Mechanics of the Pleural Space

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Origins and Early Developments ...................................................... 58
Essentials of Mechanics of Lung and Chest Wall ............................... 61
Mechanical Coupling Between Lung and Chest Wall ......................... 64
Factors holding lung against chest wall ....................................... 64
Pleural liquid pressure and pleural surface pressure .......................... 66
Pleural Membranes ...................................................................... 67
Pleural Liquid .............................................................................. 68
Volume ....................................................................................... 68
Physicochemical features ............................................................... 69
Cells ........................................................................................... 70
Thickness .................................................................................... 71
Pressure ...................................................................................... 74
Relationships between volume, pressure, and thickness in experimental hydrothorax ................................................................. 78
Exchange through pleural membranes .............................................. 80
Pneumothorax .............................................................................. 83
Pressure ....................................................................................... 83
Exchange of gas ........................................................................... 84
Pleural Surface Pressure .................................................................. 85
Methods of measurement of overall transpulmonary pressure ............... 86
Direct methods of measurement of local pleural surface pressure .......... 87
Indirect methods of measurement of local pleural surface pressure ....... 91
Overall transpulmonary pressure .................................................... 95
Topography of pleural surface pressure .......................................... 96
Nature of vertical gradient of transpulmonary pressure ....................... 100
Functional implications of vertical gradient of transpulmonary pressure 116
Changes of pleural surface pressure with age and under special conditions 118
Maximum range of pressure on pleural surface ................................. 119
Surface pressure of peribronchial and perivascular spaces .................... 120
Comparison Between Pleural Surface Pressure and Pleural Liquid Pressure at Various Lung Heights and Volumes ................................. 121

THE GREAT PROGRESS in the mechanics of breathing that followed the classic studies of Rohrer (207) and Fenn, Otis, and Rahn (83, 84, 184, 201) reached a stage about 10 years ago in which a more systematic and a deeper insight into the mechanics of the pleural space appeared essential to the advancement of our knowledge, not only of the mechanics of breathing, but also of the pulmonary circulation and gas exchange. In 1961 Mead, in his basic review on the mechanical properties of the lung (154), pointed out that “there is great need for better information as to the surface topography of lung pressure.” During the last few years many efforts have been made to solve the theoretical and experimental problems encountered in obtaining this information. This concerns one aspect of the mechanics of the pleural space: namely, the interaction between the mechanics of the lung
and of the chest wall. Since the mechanical properties of the lung were, and still are, better known than those of the chest wall, this study has been mainly undertaken through the mechanics of the lung. The mechanics of the chest wall, however, must be considered to the same extent. The other aspect of the mechanics of the pleural space concerns the nature of the coupling between the lung and the chest wall: i.e., the factors holding together these structures and providing the lubrication. This aspect involves a study of the contents of the pleural space as well as of the exchange through the pleural membranes.

Despite recent interest, the mechanics of the pleural space is an old subject, like most of the mechanics of breathing; the knowledge of its history and development is therefore essential to provide a perspective of the recent research.

I. ORIGINS AND EARLY DEVELOPMENTS

According to Haller (107) Galen maintained that air is inhaled because of active expansion of the chest wall, passively followed by the lungs. Yet this view was long disputed and was widely accepted only after the works of Mayow, Borelli, and Haller [see Fenn (85) and Perkins (188)].

Hamberger (108) maintained Galen’s view that a thin layer of gas is normally present between the pleural membranes. This view was rejected by Haller (107) and Davy (69). Recklinghausen (202) considered the pleural cavity as a lymphatic space, yet often the pleural space has been elusively defined as a virtual space. Dybkowsky (77) showed that pleural liquid with suspended particles is pumped through stomata into the lymphatics by the respiratory movements and suggested that exchanges of water and small solutes could occur also with the blood capillaries of the pleural membranes. Starling and his coworkers (136, 225) showed that the pleural membranes are size-selective barriers through which passage of liquid is determined by mechanical and osmotic forces. Having showed that isotonic or even slightly hypertonic saline solutions were absorbed through the blood and that this was not an active process, they postulated the intervention of another mechanical force. Shortly afterward Starling (224) discovered the importance of the colloid osmotic pressure of the plasma for the absorption of liquid from interstitial spaces.

A clear description of pneumothorax was provided by Mayow [see Perkins (188)]. Astley Cooper [see Davy (69)] showed that air introduced into the pleural cavity is absorbed, Davy (69) analyzed the gas of a pneumothorax, and Wintrich [see Rist and Strohl (204)] pointed out that the gas absorption should depend upon diffusion.

In 1820 Carson (48) described the first measurements of the retraction force of the lung. He connected the trachea of dead animals (cats, dogs, and calves) to a glass balloon with a vertical side pipe partly filled with water and showed that the pressure inside the lung rose above atmospheric when the chest wall was widely opened through the abdomen. He attributed this pressure to the retraction force of the lung, recognizing that this force increases with lung expansion and that, under physiological conditions, it pulls in the chest wall. In 1849–1850 Donders
January 1972 PLEURAL SPACE MECHANICS 59

(71) reported similar experiments done with a mercury manometer on dead men, with diseased lungs, and living animals. The transpulmonary pressure of men ranged from 3 to 7 cm H$_2$O. At the same time Hutchinson (122) reported that the transpulmonary pressure in a healthy man just after death was 6 cm H$_2$O. In 1882 Heynsius (114) found that the end-expiratory transpulmonary pressure in exsanguinated and partially eviscerated rabbits, dogs, calves, and cows was 3.5, 5.6, 6.5, and 9.10 cm H$_2$O, respectively. He also pointed out that the lung at the same volume could exert different retractive pressures.

In 1847 Ludwig (143) reported the first measurement of pleural pressure. He introduced between the pleural membranes of living animals a thin rubber balloon bound over a cannula. The system was filled with water and the pressure was recorded by a mercury manometer on a kymograph. The experiments of Ludwig were followed by many others, in which various kinds of cannulas were used and care was taken to minimize the pneumothorax that resulted from inserting the devices [see Wirz (259)]. Van der Brugh (241), on Einthoven's suggestion, made pressure measurements in dogs with pneumothorax of different volumes in order to get, by extrapolation, the value with no pneumothorax. His data of end-expiratory transpulmonary pressure, like most of those obtained at that time or earlier, are some centimeters H$_2$O higher than those generally found at present even with the same measuring devices. Aron (19) inserted a trocar connected with a glycerin manometer in the pleural space of a healthy man and measured about -4 cm H$_2$O at end expiration and -6.5 cm H$_2$O at end inspiration. The posture of the subject and the site of measurement are not clearly indicated.

In 1878 Luciani (142), following Ceradini's idea, made the first measurements of esophageal pressure. He introduced in the esophagus of dogs a catheter with many holes on its terminal part. In some cases he tied over this part a small balloon made of gut, but found that this was not always necessary. The catheter was connected with a Marey capsule rather than a water manometer in order to record the faster events of breathing. Like Ludwig's experiments, those of Luciani were intended to record only the tidal changes of intrathoracic pressure. In particular, Luciani compared these changes with those of abdominal pressure. Rosenthal (208) attempted to record the absolute value of pleural pressure from the esophageal tube and made measurements in men, but the errors involved were soon pointed out by Heynsius (114). Meltzer (166) measured the tidal changes of pressure in the posterior mediastinum through a catheter connected with a Marey capsule; he found that they were greater in the caudal than in the cranial part.

