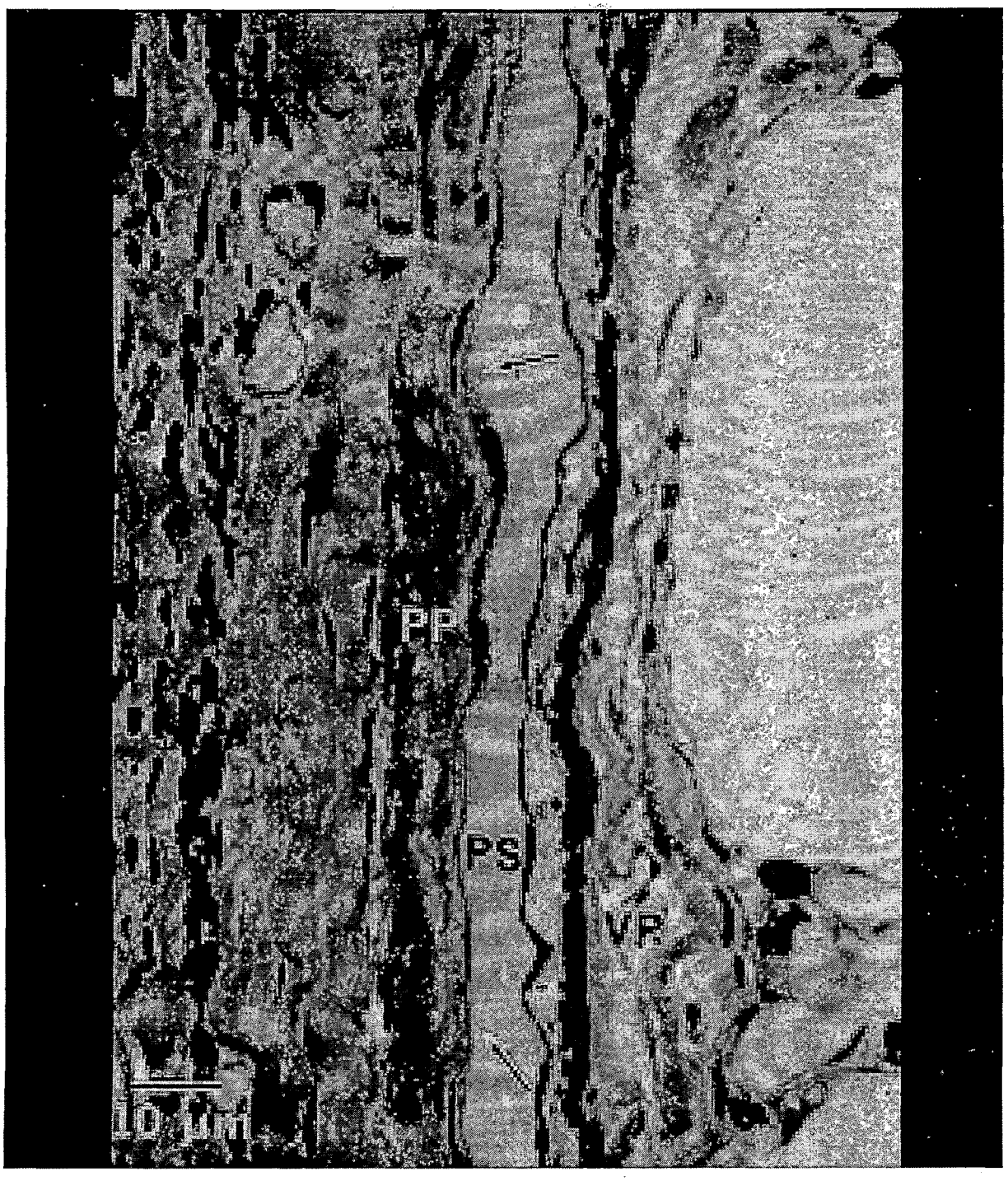
REVIEW OF LITERATURE

PLEURA – ANATOMY

Embryologically, pleural membrane develops from the mesenchyme[8]. The pleural space is a real, not potential, space that is approximately 10 to 20 μm wide and extends completely around the lung to the hilar root[4-7] (figure 1) .Below the merger of visceral and parietal pleura at the hilum, pleural reflections from the dorsal and ventral surface of the lungs usually extend to the diaphragm as a double layer of mesothelial tissue, the pulmonary ligament[8]. Both the visceral pleura, covering the lung and interlobar fissures, and the parietal pleura, covering the chest wall, diaphragm and mediastinum, have a similar area of approximately 1000 cm^2. Each membrane is covered by a single cell layer of mesothelial cells and each is nourished by a systemic circulation. They differ in one important respect: only the parietal pleura has lymphatic stomata that open directly into the pleural space. Current concepts of pleural liquid turnover have stemmed in large part from considering the anatomy of the two pleural membranes.

Parietal pleura — The parietal pleura has been proposed as the more important pleura for pleural liquid turnover in the normal physiologic state[4,10]. The reasons for this hypothesis lie in the proximity of the microvessels to the pleural space, the presence of the lymphatic stomata, and the consistent

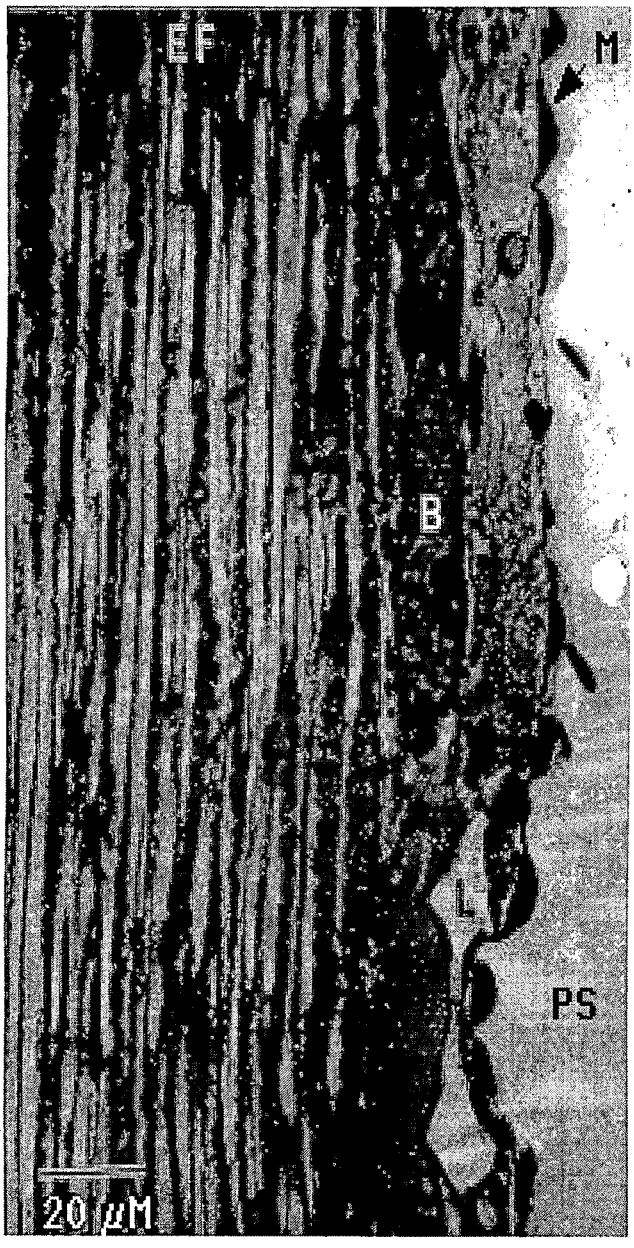


Anatomy of the pleural space
Anatomic relationships of the pleural space (PS) between the parietal and visceral pleurae (PP and VP, respectively), both of which are lined by a single layer of mesothelial cells (arrow). Courtesy of Kurt H Albertine, MD.

