The pulmonary and pleural lymphatics: A challenge to the thoracic explorer

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The Founder of The American Association for Thoracic Surgery conceived of a society of surgeons particularly interested in thoracic disease who would meet together with some representatives of related medical fields to discuss various aspects of the diagnosis and therapy of those thoracic conditions in which surgical treatment might play a role. That physiologic and pathophysiologic aspects of the intrathoracic organs would require much scrutiny was evident from the beginning. Therefore, it would seem fitting to discuss before this Association, now on the threshold of its 50th anniversary, a topic which appears to encompass physiologic and pathologic facets of major but, as yet, largely unrealized importance. Much basic information already available has not as yet been incorporated into our daily thinking and clinical practice, although many clinical applications of current knowledge about the pulmonary and pleural lymphatic channels appear feasible. It is my hope that the ensuing discussion will draw more attention to this field and, since it will be obvious that many areas require clinical and laboratory investigation, that others will be stimulated to explore the current gaps in our knowledge of this vital system. Just as the remarkable recent accumulation of information about the interrelationship of vascular changes in the lungs associated with cardiac disease has greatly enhanced our knowledge of cardiorespiratory problems, so we may anticipate that the decades ahead will witness ample rewards from a greater understanding of the intrathoracic lymphatic network. The lymphatic system is a vital accessory to the
cardiovascular system in that it plays a crucial role in returning substances of high molecular weight to the vascular compartment following loss by capillary transudation. Thus it plays an essential role in maintaining an optimum blood volume and homeostasis. The lymphatics are also concerned in attaining proper interstitial fluid relationships. Therefore, it is mandatory that the lymphatic system be studied together with the cardiovascular system of the lungs if a complete understanding of blood and fluid dynamics, so vital to respiratory function, is sought.

The aspects of the pulmonary and pleural lymphatics which I shall discuss have been drawn to my attention by certain clinical experiences and a few personal experimental observations over a period of many years. A study of the literature of the lymphatic system as a whole, however, has been crucial in drawing my attention to certain fundamental concepts about the normal and abnormal behavior of lymphatics which should be applied in greater measure to the thorax. My debt to numerous workers, including some present and past members of this Association, is herewith acknowledged. Attention will be focused primarily on some basic anatomic and physiologic concepts which have broad clinical application. The uncommon cases of lymphatic pathology which will be cited are discussed because they serve to illustrate fundamental features of the lymphatic system. The role of the lymphatics in the spread of neoplasms, which has already received much attention, is not included in this discussion.

Anatomical considerations

In the classic monograph of Miller on the lung, first published several decades ago, a chapter is devoted to the pulmonary lymphatics and contains much anatomic information which is basic for our present discussion. Lymphatic channels accompany the bronchi and the pulmonary arterial system. Lymphatics also accompany the pulmonary veins in the intersegmental septa. There is a rich lymphatic network in the pleura. The degree of dilatation and stasis in these various components of the pulmonary lymphatic network will vary with different pathologic lesions. The intersegmental lymphatics accompanying the pulmonary veins are particularly distended in cases of elevated pulmonary venous pressure, as seen in mitral stenosis and some other cardiac conditions associated with an elevated left atrial pressure. The lymphatic channels accompanying the bronchi and pulmonary arteries may show marked dilatation in certain chronic pulmonary lesions and thus lead to different clinical and radiologic findings. Congenital pulmonary lymphangiectasis presents other unique features to be discussed later. Dilated pleural and diaphragmatic lymphatics are intimately associated with the problems of pleural effusion.

Transport of lymph

A consideration of lymph transport in the lungs is important. Since the intrapulmonary and pleural lymph channels do not possess a well-developed muscular wall, slight regional changes in pressure gradients combined with the presence of valves may determine the rate and direction of lymph flow. That transport in such a system could be greatly affected by fluctuations in intrathoracic pressure and the cyclic changes associated with respiration would seem obvious. But studies to determine the effect of spontaneous respiratory pressure fluctuations and also artificial respiratory assistance on lymph movement are inconclusive, unless the influence of such pressure alterations on lymph formation is also known. Otherwise it will not be proved whether a particular pattern of intrathoracic pressure changes lessens or increases the danger of pulmonary edema.