After having determined the order of magnitude of the pressure by which the lung and the chest wall tend to move apart, attempts were made to discover the mechanism that normally holds the lung against the chest wall. West (256) noticed, in animal experiments and injured men, that occasionally the lung did not collapse despite the incision of the parietal pleura. In an attempt to explain this phenomenon, he pressed against one another two wood tablets lined with a piece of stomach (the wet serous membrane outside) and measured the force necessary to separate them. This force was greater than the retraction force of the lung, and West concluded that the lung under physiological conditions is held against the chest wall by the adhesion force between the pleural liquid and the
pleural membranes. This misinterpretation of his experiment (see below), supported by the studies of Brauer (37), Roth (209), and Bernou and Cardis (30), added confusion to the clear fundamental concepts previously established by Carson, Donders, and Ludwig. The influence of this confusion has been so strong that it has been often taught that under physiological conditions the pressure in the pleural space is not subatmospheric and that the forces holding the lung against the chest wall are the adhesion between pleural liquid and pleural membranes and the cohesion of the pleural liquid. Stoevesandt (228) and Wirz (259) cast some doubt on this view, because they maintained that the adhesion force should be negligible relatively to the retraction force of the lung. They, however, did not show where West was wrong. Wyss (265) criticized the adhesion hypothesis, but he reasoned as if the pleural membranes were impermeable to gas and to liquid. Rist and Strohl (204, 205) showed that the absorption of gases from the pleural cavity occurs by diffusion because the sum of the partial pressures of the gases in the venous part of the capillaries is subatmospheric and lower than the pressure of the gas in a pneumothorax. They believed that this was the mechanism holding the lung against the chest wall, but the pleural membranes are permeable to liquid. Bernou and Cardis (30) recognized the importance of the work of Rist and Strohl, but, in reviewing all the factors that had been considered, they concluded that no satisfactory explanation had been provided. Like Brauer and Roth, they believed that: 1) since the adhesion force between liquid and pleural membranes is greater than the retraction force of the lung, the pressure in the pleural space under physiological conditions is not subatmospheric and becomes subatmospheric only when the pleural membranes are moved apart as in a pneumothorax, and 2) the retraction force of the lung under physiological conditions acts on the chest wall and the extrapleural intrathoracic structures through the pleural membranes held together by the adhesion.

In 1927 the problem was clearly stated by Neergaard (179). He first pointed out the confusion arising from considering the pleural space a virtual space. By the same token, he noticed, the interstitial space should be called a virtual space. Then he showed that West did not measure the force of adhesion between liquid and serous membrane, but the surface tension of the air-liquid meniscus occurring at the edges of his tablets. He pressed a sheet of photographic paper against a glass tablet, lined with gelatine and wetted with pleural liquid, and measured the force necessary to separate them. The force was great, but when they were immersed into a beaker containing transudated pleural liquid the force was very small, for the air-liquid meniscus at the edges had been eliminated. This does not mean that the adhesion force between liquid and membranes is small, as Neergaard maintained, but simply that liquid can enter the space between the membranes. Neergaard pointed out that the surface tension of small bubbles is a source of error in the measurement of pleural pressure with a needle or a cannula, and he explained that the cause of the occasional absence of pneumothorax after sharp and small wounds of the chest wall is the surface tension of the small bubbles of air formed into the pleural space when the cutting agent enters it. He suggested that, besides the mechanism for gas absorption showed by Rist and Strohl (204, 205), there should be a mechanism absorbing interstitial liquid with a force
higher than the recoil of the lung. Since Krogh (134) had shown that the colloid osmotic pressure of the plasma is somewhat higher than the hydrostatic pressure of the capillaries, Neergaard suggested that the force absorbing liquid from the pleural cavity originated from this imbalance. He went even farther, speculating that the absorption of the pleural liquid should stop when the pleural membranes come into contact, because the irritation of the points of contact should produce a leakage of protein from the capillaries and hence an increase of the colloid osmotic pressure of the pleural liquid. It is noteworthy that this fundamental paper by Neergaard was not taken into consideration for about 30 years, except for a marginal quotation by Vuilleumier (248). Similarly, the other fundamental paper by Neergaard, that calling attention to the contribution of alveolar surface tension to the retraction force of the lung (180), raised some interest only after almost 30 years. Instead, another important but less original work by the same author, that on the simultaneous recording of pleural pressure and air-flow rate in two patients (181), became a classic. Indeed, this clinician from Basel was ahead of his time.

His work was probably stimulated by the systematic and quantitative treatment of the mechanics of breathing undertaken by Rohrer, who also worked for a period in Basel. With regard to the mechanics of the pleural space Rohrer (207) pointed out the advantages of a liquid coupling between lung and chest wall: 1) incompressibility, hence instantaneous transmission of forces; and 2) lubrication, hence absence of shearing forces. He calculated that the average thickness of the pleural liquid should be about 20 μ, and surprisingly he thought that this layer was thin enough as to be supported completely by the adhesion to the pleural membranes, i.e., that the pleural liquid should not undergo a hydrostatic gradient. He calculated that the flow resistance of the pleural liquid is negligible even at the highest values of ventilation. Finally, Rohrer considered the effect of the lung weight on the distribution of the transpulmonary pressure. On the basis of the lung height and density he estimated that the difference in transpulmonary pressure between top and bottom of the lung in the erect man should be at most 2 cm H₂O, but added that this was probably an overestimation because part of the weight of the lung should be supported by the hila.

The first systematic, simultaneous measurements of pressure in a pneumothorax and of air-flow rate were done by Rohrer's pupil Wirz (259) in order to study the dynamic properties of the lung. His classic article is valuable also for the comprehensive review of the old literature on the mechanics of the pleural space. The early developments of knowledge of the static and dynamic properties of the lung were reviewed by Mead (154). In 1926 Cunningham (65) reviewed the physiology of the serous membranes from the standpoint of the structure and function of the mesothelial layer and of the absorption of liquid and particles from the serous cavities.

II. ESSENTIALS OF MECHANICS OF LUNG AND CHEST WALL

The study of the mechanics of the pleural space requires a basic knowledge of the mechanics of the lung and of the chest wall. It therefore seems convenient to outline first the more pertinent topics on the mechanics of these two structures.
On the other hand, it must be realized that this knowledge has been acquired through quantitative analyses that rest on simplifications of the mechanics of the pleural space. The following review articles or monographs provide a useful general background as well as specific notions for the study of the mechanics of the pleural space: 1) mechanics of the whole respiratory system or of the chest wall (12, 47, 83, 84, 156, 160); 2) mechanics of the lung (154, 155, 169, 199); and 3) mechanical coupling between the lung and the chest wall (2, 19, 219).

The chest wall (rib cage plus abdomen-diaphragm) and the lung are placed in series and therefore the algebraic sum of the pressure exerted by these two structures gives the pressure of the respiratory system (\(Pw + Pl = Prs\)). The changes of volume of each part are equal to each other, except for any change of the intrathoracic extrapulmonary blood, and equal to that of the respiratory system (\(AVw = AVl = AVrs\)) (12). Generally the symbol \(w\) is used to indicate only the relaxed chest wall, hence \(Prs = Pl + Pw + Pmus\), where \(Pmus\) indicates the pressure contributed by the muscle contraction. The pressure exerted by a structure is given a negative sign when it decreases alveolar pressure (\(Palv\)) relative to body surface pressure (\(Pbs\)) (i.e., when it is inspiratory), whereas it is given a positive sign when it increases \(Palv\) relative to \(Pbs\) (i.e., when it is expiratory). The pressure at a boundary (alveolar, pleural, body surface) is referred to atmospheric pressure.

The pressure exerted by the lung under static conditions, or static transpulmonary pressure, is the difference between alveolar pressure and the pressure on the pleural surface (\(Pl = Palv - Ppl\)). \(Palv\) may be made equal to zero (atmospheric pressure) by holding voluntarily a given lung volume with open airways; then \(Ppl = -Pl\), and \(-Pmus = Pl + Pw\). The pressure exerted by the chest wall is the difference between the pressure on the pleural surface and that on the body surface (\(Pw = Ppl - Pbs\), and when the muscles are active \(Pmus + Pw = Ppl - Pbs\)). When the muscles are relaxed and \(Pbs\) equals atmospheric pressure, \(Ppl = Pw\) and \(Palv = Pl + Pw\) (12, 207).

The static volume-pressure relationships of the lung, of the relaxed chest wall, and of the relaxed respiratory system in the seated man are shown in Figure 1 (left). At the resting volume of the respiratory system (about 35% VC in Fig. 1) the relaxed chest wall recoils outward with a pressure equal to that by which the lung recoils inward. The resting volume of the lung alone is below 0% of VC; that of the chest wall alone is about at 55% VC; above this volume both the lung and the chest wall recoil inward (12, 201). According to Turner et al. (239) the compliance (\(C = AV/AP\)) of the chest wall decreases above 80–90% VC and the resting volume of the chest wall is higher than indicated in Figure 1 (left). If in a relaxed subject both pleural spaces were opened to the ambient, the lung would collapse and the chest wall would expand to its resting volume. If only a limited amount of air were allowed to enter the pleural space in such a way as to form a continuous layer of gas between lung and chest wall, the lung would collapse a little and the chest wall would expand a little until a new equilibrium were reached. The partitioning of this volume between the chest wall and the lung would depend on the relative compliance of these structures in the volume range involved (12, 84).
January 1972

PLEURAL SPACE MECHANICS

63

FIG. 1. Static volume-pressure curves of lung, chest wall, and respiratory system during relaxation in sitting and supine postures. [Modified from Rahn et al. (201) and Agostoni and Mead (12).]