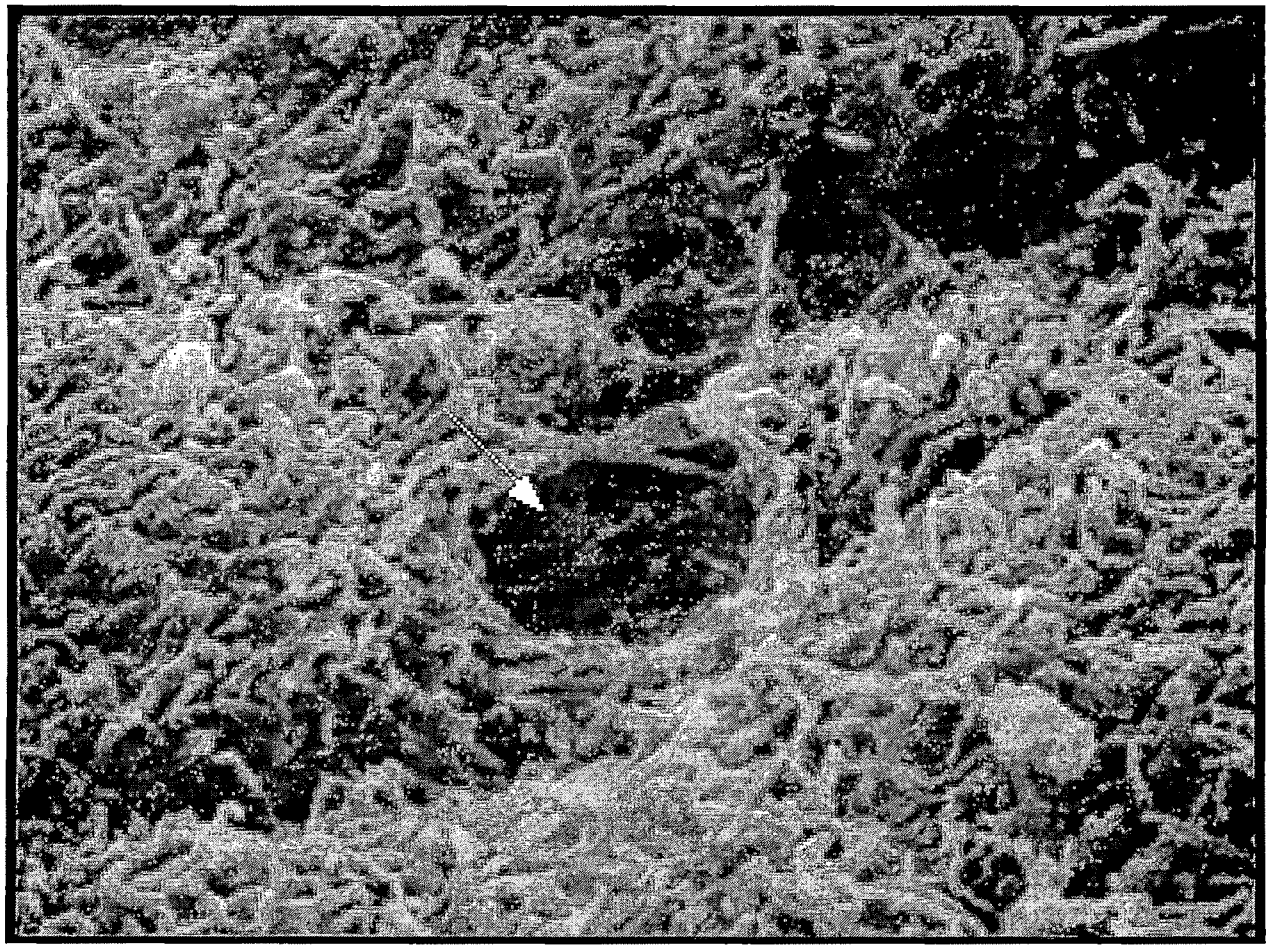
anatomy of the parietal pleura among species. The pleural membrane overlies the intercostal fascial layer and ribs. It is approximately 30 to 40 μm thick, consisting of a superficial mesothelial layer and subpleural layer[11] (figure 2). Within the subpleural layer lies loose connective tissue in which run the intercostal arteries, nerves and lymphatics. The intercostal microvessels are at a distance of about 10 to 12 μm from the pleural space.

The most interesting and unusual feature of the parietal pleura are the lymphatic stomata, holes of 2 to 10 μm in diameter that open onto the pleural space (figure 3). The stomata have been demonstrated on the parietal pleural surface with scanning electron microscopy. Each stoma is formed by a gap in the otherwise continuous mesothelial cell layer, where the mesothelial cells join with the endothelial cells of the lymphatics. Each lymphatic joins others, forming a lake or lacuna (figure 4); from the lacunae, collecting lymphatics join intercostal trunk lymphatics which travel to the parasternal and periaortic lymph nodes.

The number of stomata over the caudal pleural surfaces (chest wall and mediastinum) has been estimated at approximately $100/cm^2$[11-14]. By another estimate, one stoma is found every 500 to 1000 μm^2 in the intercostal regions,



Anatomy of the parietal pleura
The parietal pleura of the sheep, an animal with similar pleural anatomy to humans. The parietal pleura consists of a superficial single layer of mesothelial cells (M) and a subpleural layer. Within the subpleural layer lies loose and dense connective tissue of the endothoracic fascia (EF) through which run the blood microvessels (B) from the intercostal arteries) and lymphatic lacunae (L), which open into the pleural space (PS) via stomata. The intercostal microvessels are about 10 to 12 μm from the pleural space. (Staub, NC, Wiener-Kronish, JP, Albertine, KH, in: The Pleural in Health and Disease, Chretien, J, Bignon, J, Hirsch, A (Eds), Marcel Dekker, New York, 1985, by courtesy of Marcel Dekker, Inc.)



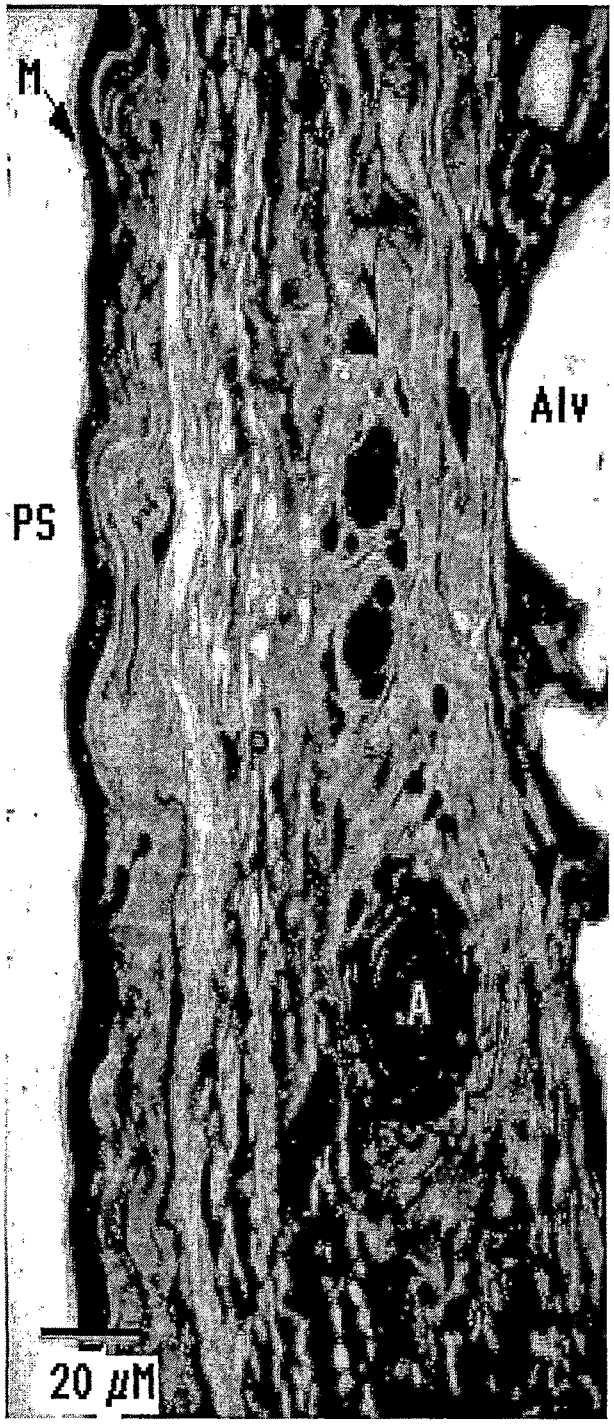
Lymphatic stomata in parietal pleura Scanning electron micrograph showing a lymphatic stoma on the surface of the parietal pleura (arrow). The stomata are holes in the otherwise continuous mesothelial layer that open onto the pleural space; they are the primary site of removal of pleural liquid from the pleural space. Courtesy of Kurt H Albertine, MD.

which would be equivalent to a density of 100,000 to 200,000/cm^2[11].