The effect of respiration on lymph flow is a topic which deserves much attention because of its tremendous, but as yet largely unappreciated, importance. It is important to bear in mind that much of the lymph drainage from the abdominal area and infradiaphragmatic portion of the human body is carried by the thoracic duct, whereas the
chief avenue of lymph drainage from the thoracic viscera, and especially the lungs, is via the right lymphatic duct. The influence of respiratory motion and intrathoracic pressure on these two networks may not be entirely identical. The thoracic duct has been shown by cinegraphic studies to possess a propulsive mechanism due to its relatively well-developed muscular wall, but a similar mechanism is not operative in the transport of lymph within the lungs. The classical studies of Drinker several decades ago clearly demonstrated that blood and lymph stasis occurred in the dependent portions of the lungs of the immobilized anesthetized animal. Similar lymph stasis is seen clinically, especially after long operative procedures, and is associated with the immobility of the bed-ridden patient. Drugs which are respiratory depressants also play a significant role.

Several basic facts must be borne in mind in evaluating the significance of an alteration in the lymphatic drainage from an organ or serous cavity. No conclusion concerning the rate of lymph formation is justified on the basis of determinations of lymph drainage alone. Obviously, if the rate of increase in lymph production is of greater magnitude than the increase in lymph drainage from the part, an organ may be becoming more edematous in spite of greater outward lymph flow. Thus one of the areas in which more data are particularly required concerns the multiple factors influencing lymph formation. Here studies with isotopes may play an important role in the future. The interpretation of experimental studies is complicated by the variations in lymph flow resulting from anesthesia, character of respiration, and the effect of exercise. Species differences also cannot be ignored.

At a time when much thought is being given to the important problem of pulmonary edema associated with prolonged cardiopulmonary bypass, it would seem most appropriate to give greater attention to the role which lymph stasis may play in this morbid state. How actually does an immobile lung in an open chest transport its lymph? Re-establishment of lymph flow is also an important problem in the autotransplantation and homotransplantation of hearts and lungs.

**Lymphatic regeneration**

An analysis of the various types of cases manifesting abnormalities of the lymphatic vessels leads to the conclusion that some patients do not possess a normal potential to regenerate lymphatics. The usual remarkable regenerative ability of the lymphatics should not be permitted to obscure the fact that some individuals are not so well endowed. A congenital and, in some instances, probably inherited defect may exist. Current information is inadequate to determine whether this defect is usually limited to the lymphatics of one or more organs or whether it is more likely to be a generalized tissue alteration. The literature contains a number of cases in which rather diffuse abnormalities of lymphatic vessels are apparent. With longer periods of observation, multiple sites of lymphatic maldevelopment have at times become manifest. The recent increase in the utilization of lymphangiography has demonstrated abnormal lymphatic channels in areas which had not been clinically suspected. In those cases of chylothorax which are not due to trauma or neoplasm, pathologic lymphatic vessels in the infradiaphragmatic region may at times be demonstrated. It appears evident that more thorough diagnostic work-up, especially with lymphangiography, will be necessary in the future in patients with thoracic lymph vessel pathology. Also, a long follow-up is necessary before final conclusions can be drawn about the ultimate effects of surgical procedures which interrupt large lymph channels, such as the thoracic duct. Here again a distinction must be made between those patients with normal lymphatic regenerative potential and those uncommon individuals with congenital lymphatic aberrations. In this latter group, full knowledge of the distribution and nature of the lymph vessel pathology is necessary before a decision is made as to the proper form of
therapy. Ligation of the thoracic duct may be indicated, and even life-saving, in certain cases of persistent chylothorax. In some other cases of chylothorax of different etiology, however, ligation of the thoracic duct may not be indicated or even contraindicated. There has been a failure to differentiate instances of chylothorax due to rupture or severance of a major lymph duct from other cases in which chylothorax is caused by diffuse transudation or seepage from engorged lymph channels. It is interesting to note in retrospect that the patient of Lampson, who was the first one reported to have had a chylothorax successfully treated by ligation of the thoracic duct, died 2 years later of a diffuse pulmonary lesion clinically similar to the lymphangiectasis of the lungs which will be discussed later.

