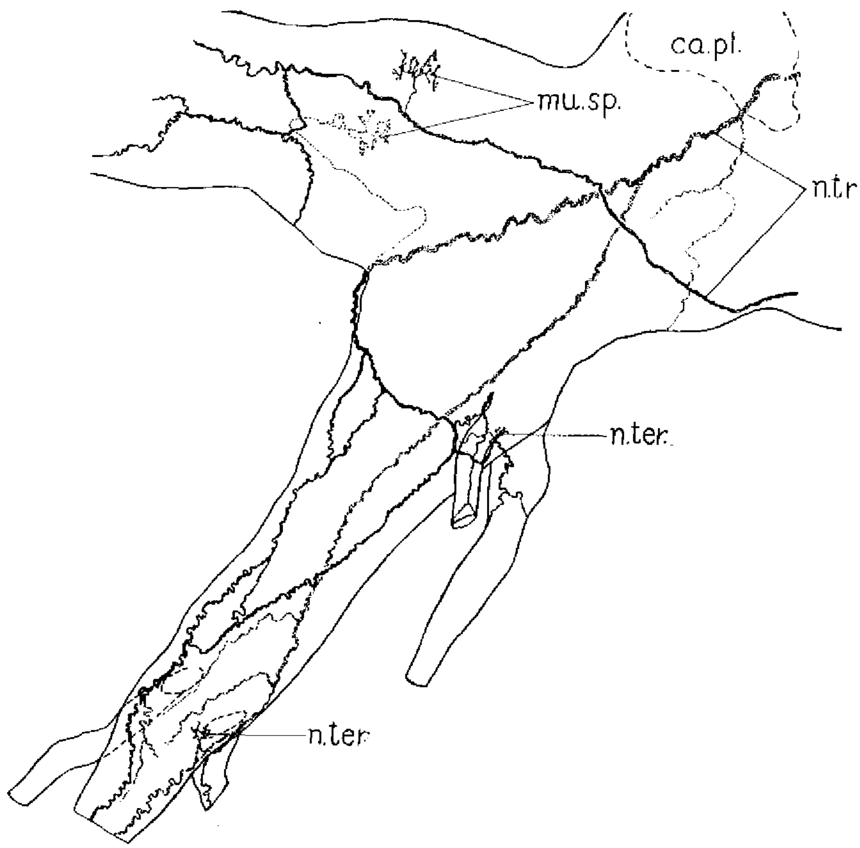


Fig. 9 Portion of the bronchial tree, mounted entire, showing the nerve plexuses on bronchi of about 0.8 mm. to 0.4 mm. mean diameter. Rabbit. Methylene blue. Edinger-Leitz projection apparatus. Reduced to × 28.

muscle bands (figs. 11 and 12). The unmyelinated fibers are derived from the various ganglia, including the subchondrial, the extrachondrial, and the ganglia of the pulmonary plexuses. The terminations of these fibers are in the smooth muscle of the bronchi (fig. 5), as has been shown by the writer in a previous communication ('21).

The smaller bronchi which do not have cartilaginous plates show a blending of the two plexuses (fig. 9). But for the presence of more numerous myelinated fibers than are found in the subchondrial plexuses elsewhere, the statement would appear to

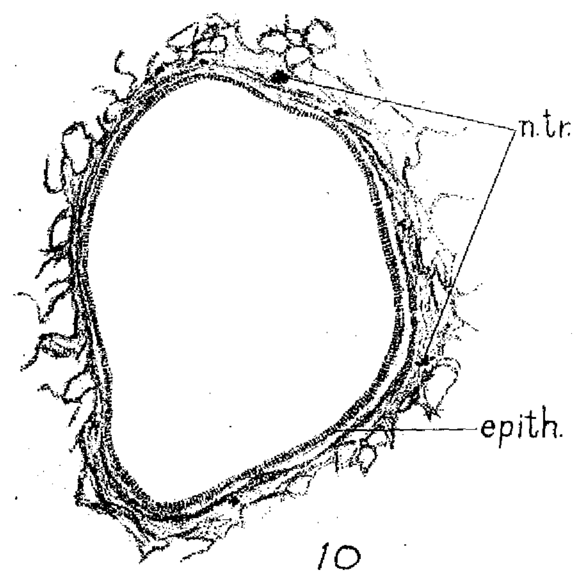


Fig. 10 Transverse section of a bronchus of 0.9 mm. mean diameter showing the distribution about it of the bundles of myelinated fibers. Rabbit. Osmium tetroxide. Section 108μ. Camera lucida. Reduced to $\times$ 46.

be justified that the extrachondrial plexus gives place in these bronchi to the subchondrial. The absence of ganglion cells adds weight to this interpretation. However, the main nerve trunks are somewhat larger than in those portions of the bronchial tree where the two plexuses are distinct (cf. figs. 4 and 9), and the myelinated fibers have the arrangement characteristic of the extrachondrial plexus, namely, in bundles of a considerable number of fibers (fig. 10).