The static volume-pressure relationships of the lung, of the relaxed chest wall, and of the relaxed respiratory system in the supine man are shown in Figure 1 (right). That of the lung is essentially the same as in the upright posture, whereas that of the chest wall is changed. The resting volume of the chest wall is lowered to about 30% VC and the compliance of the chest wall in the midvolume range is increased. The resting volume of the respiratory system is lowered to about 22% VC. These changes are mainly due to the effect of gravity on the abdomen. From the mechanical point of view the abdomen can be likened to a container filled with liquid and with part of its wall distensible. In the upright posture the gravitational effect is inspiratory on the abdomen and expiratory on the rib cage; in the supine posture it is expiratory on both the abdomen and the rib cage (12).

By plotting $P_l$, instead of $P_i$, a volume-pressure diagram in terms of pressure on the pleural surface is obtained (Fig. 2): this applies to both the static and dynamic conditions. The loop $P_{dyn}(l)$ in Figure 2 represents the path of the pressure on the pleural surface during a spontaneous breath through the nose in the sitting posture, whereas the loop $P_{dyn}(w)$ represents the path of the pressure on the pleural surface during an artificial cycle obtained by changing the alveolar pressure relative to the body surface pressure in such a way as to simulate the volume events during the spontaneous cycle (156).

For analytical purposes the pressure has been considered equal on the entire surface of the lung, but this occurs only when the whole lung is separated from the chest wall by a continuous layer of gas. It is in fact conceivable that under physiological conditions the pressure varies at different sites because of the effect of gravity and of any difference of shape between the lung and the chest wall (76, 154, 207). In other words, the balance between the lung and the chest wall under
physiological conditions occurs through a wide distribution of stresses (see sect. VII). In each site, under static conditions, the force of the visceral side must balance that of the parietal one.

Moreover, there is a factor that makes the relationship between volume and pressure not unique, which is the previous volume history of the respiratory system. The pressure at a given volume under static conditions is higher after deflation than after inflation; hence, static (stepwise) inflation volume-pressure curves are not superimposed on static deflation curves, but form a static hysteresis loop. Static hysteresis occurs both in the lung (22, 39, 44, 49, 55, 164, 180, 213, 221, 223, 244) and in the chest wall (44, 223, 244).

II. MECHANICAL COUPLING BETWEEN LUNG AND CHEST WALL

A. Factors Holding Lung Against Chest Wall

At the resting volume of the respiratory system the opposed recoils of lung and chest wall tend to separate the visceral from the parietal pleura. Since the pleural membranes are permeable to gases and interstitial liquid, the lung can be held against the chest wall only if there are mechanisms preventing gas and liquid collection in the pleural space (12, 179, 219, 220).

The mechanism by which the pleural space is kept free from a gas phase was first described by Rist and Strohl (204, 205). Because of the shape of the blood dissociation curves for O\textsubscript{2} and CO\textsubscript{2}, the total gas pressure in the venous blood is about 60 cm H\textsubscript{2}O less than that in the arterial blood, which in turn is about 10 cm H\textsubscript{2}O less than atmospheric owing to the alveolar-arterial O\textsubscript{2} gradient. As a result
January 1972  PLEURAL SPACE MECHANICS  65

the total gas pressure in the venous blood is about 70 cm H2O below atmospheric. The total gas pressure in the interstitial liquid and hence in the pleural liquid should be even lower because the gradient between tissues and blood is higher for O2 than for CO2. The gas pressure in a closed, relatively small pneumothorax depends on the retraction force of the lung involved and is therefore only a few centimeters of water subatmospheric. Thus, if the gas pressure in a pneumothorax is \(-2\) cm H2O, the gas diffuses from the cavity into the blood under a pressure of about 70 \(- 2 = 68\) cm H2O. The volume of the pleural space decreases as the gas diffuses out of it until all the gas phase disappears. Actually the kinetics of the phenomenon is more complex because different gases are involved, as first elucidated by Rist and Strohl (204; see sect. viB).

Under physiological conditions there is only a small amount of liquid into the pleural cavity (see sect. vA), suggesting that there is a mechanism absorbing liquid from it and another preventing a complete removal (179). Cohesion forces of the pleural liquid and adhesion between the pleural liquid and pleural membranes could play a role at equilibrium only if the pleural membranes were impermeable to liquid and to gases, which is not the case. At the boundary between the pleural liquid and the pleural membranes the interfacial tension is extremely weak and tends to diminish the pulmonary surface and volume, i.e., to have the same effect as the inward recoil of the lung (12, 219). Neergaard (179) suggested that the mechanism absorbing liquid from the pleural cavity should be provided by the difference between the plasma colloid osmotic pressure and the hydrostatic pressure. Since the latter in the pulmonary capillary is low (see sect. vG) and the colloid osmotic pressure of the pleural liquid is only a few millimeters Hg (see sect. vB), the net absorbing pressure is greater than the opposed recoil of the lung and of the chest wall at FRC (12, 17, 219).

When isotonic saline solution is introduced into the pleural space, the lung and the chest wall move apart and the pressure in the hydrothorax reflects the recoil forces of the lung and chest wall. As the liquid introduced is absorbed, the lung and the chest wall are pulled together into contact at several points (see sect. vD). That is, at these points the walls of the pleural cavity push on each other. A further removal of liquid, and hence a tighter fitting of the lung with the chest wall, elicits deformation forces in the walls of the pleural cavity. These forces oppose a closer apposition of the pleural membranes. Hence, as the volume of the pleural liquid is reduced, its pressure decreases below that determined by the recoil of the lung and of the chest wall and tends to an equilibrium with the absorption pressure (see sect. vG). The equilibrium volume of the pleural liquid should therefore be set by the deformation forces elicited by the contact between lung and chest wall (12, 219, 220).

The essential mechanisms holding the lung against the chest wall are therefore those keeping the pleural space gas free and nearly liquid free. The mechanism preventing a complete removal of liquid from the pleural space secures the lubrication of the coupling system (12). The liquid coupling provides an instantaneous transmission between the walls of perpendicular forces and allows slide in response to shearing forces. Any nonperpendicular force applied to the chest.
wall or to the lung may be divided into a vector component perpendicular to
the surface and another one parallel to the surface. The latter makes the walls
slide on each other until a new equilibrium is reached (207). Little is known about
the frictional forces between the pleural membranes. The static coefficient of
friction has been found to be $0.086 \pm 0.013$ (sd) (35), but the experimental
conditions were far from physiological. The pressure that the diaphragm must
exert to overcome the kinetic friction has been roughly calculated by Rohrer
(207) to be of the order of 0.1 cm H$_2$O at the highest flow rate. Since the thick-
ness of the pleural liquid over most of the pleural surface is generally smaller
than the average value assumed by Rohrer and its relative viscosity higher (see
sect. vB, D), this pressure should be higher than provided by Rohrer, but still
negligible.

B. Pleural Liquid Pressure and Pleural Surface Pressure

From the above considerations on the forces absorbing liquid from the pleu-
ral cavity and those preventing a complete removal of the liquid, it appears that
under physiological conditions the pressure of the pleural liquid in a given region
is lower (more subatmospheric) than the pressure due to the recoil of the lung
and the chest wall (219, 220). The latter has been termed pleural surface pressure
(12) and is the force per unit surface area of the lung or of the chest wall, as de-
finied by Carson (48), Donders (71), Wirz (259), and Rohrer (207). The difference
between pleural liquid pressure and pleural surface pressure is the deformation
pressure, i.e., the pressure due to the deformation forces elicited in the walls when
they contact. Evidence of the difference between pleural liquid and pleural sur-
face pressure has been provided by measurements of pleural liquid pressure (4,
7, 14, 219), pleural liquid thickness (4, 10, 14), and pleural surface pressure (3,
5, 8, 67) (see sect. v, vii, and viii). The difference between liquid and surface pres-
sure as well as the deformation forces have been illustrated by mechanical models
(4, 12, 219, 220) and in the excised esophagus (189; see sect. vE).

This distinction has been extended by Guyton (103–105) and by Scholander
(218, 231) to the interstitial spaces, although the conditions of the interstitial
spaces, particularly outside the lung, differ from those of the pleural space. The
importance of the distinction between surface and liquid pressure was recognized
also by West (252) in his studies on the perivascular and peribronchial spaces.
Wood and his associates (26, 211, 212), however, did not recognize this distinc-
tion. This failure led to some confusion in the discussion of the vertical gradient
of transpulmonary pressure (see sect. vE and vii).