Visceral pleura — The visceral pleura invests the lungs everywhere except the hilum, where the bronchi, pulmonary vessels and nerves enter the lung substance[9]. The visceral pleura in humans is approximately 20 to 80 µm thick and consists of a mesothelial layer and subpleural connective tissue layer[6,15] (figure 5). The thickness varies considerably over the lung, being greatest in the caudal regions and least in the cephalic regions. The subpleural connective tissue layer contains both collagen and elastin as well as the bronchial artery capillaries and subpleural lymphatics (which do not connect to the pleural space). The alveoli and the pulmonary circulation lie beneath the membrane. Both the bronchial microvessels and lymphatics are at a greater distance from the pleural space (20 to 50 µm versus 10 to 12 µm in the parietal pleura).

The bronchial microvessels drain into the pulmonary veins, a feature that may have two consequences on pleural liquid formation:

1. Because of the normally low pulmonary venous pressure, the bronchial arterial driving pressure is probably lower than in other systemic microvessels which have a systemic drainage. This may mean that, in the normal



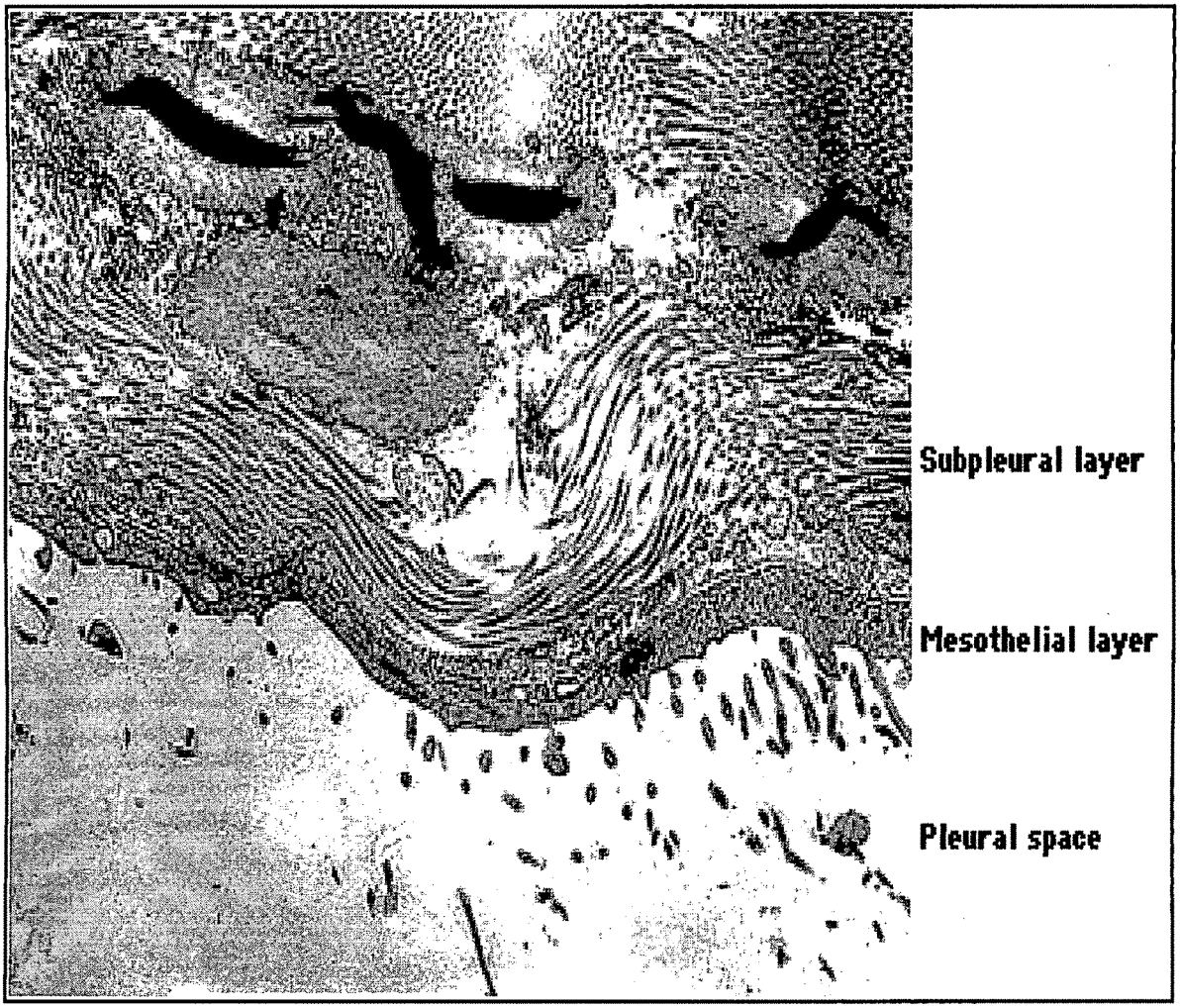
Anatomy of the visceral pleura The visceral pleura (VP) of the sheep, an animal with similar pleural anatomy to humans. The visceral pleura lies between the pleural space (PS) and the alveoli (Alv). It is approximately 20 to 80 μm thick and consists of a single mesothelial layer (M) and a subpleural connective tissue layer. The subpleural connective tissue layer contains both collagen and elastin as well as the bronchial arteries (A, which drain into pulmonary veins) and subpleural lymphatics (which do not connect to the pleural space). The bronchial microvessels and lymphatics are relatively far from the pleural space (20 to 50 μm versus 10 to 12 μm in the parietal pleura). (Staub, NC, Wiener-Kronish, JP, Albertine, KH, in: The Pleural in Health and Disease, Chretien, J, Bignon, J, Hirsch, A (Eds), Marcel Dekker, New York, 1985, by courtesy of Marcel Dekker, Inc.)

situation, less liquid flows from the visceral pleura than from the parietal pleura.

2. When the pulmonary vascular pressures rise, the bronchial arterial driving pressure and visceral pleural liquid flow could be increased.

Interestingly, visceral pleural anatomy differs dramatically among species of mammals. In small mammals (mice, rabbits, dogs), the visceral pleura is quite thin (5 to 10 μm), with almost no subpleural layer. One likely possibility for the major difference in anatomy is structural; in large mammals, the thick visceral pleura may offer necessary support for the lung tissues. The visceral pleural connective tissue may withstand and dissipate stresses in the lung, minimize overexpansion of weaker portions of lung (thereby reducing the risk of pneumothorax), and smooth out the relative expansion of different areas of lung and the distribution of ventilation. In small mammals with a thin visceral pleura, there is no pleural bronchial circulation, and the pleura is supplied only by the underlying pulmonary circulation.

Pleural mesothelial cell — The continuous lining cell of both pleurae is the mesothelial cell[6] (figure 6). Not unique to the pleural space, the mesothelial cell lines the other two coelomic spaces in the body, the pericardial and peritoneal



Pleural mesothelial cell layer Both pleurae are lined by a continuous mesothelial cell layer. The mesothelial cell is a flat cell one to 4 μm thick with a variable covering of microvilli (up to 3 μm long). Courtesy of V Courtney Broaddus, MD.

spaces also. There are no differences yet described among mesothelial cells from these three locations or between the parietal and visceral locations. The mesothelial cell is a flat cell (1 to 4 μm thick) with a variable covering of microvilli (up to 3 μm long). Microvilli, enmeshed in a matrix of glycoproteins, serves as a lubricant and as a device to increase pleural surface area available for fluid transport[8]. The shape and area of the (visceral) cell change with lung inflation, with a range of diameters of 27 μm at a transpulmonary pressure of 1.5 cm H_2O to 39 μm at 12 cm H_2O in isolated rabbit lungs[16].

Similar to that of the other two lining cell types, ie, the endothelial and epithelial cells, the mesothelial cell has been found to have many functions.