This union of the extrachondrial plexus with the subchondrial makes Budde's term 'peribronchial' (p. 106) undesirable, as applying to either of the two component plexuses alone. If applied to the united plexuses, it would appear more properly used. In order to avoid confusion, however, the writer will not employ it, even in this sense.

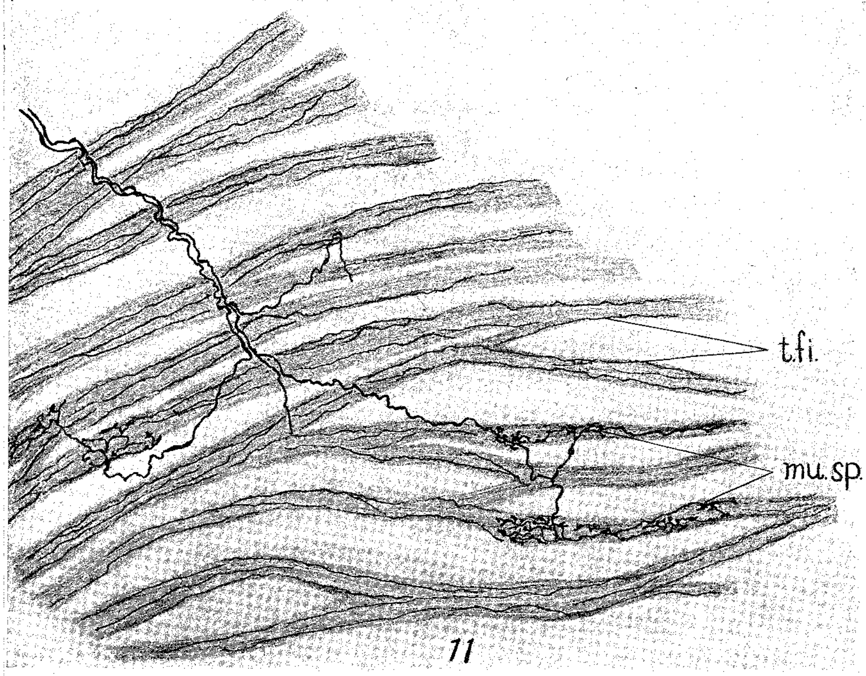
In the smaller bronchi the myelinated fiber bundles break up into nerve strands of two or three fibers, or into individual filaments. The individual fibers terminate as sensory endings in the epithelium or in the smooth-muscle bands (figs. 9, 11, 12).

Sensory nerve terminations in smooth muscle. Reference has been made a number of times to nerve terminations of sensory type in the smooth muscle bands of the bronchial tree. In addition to the sensory terminations in the epithelium, which were described in a preceding article already cited, another type of ending, which is apparently sensory, is present in the bands of muscle (muscle of Reisseisen) which surround the various subdivisions of the bronchial tree. These nerve endings were brought to view by the method already described, of preparing whole mounts of the bronchi and their branches, after staining with methylene blue.

Myelinated fibers which are derived from the main nerve trunks of the extrachondrial plexus pass individually, or in small strands of several fibers, for a greater or less distance over the outer surface of the bronchial muscle. In the smaller bronchi where the extrachondrial and the subchondrial plexuses have united, the fibers which give rise to the type of nerve endings under consideration can be easily followed for considerable distances (fig. 9). The individual fibers divide into relatively short branches which are distributed to different muscle bands (fig. 11). The branches terminate upon and within the muscle bands as spindle-like nerve endings.

No distinction could be made between the fibers which lead to terminations in the muscle, and those which terminate in the sensory endings of the bronchial epithelium. The fibers in both cases are myelinated and are of medium to large size.

The smooth-muscle nerve spindles, as we may call the nerve-terminations under consideration (figs. 11 and 12), are composed



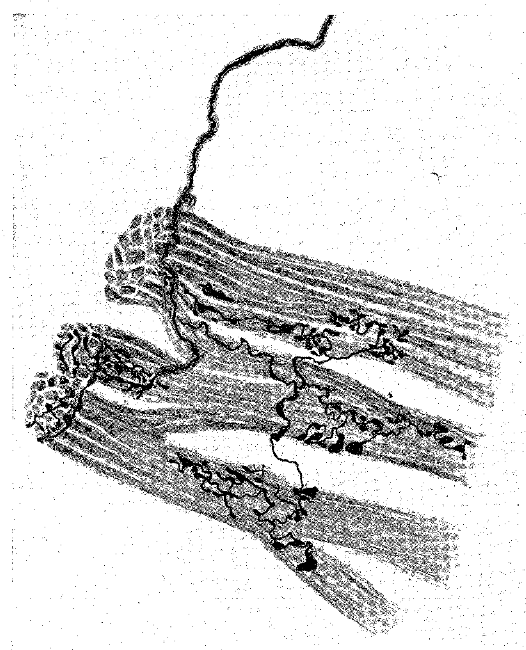


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Fig. 11 Nerve endings (smooth-muscle nerve spindles) in the smooth muscle bands of a bronchus 1 mm. in diameter, mounted entire. Rabbit. Methylene blue. Camera lucida. Reduced to × 109.