From the standpoint of transmission of mechanical forces between the chest
wall and the lung, it is pleural surface pressure that matters. All intrathoracic
extrapulmonary structures, such as extrapulmonary airways, esophagus, great
vessels, heart, etc., are affected by the pleural surface pressure, i.e., by the pressure
exerted by the lung or by the chest wall (12). It is convenient to consider that in-
trapulmonary airways and vessels are also subject to pleural surface pressure, but
the surface pressure of the peribronchial and perivascular spaces may differ from
pleural surface pressure (161; see sect. viiJ).
IV. PLEURAL MEMBRANES

This section summarizes some notions on the morphology of the pleural membranes that may be of some interest in the study of the mechanics of the pleural space. The pleural membranes are lined with a single layer of flat mesothelial cells. This layer is important for mobility of the lung because adhesion of the pleural membranes seems to occur when it is lacking (65, 148). After a disruption of the layer the mesothelial cells cover the defect by migration and proliferation (53). The mesothelial cells are 15–30 μ wide and 6–7 μ thick (82, 113, 195). Among the polygonal cells are islets (0.1–0.5 mm in diameter) of smaller round cells with little cytoplasm (112). Although Lippman and Plesch (140) maintained that the mesothelial cells may become similar to lymphocytes and monocytes, Cunningham (65) concluded that this transformation does not occur. According to Cunningham (65) the mesothelial cells share some properties of the fibrocytes. The presence of cilia on the mesothelial cells, first described by Kolossov (132), was found by many investigators [see Cunningham (65)]. Cilia up to 2 μ long on the free border of the cells, lipid droplets up to 1 μ in diameter just inside the free border, several micropinocytosis vesicles on the opposite side of the cells, and small desmosomes between the cells have been observed by electron microscopy on the large mesothelial cells of human visceral pleura (70). The renewal process of the mesothelial cells is not clear (70, 247). The width of the intracellular cleft of the surface layer is variable and the intercellular substance rather yielding. Lymphocytes (112) and probably also monocytes (65) have been observed crawling in the widened intercellular clefts, particularly in the islets of smaller cells (112, 113). The intercellular space, stained with silver nitrate, forms a continuous net (202). After several hours of pneumothorax the mesothelial cells bulge and contract until they lose mutual contact (235), as they do whenever they are irritated (65). After a few days the normal intercellular net reappears in spite of the persistence of the pneumothorax (235).

In the parietal pleura the mesothelial cells lie on a connective tissue layer of collagen and elastic fiber networks. This layer may be further divided into a superficial and a deep one. The mediastinal part of the deep layer is mainly collagenous (109). In the mediastinal region and on the ribs there is some vacuolar adipose tissue (113). The deep connective fibers of the parietal pleura mingle with the endothoracic fascia. Over the pleural cupola this fascia becomes thick and it is attached to the arch of the first rib and to the transverse process of the seventh cervical vertebra by the costopleural and vertebropleural ligaments, respectively (113, 133). The lymphatic vessels are mainly subjacent to the intercostal muscles and the muscular part of the diaphragm, whereas the blood vessels are mainly to the ribs (113).

The visceral pleural consists of the aforementioned layer of mesothelial cells and of a connective layer with a network of collagen and elastic fibers (113). The elastic fibers in man increase during the first few months of life (82). In the guinea pig, and to a minor extent in the cat and dog, there are also bundles of smooth muscle fibers (82). They have been found also in man (25), but rarely (113). According to the data of Policard and Galy (195) the connective layer in
man is 30–40 μ thick. In some mammals such as rodents, cats, dogs, and monkeys it is thinner; these animals also lack interlobular septa. In animals with a thick visceral pleura, including man, the connective layer is attached to the interlobular septa, which run from the surface of the lung to various depths. The interlobular septa are well developed in pigs and calves (113, 151). According to Hayek (110) the lobules can move a little against each other, and this could be important in reducing internal shearing forces when the shape of the lobe changes. In the superficial part of the connective layer, the collagen fibers run predominantly in a given direction, which changes according to the location, whereas in the deep part the collagen fibers form a uniform net like the elastic fibers do (33, 245). The pleura may be separated from the lung rather easily, particularly in an animal with a thick pleura (113). Between the connective tissue layer of the pleura and the limiting membrane of the lung there is a region, 20–50 μ thick (195), with blood vessels and lymphatics. The diameter of these blood capillaries is about 3 times that of other capillaries, although the features of their wall are similar (111, 113). Except for the hilar region and part of the mediastinal and interlobar regions the blood supply to the visceral pleura comes from the pulmonary artery (113, 133, 195). According to Miller (173) and McLaughlin et al. (151), however, this is the case for dogs, cats, and monkeys, whereas in men, sheep, horses, cows, and pigs (species with thick pleura) the main blood supply to the visceral pleura comes from the bronchial arteries. The blood reaching the visceral pleura either from the pulmonary or bronchial arteries is drained by the pulmonary veins (195, 173). At the lobar margins the pleura is thicker and may form villi (82).

In Asian and African elephants the pleural cavity was found obliterated by connective tissue (34, 210, 216); whether this reflects the normal condition is controversial, however (95, 96, 97, 192). It has been maintained that the pleural space is also partially obliterated in large cetaceans [see Favaro (82) for the old literature]; however, R. Elsner (personal communication) observed in a 15-m sperm whale that the lungs separated from the ventrolateral surfaces of the chest wall when this was opened and that the dorsal and diaphragmatic surfaces did not show signs of laceration when the lungs were removed. Such signs are also lacking in a photograph of lung removed from a 24-m fin whale (217). According to D. Leith (personal communication) in several kinds of whales there is a complete pleural space; in the sperm whale, however, the space is obliterated in the apical region.

V. PLEURAL LIQUID

A. Volume

According to Rohrer (207) the volume of liquid in a single pleural space of man is about 2 ml. Unfortunately no mention is made of how the volume of liquid was determined. Yamada (266) in a group of healthy Japanese soldiers punctured the 9th or 10th intercostal space in the dorsal axillary line and was
able to obtain some liquid in about 30% of the cases after a period of rest and in about 70% of the cases after a period of exercise. He generally collected from one pleural space only a few drops of foam (hence probably less than 1 ml of liquid), but in a few cases he collected up to 10-20 ml of liquid. The finding of about 150 neutrophil granulocytes per mm³ suggests that the liquid collected was slightly contaminated by blood. He did not mention whether the liquid was examined for red cells. Obviously this approach does not enable the collection of most of the pleural liquid; the few cases in which several milliliters were found are difficult to explain, unless abnormal.

Stewart and Burgen (227) attempted to measure the volume of the pleural liquid in dogs by two methods. The first consisted of collecting the pleural liquid after having carefully opened the chest wall. Nevertheless the liquid collected must have been contaminated by blood because they found an average of 6300 red cells/mm³. The geometrical mean of the volume of liquid collected from both sides was 1.3 ml. In the two cases in which the contamination was small the volume collected was 0.2 and 0.3 ml. They did not mention the posture in which the liquid was collected. The second method was based on dilution of the injected label immediately after intrapleural injection of a known volume of liquid. No information is given on the criterion used to establish that mixing was complete. The geometric mean of the volume of pleural liquid (both sides) calculated with this method was 2.7 ml. According to Stewart and Burgen, the difference between the two methods was probably due to the layer of liquid moistening the pleural surfaces that was not measured by the first method.

Miserocchi and Agostoni (176) collected liquid from the dorsal part of the costodiaphragmatic sinus of head-up rabbits and dogs after having opened the chest wall in such a way as to avoid contamination. The volume collected was 0.46 ± 0.04 (se) ml in rabbits (body wt 2.2 kg) and 0.55 ± 0.12 ml in dogs (body wt 9.3 kg). No red cells were found in the samples. They also determined the volume of liquid adherent to a unit of pleural surface by measuring the increase of weight of a piece of filter paper applied to the pleural surface until it appeared dry. Multiplying this volume by the surface area of the pleural membranes (Table 1), they calculated the volume of liquid adherent to the pleural surface after having opened the chest wall. This was 0.52 ml in rabbits and 1.8 ml in dogs. Hence the volume of the pleural liquid under physiological conditions was 0.98 ml in rabbits and 2.35 ml in dogs (Table 1). By means of the data of pleural liquid thickness, measured directly after quick freezing (see sect. vD), and of the area covered by the liquid under physiological conditions, they calculated the volume of pleural liquid in the "surface" region, i.e., that outside the lobar margins, the sinuses, and the hila, which in turn they termed the "margin" region. Subtracting the volume of the surface region from the total volume of pleural liquid they obtained the volume of the margin region (Table 1).