1. It produces a wide array of extracellular matrix molecules and may participate in the production of the submesothelial connective tissue[17]. For this, it migrates to post-injury denuded areas and secretes growth factors which lead to increase secretion of collagen and elastin for rebuilding. In addition, mesothelial cell matrix metalloprotienases contribute to the remodeling of connective tissue matrix.

2. It regulates local blood flow by producing thromboxane and prostacyclin[13].

3. The mesothelial cell is phagocytic[18].

4. It may function as an inflammatory cell, directing movement of other inflammatory cells into the pleural space by releasing cytokines and expressing adhesion molecules[19-20]. The mesothelial cell may also recruit fibroblasts[21].

5. Mesothelial cells may contribute to the balance between procoagulant and fibrinolytic activities in the pleural space[23].

Compared to all these known or potential functions, however, the mesothelial cell has no documented active role in entry or exit of fluid from the pleural space. There is no evidence for active transport by the mesothelial cell. Furthermore, the mesothelial surface is leaky to protein and liquid, as, for example, is necessary for successful dialysis in the peritoneal space. A leaky membrane implies a passive role for the mesothelium in the movement of liquid and protein.

Nerve supply of pleura[8]

Pain fibres are present in the connective tissue layer of parietal pleura but not the visceral pleura. These fibres have different origins, depending on the part of the thorax that they innervate: the costal pleura and peripheral rim of the diaphragmatic pleura are innervated by the intercostals nerves; painful stimuli in these regions are sensed in the adjacent chest wall. The central part of the diaphragm is innervated by the phrenic nerve; stimuli in these areas elicit pain in the ipsilateral shoulder.

FUNCTIONS OF THE PLEURAL SPACE[8]

1. Important role in mechanism of breathing. The negative pressure generated in this space due to expansion of the thorax during inspiration helps expand the lung. Conversely, the intrapleural positive pressure generated during expiration helps passive decrease in lung volume and exhaling of air.
2. Smoothing the movements of the lungs in the thorax during breathing.
3. Coupling the lungs to the chest wall.

PLEURA - PHYSIOLOGY

Pleural fluid is formed from the systemic vessels of the pleural membranes at an approximate rate of 0.6 mL/h and is absorbed at a similar rate by the pleural lymphatic system. Normally, the pleural spaces contain approximately 0.1-0.2 ml/kg of a low protein liquid. Disturbances in either formation or absorption result in the accumulation of excess pleural fluid.

Normal pleural liquid — The volume of pleural liquid is small, approximately 0.1 to 0.2 mL/kg in different species. One study in normal humans found a mean pleural fluid volume of 8.4 mL per hemithorax[24]. The WBC count was approximately 1700 per mm3 with a median differential of approximately 75 percent macrophages and 23 percent lymphocytes. The protein concentration of the liquid is low, approximately 15 percent of the plasma protein concentration.

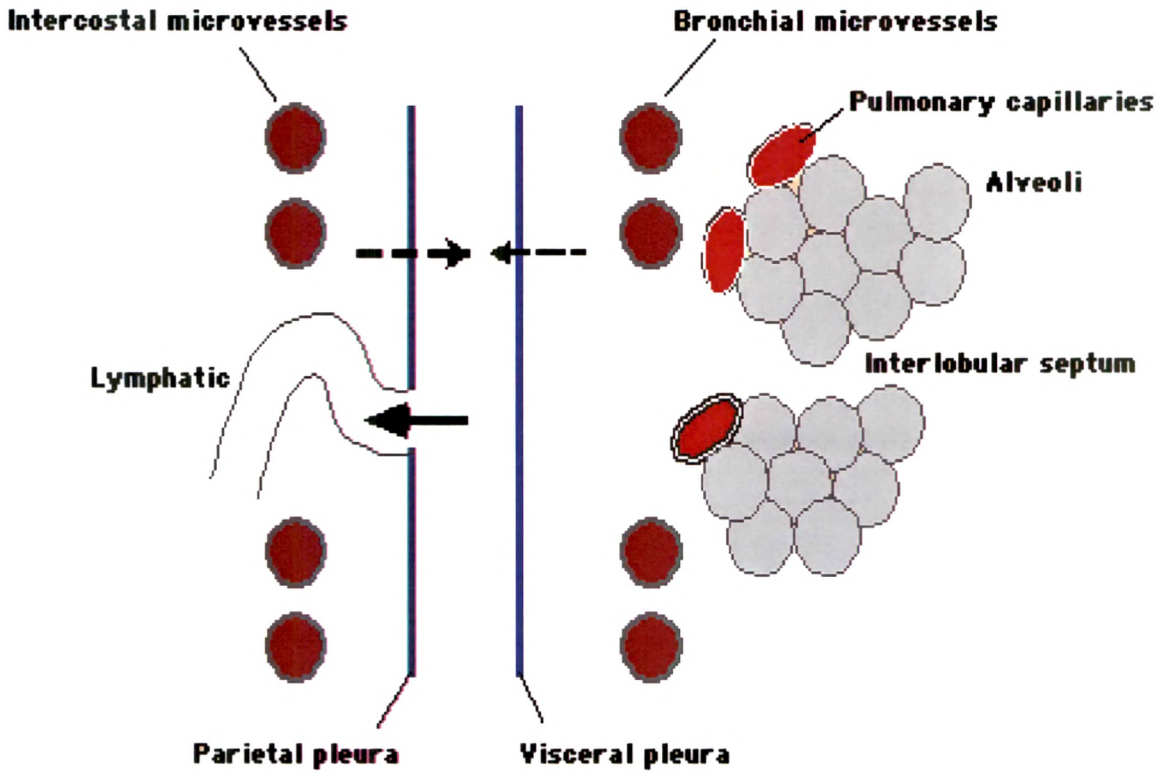
Rate of formation — In noninvasive studies using equilibration of radiolabeled albumin from the plasma to the pleural liquid, pleural liquid forms at 0.01 mL/kg per h, or the equivalent of 0.6 mL/h in a 60-kg person. This

constitutes a turnover rate of 11 percent of the pleural liquid volume per hour.

Origin of pleural liquid — The current consensus of pleural liquid formation is that the liquid originates from the systemic vessels of the pleural membranes, not from the pulmonary vessels[10]. In other words, pleural liquid is interstitial fluid of the systemic pleural microvessels (figure 7). There are three major considerations in support of this hypothesis:

1. The systemic vessels are adjacent to the pleura, and are much closer than the pulmonary vessels.

2. The low pleural liquid protein concentration (1 g/dL) and ratio to the plasma protein concentration (0.15) are consistent with a filtrate from high-pressure systemic vessels. If liquid and protein are filtered at high pressure and high flow across a semipermeable membrane, large particles will be sieved and held back. Thus, plasma proteins, being large, will be retarded much more than the liquid in their movement across a membrane, and the protein concentration of the resultant filtrate will be low. On the other hand, if liquid and protein are filtered at low pressure and low flow, proteins are retarded less, and the resultant protein concentration of the filtrate is higher.



Pathways of pleural liquid turnover Schematic representation of the pathways of normal pleural liquid turnover. Pleural liquid appears to originate fro the systemic vessels of both the parietal and visceral pleural membranes (dashed arrows). The parietal vessels (intercostal microvessels) are thought to be of primary importance because they are closer to the pleural space and have a higher filtration pressure than the bronchial microvessels of the visceral pleura. Pleural liquid is initially partially reabsorbed by the microvessels; the remaining fluid exits the pleural space via the lymphatic stomata in the parietal pleura (solid arrow).

Filtrates from low pressure pulmonary vessels, eg, lung lymph, have a high protein concentration (4.5 g/dL) and ratio (0.7) compared to filtrates from systemic vessels and to pleural liquid.

Of note in this argument, pleural liquid formation is described as high flow whereas its measured rate is relatively slow (0.01 mL/kg per h). However, it is the filtration at the systemic microvessels that is described as high, or at least higher than filtration across pulmonary microvessels. Some of that filtrate is reabsorbed into the low pressure postcapillary venules, and some is removed by bulk flow via the local lymphatic vessels. It is only the remainder that moves into the low pressure pleural space.

3. In situations where systemic pressure varies, the pleural liquid protein concentration varies in concert. During development from the fetus to the adult, the systemic pressure generally rises and pulmonary pressure falls. In a study in sheep, the pleural protein ratio decreased with development, as would be expected if the pleural liquid originated from the high-pressure systemic vessels[27].