Fig. 12 Nerve endings (smooth-muscle nerve spindles) in smooth muscle bands of bronchus 0.32 mm. diameter, more highly magnified. The figure was drawn from a preparation in which the muscle bands had been cut in such a manner as to show the continuation of the nerve fibers between the individual muscle cells, as described in the text. Rabbit. Methylene blue. Camera lucida. Reduced to × 360.

of numerous short terminal branches. Some of these rami wrap about the muscle, to terminate upon the bundle as a whole, as knobs or plates. Other rami penetrate between the individual smooth-muscle fibers which compose the muscle band. These terminate among the smooth-muscle fibers also in knobs or leaf-like expansions, as shown in figure 12.

Miller ('21) has recently pointed out that "the bronchial musculature is not arranged in the form of distinct bands which encircle the bronchi and bronchioli, neither is it in the form of a continuous sheet, but it is in the form of a net-work." The smooth-muscle spindles are found at various points in this network of the bronchial muscle. A single nerve fiber, as shown in figure 11, may give rise to a considerable number of endings, each located in a different band of the network.

Terminations of this type were found in bronchi as small as 0.19 mm. in diameter. They may be present in smaller branches also, but in the writer's preparations most of the bronchi and bronchioli of smaller size than this had been unavoidably torn off in dissecting away the parenchyma. They are present wherever the muscle bands are found, in those portions of the bronchi and their branches which it was possible to examine. This is in contrast to the sensory terminations in the bronchial epithelium, which are characteristically present, in the smaller bronchi, only at the division points of the bronchial passages.

A rough approximation of the number of this type of nerve endings was obtained by counting them in a few of the most favorably stained portions of bronchi of various sizes. The results are indicated in the following tabulation:

MEAN DIAMETER OF PORTION OF BRONCHUS	LENGTH OF PORTION OF BRONCHUS	APPROXIMATE AREA	NUMBER OF TERMINATIONS
mm.	*mm.*	*sq. mm.*	
2	8.9	55.92	14
0.9	5.8	16.40	10
0.7	2.2	4.84	8
0.5	6.8	12.78	9

It will be seen that there is one nerve termination for 3.99 sq. mm., one for 1.64 sq. mm., one for 0.605 sq. mm., and one for

1.42 sq. mm., respectively. It must also be borne in mind that some of the terminations, even in the most favorably stained portions of the preparations may not have been stained.

Cuccati ('88) has described very small terminal nerve plates in the smaller smooth muscle bands of the frog's lung. So far as I am aware, this is the only reference in the literature to nerve-terminations approaching the type above described. As they appear to correspond to the nerve-muscle spindles of skeletal muscle, the term 'smooth muscle nerve spindles' is suggested as a convenient name by which to designate them.

Smirnow ('88), and Cuccati in the reference cited in the preceding paragraph, have described terminal skeins and plates in the connective tissues enveloping the smooth-muscle bands in the frog's lung, and Ploschko ('97) found 'intermusculäre Endbäumchen' between the bundles of smooth muscle in the trachea of the dog. Carpenter ('18) has described sensory terminal skeins in the longitudinal muscle layer and in the serous coat of the cardiac stomach of the cat. He also found terminal tufts, apparently of sensory type, connected with nerve fibers in the corresponding coats of the intestine of the dog. Both of these types of terminations appear to lie in the connective tissue, rather than in relation to the muscle fibers, even when located in the muscular layer. So far as Carpenter's description and figures indicate, neither terminal tufts nor nets in the stomach, nor the end tufts in the intestine, are in intimate relation with the smooth-muscle fibers themselves. This appears to be true also of the endings described by Smirnow, Cuccati, and Ploschko, with the exception of the one type which Cuccati calls 'piccolissima piastra,' to which reference has been made.

It does not appear impossible that the smooth-muscle nerve spindles in the bronchial musculature may exert a regulatory influence on the respiratory movements, through the action upon them of the contracting or relaxing muscle bands during inspiration or expiration.