R. Physicochemical Features

Yamada (266) found that the protein concentration of the pleural liquid in men was 1.77 g/100 ml (range 1.38–3.35). Stewart and Burgen (227) found
**TABLE 1. Volume of pleural liquid and surface area of visceral pleura of both sides (176)**

<table>
<thead>
<tr>
<th>Species</th>
<th>Body Wt, kg</th>
<th>Volume, ml</th>
<th>Area, cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Collected</td>
<td>Adherent</td>
<td>Total</td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.9-2.5</td>
<td>0.46</td>
<td>0.32</td>
</tr>
<tr>
<td>Dog</td>
<td>6.5-12.5</td>
<td>0.55</td>
<td>1.80</td>
</tr>
</tbody>
</table>

* The regions of the lobar margins, sinuses, and hila are termed “margin,” the others “surface.”
† At a transpulmonary pressure of 5 cm H₂O.

in dogs a geometric mean of 1.39 g/100 ml (range 0.5–3.5). Since the liquid was contaminated by blood, these values are probably a little too high. Miserocchi and Agostoni (176) found 1.33 ± 0.04 (SE) g/100 ml in rabbits (76.1% albumin, 21.5% globulin, and 2.4% fibrinogen) and 1.06 ± 0.11 g in dogs (57.2% albumin, 35.8% globulin, and 7% fibrinogen). The computed colloid osmotic pressure was 4.8 cm H₂O in rabbits and 3.2 cm H₂O in dogs.

According to Yamada (266) the contents of Na⁺, K⁺, and Ca²⁺ are similar to those of the interstitial liquid, whereas pH is 7.64 and total CO₂ (hence the bicarbonates) higher than in plasma. High values of pH and bicarbonates have been found also in the pleural liquid of rats (L. L. Rolf, personal communication). These findings suggest an active transport by the pleural membranes.

The density and the surface tension of the liquid collected from the costodiaphragmatic sinus of rabbits are 1.03 ± 0.01 g/ml and 57.8 ± 1.0 dynes/cm, respectively (176). The relative viscosity in man is 1.24 (266).

C. Cells

In the pleural liquid there are mesothelial cells and cells similar to monocytes and lymphocytes (176, 266). The number of cells and the percentage of the various cells in the liquid collected from the costodiaphragmatic sinus are shown in Table 2. Since the cells come from or through the pleural membranes, it could be that the cells are not uniformly distributed per unit of liquid volume, but are rather more closely related to the unit of surface area. Since the area-to-volume ratio in the surface region (see sect. vA) is several times that in the margin region, the cells per unit volume of pleural liquid in the surface region could be more than those in the margin region, in spite of mixing. Moreover the surface region could produce more cells per unit area and time than the margin region because of the greater mechanical stimulus (176). Indeed, there is some evidence suggesting that in the surface region of rabbits the concentration of cells is more than twice that found in the liquid collected from the costodiaphragmatic sinus and that most of them are mesothelial cells (G. Miserocchi, unpublished observations). The hypothesis has been made that the cells of the pleural liquid could provide most of the points of contact between the pleural membranes (176; see sect. vD). Moreover, the monocytes probably get rid of the deteriorated cells by phagocytosis.
Table 2. Cells of liquid collected from costodiaphragmatic sinus

<table>
<thead>
<tr>
<th>Species</th>
<th>Cells/mm³</th>
<th>Mesothelium, %</th>
<th>Monocytes, %</th>
<th>Lymphocytes, %</th>
<th>Unclassified, %</th>
<th>Granulocytes, %</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>4500</td>
<td>(1700–6200)</td>
<td>2208</td>
<td>31.8</td>
<td>2472</td>
<td>3.1</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>668</td>
<td>3</td>
<td>53.7</td>
<td>10.2</td>
<td>29.5</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>5395</td>
<td>±31.8</td>
<td>78.9</td>
<td>24.4</td>
<td>0</td>
<td>0</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>2208</td>
<td>±9.1</td>
<td>60.8</td>
<td>7.4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>37.4</td>
<td>±7.7</td>
<td>69.6</td>
<td>28.2</td>
<td>2.2</td>
<td>0</td>
<td>176</td>
</tr>
</tbody>
</table>

Values for man are means with ranges in parentheses; values for rabbit and dog are means ± SE.

D. Thickness

Rohrer (207) calculated from the volume of liquid of one pleural space (2 ml) and the surface of one lung (1000 cm²) that the average thickness of the pleural liquid should be roughly 20 μ. This approach cannot provide data on the thickness of the pleural liquid in the various sites. On the other hand, conventional histological methods do not seem to measure reliably the thickness of the pleural liquid because they could alter the relative position of the pleural membranes.

In order to measure the thickness of the pleural liquid in different parts of the costal region the following method was developed (10). Animal chests were quick-frozen and cores drilled out; the cores, always kept at low temperature, were cut and examined directly through a reflex light microscope in a special cryostat. Since the pleural contents reflect less light than the surrounding tissues, the pleural space appears as a dark band that becomes wider when the thickness of the pleural liquid is artificially increased. This approach does not allow measurements at or near the lobar margins. Both in the lateral and the supine postures, the thickness of the pleural liquid in the superior part was about equal to that in the dependent part (Fig. 3); but, when 2.5–5 ml of isotonic saline solution were introduced into the pleural space, the thickness increased only in the dependent part (4, 10, 14). These findings agree with the mechanism illustrated (see sect. III), namely that the volume of the pleural liquid is reduced until the forces elicited by the contact between lung and chest wall prevent a further reduction. In fact, if the pleural membranes would not be pulled into contact and therefore the pleural liquid pressure were not less than but equal to the pleural surface pressure, the thickness of the pleural liquid (which is more dense than the lung) should be markedly greater in the dependent part, even under physiological conditions (4, 10). In all species examined the peak of the frequency distribution of the thickness over most of the costal region (except at the lobar margins) was 5–10 μ. In some cases the frequency distribution of the thickness may look like a Poisson distribution, but it is not (the mean is different from the variance). In dogs, cats, and mice the average thickness of the pleural liquid over most of the costal region (except at the lobar margins) was about 10 μ, with widenings up to 40. μ In rats
The average thickness was about 15 $\mu m$ and in rabbits about 27 $\mu m$. In many rabbits the widenings were more common than in the other species and occasionally reached 120 $\mu m$. They occurred both in the superior and the dependent parts and are probably due to the mechanical inhomogeneity of the tissues involved (10, 14). At the lobar margins the thickness of the pleural liquid is large—more than 100 $\mu m$ (10).

The thickness of the pleural liquid found over most of the costal region suggests that the pleural liquid behaves as a continuous system (see sect. vE). A few regions 10–50 $\mu m$ long where the dark band, corresponding to the pleural space, disappeared were observed occasionally (less than 1%) (10, 14). In these regions the thickness of the pleural liquid should be less than 1 $\mu m$. Somewhere in these regions contacts between the lung and the chest wall could occur; i.e., in these regions the lung and the chest wall should push each other. When the pleural membranes are moving, contacts could take place through a load-carrying film of liquid, i.e., through a hydrodynamic action (10); since the walls are soft one should have an elastohydrodynamic kind of lubrication. The regions where the thickness is less than 1 $\mu m$ were observed so seldom that it does not seem likely that contacts occur only in these regions. First, it would be difficult to understand why the thickness of the pleural liquid is 5–10 $\mu m$ over most of the costal surface in all the species examined. Second, the pressure at such areas of contact would be enormous because of their small size. Since there are cells in the pleural liquid (see sect. vC), most of the contacts between lung and chest wall may take place through these cells; i.e., they may prevent a further apposition of the pleural membranes (176). The monocyte-like cells have an almost spherical shape with a diameter of 10–15 $\mu m$ (176) and the mesothelial cells are 6–7 $\mu m$ thick (see sect. iv).
The fact that the thickness of the pleural liquid is mostly 5–10 μ fits with this hypothesis, provided that the cell concentration in the "surface" region is higher than that in the liquid collected from the costodiaphragmatic sinus (see sect. vC).