**The pleural cavity and the lymphatic system**

Some investigators many years ago regarded the serous cavities as a physiologic component of the lymphatic system. But since certain substances, especially those of lower molecular weight, introduced into the pleural or other serous cavities can be absorbed directly into the blood stream, it is obvious that such serous spaces, although intimately related to the lymphatic system, possess unique properties.

A brief consideration of the functional advantage of the peritoneal, pleural, and pericardial serous cavities seems in order. These serous cavities permit motion of the viscera projecting into these potential spaces. The presence of a rich network of subserous vessels and lymphatics permits the transudation of fluid into the serous cavity in various pathologic states. The importance of this process has been given too little attention. One tends to regard a pleural or peritoneal effusion as a complication, often forgetting the beneficial side of this ability to drain off excess fluid from the viscera by such a mechanism. One must realize the serious or even fatal pulmonary edema which might readily ensue if there were no other route than the usual lymphatic channels to carry off excess interstitial fluid from the lungs. Hence, one should appreciate the fact that an obliterated pleural space leaves a person potentially more susceptible to acute pulmonary edema in some pathologic states. However, lymphatic channels may develop in pleural adhesions, and, in certain adhesions of long standing, considerable lymph may traverse such adhesions. This is demonstrated by the delineation of such lymphatic pathways by anthracotic particles which may be noted in the parietal pleura. Recent lymphangiographic studies have also shown such channels under special conditions. The normal pleural space contains only a few cubic centimeters of fluid but vigorous exercise with increased pulmonary and thoracic motion will result in some increase in the amount of pleural fluid, usually with an alteration in its protein content. This was demonstrated by pleural puncture in several clinical research studies on many Japanese soldiers done several decades ago.

Lymphatic flow is known to be affected by the intrapleural pressure, but knowledge concerning the varied effects of different types of ventilatory patterns awaits controlled studies. Pathologic alterations in the pleural surfaces can also have a profound effect on pleural interchange. Hence, the absorption of substances, such as chemotherapeutic agents and antibiotics, administered intrapleurally can vary greatly. Likewise, the toxic absorption from the pleural cavity in the presence of a chronic suppurative pleuritis may be much less than in a patient without previous pleural reaction. The presence of uncomplicated pneumothorax decreases the rate of pleural absorption. Dyspnea, however, with its increased lymph transport, increases the rapidity of absorption of fluids from the pleural space.

A study of the pleural cavity quickly focuses attention on the rich lymph vessel network on the diaphragm and its important role in lymphatic transport. The usual direction of lymphatic flow is cephalad, and pleural effusions secondary to the ascites of Meigs' syndrome and in some cases of cirrhosis of the liver and acute pancreatitis
are examples of this process. In these situations there is much evidence that the pleural effusion is due in part to the transudate of lymph from the distended diaphragmatic lymphatics which are attempting to remove the excess of peritoneal fluid. In cases of intrathoracic lymphatic blockage, retrograde flow from the chest to the subdiaphragmatic lymphatics may occur. This is illustrated by the occasional finding of inhaled silicotic particles in the infradiaphragmatic lymphatic tissues.

**Congenital pulmonary lymphangiectasis**

An analysis of the literature on congenital lymphangiectatic lesions of the lung, together with a consideration of the evolution of the pulmonary pathology associated with lymphatic aberrations developing in adults, suggest the following sequence of pathologic changes. An abnormal development of the lymphatics of the lung may occur in fetal or post-natal life. The lymphatic vessel abnormality may be predominantly in one organ, one organ system, or be manifest in several organs or rather diffusely throughout the body. The lymph stasis produced by the pathologic development of the lymphatics may result in other secondary tissue changes, and, since these may take a considerable time to develop, the pathologic findings of congenital lymphangiectasis will vary somewhat from those of lymph vessel abnormalities noted in adults in whom acquired processes may be superimposed on the pre-existing subclinical lymphatic aberrations.