Innervation of blood-vessels, glands, and lymphatics of the lung. Attention has already been called to the plexus of nerve trunks about the pulmonary blood-vessels. The roots of the larger vessels, particularly the arteries near the hilum of the lung, have nerve trunks of considerable size, as shown in figure 13. Many of the fibers of these trunks are myelinated (fig. 16). Bundles of fibers branch at intervals from the main trunks and break up into individual filaments. These fibers in turn

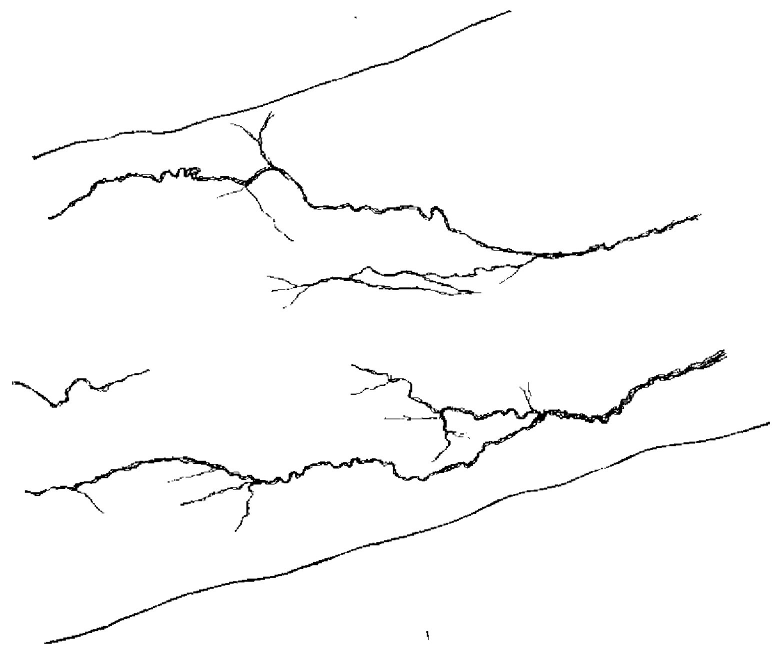


Fig. 13 Nerve plexus on the main pulmonary artery of one of the lobes of the dog's lung. The artery had been split open longitudinally and mounted entire. Methylene blue. Edinger-Leitz projection apparatus. Reduced to × 14.

give off branches which finally give rise to the terminal rami. The terminal twigs pass to the smooth muscle of the tunica media, both in the larger vessels and in the arterioles, as has been described and figured by the writer in a previous contribution. The pulmonary veins have but few nerve fibers, in contrast to the rich plexus on the arteries.

Sensory nerve-terminations are present in the walls of the larger pulmonary arteries, near the hilum of the lung. These have been described and figured by Schemetkin, a student of Dogiel, and reported by the latter (Dogiel, '98). The present writer has also referred to them previously ('21).

The bronchial artery has essentially the same type of innervation as is present in the pulmonary arteries. A relatively small bundle of delicate nerve fibers may usually be seen in favorably stained methylene-blue material (fig. 14). As shown in the figure, individual fibers are given off from the bundle. They in turn give off a number of terminals which end in relation to the smooth muscle cells of the arterial coat, as small terminal knobs. Berkley ('93) found in the rat a richer innervation of the bronchial arteries than of the pulmonary vessels. This does not hold true in the dog and the rabbit.

Bronchial glands. Nerve terminations are also present in the bronchial mucous glands. Small bundles of fibers which arise from the subchondrial plexus, find their way to the glands of the bronchi. On reaching one of the glands, the bundle breaks up, as shown in figure 15, into individual fibers. These are distributed to the alveoli of the gland, where they terminate in relation to the epithelial cells, in a number of short end-fibers.

Lymphatics. Some nerve fibers have been observed in the writer's preparations, which terminate apparently in the larger pulmonary lymphatic vessels. These fibers are of small size and are few in number. No thorough study of them was possible.

B. Innervation of the pleura pulmonalis

Dogiel ('03) has described nerve fibers and nerve terminations of several types in the costal pleura, but makes no mention of the pulmonary pleura in this connection. The visceral pleura is usually considered insensitive to pain-producing stimuli.