When the lung volume is about 3 times that at the resting volume of the respiratory system in the supine posture, the thickness of the pleural liquid is about halved (10). This finding may be explained on pure geometrical grounds, because when the volume increases 3 times the area increases $3^{1/3} = 2.08$ times. Since the volume of the pleural liquid cannot change appreciably during the few minutes between inflation and freezing, the same amount of liquid is spread over about twice the area. Hence one would expect that the thickness of the pleural liquid would be about halved when the lung volume is increased about 3 times. This result is further evidence of the validity of the technique. Furthermore, it shows that the liquid at the lobar margins undergoes the same forces as does the liquid in the other regions; in fact if this were not the case, and the liquid at the lobar margins acted as a free pool, liquid should be displaced from the pool and the thickness in the other regions would decrease less when the lung volume is increased. Consistent with this interpretation is the fact that the reduction in the thickness of pleural liquid produced by the increase of lung volume in rabbits did not involve the widenings only (10).

In newborn cats the average thickness of the pleural liquid was about 40 μ and the frequency distribution of the thickness was more symmetrical, with a peak close to the mean, suggesting that at birth no mechanism reducing the liquid to a minimum is operating. Actually this mechanism is not required because in the mature fetus the lung and the chest wall do not pull apart (see sect. viH). In cats 2 weeks old the average thickness of the pleural liquid was about 10 μ as in the adult, and the frequency distribution of thickness was also similar to that of the adult (F. Agostoni, E. D’Angelo, and M. V. Bonanni, unpublished observations).

Wunder et al. (264) measured the sedimentation rate of microspheres of various density and diameter in the lower half of the pleural space of dogs. Since the sedimentation rate for microspheres of diameter up to 550 μ complied with Stokes law, they inferred that the thickness of the pleural liquid in the lower half of the space should be about 800 μ. This approach, however, seems inadequate to measure the thickness of the pleural liquid occurring under physiological conditions because the walls of the cavity tend to move apart when some fluid is allowed to enter it. The internal diameter of the catheter introduced into the pleural space to inject the microspheres was at least 250 μ larger than the diameter of the microspheres. Considering also the liquid present between the spheres, the volume of liquid introduced with the microspheres of diameter up to 550 μ was equal to or greater than the volume of the microspheres. Hence the volume of the liquid in the pleural space during the measurement was artificially increased. Besides, there are two simple arguments against these findings that seem stronger than any theoretical considerations of the validity of this approach. First, as mentioned by the authors themselves, if the thickness of the pleural liquid in the lower half were about 800 μ, the order of magnitude of the volume of the pleural liquid
in dogs should be 100 ml. Second, it is possible to make an incision in the parietal pleura without producing a pneumothorax (3). This would not be possible if the thickness of the pleural liquid were 800 μ or even if it were 500 μ, because the meniscus of the air-liquid interface at the rims of the incision would be too large (for explanation see sect. vE and vnB).

Finally, Miserocchi and Agostoni (176) found that the average thickness of the pleural liquid over the whole space, obtained by dividing the volume of the pleural liquid by the surface area (see sect. vA), was 53.5 μ in rabbits and 27 μ in dogs. Considering that the thickness in the margin region is much greater than that in the surface region, these data fit with those of 27 and 10 μ, respectively, obtained in the surface region with the quick-freezing approach (14; see above).

E. Pressure

Setnikar et al. (220) were probably the first to measure the pressure of the pleural liquid. They introduced a cannula filled with saline solution into the pleural space of dogs under a layer of liquid and were therefore sure that no air and only a small amount of liquid entered the pleural space. Then they waited until the liquid was reabsorbed and equilibrium was reached. Although their instrumentation was in part inadequate, they were first to show that pleural liquid pressure is lower than that determined by the lung recoil and that the vertical pressure gradient of the pleural liquid is about 1 cm H₂O/cm.

When a device is introduced into the pleural space it produces a distortion in the normal geometry of the space, and hence the conventional methods for measuring pleural liquid pressure could be subjected to criticism. Recently, however, Agostoni et al. (7) developed a method to measure the pressure of the pleural liquid without introducing anything into the pleural space. They took advantage of the fact that an incision made with a minimum of pressure on the parietal pleura of an apneic animal does not cause a pneumothorax because the surface tension of the air-liquid meniscus at the rims of the incision prevents the lung and the chest wall from moving apart (3; see sect. vnB). They fixed a capsule on the tissues surrounding the incision and lowered the pressure in it below the probable value of the pleural liquid pressure. Then they substituted some air of the capsule with an equal volume of isotonic saline solution and slowly raised the pressure in the capsule. When the pressure of the liquid on the incision was just above that of the pleural liquid, the liquid of the capsule started to enter the pleural space. The values of the pressure of the pleural liquid thus obtained were similar to those obtained through cannulas 1 mm in external diameter. This suggests that the liquid surrounding the cannula communicated with that in the undistorted regions.

The data that follow were obtained from measurements through cannulas, needles, or catheters 1–1.5 mm in external diameter connected to a low-compliance pressure transducer, the whole measuring system being filled with liquid. While in the works of Agostoni and his associates (4, 14) the cannulas were introduced under a layer of liquid, this precaution was not used by Surprenant and
Rodbard (232) nor by Wood and his associates (26, 211, 212), who nevertheless took particular care to avoid the entrance of air into the pleural cavity.

A vertical pressure gradient of about 1 cm H$_2$O/cm has been found in dogs in the lateral (14, 211, 212), supine (14), prone (211), head-up, and head-down (232) postures. On the other hand, Rutishauser et al. (211, 212) found a mean gradient of only 0.64 cm H$_2$O/cm in the supine posture, and Banchero et al. (26) found in 3 of 5 dogs in the head-up posture that the gradient was almost nil above the cranial part of the heart and about 1 cm H$_2$O/cm below this level. In some instances they obtained the same results in the esophagus by measuring the pressure through a liquid-filled catheter. Moreover, Rutishauser et al. (212) in dogs exposed to ventral, dorsal, right lateral, and left lateral accelerations of 2.1, 4.3, and 6.7 g for 60 sec found that the vertical gradient increased proportionally to the acceleration. That is, the mean values of the vertical gradient, expressed in cm H$_2$O/(cm·g), were almost 1 in the lateral and prone postures and 0.7 in the supine posture, confirming their previous finding at 1 g. A gradient of 1 cm H$_2$O/cm of vertical distance has been also found in cats and rabbits in the lateral (14), supine, and head-up (4, 67) postures, and in rats (14) and rams (E. Agostoni and E. D’Angelo, unpublished data on 3 animals) in the lateral posture.

On the basis of finding a vertical gradient smaller than 1 cm H$_2$O/cm in some postures and, particularly, of finding in some cases a vertical gradient less than 1 above the upper border of the heart and about 1 below this level, Wood and his associates (26, 211, 212) maintained that the vertical gradient depends on the weight of the average thoracic contents and that therefore they were not measuring the pressure of the pleural liquid. More recently they seem to have recognized that they were measuring the pressure of the pleural liquid, when the vertical gradient was 1 cm H$_2$O/cm, but only on the basis of their belief that the pleural liquid is about 800 μ thick (264; see sect. vD). Actually there are arguments against their interpretations. 1) Their experimental approach would measure the pressure of the pleural liquid, even if its thickness were 100 times less (14, 189, 219, 220). 2) The average thoracic contents would have to act as a fluid of appropriate density in order to produce the vertical pressure gradient found. This, however, is not the case for the lung (see sect. viF) and the heart behaves even more like a solid in this respect (14). 3) The fact that the vertical gradient increased proportionally to the acceleration proves only that the vertical pressure gradient is gravity dependent: if the vertical gradient depended on the weight of the liquid, and not on the weight of the thoracic contents, it should also have increased proportionally to the acceleration (14). 4) The very low vertical pressure gradient found by them in some head-up dogs above the upper border of the heart could indicate that in the superior part the pleural liquid did not behave as a continuous system, at least under their experimental conditions. That this may occur is suggested by the finding of Permutt et al. (189) on the excised esophagus.

These authors suspended vertically a dog esophagus, displaced all the air contained in its lumen by injecting water from the bottom, and tied the upper
end over a rigid tube, connected to a pressure transducer. The system was filled with water and the transducer was kept at the same height as the tip of the tube and moved with it along the esophagus. The water contained in the esophagus was then allowed to drain until no more liquid came out through the tube inserted at the lower extremity of the esophagus. After having closed the drain, the pressure of the liquid left between the walls of the collapsed esophagus was measured. The pressure was subatmospheric at all the heights of the esophagus and decreased by 1 cm H$_2$O/cm vertical distance up to a given height, above which it remained almost constant. That is, above this level the liquid in the anfractuositites between the contacting walls of the esophagus no longer behaved as a continuous system. The value of liquid pressure at which the liquid channels were interrupted was lower (more subatmospheric) the greater the longitudinal tension of the esophagus. This finding is interesting in connection with the fact that the thickness of the pleural liquid decreases when the lung volume is suddenly increased (see sect. vD): when the lung volume increases the pleural membranes are tensed, and therefore the continuity of the pleural liquid might be preserved up to a certain extent in spite of the smaller volume of liquid per unit of pleural surface. Finally, since the pressure acting on the surface of the excised esophagus was atmospheric, the simple experiment of Permutt et al. (189) provides a clear demonstration of the difference between liquid pressure and surface pressure (see sect. iii).

