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SOME ASPECTS OF THE INNERVATION OF THE LUNG

O. LARSELL, PH. D.

PORTLAND, ORE.

Anatomical Laboratory, University of Oregon Medical School

There are certain features of the nerve supply of the lung which should be of interest to both the internist and the surgeon who has occasion to deal with this organ. The information to be found on the subject in treatises on anatomy is limited, and the physiologists have not always agreed among themselves on this subject. It is with the hope, therefore, of throwing some light from an anatomic standpoint on certain obscure conditions and relations within the lung that this summary is presented.

The investigations on which it is based necessitated special neurologic technic, particularly the intravitam methylene-blue method of staining. As human material was not available soon enough after death to make possible success with this method, dogs, cats and rabbits were employed for most of the work. Sufficient study of human material by other histologic methods was possible so that a general similarity of distribution and arrangement of nerve fibers in the human lung and the lungs of the animals employed is indicated. There are certain points of difference, but these need not enter into the present account.

The researches of Dr. W. S. Miller, extended over a period of more than thirty years, have given us a comprehensive account of the structure of the lung, including its blood-vascular supply, its lymphatic system, and the arrangement of the bronchial musculature, and also clean-cut ideas regarding the bronchial tree and air-sacs. We shall therefore attempt to follow only the nerve trunks and their branches from the point of entrance into the lung, at the hilum, to their various terminations, motor and sensory, with some attention to the intrapulmonary ganglia and the relations of the plexuses.

The anterior and posterior pulmonary plexuses send their fibers into the lungs along the main bronchi and the bases of the pulmonary arteries. Within the lung these fibers are rearranged into two main plexuses, one about the main stem bronchus, and the other about the pulmonary artery and its branches. The plexus about the bronchus may be subdivided into two portions, according to their position with respect to the cartilaginous plates which form the framework of all save the smallest bronchi and the bronchioles. The larger nerve trunks, composed in large part of myelinated fibers, form a network of longitudinal mesh outside the layer of cartilage plates—therefore between these plates and the lung parenchyma—which we may designate the extrachondrial plexus. Numerous clusters of ganglion cells are found in this plexus, usually located at the points of anastomosis of the nerve trunks which compose it. No ganglion cells are found beyond the bronchi of the third order, and only few and scattering ones are usually found distal to the secondary bronchi.

The fibers of the extrachondrial plexus are derived from the vagus. They consist of afferent fibers and preganglionic efferent fibers. The cells of the afferent fibers are located in the nodose ganglion, while the preganglionic efferent fibers have their origin from cells in the motor X nucleus of the medulla oblongata. The afferent fibers terminate as afferent receptors in different branches of the bronchial tree, as will be described below. The preganglionic efferent fibers terminate about the ganglion cells, to which reference has just been made, as pericellular synaptic networks. Axonic processes from these cells relay the impulse to the motor terminations in the smooth muscle cells of the bronchial musculature, and possibly to the mucous glands, as will be more fully described below. On the efferent side there is present, therefore, a typical preganglionic and postganglionic neurone chain.

The second of the two plexuses about the bronchi lies between the cartilage plates and the bronchial muscle bands, with some of its fibers extending to the epithelium. It will be designated as the subchondrial plexus. The plexus is also made up of two kinds of fibers, afferent and efferent. The afferent fibers are continuations of the afferent fibers which course thru the extrachondrial plexus, to terminate in the epithelium or muscle bands as receptor organs. The efferent fibers of the subchondrial plexus are the postganglionic fibers to which reference was made in the preceding paragraph, which have their origin for the most part in the ganglionic cells of the extrachondrial plexus. A relatively small number apparently have as their source cells of the posterior and anterior pulmonary plexuses. The ganglia of these plexuses differ

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from those within the lung, to all appearance, only is position. A few ganglion cells are also found in the subchondrial plexus in some forms, and these also give rise to fibers which terminate in the same manner as those above named.

The extrachondrial and subchondrial plexuses are separate as far peripherally in the course of the various orders of bronchi as cartilaginous plates are present. Beyond these points such fibers of the extrachondrial plexus as remain fuse with the subchondrial plexus, and the two continue distally as a single network. This gives off afferent and efferent fibers at various points in the smaller bronchi. These points correspond to those of the larger bronchi which are innervated by the several types of nerve fibers respectively.