Of the two pleural membranes, the parietal is thought to be more important than the visceral for normal pleural liquid formation. The arguments in favor of this view are as follows:

1. The parietal pleural microvessels are closer to the pleural space (10 to 12 μm) than are those of the visceral pleura (20 to 50 μm).

2. The parietal pleural microvessels probably have a higher filtration pressure than do the visceral bronchial microvessels, which are known to empty into the low pressure pulmonary veins.

3. The parietal membrane has a consistent anatomy and thickness over its extent in the body and among different species; the visceral membrane varies greatly.

The formation of pleural liquid is dependent upon a balance of hydrostatic pressures (microvascular minus pleural) opposed by the counterbalancing osmotic pressures (microvascular minus pleural). These pressures can be quantified by application of Starling's equation.

For the pleura, *Starling's Equation*[22] can be written as follows:

$$F = k[(P_{cap} - P_{pl}) - \sigma(\pi_{cap} - \pi_{pl})]$$

where

F = the rate of fluid movement

P = the hydrostatic pressure (25 mmHg in cap of parietal pleura; -3 mmHg
Intrapleural)

π = the oncotic pressure

k = the filteration coefficient

σ = osmotic reflection coefficient for protein (about 0.9)

cap = capillary

pl = the pleural space

Osmotic force = $\sigma(\pi_{cap} - \pi_{pl}) = 0.9(28-5) = 21$ mmHg

In visceral capillaries, even though oncotic pressures are the same, the hydrostatic pressures are lower (about 10 mmHg) thereby reversing the pressure gradient and favouring absorption on fluid.

Alterations of the balance that could increase pleural liquid formation include: an elevation of systemic microvascular pressure (eg, from systemic venous hypertension), a decrease in pleural pressure (eg, in atelectasis), or a decrease in systemic protein

concentration (eg, with hypoproteinemia). (The fourth possibility, an increase in pleural liquid protein concentration, is not relevant clinically.) The alteration in balance would presumably be transient and followed by a new balance at a different combination of hydrostatic and countering osmotic pressures.

PLEURAL LIQUID ABSORPTION — Because the normal situation is at steady-state, the absorption rate of pleural liquid should equal the formation rate. If excess liquid is introduced into the pleural space, however, the rate of absorption increases several fold, from the baseline rate of 0.01 to 0.02 mL/kg per h to 0.22 to 0.28 mL/kg per h [28-29].

The route of exit of the pleural liquid has been debated, in part because of the difficulty studying the pleural space. Various proposals have included reabsorption by the mesothelial cells themselves, and passive flow of pleural liquid into the "low" pressure interstitial tissues of the lung. According to one theory, both sodium and chloride are actively transported out of the pleural fluid via a Na^+/H^+ and Cl^-/HCO_3^- double exchange on serosal surface and a Na+/K+ pump on the interstitial side of the mesothelium[25]. This leads to solute-coupled fluid absorption.

Nonetheless, current evidence supports the conclusion that the liquid exits the pleural space via the lymphatic stomata

of the parietal pleura. This conclusion is based upon knowledge of the physical forces operating at the pleural tissue and the evidence for bulk flow as opposed to diffusion.

Physical forces — Our current understanding of the physical forces operating at the pleural spaces do not support an important role for active transport or uptake by capillaries in the absorption of pleural liquid.

1 The intrapleural pressure is lower than the interstitial pressure of either of the pleural tissues. With this pressure difference, a gradient of pressure directs liquid movement into but not out of the pleural space.

2 The pleural membranes are leaky, offering little resistance to the movement of liquid and protein[30], as has been shown for peritoneal mesothelium. Such a condition favors the passive movement of liquid, proteins, and other molecules. This is the underlying characteristic necessary for successful dialysis across the peritoneal membranes.

3 Mesothelial cells have not been shown to generate an electric potential difference, as would be expected if mesothelial cells moved ions by active transport. Although pleural liquid has been reported to be alkaline with a higher

bicarbonate concentration than plasma, there is no evidence yet for mesothelial participation in generating a bicarbonate gradient. Furthermore, it is difficult to explain how the mesothelium could maintain a transport gradient since it is a leaky membrane.

Evidence for bulk flow — The majority of liquid appears to exit the pleural space by bulk flow, not by diffusion. At least four findings underlie this assertion.

1 Pleural liquid protein concentration does not change as a hydrothorax is absorbed[28]. With bulk flow, liquid and protein are removed together, and the protein concentration of the liquid remaining in the pleural space does not change. With diffusion, however, proteins would diffuse at a slower rate than the liquid, resulting in a progressive increase in protein concentration.

2 The absorption rates of pleural liquid are constant despite differences in protein concentration[29]. If diffusion were predominant, the presence of protein would slow the removal of the pleural liquid because the higher protein osmotic pressure would reduce the pressure gradient for flow out of the pleural space.

3 Absorption rates are constant despite changes in pleural liquid volume, at least once the liquid volume rises above some threshold[29]. If diffusion were the predominant mechanism of absorption, the absorption rate should change with volume, as the pleural liquid pressure gradient changed.

4 Erythrocytes are absorbed intact from the pleural space and at nearly the same rate as the liquid and protein. This relatively free exit of erythrocytes from the pleural space indicates that the major route of exit is via holes large enough to accommodate erythrocytes (6 to 8 μm for the sheep erythrocytes used in the study). The only possible route then is via the parietal pleural stomata (2 to 10 μm) and the lymphatics.

Lymphatic flow is influenced both by intrinsic contractility of the lymph vessels and by extrinsic respiratory movements. Intrinsic contractility could potentially be altered by hormones, cytokines, or adrenergic stimulation. Respiratory movements may assist lymphatic flow by applying an alternating pressure on the subpleural lymphatics or by expanding and contracting the openings of the lymphatic stomata. Respiratory movements also promote a continuous intrapleural circulation of pleural liquid, which may favor delivery of pleural liquid to the stomata[29-30].

TRANSUDATIVE PLEURAL EFFUSION

Pleural fluid formed through a normal capillary membrane is a transudate. Transudates occur when normal relationships between capillary hydrostatic pressure and colloid osmotic pressure are upset.

Causes –

Increased hydrostatic pressure

Congestive cardiac failure
Constrictive pericarditis
Pericardial effusion
Constrictive cardiomyopathy
Massive pulmonary embolism

Decreased capillary oncotic pressure

Cirrhosis
Nephrotic syndrome
Malnutrition
Protein-losing enteritis
Small bowel disease

Transmission from peritoneum

Any cause of ascitis

Peritoneal dialysis

Liver transplantation

Increased capillary permeability

Small pulmonary emboli

Myxedema

Obstructed lung lymphatics

Lung transplantation

Congestive cardiac failure – This is the most common cause of a transudative pleural effusion. The presence of effusion in CCF is best correlated with the development of pulmonary venous hypertension[31]. It may be bilateral in severe failure, cardiac failure being the most frequent cause of bilateral pleural effusions. Bilateral effusions are rarely due to cardiac failure if the cardiac size is not increased (constrictive pericarditis being an exception)[32]

Massive pulmonary embolism – Embolism leads to transudate in only one-third of cases, the rest being

exudates. The fluid may contain a high proportion of eosinophils.

Hypoalbuminemia – Hypoalbuminemia in Nephrotic Syndrome and Cirrhosis of liver leads to development of pleural effusion. However, the massive hydrothorax that sometimes complicates the ascites of hepatic cirrhosis presumably occurs by passage of ascitic fluid into the pleural space either through defects in the diaphragm or via lymphatics; usually the hydrothorax associated with ascites is on the right side.

Hydronephrosis – Urine dissects cephalad and enters pleural space (as above). Although classified as a transudate because of its low protein content, the effusion has a high creatinine level and is actually a urothorax.

Meig's syndrome – hydrothorax is associated with ascitis and benign ovarian tumor; usually on the right. The classic effusion in Meig's syndrome is transudate, but the effusions associated with some ovarian tumors may be exudates.

Peritoneal Dialysis – Pleural effusion associated with peritoneal dialysis has the chemical composition of the dialysate used[33].

Myxedema – Myxedema may cause pleural effusion, either as a consequence of ascitis or pericardial effusion or, very rarely, as a direct effect on pleural capillary permeability[34].