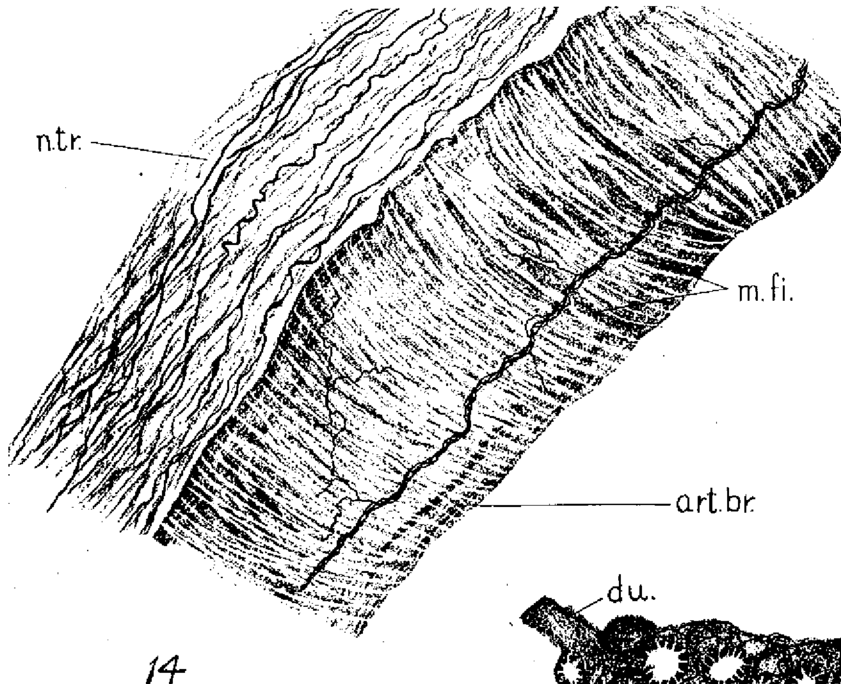
Capps ('11) has explored the pulmonary pleura in over fifty cases of thoracentesis in human subjects, with especial reference to the pain sense. He states, "Neither pressure nor other forms of irritation produced any feeling of discomfort except when adhesions to the costal pleura were present." The presence of nerve fibers and of sensory endings might, therefore, not be expected in the immediate covering of the lungs.

That they are present in some regions of the visceral pleura, however, can be demonstrated in the dog and rabbit, both by staining with methylene blue and with osmium tetroxide. The latter stain shows only that myelinated fibers are present, but in methylene-blue material nerve-terminations, as well as nerve trunks and fibers, may be seen.

The nerve trunks which form the pleural bundles emerge from the plexus which surrounds the pulmonary arteries and pass into the pulmonary pleura, near the hilum of the lung. They run for some distance as fairly compact trunks, then break up into smaller bundles or into individual fibers. Figure 16 shows such a plexus from the rabbit. The figure represents a reconstruction from twelve serial sections of a lung which had been fixed and stained with osmium tetroxide. As will be noted from the figure, the main nerve trunks follow the pleura which bounds the fissures between the lobes of the lung. The source of the pleural nerves, namely, from the periarterial plexus, is also shown in the reconstruction.

In figure 17 is represented a section through a main nerve trunk from the dog's pleura, and in figure 18 portions of two secondary branches of the pleural nerves from the same species. The main trunks break up into secondary bundles of smaller size. These in turn subdivide, frequently as individual fibers. The individual filaments pass to sensory terminations in the pleural membrane. In the dog the main nerve bundles follow the larger pleural blood-vessels (fig. 17), but in the rabbit no such relation was noted. This is no doubt due to the exceedingly thin pleura of this animal and the lack of large vessels therein.

Measurement of individual fibers of the pleural nerves shows a diameter of the myelin sheaths of 2μ to 7μ in the dog, and about 4μ to 6μ in the rabbit. In the dog a few larger fibers were also observed, but none beyond 10μ in diameter were found. Ranson and Billingsley ('18) have shown that in the cat "the sensory fibers of the white rami may be said to be of all sizes from 1.5 to 8 or 10μ, no one size greatly predominating over the others.



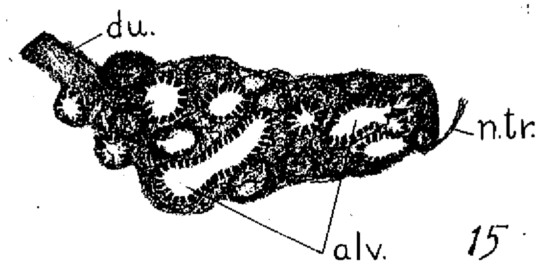


Fig. 14 Bronchial artery and accompanying nerve trunk in lung of the rabbit. Methylene blue. Section 72μ. Camera lucida. Reduced to $\times$ 270.

Fig. 15 Nerve fibers and terminations in a bronchial gland of the dog. Methylene blue. Section 108μ. Camera lucida. Reduced to $\times$ 178.