Without entering into details of structure we may now consider the afferent receptors and their points of location. The first to be encountered within the bronchus proper is found in the epithelium of the bronchial wall. It is a free nerve ending, the terminal twigs of which branch out among the columnar epithelial cells of the bronchial mucosa. These endings are apparently stimulated by objects which may come into contact with the epithelial surface, such as foreign bodies and masses of mucus. Nerve terminations of somewhat different type are found at the division points of the bronchi into their primary, secondary and tertiary branches. At these points the nerve endings are less diffuse in their branching, and the entire structure has a somewhat rounded contour, altho no capsule is present. They are located in the epithelium at the apex of the crotch between dividing bronchi. Their appearance and location give one the impression that these endings receive their stimulation ordinarily from pressure of the bronchus on either side, as the lung collapses in expiration.

W. S. Miller has repeatedly called attention to the division points of the bronchi as the key points of pulmonary anatomy. In addition to other structures, here are found aggregations of lymphoid tissue, frequently in the form of small nodules. Enlargement of such nodules as a result of infection, as in tuberculosis, undoubtedly produces pressure on the neighboring nerve endings in the crotches of the bronchi. This may, in part at least, account for the sensation of deep seated pain in certain pulmonary conditions.

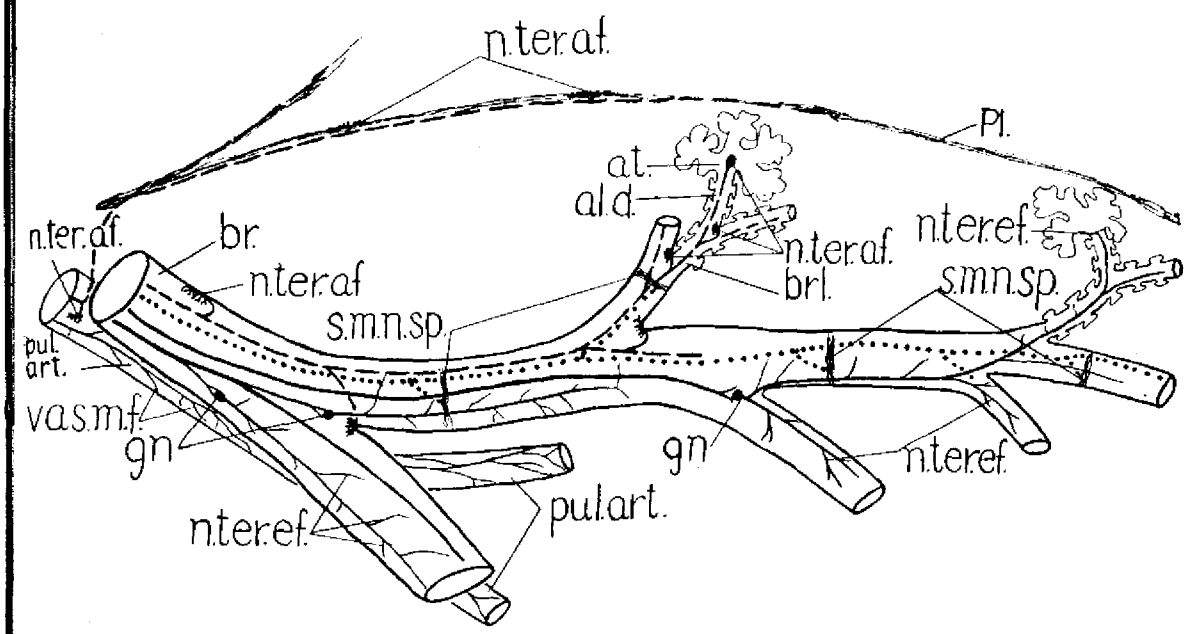
Nerve terminations at the division points of the bronchi are found as far peripherally as the points of bifurcation of the respiratory bronchioli to form the alveolar ducts. This far distally they are of very small size, and are only occasionally encountered in my preparations.

In the walls of the atria or air-spaces, into which the alveolar ducts open, and which are lined with respiratory epithelium, there is present a quite different type of nerve ending. This type is oval in outline and is flattened. It is covered by a thin capsule, part of which is formed by the squamous epithelium of the atrial wall. Beyond this point no nerve endings of any kind were observed.

The afferent receptors in the epithelium of the bronchi of the various orders would appear to be responsible, on proper stimulation, for initiating the cough reflex. Chevalier Jackson has shown clinically that stimulation of the bronchi, either by contact or by inflammatory processes, will produce coughing for a short period. If the stimulating agent is continued at one point for a number of minutes, a "tolerance" is established, but the reflex may be again elicited by stimulating another portion of the epithelium. Dr. Burget and I have obtained similar results in experimental animals, in work as yet unpublished. In these animals the point stimulated was observed with the aid of the fluoroscope.