Although the data available at present are inadequate for final conclusions, it already seems apparent that genetic factors may play a role in the etiology of this group of pathologic conditions. Hence greater attention to family histories, especially in regard to abnormalities which might involve the lymphatic or vascular systems, is desirable in the future. Also, the association of congenital lymphatic lesions with congenital ovarian abnormalities is interesting since there seems to be a predominance of females, often with a history of gynecologic pathology, among a unique group of adults with chylous reflux into the lung, chylothorax, and certain intrapulmonary lymphatic pathologic findings. Other hormonal factors as yet undetermined may well play a role.

Laurence has described the gross and microscopic findings in congenital pulmonary cystic lymphangiectasis. These lungs which are larger than normal and firm in consistency show numerous small cysts which are often confused with emphysematous blebs containing edema fluid. Histologic examination shows that the cysts are primarily situated in areas of abnormally abundant connective tissue and are often in a close relationship to blood vessels. The cysts are lined with flat endothelium with a surrounding network of elastic, collagen, and occasional smooth muscle fibers. The blood vessels may appear normal and serial sections show no connection between the air passages and the cysts. Laurence stressed the error of assuming that congenital pulmonary cystic disease is entirely an anomaly of air passages. Occasionally pulmonary lymphangiectasis is responsible for pleural effusion in the early hours of neonatal life. Chylothorax in the newborn may also be associated with congenital maldevelopment of the thoracic duct.

**Complications of lymph stasis**

That congenital hypertrophy of the lymphatics in a part of the body may result in hypertrophy of the tissues in that area is well known. That lymph stasis leads to connective tissue proliferation is also documented. That lymph stasis in the lungs may be responsible, at least in part, for marked smooth muscle hypertrophy in the lungs in association with pulmonary fibrosis seems to be shown by the occasional demonstration of such myosis developing after longstanding lymph stasis within the lung. The interaction of lymph stasis and neoplasia awaits elucidation. Carcinoma of the lung of an unusual diffuse type is occasionally found in patients with so-called idiopathic pulmonary fibrosis. Is this similar in eti-
ology to the angiosarcoma of the arm in the lymphedematous limb following therapy for mammary carcinoma? Diffuse local neoplastic involvement has also been reported in cases of chronic lymphedema of other etiology.

It is a well-established clinical fact that an extremity which is the site of lymphedema is susceptible to recurrent infections. Similar occurrences complicating lymphedema of certain internal organs have also been documented. One would therefore expect to encounter a similar sequence of events in lungs which were the seat of lymph stasis. That such situations are not recognized can be readily attributed to the similarity of the clinical features to common pulmonary infections and to the rarity with which careful microscopic studies in lung biopsies are directed to an attempt to evaluate the state of the pulmonary lymphatics. The following case illustrates the type of clinical and pathologic picture which may be encountered.

Case report

A 64-year-old rural letter carrier had noted cough for 1 year. A hemoptysis had occurred on one occasion. The interesting feature of the history was that the patient had had repeated episodes characterized by chills and fever. Wheezing and chest discomfort were absent. Slight dyspnea was noted during the acute episodes. A diagnosis of bronchostenosis was entertained and thoracic roentgenograms and bronchograms were done but repeatedly failed to demonstrate any bronchial lesion. Bronchoscopy was likewise negative. A thoracotomy revealed linear fibrotic areas on the pleural surface of the upper lobe and superior segment of the lower lobe corresponding to the course of the ribs and intercostal spaces. In these fibrotic areas the presence of anthracotic pigment was pronounced as compared to the pleural areas of normal consistency. There were no pleural adhesions. Biopsy of the abnormal areas of the lung showed considerable thickening of the pleura with focal chronic inflammatory cellular infiltration around many enlarged and dilated lymph channels. Hence the final diagnosis was recurrent pulmonary lymphangitis. The patient responded to antibiotic therapy.