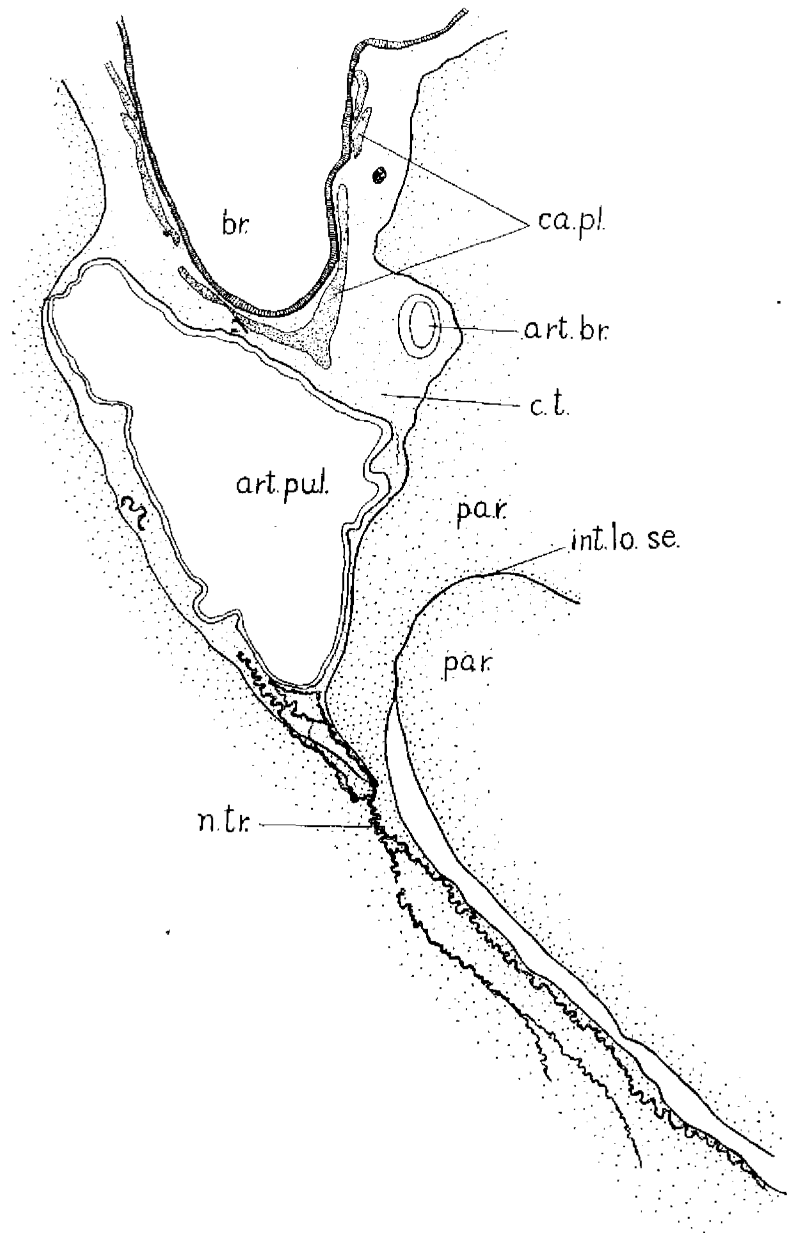


Fig. 16 Reconstruction from twelve serial sections, cut transversely to main-stem bronchus at 108μ, to show the nerve trunks passing to the pleura. Rabbit. Osmium tetroxide. Edinger-Leitz projection apparatus. Reduced to × 9.25.

In some rami as in the upper thoracic larger fibers up to 13μ may be present." This range of variation corresponds approximately with that of the myelinated fibers of the nerve bundle of the pleura illustrated in figure 17.

The principal areas of distribution of fibers from the pleural nerve trunks are apparently the margins of the pulmonary lobes and the immediately neighboring regions, particularly on the