Jackson states that "the finer subdivisions of the tracheobronchial tree, which together with the alveoli are not enterable with a bronchoscope but are enterable with a slender instrument, show decidedly less cough production from instrumental contact, and in most cases all peripheral areas show no cough reflex unless the proximity of the visceral pleura is reached and pushed on. This pleural reflex is very rarely observed, and its existence is somewhat doubtful." The statement concerning the pleural reflex is very interesting, in view of the limited distribution, anatomically, of nerve fibers and endings in the visceral pleura, as will appear below.

We may now turn our attention to quite a different type of termination, which is found in the bands of smooth muscle that make up the bronchial musculature or muscle of Reisseisen. The fibers which lead to these endings are large and myelinated. On approaching their destination they subdivide into a number of branches. Each branch reaches a separate muscle band, on which it forms a spindle-shaped termination. Some of the short terminal twigs of this ending embrace the muscle band, others penetrate between the individual smooth muscle fibers to terminate as small knobs among the latter. I have called these endings "smooth-muscle



This paper as read was illustrated by twenty-four lantern slides. The principal features of these slides are here combined in diagrammatic form. This diagram is of a portion of the bronchial tree and accompanying pulmonary artery and of a portion of the pulmonary pleura, to illustrate the distribution of the nerve plexuses and nerve terminations of various types. Adapted in part after W. S. Miller.

al.d., alveolar duct; **at.**, atrium; **br.**, bronchus; **brl.**, bronchiole; **gn.**, ganglion; **n.ter.af.** nerve termination of afferent fiber; **n.ter.ef.**, nerve termination of efferent fiber; **Pl.**, visceral pleura; **pul. art.**, pulmonary artery; **s.m.n.sp.**, smooth muscle nerve spindle; **vas.m.f.**, vasomotor fibres.

The motor fibers to the bronchial musculature, both pre- and postganglionic, are indicated as solid lines, as are also the vasomotor fibers on the pulmonary artery. The afferent fibers from nerve terminations in the epithelium of the bronchial rami are represented in broken lines, as are the fibers which lead to the nerve endings in the pleura. The fibers to the smooth muscle spindles, in the bronchial muscle bands, are indicated by dotted lines.

nerve spindles" because of their general similarity to the nerve-muscle spindles of striated muscle, and to the sensory spindles in tendon, both of which have long been known. "Smooth-muscle nerve spindles" are present in the muscle bands of all the orders of bronchi, down to bronchioles. I have not found them in the latter or in the alveolar ducts. From their position and the relation of the terminal twigs they are apparently stimulated by contraction or relaxation of the muscle bands, in much the same manner as the neuromuscular spindles of skeletal muscle.

If we examine the pulmonary pleura after vital staining with methylene-blue, we again find a nerve plexus in certain regions, and nerve endings of afferent type. The plexus is derived from the second chief plexus, to which reference was made in the early part of this paper, namely, the plexus about the pulmonary artery. Myelinated fibers from this plexus pass to the visceral pleura in the region of the hilum, reaching the interlobar pleura. They are distributed especially along the interlobar margins. None have been observed in the pleura of the lateral or the diaphragmatic surfaces of the lung, or even on the diaphragmatic margins. The main bundles break up into smaller ones, which in turn ramify as individual fibers. The fibers terminate in endings of the free-branching afferent type, in the regions noted. This is true of dogs and rabbits. In the human I have been unable to demonstrate nerve endings anywhere in the pleura, but I ascribe this to the usually embalmed autopsy material, which was unsuited to the special methods of technic necessary to bring out nerve terminations. Fresh material, when available within a few hours after death, will undoubtedly reveal pleural nerve endings in the human also.

The source of the fibers to these various receptors is of interest to physician and physiologist alike. Molhant and Möllgaard have shown that nerve cells in the nodose ganglion undergo chromatolytic changes on ablation of one or more lobes of the lung. It has also been demonstrated (Larsell and Mason) that nearly all of the nerve terminations within the rabbit's lung disappear after experimental degeneration of the vagus. This, however, does not hold true for the endings in the visceral pleura, which appear to be just as numerous in well stained preparations after vagotomy as in normal animals. Möllgaard has demonstrated in dogs and kittens that the lungs receive fibers from 1st., 2nd. and 3rd. thoracic spinal ganglia. These fibers pass thru the

white rami to the middle and inferior cervical ganglia, and thence to the lungs by way of the pulmonary plexus.