Since the pleural liquid is in equilibrium with the pulmonary capillaries, a vertical gradient of 1 cm H$_2$O/cm could be the expression of the vertical gradient in the pulmonary capillaries and therefore does not prove the continuity of the pleural liquid (10, 189). On the other hand, if a small amount of saline is introduced into the pleural space, the pressure of the pleural liquid increases by the same amount in the dependent part, where the thickness of the pleural liquid is increased, and in the superior part, where the thickness is still normal (4). This suggests that the pleural liquid, in the species examined, behaves like a continuous system, as shown by the values for the thickness of the pleural liquid. When a gradient of less than 1 cm H$_2$O/cm is found, it should indicate either a discontinuity of the pleural liquid and a less than hydrostatic gradient of pulmonary capillary pressure or a vertical flow of pleural liquid. The lack of vertical gradient in the pulmonary capillaries could occur in the superior part of the lung of a relatively large animal in the head-up posture because these capillaries are not perfused (90, 255). On the other hand, there is no evidence of an appreciable vertical flow of pleural liquid (222).

In the lateral posture the end-expiratory pressure of the pleural liquid in the most dependent part of the space was about the same in all the species studied (cats, dogs, rabbits, rams, rats): the average value for each species ranged from about $-1$ to $-2$ cm H$_2$O (14; E. Agostoni and E. D’Angelo, unpublished observations). Similar data have been found in supine cats, dogs, and rabbits (4, 14, 67). Although only slightly subatmospheric, these values are lower than pleural surface pressure (see sect. viii). The relatively high pleural liquid pressure at the bottom in the lateral and supine postures suggests that the difference between the colloid
osmotic pressure of the plasma and the pulmonary capillaries pressure in the most 
dependent part of the lung is small and/or that the resistance to the flow of liquid 
through the parietal pleura is not high relative to that through the visceral pleura 
(see sect. vG). Since the vertical pressure gradient is about 1 cm H₂O/cm, the 
taller the chest the lower the pressure of the pleural liquid in the upper part of 
the space, at least in the species studied. In rams in the lateral posture the height 
of the pleural space was about 22 cm and the pressure of the pleural liquid at the 
top was −24 cm H₂O (E. Agostoni and E. D’Angelo, unpublished observations).

In the head-up posture the end-expiratory pressure of the pleural liquid of 
cats and rabbits at any distance from the bottom was 2–4 cm H₂O lower than in 
the lateral or supine posture (2, 67). This indicates a greater pressure for ab-
sorbing liquid from the pleural space and hence a lower pressure in the pulmonary 
capillaries. This could depend on the smaller central blood volume occurring 
in the head-up posture. It must be considered that these data refer to anesthe-
tized animals and that the situation in conscious man could be somewhat differ-
ent. When an animal is placed in the head-up posture, a decrease of pressure in 
the pleural liquid occurs immediately, too soon to be accounted for by a change 
of pressure in the pulmonary capillaries, because this requires some time to produce 
an effect on the pleural space. In this connection it must be considered that when 
the animal is moved from the supine to the head-up posture, the end-expiratory 
lung volume increases. Besides the increase of lung recoil, this involves a decrease 
of the thickness of the pleural space (see sect. vD) and an increase of the deforma-
tion forces. Hence, the pleural liquid pressure decreases. The decrease in the 
pleural liquid pressure that occurs just after the shift to the head-up posture is 
due to the increase in lung volume. If this posture is maintained for 
about half an hour, the pleural liquid pressure comes into a new equilibrium with 
the pressure in the pulmonary capillaries. Since the pressure has also decreased 
in the capillaries, the pleural liquid pressure changes little to reach the equilibrium 
(2). Similarly the increase of lung volume produced by inspiration causes a de-
crease in the pressure of the pleural liquid (13, 14; see sect. viii).

It is worthwhile to compare the pressure of the pleural liquid with that of the 
interstitial liquid of the lung, although we know little of the latter. The interstitial 
space of the lung is very small (165, 249), hence a small change of volume of the 
liquid may produce a marked change in the protein concentration. The changes 
of the colloid osmotic pressure of the interstitial liquid after the changes of its vol-
ume have been computed by Wiederhielm (257) assuming a constant compliance 
for the interstitial space. It must be considered, however, that the compliance 
should decrease markedly when the walls of the interstitial spaces begin to contact. 
If the pressure of the interstitial liquid were not subatmospheric, it seems likely 
that the alveoli would draw liquid into the interstitial space through the same 
mechanism by which they maintain patency of collapsible vessels (40, 141, 185); 
morover, the surface tension of the alveolar air-liquid interface would draw liquid 
into the alveoli. The data of Meyer et al. (167) indicate that the pressure of the in-
terstitial liquid in dog lungs is about −15 cm H₂O. No indication is given on the 
height of the lung at which these measurements were taken. Moreover, these data
should be taken with reservation because of the trauma produced by the implanted capsule. Stromberg and Wiederhielm (230) maintained that part of the negative pressure recorded in implanted capsules may result from difference in colloid osmotic pressure between capsule liquid and interstitial liquid. On the other hand, apart from considerations on the validity of their arguments, the interstitial liquid pressure measured in subcutaneous tissue with the "wick" technique (231), which should not be affected by the capsule artifact, was similar to that found in capsules implanted in subcutaneous tissue. Indirect data of Levine et al. (138) and Mellins et al. (165) suggested that the pressure of the interstitial liquid in dog lung is about -12 cm H₂O; moreover, Levine et al. (138) calculated that the colloid osmotic pressure of the interstitial liquid of the lung is only a few cm H₂O as in other tissues. On the other hand, Lunde and Waaler (144), on the basis of experiments on isolated perfused lung of rabbits, postulated a relatively high colloid osmotic pressure and a nearly atmospheric hydrostatic pressure in the interstitial space, as formerly suggested by Hughes et al. (121), who, however, did not consider the possibility that the pressure of the interstitial liquid could be subatmospheric. It should be taken into account in this connection that the determination of the pressure of the interstitial liquid from measurements of water accumulation in the lung may be misleading, because a considerable amount of liquid accumulates in the interstitial space only when the pressure of the interstitial liquid is nearly atmospheric (104, 165).

F. Relationships Between Volume, Pressure, and Thickness in Experimental Hydrothorax

The change in pressure of the pleural liquid per unit of volume of liquid introduced into the space decreases progressively as the volume of liquid increases, and then becomes almost constant (Fig. 4). This is because the increase of pressure produced by the first amount of liquid introduced depends on the release of the deformation forces related to the contact between the lung and the chest wall, whereas the increase of pressure produced by the introduction of further liquid is mainly related to the decrease of lung volume in the dependent part, where the lung no longer contacts the chest wall (4, 220). Rutishauser et al. (211, 212) did not find an increase of pleural liquid pressure after the introduction of 0.02 ml of heparinized saline solution into the pleural space and emphasized this finding against the distinction between pleural liquid and pleural surface pressure. In a subsequent work (26), however, they found an increase of pleural liquid pressure in some cases.

The thickness of the pleural liquid at different heights in the pleural space after the introduction of various amounts of isotonic saline solution in supine cats is shown in Figure 5. At a given height and for a given volume of liquid introduced, the thickness of the liquid layer was about the same in the cranial and caudal parts (4). The introduction of small amounts of saline solution, up to about 0.7 ml into the pleural space of supine cats did not increase appreciably the thickness of the pleural liquid in the most dependent part. This suggests that the first liquid introduced flowed to the lobar margins, where the thickness was not measured and the lung pull was bigger. The finding that the introduction of 0.7 ml of liquid does not
increase appreciably the thickness of the pleural liquid, but does increase its pressure (Fig. 4), is further proof that pleural liquid pressure is lower than pleural surface pressure even in the most dependent part of the pleural space. When the deformation forces acting at the lobar margins are in part released, the liquid starts to collect on the flat surface of the lowermost part. From this stage on, up to a relatively large hydrothorax (20 ml), the thickness of the liquid layer in the lowermost part
of the pleural space increased approximately with the logarithm of the volume of liquid introduced (4).