Ex vacuo effusion – Pleural adhesions sometimes prevent the reexpansion of the lung after pneumothorax. The continuous absorption of the intrapleural gas then produces markedly subatmospheric pleural pressures that favour the formation and accumulation of a transudate.

Causes of Transudative Pleural Effusions

Effusion always transudative	Comment
Congestive heart failure	Acute diuresis can result in pseudoexudate
Hepatic hydrothorax	Rare without clinical ascites
Nephrotic syndrome	Usually subpulmonic and bilateral
Peritoneal dialysis	Acute massive effusion develops within 48 hours of initiating dialysis
Hypoalbuminemia	Edema fluid rarely isolated to pleural space
Urinothorax	Caused by ipsilateral obstructive uropathy
Atelectasis	Caused by increased intrapleural negative pressure
Constrictive pericarditis	Bilateral effusions; may be exudative
Trapped lung	A result of remote or chronic inflammation; may be exudative
Superior vena caval obstruction	May be due to acute systemic venous hypertension or acute blockage of thoracic lymph flow

"Classic" exudates that can be transudates	Comment
Malignancy	Due to early lymphatic obstruction, obstructive atelectasis, or concomitant disease (CHF)
Pulmonary embolism	23 percent incidence; due to atelectasis
Sarcoidosis	Stage II and III disease
Hypothyroid pleural effusion	From hypothyroid heart disease or hypothyroidism per se

EXUDATIVE PLEURAL EFFUSIONS

Causes –

Infections

Pneumonia, abscess

Tuberculosis

AIDS

Hantavirus syndromes

Fungal and actinomycotic disease

Subphrenic abscess

Hepatic amoebiasis

Neoplasms

Mesothelioma, very rarely pleural sarcoma

Metastases

Lymphoma

Immune disorders

Post-myocardial infarct / cardiotomy syndrome

Rheumatoid disease

Systemic lupus erythematosus

Wegener's granulomatosis

Rheumatic fever

Abdominal diseases

Pancreatitis

Uremia

Other causes of peritoneal exudates

Pulmonary embolism and infarction

Other causes

Sarcoidosis

Drug reactions

Radiation therapy

Asbestosis exposure

Recurrent polyserositis

Oesophageal rupture

Yellow nails syndrome

Bacterial pneumonia – Associated with pleural effusion in 40 % of cases. It is initially sterile, amber-coloured with predominantly polymorphs. However, it may frequently be invaded by causative organisms, leading to empyema or eventual healing by fibrosis. For this reason, aspiration to

dryness (or as near as possible) is necessary at the time of presentation.

Tuberculosis – pleural effusion may occur as a complication of tuberculosis in four situations. In all cases, the disease is due to actual infection of the pleura by tubercle bacilli, though tuberculin hypersensitivity probably plays a part in potentiating the reaction.

1. Effusion occurring as a part of primary tuberculosis in children, when a peripheral focus or a caseating lymph node ruptures into the pleura, usually occurring 3-6 months after infection. Nowadays, this syndrome is seen more frequently in middle-aged and elderly subjects who may have lost their tuberculin sensitivity.

2. Effusion may present in adolescents and young adults (less common after the introduction of BCG). Upto two-thirds of these patients develop active pulmonary tuberculosis within the ensuing 5 years[35-36].

3. This type of effusion occurs when a tuberculous cavity ruptures into the pleura. Complications like bronchopleural fistula and chronic fibrothorax with extensive calcification are common.

4. Effusion as a manifestation of disseminated tuberculosis in patients with AIDS. These patients re very ill and deteriorate very rapidly. The effusion may contain large numbers of bacilli.

Effusion in tuberculosis usually occupies one-third to half of the hemithorax. The fluid is usually serous with more than 5 g/dl protein and predominant lymphocytosis. The tuberculin test is almost always positive except in very early cases when the circulating lymphocytes suppress the activity of tuberculin-sensitized T lymphocytes. Culture of fluid is often negative; however, pleural biopsies show granulomas in about two-thirds of the patients.

Fungal infections – Effusions in these cases are mainly seen in immunosuppressed patients. They mimic tuberculosis clinically, radiographically and in the features of pleural fluid. Effusions have been noted in infections like blastomycosis, coccidioidomycosis and rarely in histoplasmosis and cryptococcosis.

Subphrenic infection – Usually due to a perforated abdominal viscus, it may spread up through the

diaphragm. It initially contains polymorphs but no organisms but can progress to empyema if untreated. Usual organisms isolated are coliforms, streptococci and clostridia.

Hepatic amoebiasis – effusion usually seen on the right side. Hepatic abscess may rupture into the pleura occasionally leading to a hepatobronchial fistula and leading to 'anchovy sauce' sputum.

Neoplasms – A primary pleural tumour is almost always a mesothelioma. Metastesis occurs commonly from bronchial, breast, stomach and ovarian carcinoma[37]. Lymphoma may cause effusion without necessarily causing pleural infilteration. Malignant pleural effusions are usually, though not always, blood-stained and recur after aspiration.

Rheumatoid arthritis – RA is accompanied by pleural effusion in 15% of makes but only 2% of females. Typically, the effusion occurs within about 5 years of the start of the disease. The fluid is straw-coloured, has a low pH and glucose and a high lactate dehydrogenase. Rheumatoid factor and immune complexes may be found

often as a higher titre than in blood[38-39]. Biopsy shows typical rheumatoid histology while thoracoscopy shows a typical granular appearance of parietal pleura due to palisaded epithelial cells and occasional giant cells.

Systemic lupus erythematosus – Effusion is more common in women than men[40-42]. The usual presentation is small bilateral effusions seen in about 40% of cases at some stage of the disease. Lupus cells may be demonstrated in fluid. High titre of antinuclear antibodies is diagnostic[43]. Antibodies may be absent if the effusion is due to some complication related to lupus like uremia or pneumonia. Fluid tends to have a normal glucose and low LDH concentration.

Post-myocardial infarct / cardiotomy syndrome – Malaise, fever and pleural and pericardial pain usually coming on about 3 weeks after the cardiac injury. The fluid is usually bloody with high glucose and pH, difficulty arises to differentiate it from effusion resulting in pulmonary infarct. Responds well to corticosteroids.

Pancreatitis – Acute and chronic pancreatitis can lead to pleural effusion due to transmission of inflammation

through the diaphragm. High amylase levels in the fluid, often higher then serum levels, help in the diagnosis.

Sarcoidosis – effusions are usually small and contain predominantly lymphocytes. Biopsy may show granulomas that can lead to confusion with tuberculosis. Usually tuberculin test is negative and Kveim test or biopsy of the other tissues confirms the diagnosis.

Drugs – Methysergide, practolol, eosinophilic reactions induced by nitrofurantoin, sulphonamides, salicylates, β-blockers and para-aminosalicylic acid.

Oesophageal rupture – Oesophageal rupture leads to mediastinitis with infection of the pleura and effusion containing a high level of salivary amylase, epithelial cells and often food particles[44-46]. It is important to recognize this condition early, as it is usually fatal if surgical repair and mediastinal drainage are not instituted promptly.