It is evident, therefore, that the vagus supplies the afferent fibers to the bronchial tree, and the visceral pleura is supplied thru the mediation of the sympathetic trunk. The possibility remains that the few nerve endings which remain within the lung after degeneration of the vagus on one side are also derived from the sympathetic trunk. It appears far more likely that they represent the terminations of fibers which have crossed over from the opposite vagus. There is considerable crossing of vagus fibers in the pulmonary plexuses, as Schiff pointed out many years ago.

The position of nerve terminations at the division points of the bronchi and at the interlobar marginal surfaces of the visceral pleura suggest interesting relations of the nervous system to respiratory regulation. These, however, we must leave to the physiologist. A complete anatomic basis for the Hering-Breuer phenomena appears to be present. The slow, deep inspiration which follows double vagotomy is conceivably arrested at its maximum thru stimulation of the nerve endings in the visceral pleura by contact of the interlobar margins. Afferent fibers from the sympathetic trunk may thus in a sense take over certain functions which normally belong to the vagus, but at a lesser degree of distention of the lung.

Turning our attention to the efferent nerve fibers which are present in the lung, we find that preganglionic fibers from the vagus terminate as pericellular synaptic networks, as already noted, about the ganglion cells in the bronchial walls. These networks disappear almost entirely after unilateral degeneration of the vagus. The few which remain without doubt are derived from the opposite vagus.

The ganglion cells send their axones, which thus constitute postganglionic fibers and which make up the greater part of the subchondrial plexus, to the muscle bands of the bronchi, where the terminal twigs end in relation to the individual smooth muscle cells in the typical manner of smooth muscle motor nerve endings. Such nerve fibers are present in all branches of the bronchial tree as far distally as the ends of the alveolar ducts, where the latter open into the atria. Miller has described at this point a sphincter-like band of muscle, but beyond this point no muscle is to be found which belongs to the bronchial tree.

The bronchial mucous secreting glands also receive excitor fibers from the subchondrial plexus. Concerning the source of the fibers to the glands whether from intrapulmonary ganglion cells o from ganglia of the sympathetic trunk, I have n clear evidence. Irrespective of their origin, the are probably of importance in accounting in part at least, for the large amount of secretion at certai stages of tuberculosis. Miller has pointed out th relation of lymphoid tissue and areas of inflamma tory processes within the lung to many of the nerv trunks, in a case of pulmonary tuberculosis. H suggests that the increased activity of the mucou glands may be due to irritation of the nerves an ganglia by the zones of inflamed tissue, thru whic some of the nerve trunks pass. The demonstratio of fibers of motor type terminating in the bronchia mucous glands merely emphasizes Miller's sugges tion. The anatomic basis is present in complet detail.

The second main plexus to which attention wa called at the beginning of this paper, namely, tha surrounding the pulmonary artery, is composed en tirely, to all appearance, of fibers from the sympa thetic trunk. No ganglia are found in this plexu Near the hilum of the lung, where the artery separated from the main bronchus by a relativel thin mass of connective tissue; ganglia are prese which might be considered as belonging to the arter A study of the distribution of their fibers, howeve shows that they are bronchial ganglia.

The periarterial plexus contains numerous myelin ated fibers, together with unmyelinated, near th base of the artery, but more distally unmyelinate fibers only are present. The myelinated fibers pas in part, to afferent terminations in the wall of th base of the pulmonary artery itself; and in large part to the interlobar pleura, where they give ri to the plexuses and terminations above described i the pleura.

The unmyelinated fibers pass to the tunica med of the pulmonary artery and its branches, there terminate as motor endings in the smooth musc cells. Such terminations are found in all branch of the artery, including the arterioles. I have al observed some evidence of a very delicate plexus nerve fibers on the pulmonary capillaries.

The question of vasomotor control within th lung has been a mooted one. It is only recent that Wiggers has summarized the evidence on th subject, which on the whole favors the view th a mechanism for such control is present, from th standpoint of the physiologist. The demonstratio of nerve fibers terminating in the smooth musc cells of the arterioles gives also an anatomic ba

for the assumption that vasomotor action is present within the lung.

The possible bearings of this fact on certain pulmonary conditions will present themselves. Also the question is raised if the relief obtained from the administration of adrenalin in certain cases of asthma may not be due in part to the constrictor action of this drug on the pulmonary arterioles, rather than altogether to its opposite action on the bronchial musculature.

The presentation of the nerve supply of the lung from an anatomic standpoint, it is hoped will give the physiologist and the physician a firm foundation, on which to build a structure of experimental and clinical observation which may add to our knowledge of the hitherto obscure role of the nervous system in the activities and disorders of the lung.

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