Pulmonary lymphatics and dyspnea

The interrelationship between distension of the intrapulmonary lymphatics and dyspnea is evident in a variety of pathologic conditions. A graphic example of this is seen in patients with diffuse lymphangitic metastases who have no bronchial obstruction and little pulmonary infiltration to explain the pronounced respiratory symptoms. Such patients may show septal thickening in the lung fields on the roentgenograms. These septal lines which may differ from those seen in mitral stenosis have been shown to be due to dilated lymphatics with adjacent fibrosis. Marked alteration in the pulmonary compliance caused by the septal thickening accounts for the dyspnea in large part. With lymphangiectatic metastases secondary to mammary carcinoma, the dyspnea and pulmonary compliance may definitely improve with hormone therapy if the neoplasm is hormone dependent. Other examples of dyspnea associated with distension of the septal and pleural lymphatics which causes stiffening of the lung and reduced pulmonary compliance might be cited. One of these is the recently recognized tachypnea of the newborn which may clear spontaneously as the lymphatics help to remove the excess fluid from the lungs which is present at birth.1

Interrelationship of pulmonary fibrosis and lymphatic pathology

A study of the intrapulmonary lymphatics in cases of "idiopathic" pulmonary fibrosis appears overdue. Many detailed descriptions of the gross and microscopic findings in cases of pulmonary fibrosis of various, and often obscure, etiology fail to make any reference to the state of the lymphatic channels. This is reminiscent of the common disregard of the pulmonary vasculature in reports on congenital cardiac cases a few decades ago. Although it may at times be difficult to differentiate on microscopic examination between a dilated lymphatic in the lung and an abnormal alveolar space, it should be a part of a complete microscopic tissue study to report on the status of the lymphatic system in non-neoplastic pulmonary lesions just as is customary in examinations of malignant tumors. The necessary educational step is to make a determined
effort to identify the lymphatic channels when examining any section of pulmonary tissue.

Pathologic evidence of the production of pulmonary fibrosis as a result of long-standing chronic obstruction of one or more pulmonary veins is already at hand. It is interesting to note that when the pulmonary veins of only one lung are obstructed, it is only that lung which may show pulmonary fibrosis. Thus again the interrelationship of chronic stasis in the pulmonary veins and the occurrence of fibrosis is demonstrated.

Whenever chronic stasis in the pulmonary lymphatic system is being evaluated, attempts must also be made to study the valves in the lymphatic channels. In such a low pressure system as the pulmonary lymphatic network, valves may play a significant role in determining the direction of lymph flow. It is interesting to recall that Miller's monograph on the lung\textsuperscript{8} published many years ago contains tables recording the lymphatic valve count in different portions of a minutely studied lung.

**Chylous reflux into the lungs and pleura**

In discussions of chylothorax, consideration of the source of the chyle is usually limited to lesions of the thoracic duct or other large lymphatic channels within the mediastinum. The possibility that occasionally chylous fluid in the pleural cavity might be, at least in part, due to reflux of chyle into the lungs and hence into the pleural space is not discussed. That such may at times occur was first suggested to me by a case of pulmonary fibrosis in which the patient, after several years' observation, began coughing up milky fluid. Later chylous fluid appeared in one pleural cavity and, associated with this, there was a cessation of expectoration of milky fluid. Shortly after the chylothorax was treated by surgical obliteration of the pleural space on the side of the effusion, the milky fluid was again expectorated. This chylous expectoration continued for almost a year and a half when it ceased, as chyle now appeared in the opposite pleural cavity. Following a second operation to obliterate the pleural space on the second side, the patient had marked dyspnea and died 2 weeks later. Autopsy revealed casts of soft coagulated gray-white material in the bronchial tree. The lung biopsies taken at the time of operation and the lungs at autopsy showed markedly dilated lymphatics, together with chronic pulmonary fibrosis. At autopsy the lungs also showed a lobular pneumonia. No neoplasm was present. This case demonstrated that preventing the refluxed chyle from seeping from the lung into the pleural cavity may aggravate the pulmonary condition by increasing the retention of chyle within the lung.