Causes of Exudative Pleural Effusions

Infectious
- Bacterial pneumonia
- Tuberculous pleurisy
- Parasites
- Fungal disease
- Atypical pneumonias (viral, mycoplasma)
- Nocardia, Actinomyces
- Subphrenic abscess
- Hepatic abscess
- Splenic abscess
- Hepatitis
- Spontaneous esophageal rupture

Iatrogenic
- Drug-induced
- Esophageal perforation
- Esophageal sclerotherapy
- Central venous catheter misplacement/migration
- Enteral feeding tube in pleural space

Malignancy
- Carcinoma
- Lymphoma
- Mesothelioma
- Leukemia
- Chylothorax
- Paraproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia)

Other inflammatory disorders
- Pancreatitis (acute, chronic)
- Benign asbestos pleural effusion
- Pulmonary embolism
- Radiation therapy
- Uremic pleurisy
- Sarcoidosis
- Postcardiac injury syndrome
- Hemothorax
- Acute respiratory distress syndrome (ARDS)

Increased negative intrapleural pressure
- Atelectasis
- Trapped lung
- Cholesterol effusion

Connective tissue disease
- Lupus pleuritis
- Rheumatoid pleurisy
- Mixed connective tissue disease
- Churg-Strauss syndrome
- Wegener's granulomatosis
- Familial Mediterranean Fever

Endocrine dysfunction
- Hypothyroidism
- Ovarian hyperstimulation syndrome

Lymphatic abnormalities
- Malignancy
- Chylothorax
- Yellow nail syndrome
- Lymphangiomyomatosis
- Lymphangiectasia

Movement of fluid from abdomen to pleural space
- Pancreatitis
- Pancreatic pseudocyst
- Meigs' syndrome
- Carcinoma
- Chylous ascites
- Subphrenic abscess
- Hepatic abscess (bacterial, amebic)
- Splenic abscess, infarction

DIAGNOSTIC EVALUATION OF PLEURAL EFFUSION

Determining the cause of a pleural effusion is greatly facilitated by the ability to analyze the pleural fluid. Thoracentesis, a simple bedside procedure, permits fluid to be rapidly sampled, visualized, examined microscopically, and quantified. A systematic approach to analysis of the fluid in conjunction with the clinical presentation should allow the clinician to diagnose the cause of an effusion in about 75 percent of patients at the first encounter[47]. A definitive diagnosis, provided by the finding of malignant cells or specific organisms in the pleural fluid, can be established in approximately 25 percent of patients. However, a presumptive diagnosis, based on the pre-thoracentesis clinical impression, can be substantiated by pleural fluid analysis in an additional 50 percent of patients. Even with a nondiagnostic thoracentesis, pleural fluid analysis can be useful in excluding other possible causes, such as infection. Thus, clinical decision-making information can be gained from pleural fluid analysis in over 90 percent of patients[47].

INDICATIONS — The indication for diagnostic thoracentesis is the new finding of a pleural effusion. Observation, in lieu of diagnostic thoracentesis, may be warranted in uncomplicated congestive heart failure and

viral pleurisy. In the former setting, the clinical diagnosis is usually secure; in the latter, there is typically a small amount of fluid. However, if the clinical situation is atypical or does not progress as anticipated, thoracentesis should be performed[48].

Definitive diagnoses — Only a select number of diagnoses can be established definitively by thoracentesis[49]. (figure 8)

OBSERVATION OF THE ASPIRATE — Initial diagnostic clues can be obtained by gross inspection of pleural fluid as it is being aspirated from the patient's chest[49]. Observations that are helpful for diagnosis are listed (figure 9).

SEPARATION OF TRANSUDATES AND EXUDATES — The pleural fluid is next characterized as either a transudate or an exudate.

Transudates — Transudates are largely due to imbalances in hydrostatic and oncotic pressures in the chest. However, they can also result from movement of fluid from the peritoneal or retroperitoneal spaces, or from iatrogenic causes, such as crystalloid infusion into a central venous catheter that has migrated[48]. Nevertheless, transudates have a limited number of diagnostic possibilities that can usually be discerned from the patient's clinical presentation (figure 10).

Diagnoses Established "Definitively" by Pleural Fluid Analysis

Disease	Diagnostic pleural fluid tests
Empyema	Observation (pus, putrid odor); culture
Malignancy	Positive cytology
Lupus pleuritis	LE cells present; pleural fluid serum ANA >1.0
Tuberculous pleurisy	Positive AFB stain, culture
Esophageal rupture	High salivary amylase, pleural fluid acidosis (often as low as 6.00)
Fungal pleurisy	Positive KOH stain, culture
Chylothorax	Triglycerides (>110 mg/dL); lipoprotein electrophoresis (chylomicrons)
Hemothorax	Hematocrit (pleural fluid/blood >0.5)
Urinothorax	Creatinine (pleural fluid/serum >1.0)
Peritoneal dialysis	Protein (<1g/dL); glucose (300 to 400 mg/dL)
Extravascular migration of central venous catheter	Observation (milky if lipids are infused); pleural fluid/serum glucose >1.0
Rheumatoid pleurisy	Characteristic cytology

Observations of Pleural Fluid Helpful in Diagnosis

Color of fluid	Suggested diagnosis
Pale yellow (straw)	Transudate, some exudates
Red (bloody)	Malignancy, benign asbestos pleural effusion, postcardiac injury syndrome, or pulmonary infarction in absence of trauma
White (milky)	Chylothorax or cholesterol effusion
Brown	Long-standing bloody effusion; rupture of amebic liver abscess
Black	Aspergillus
Yellow-green	Rheumatoid pleurisy
Dark green	Biliothorax
Color of:	
Enteral tube feeding	Feeding tube has entered pleural space
Central venous catheter infusate	Extravascular catheter migration

Character of fluid	Suggested diagnosis
Pus	Empyema
Viscous	Mesothelioma
Debris	Rheumatoid pleurisy
Turbid	Inflammatory exudate or lipid effusion
Anchovy paste	Amebic liver abscess

Odor of fluid	Suggested diagnosis
Putrid	Anaerobic empyema
Ammonia	Urinothorax

Exudates — In contrast, exudative effusions present more of a diagnostic dilemma. Disease in virtually any organ can cause exudative pleural effusions by a variety of mechanisms, including infection, malignancy, immunologic responses, lymphatic abnormalities, noninfectious inflammation, iatrogenic causes, and movement of fluid from below the diaphragm[48] (figure 11).

Exudates result primarily from pleural and lung inflammation (resulting in a capillary protein leak) or from impaired lymphatic drainage of the pleural space (resulting in decreased removal of protein from the pleural space)[48]. Exudates can also result from movement of fluid from the peritoneal space, as seen with acute or chronic pancreatitis, chylous ascites, and peritoneal carcinomatosis.

Diagnostic criteria — The most practical method of separating transudates and exudates is measurement of serum and pleural fluid protein and LDH. If at least one of the following three criteria is present, the fluid is virtually always an exudate; if none is present, the fluid is virtually always a transudate[1]:

- Pleural fluid protein/serum protein ratio greater than 0.5.

- Pleural fluid LDH/serum LDH ratio greater than 0.6.

- Pleural fluid LDH greater than two thirds the upper limits of normal of the serum LDH.

A meta-analysis involving 1448 patients in eight studies used receiver operating characteristic (ROC) analysis, and found that three tests on a single pleural fluid sample could each discriminate as well between transudates and exudates as using paired and triplet combinations[50]. An exudate in this study was best determined by any one of the following:

- Pleural fluid protein >2.9 g/dL (29 g/L)

- Pleural fluid cholesterol >45 mg/dL (1.16 mmol/L)

- Pleural fluid LDH >60 percent of upper limits of normal serum value

CHEMICAL ANALYSIS — The measurement of pleural fluid protein and LDH, glucose, pH, and amylase can provide useful information.

Pleural fluid protein — Most transudates have absolute total protein concentrations below 3.0 g/dL; however, acute diuresis in congestive heart failure can elevate protein levels into the exudative range[51-53].

• Tuberculous pleural effusions virtually always have total protein concentrations above 4.0 g/dL[1].

• When pleural fluid protein concentrations are in the 7.0 to 8.0 g/dL range, Waldenstrom's macroglobulinemia and multiple myeloma should be considered[54-55].

Pleural fluid LDH — Several specific disease associations have been noted with pleural fluid protein and LDH levels:

• Pleural fluid LDH levels above 1000 IU/L (with upper limit of normal for serum of 200 IU/L) are characteristically found in empyema[56], rheumatoid pleurisy[57], and pleural paragonimiasis[58], and are sometimes observed with malignancy.

• Pleural fluid secondary to Pneumocystis carinii pneumonia has the characteristic finding of a pleural fluid/serum LDH ratio greater than 1.0 and a pleural fluid/serum protein ratio of less than 0.5[59]. Urinothorax is another cause of elevated pleural fluid LDH associated with low pleural fluid protein levels[60].

Pleural fluid glucose — A low pleural fluid glucose concentration (less than 60 mg/dL (3.33 mmol/liter), or a pleural fluid/serum glucose ratio less than 0.5) narrows the

differential diagnosis of the exudate to the following possibilities[61]:

- Rheumatoid pleurisy
- Complicated parapneumonic effusion or empyema
- Malignant effusion
- Tuberculous pleurisy
- Lupus pleuritis
- Esophageal rupture

All transudates and all other exudates have pleural fluid glucose concentration similar to that of blood glucose.