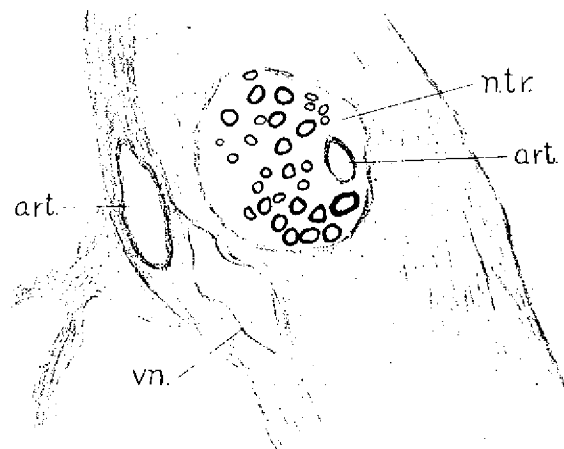


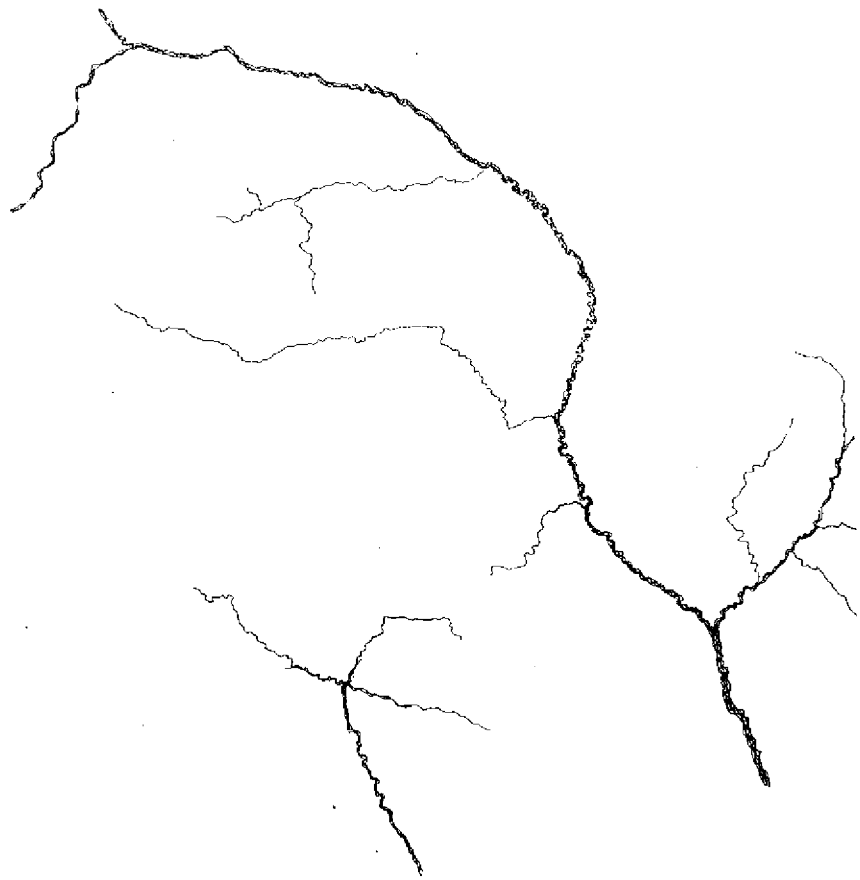
Fig. 17 Transverse section through a nerve trunk in the pulmonary pleura of the dog. Vom Rath's fluid, after formalin fixation. Section 50μ. Camera lucida. Reduced to × 540.

inner surfaces of the lobes. Very few fibers or nerve endings were found on the exposed surfaces of the lobes, although practically the entire pleura was systematically removed, strip by strip, from both the inner and the outer surfaces of several well-stained lungs. Such nerve fibers and terminations as were found were obtained from the pleura of the margins of the lung, and were most numerous in the dorsal margins of the lobes near the hilum. None were encountered on the caudal or caudo-ventral margins.

In the rabbit the nerve-terminations are small and of simple structure, but in the dog the size is greater and the elaboration of structure is considerable. As illustrated in figure 19, the nerve fiber, which in the case illustrated was myelinated almost to the point at which it nearly doubles upon itself, divides into a number of very slender filaments. Each of these filaments gives off numerous terminal branches. The terminal rami each end in a knob-like expansion in the tissue of the pleura, within which the entire nerve termination is situated. These nerve-terminations have the aspect of sensory endings. Moreover, neither glandular structure nor muscle is present to be innervated by them, were they motor.

The experimental method which Capps employed in the work above cited, namely, stimulation with the blunt end of a stiff wire which had been passed through the thoracic wall, would not readily lend itself to examination of the interlobar surfaces, or to exploration of the margins of the lobes. If the distribution of the visceral pleural nerves is similar in the human to that in the dog and rabbit, it is possible that the negative results obtained by Capps were due to the probability that he was able to explore only the costal surfaces of the pulmonary lobes. Also the possibility must be borne in mind that, as Head ('20) has pointed out for visceral sensation in general, these terminations may not give rise to painful sensations, and possibly not to conscious sensations of any type which could be referred to the pleura.

The source of the nerves to the pulmonary pleura is usually stated to be from the vagi and the sympathetic trunks, via the pulmonary plexuses. Degeneration experiments conducted by the writer, whose object was in part to ascertain more specifically the origin of these fibers, have not given conclusive results. Several lines of evidence point pretty strongly, however, to the indication that they are derived in large part, at least, from the dorsal root ganglia of the upper thoracic spinal nerves, and pass to the lungs via the sympathetic trunks and the stellate and inferior cervical ganglia. In the rabbit the writer has found the nerves to be substantially as numerous, so far as could be judged



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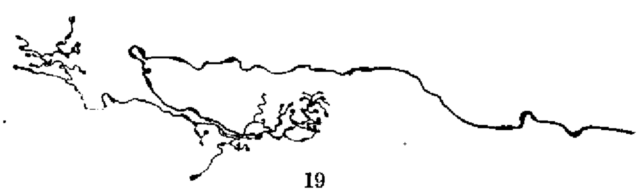

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Fig. 18 Portion of the nerve plexus of the pulmonary pleura of the dog, showing secondary and tertiary branches from the main trunks, and also individual fibers. Whole mount of a portion of pleura from the inner side of dorsal margin of lung, near the hilum. Edinger-Leitz projection apparatus. Methylene blue. Reduced to × 18.