Obviously several abnormal conditions must be present if chyle reflexes into the lungs. On the basis of the fragmentary observations to date, it would appear that obstruction to lymph drainage at the base of the neck combined with unusual communications between the thoracic and other mediastinal lymph ducts with resultant lymphangiectasis and incompetency of the lymphatic valves may permit chylous reflux into the lungs. Thrombophlebitis of the subclavian or innominate veins has been a definite forerunner of the clinically manifest pulmonary pathology in some cases.\textsuperscript{2-10} Several years may elapse between the initial lymphatic obstruction in the mediastinum or neck and the development of recognized pulmonary lymphangiectasis. Whether the lungs of such patients were originally normal cannot be stated at this time.

Although chylous reflux into the lungs is very unusual, it is evident that the expectoration of yellow sputum, so common with bronchopulmonary disease, rarely suggests to the physician that chyle may also be present. Two patients observed by me first called my attention to the fact that their expectoration was "milky." One of these patients in whom we established a diagnosis of marked pulmonary fibrosis with dilated lymphatics by lung biopsy 14 years ago continues to do well; in that case the "milky" expectoration was never large, the pulmonary function improved after removal of an ovarian cyst, and chylothorax has not occurred. The consistency of expectoration,
or the character of the material found in the tracheobronchial tree, may vary with the amount and concentration of chyle mixed with other secretions.

**Chylopericardium**

Chylopericardium may be present in association with chylothorax or rarely appear to be the only serous cavity so involved. In some of these unusual cases, the mechanism of chylous transudation into the pericardial cavity may be similar to that present in some cases of so-called idiopathic chylothorax. Ligation of the thoracic duct or abnormal lymph channels may be curative.

Obstruction to lymph drainage from the heart may be potentially dangerous, aside from the production of cardiac tamponade. Cardiac arrest during operation may occur, apparently due to altered myocardial metabolism. The recent investigations of Miller and associates on the pathologic alterations in the heart resulting from experimentally induced lymph stasis in the myocardium are of great interest in regard to etiologic factors in endocardial fibroelastosis, valve lesions, and the susceptibility to bacterial endocarditis.

**Protein-losing enteropathy secondary to chronic constrictive pericarditis**

Another clinical syndrome in which current evidence points to a diffuse lymph vessel abnormality is the combination of constrictive pericarditis and intestinal lymphangiectasis. Although it has long been recognized that hypoproteinemia may result from chronic constrictive pericarditis, it has only recently been appreciated that in some of the cases the abnormally low serum albumin is due to a large loss from dilated lymphatics in the intestinal wall. Because of the fact that the etiology of the chronic constrictive pericarditis is often obscure in these cases which occur predominantly in a young age group, and since an intestinal biopsy may indicate a lymphangiectasia of the bowel wall, one might suspect that a pathologic change in the lymphatics draining the pericardium plays a role in the etiology of the constrictive pericarditis in these unusual cases. The frequent association of lymphocytopenia with this condition also suggests impairment of lymph drainage back into the veins.

**Conclusion**

Although this presentation has included reference to a variety of rare abnormalities of the pulmonary and pleural lymphatics, these cases have been cited to stress the wide spectrum of lymph vessel abnormalities and to point to the vast importance of the thoracic lymphatic system in everyday practice. Since the function of the lungs as a respiratory organ is intimately related to the integrity of the vascular system, it follows that the lymphatic system which is crucial in maintaining interstitial fluid homeostasis, and aiding in removing abnormal fluid from the alveoli, is also vital to lung function. Although many pioneers in the investigation of the physiology and pathology of the lymphatic system have pointed the way to future knowledge, we have thus far failed to apply clinically much of this basic information. In reports on the pathologic examination of the lungs and pleura in non-neoplastic conditions often no mention is even made of the state of the lymph vessels, although lymphatic abnormalities are obvious in some of these cases to the observer who is properly oriented. Physiologic studies often ignore the effect which lymph stasis may have on respiratory function. Here is a potentially rewarding field of the future for those who can correlate basic science with clinical problems and then, as questions arise, envision the avenues for further research. When the thoracic explorers of the future, be they physiologists, pathologists, surgeons, or among those schooled in other fields of research, have conquered the problem of pulmonary edema and other fluid aberrations in the lungs, and have given the pulmonary and pleural lymphatics the attention this vital system merits, a significant reduction in the morbidity and mortality of thoracic disease will be attained.
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