The mechanism responsible for a low pleural fluid glucose depends upon the underlying disease. Specific examples include:

- Decreased transport of glucose from blood to pleural fluid with rheumatoid pleurisy[62-63] or malignancy[64].
- Increased utilization of glucose by constituents of pleural

fluid, such as neutrophils, bacteria (empyema), and malignant cells[65].

The lowest glucose concentrations are found in rheumatoid pleurisy and empyema, with glucose being undetectable in some cases. In comparison, when the glucose concentration is low in tuberculous pleurisy, lupus pleuritis, and malignancy, it usually falls into the range of 30 to 50 mg/dL (1.66 to 2.78 mmol/liter)[61].

Pleural fluid pH — Pleural fluid pH should always be measured in a blood gas machine rather than with a pH meter or pH indicator paper, as the latter will result in inaccurate measurements[66]. A pleural fluid pH below 7.30 with a normal arterial blood pH is found with the same diagnoses associated with low pleural fluid glucose concentrations[67]. The pH of normal pleural fluid is approximately 7.60, due to a bicarbonate gradient between pleural fluid and blood[68]. Thus, a pH below 7.30 represents a substantial accumulation of hydrogen ions. Transudates generally have a pleural fluid pH in the 7.40 to 7.55 range, while the majority of exudates range from 7.30 to 7.45[67].

The mechanisms responsible for pleural fluid acidosis (pH <7.30) include;

- Increased acid production by pleural fluid cells and bacteria (empyema)[65,69].

- Decreased hydrogen ion efflux from the pleural space, due to pleuritis, tumor, or pleural fibrosis. Specific examples include malignancy[64], rheumatoid pleurisy[62,63], and tuberculous pleurisy.

A low pleural fluid pH has diagnostic, prognostic, and therapeutic implications for patients with parapneumonic and malignant effusions[70]. Patients with a low pleural fluid pH malignant effusion have a high initial positive yield on pleural fluid cytology and tend to have a shorter survival and poorer response to chemical pleurodesis than those with a pH >7.30, although the strength of these associations has been questioned[71-73].

Clinicians should not use the pleural fluid pH as the sole criterion for the decision to recommend pleurodesis. A parapneumonic effusion with a low pleural fluid pH indicates a high likelihood of necessity for pleural space drainage.

Pleural fluid amylase — The finding of an amylase-rich pleural effusion, defined as either a pleural fluid amylase

greater than the upper limits of normal for serum amylase or a pleural fluid to serum amylase ratio greater than 1.0, narrows the differential diagnosis of an exudative effusion to the following major possibilities[48]:

- Acute pancreatitis
- Chronic pancreatic pleural effusion
- Esophageal rupture
- Malignancy

Other rare causes of an amylase-rich pleural effusion include pneumonia, ruptured ectopic pregnancy, hydronephrosis, and cirrhosis[74]. Pancreatic disease is associated with pancreatic isoenzymes, while malignancy and esophageal rupture are characterized by a predominance of salivary isoenzymes[74].

Pleural fluid Adenosine Deaminase (ADA) –

Pleural fluid adenosine deaminase (ADA) concentrations are elevated in tuberculous pleural effusions[75-76]. Some large series suggest that ADA is 100 percent sensitive and 95 to 97 percent specific when a value above 45 to 60 U/L is found[76-79]. However, one report found levels above 43 U/L in

only 68 of 87 cases (78 percent sensitivity)[80], while other series found specificities in the range of 85 to 89 percent[81-82].

Specificity is decreased by high ADA levels that occasionally occur in other conditions, including rheumatoid effusion, empyema, mesothelioma, lung cancer, parapneumonic effusion, and hematologic malignancies. Choosing a lower ADA cutoff value will increase sensitivity at the expense of specificity.

These variable findings may in part reflect failure to distinguish between the two principal isoenzymes, ADA-1 and ADA-2. ADA-2 is increased in tuberculous effusions, while ADA-1 rises in empyemas[83]. Most studies have reported only the total ADA level.

At present, pleural fluid ADA remains "an aid to differential diagnosis," as it was originally described in 1978[75]. It is most useful in the 10 percent of patients with tuberculous pleurisy who have negative standard diagnostic studies, ie, negative pleural histology and culture.

PLEURAL FLUID NUCLEATED CELLS — The total pleural fluid nucleated cell count is virtually never diagnostic. There are, however, some settings in which the count may be helpful:

- Counts above 50,000/μL are usually found only in complicated parapneumonic effusions, including empyema.

- Exudative effusions from bacterial pneumonia, acute pancreatitis, and lupus pleuritis usually have total nucleated cell counts above 10,000/μL[48,84].

- Chronic exudates, typified by tuberculous pleurisy and malignancy, typically have nucleated cell counts below 5000/μL[48,84].

The timing of thoracentesis in relation to the acute pleural injury determines the predominant cell type. The early cellular response to pleural injury is neutrophilic. As the time from the acute insult lengthens, the effusion develops a mononuclear predominance if the pleural injury is not ongoing[48].

Pleural fluid lymphocytosis — Pleural fluid lymphocytosis, particularly with lymphocyte counts representing 85 to 95 percent of the total nucleated cells, suggests tuberculous pleurisy, lymphoma, sarcoidosis, chronic rheumatoid

pleurisy, yellow nail syndrome, or chylothorax[48,49,85]. Carcinomatous pleural effusions will be lymphocyte-predominant in over one-half of cases; however, the percentage of lymphocytes is usually between 50 and 70 percent[85].

Pleural fluid eosinophilia — Pleural fluid eosinophilia (defined by pleural fluid eosinophils representing more than 10 percent of the total nucleated cells) usually suggests a benign, self-limited disease, and is commonly associated with air or blood in the pleural space[86-87]. However, two studies have noted that malignancy is as prevalent in eosinophilic as noneosinophilic pleural effusions[88-89]. The differential diagnosis of pleural fluid eosinophilia includes[86-87]:

- Pneumothorax
- Hemothorax
- Pulmonary infarction
- Benign asbestos pleural effusion
- Parasitic disease

- Fungal infection (coccidioidomycosis, cryptococcosis, histoplasmosis)

- Drugs

- Malignancy (carcinoma, lymphoma)

Pleural fluid eosinophilia appears to be rare with tuberculous pleurisy on the initial thoracentesis[86-87].

Mesothelial cells — Mesothelial cells are found in small numbers in normal pleural fluid, are prominent in transudative pleural effusions, and are variable in exudative effusions. The major clinical significance of mesothelial cells in exudates is that tuberculosis is unlikely if there are more than five percent mesothelial cells[85,87,90,91].

NEED FOR BETTER ACCURACY

In the past, transudates were separated from exudates by the specific gravity, cell count and presence or absence of clotting of fluid. In 1972, Light *et al*[1] developed a criterion for the diagnostic separation of transudates from exudates. Thereafter it was found that Light's criteria misclassified large number of effusions which may lead to unwarranted invasive interventions in 20% to 30% of patients with transudates[92-93]. Therefore some doubts were cast on the universal applicability of Light's criteria. Subsequently, Romero *et al*[93] used modified Light's criteria using new cut-off values. However Vives *et al*[94] found that changing the classic Light's criteria with different cut-off values offered no advantage for differentiating transudates from exudates.

For this reason, over the last few years, new parameters have been tried to ensure better sensitivity and specificity. These parameters include :

1. Pleural fluid cholesterol level.
2. Pleural fluid to serum cholesterol ratio.
3. Pleural fluid to serum bilirubin ratio.
4. Serum-effusion albumin gradient.
5. Alkaline phosphatase value.

RATIONALE FOR CONSIDERING CHOLINESTERASE LEVEL:

Cholinesterase is found in plasma and most tissues of the body[95]. It is synthesized in the liver and its levels are remarkably constant in well-fed healthy individuals. Measurement of serum ChE activity can serve as sensitive measures of the synthetic capacity of the liver. The cholinesterase activity may vary widely from individual to individual, but it tends to remain fairly constant in any one individual[96-99].

In case of an exudates formed from an inflamed tissue, the level of cholinesterase synthesized locally increases. So, in case of an exudative pleural effusion, the pleural fluid cholinesterase is higher and its ratio with serum level in a given individual may help in distinguishing it from transudative causes.