Fig. 19 Nerve termination in the pulmonary pleura of the dog. Methylene blue. Whole mount of a portion of interlobar pleura. Camera lucida. Reduced to × 270.

from serial sections of the lung, following degeneration of the vagus nerve, as in the normal lung. This fact would point to an origin such as above suggested, or to a very great crossing over from the contralateral vagus.

Möllgaard ('12), as previously noted, has found that some of the cells of the second and third thoracic spinal ganglia undergo chromatolysis on ablation of one or more lobes of the lung in kittens and puppies. The nerve fibers to the pleura are also given off, as already stated, in large part from the periarterial plexus. This plexus is apparently composed of fibers from the sympathetic trunk.

The final solution of the question presents unusual difficulties, both of experiment and of interpretation. This is due to the relatively few fibers of the pleura, scattered over a wide area, and particularly to the intermingling of fibers from the sympathetic trunks of both sides with branches of the two vagi in the pulmonary plexuses.

It has been shown by experimental degeneration, as already noted, that fibers of the vagi cross through the pulmonary plexuses to the contralateral side. Physiological experiments by a number of workers also indicate that this is true. Möllgaard ('12) states that there is a similar crossing over of sympathetic fibers in the pulmonary plexuses of the dog, but that in the cat the sympathetic innervation of the lung is apparently unilateral. Accordingly, section of the thoracic roots, or extirpation of the sympathetic ganglia of one side, could give only ambiguous results except possibly in the cat. Such experimental work on this animal must await a detailed study of the distribution of the nerves and terminations in its lung and pleura, corresponding to that reported for the dog and rabbit.

SUMMARY

1. The nerves which enter the lung from the anterior and posterior pulmonary plexuses become segregated within the organ, near the hilum, into three groups of plexuses, namely: 1) a bronchial group; 2) a vascular group; and 3) a plexus which is distributed to the pleura pulmonalis.

2. The bronchial plexuses are two in number, an extrachondrial and a subchondrial. The extrachondrial plexus lies between the cartilaginous plates of the bronchi and the lung parenchyma. It is composed of relatively large nerve trunks which anastomose to form a plexus of longitudinal mesh about the bronchi. It contains many myelinated fibers and numerous clusters of ganglion cells. The subchondrial plexus lies between the layer of cartilaginous plates and the layer of the bronchial muscle. It is composed of smaller nerve trunks which consist of unmyelinated fibers, myelinated fibers and, in the rabbit, some ganglion cells. The unmyelinated fibers pass to the smooth muscle of the bronchi, the myelinated fibers pass to sensory terminations in the epithelium of the bronchi and in the smooth-muscle bands. About the smaller bronchi which do not have cartilaginous plates, the two plexuses blend into one. This retains, however, many of the distinctive features of each of the component plexuses.

3. The intrapulmonary ganglia are found chiefly in the extrachondrial plexus, but in the rabbit some are present also in the subchondrial plexus. These ganglia are characteristically located at the division points of the bronchi, and at the points of junction of the larger nerve trunks of the plexuses. Ganglionic cells are rarely found beyond the points of origin of the bronchi of the third order. They are surrounded by pericellular baskets, which represent the terminal arborizations of preganglionic fibers from the vagus nerve. The axonic processes of these nerve cells are distributed to the smooth-muscle cells of the bronchial muscle, and probably to the bronchial mucous glands.

4. The mucous glands of the intrapulmonary bronchi receive their nerve fibers from the subchondrial plexus. The fibers terminate in relation to the epithelium of the alveoli.

5. A type of sensory termination, which appears to correspond to the muscle spindles of striated muscle, is present in the smooth-muscle bands of the bronchial muscle. These terminations are designated 'smooth muscle nerve spindles.' They are the terminations of myelinated fibers of large size.

6. Nerve plexuses are present about the vascular tubes of the lung. A rich plexus extends over the various branches of the pulmonary artery, including the arterioles. The nerve fibers terminate in relation to the smooth-muscle cells of the tunica media of these vessels. Sensory nerve endings are also present in the walls of the pulmonary artery, near the hilum of the lung.

The bronchial artery is supplied by a nerve plexus whose terminal fibers end in relation to the smooth-muscle cells of the tunica media.

The pulmonary veins and lymphatics have but few nerve fibers, but the relation appears to be the same as in the arteries.

7. The pleura pulmonalis receives nerve trunks from the periarterial plexus. The fibers, chiefly myelinated, pass to the margins of the pulmonary lobes. They terminate as sensory endings near the lobar margins principally on the dorsal and interlobar margins of the lobes.

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