When liquid is introduced into the pleural space the level at which the pressure in the pleural liquid is zero rises more than the lowermost part of the lung does; hence, an appreciable part of the lung is compressed. For instance, after the introduction of 20 ml of liquid into the pleural space of supine cats, the level of zero pressure was 10 mm above the lower border of the lung; i.e., pleural surface pressure was positive over about 1/6 of the lung height (4).

The relationship between the pressure and the thickness of the pleural liquid in hydrothoraces of small and medium size in the supine posture is illustrated by Figure 6. From this relationship and the preceding data it can be inferred that, within a wide range of hydrothorax size, the respiratory system may be divided into three zones. 1) In the upper zone, the thickness of the pleural liquid is normal; the pressure of the pleural liquid is higher than normal but lower than the pleural surface pressure because over this region the lung contacts the chest wall. 2) In the middle zone, which extends from the level at which the thickness of the pleural liquid is increased to such an extent as to eliminate the points of contact to the level of zero pressure, pleural liquid pressure equals pleural surface pressure. 3) In the lower zone, the pressure of the liquid is positive; therefore, both the lung and the chest wall are pushed apart by the pressure of the pleural liquid (4).

G. Exchange Through Pleural Membranes

The old literature on this subject was reviewed by Cunningham (65). The absorption of liquid from the pleural cavity may occur through the lymphatics.

![Figure 6](http://physrev.physiology.org/)
and the blood, that of particles and large molecules only through the lymphatics (77). Starling and his coworkers (136, 225) established the following fundamental facts. 1) The removal of liquid through the blood is faster than that through the lymphatics. 2) Isotonic and slightly hypertonic saline solutions are removed without active transport; hence the pleural membranes act as size-selective barriers through which the passage of liquid is determined by mechanical and osmotic forces. 3) The pleural membranes are less permeable to electrolytes and glucose than to water, as is the case for the alveolar membrane (52; see below).

The lymphatic drainage from the pleural cavity was reviewed in 1954 by Courtice and Simmonds (63) and therefore only the points of more direct interest are summarized here. Nearly all lymphatic absorption takes place in the parietal pleura. The communications between lymphatics and pleural cavity do not seem permanent, as had been believed by Dybkowsky (77), but are due to temporary dehiscences of adjoining mesothelial cells occurring when the pleura is stretched. Allen and Vogt (18) showed that the intercostal lymphatics could be filled by placing a carbon suspension over the pleura on the excised part of the chest wall and stretching the tissues. The importance of the respiratory movements for the passage of liquid and particles through the mesothelial lining and subserous tissues into the lymphatics and for the propulsion of the lymph stream is paramount; rhythmic contraction of the wall of the larger lymphatics could also occur (63, 73).

Courtice and Simmonds (63) showed in cats that lymphatic flow was increased by hyperventilation and decreased by hypoventilation. Stewart and Burgen (227) calculated the lymphatic flow from the disappearance of labeled proteins injected into the pleural space and from the appearance of these proteins in the circulating blood. After injection of a rather large quantity of plasma into the pleural space, they found that the injected liquid was absorbed by the lymphatics, while a somewhat smaller amount of liquid filtered from the blood into the pleural space. The lymphatic flow was not affected by the composition of the injected liquid, but was increased by the rate and depth of the respiratory movements. It is not clear, however, why the lymphatic flow was elevated for many hours after the end of hyperventilation. The flow of liquid from the blood to the pleural space was markedly reduced and in some cases even reversed if saline solution, instead of plasma, was injected into the space. Unfortunately in all these experiments signs of increased permeability of the blood capillaries appeared and therefore, as pointed out by Stewart and Burgen (227), their results do not apply to physiological conditions.

In conclusion, the lymphatics seem to be a way for the drainage of pleural liquid, proteins, and particles, without a selective absorbing action. They may be an important emergency mechanism. They probably are not directly involved in setting the pressure and volume of the pleural liquid under normal conditions (219).

The surface of the lung in open-chest dogs absorbs isotonic saline solution with a pressure related to the difference between plasma colloid osmotic pressure and pulmonary capillary pressure (17). This finding was confirmed in isolated lobes of dog lungs with artificial perfusion (15). Since the visceral pleura of dogs is mainly supplied by the pulmonary circulation, the pressure in its capillaries is relatively low. As mentioned previously (sect. iv) some morphologists maintain that in
some species (including man) the visceral pleura is mainly supplied by the bronchial arteries. However, since the blood from the pleural capillaries is mainly drained by the pulmonary veins it is conceivable that in the pleural capillaries the pressure is relatively low regardless of the supply. Unfortunately the value of the pulmonary capillary pressure is defined only within broad limits. In the supine dog the pressure in the pleural capillaries at the height of the left atrium should be about 12 cm H₂O (15, 17). The colloid osmotic pressure of the plasma is about 29 cm H₂O (15, 17) and that of the pleural liquid is about 3 cm H₂O (176); hence the net colloid osmotic pressure through the visceral pleura should be 26 cm H₂O, and the net absorbing pressure of the pleural capillaries should be 26 - 12 = 14 cm H₂O. If the parietal pleura were impermeable to liquid the equilibrium should be reached when the pressure of the pleural liquid at the height of the left atrium were -14 cm H₂O. Actually at this height in a supine dog the pressure of the pleural liquid is about -10 cm H₂O. This indicates that the overall net pressure driving liquid out of the cavity through the visceral pleura is about 4 cm H₂O and implies that there must be a flow of liquid through the parietal pleura into the cavity. Since the pressure in the capillaries of the parietal pleura at the height of the left atrium should be about 26 cm H₂O, and the other factors are the same as those across the visceral pleura, the overall net pressure driving liquid into the cavity through the parietal pleura should be about 10 cm H₂O. At equilibrium the flow of liquid through the two membranes must be equal (except for the drain through the lymphatics that under normal conditions should be nearly negligible); hence these values of net driving pressure would indicate that the flow resistance through the parietal pleura is greater than that through the visceral pleura, although not so much as one would expect on anatomical ground because of the greater extent and vascular supply of the visceral pleura. The data of capillary pressure are not precise enough for this comparison: they have been used only to illustrate the forces exchanging liquid through the pleural membranes. It appears from the above considerations that the higher the flow resistance through the parietal pleura, the lower the pressure of the pleural liquid. Since the gravitational effect operates both on the capillaries of the membranes and on the pleural liquid the values of the net pressure driving liquid across each membrane should be equal at various heights (219, 222). An analysis in postures other than the supine is prevented by lack of information on the capillary pressure.

When saline solution is introduced into the pleural space the equilibrium is disturbed; the pressure of the pleural liquid rises and therefore the net driving pressure across the visceral pleura increases while that across the parietal pleura decreases. As a consequence, the outflow of liquid through the visceral pleura should become higher than the inflow through the parietal one. The volume of the liquid is then reduced until the deformation forces produced by the contact between the membranes lower the pressure of the pleural liquid to its original value, preventing a further reduction of its volume (see sect. 11.4). The equilibrium is thus reestablished. The conductance of the visceral pleura plus the walls of capillaries for isotonic saline solution in open-chest dogs and isolated lung lobes has been found to be, respectively, \(0.4 \times 10^{-3}\) and \(0.9 \times 10^{-3}\) ml/hr per cm H₂O per cm² of
pleural surface (15, 17). The rate at which saline solution is removed from the pleural cavity of animals has not been studied systematically. From a few unpublished observations of this laboratory the scattering seems great.

The essentials of the exchange of liquid between the interstitial space of the lung and the alveoli are summarized here for comparison. Since Colin (60) found that a horse tolerated the intratracheal administration of 21 liters of water in 3.5 hr, several investigators have confirmed the rapid absorption of water or isotonic saline solution from the lung (63). Most of this absorption must occur through the pulmonary capillaries because the lymphatic drainage is relatively slow [the lymphatics do not reach the alveoli: the liquid flows through interstitial paths and reaches the lymphatics in the peribronchial and perivascular spaces (226)]. Although Uter et al. (240) did not find a relationship between the exchange of liquid through the pulmonary capillaries and plasma colloid osmotic pressure, the results of several investigations show that these exchanges occur according to the Starling equilibrium (94, 106, 121, 138, 144, 165, 106). The earliest manifestation of pulmonary edema is the accumulation of liquid in the interstitial space (246), between the basement membrane and the alveolar epithelium (62) and in the perivascular and peribronchial spaces (120, 226, 254); in these last places the surface pressure may be lower than in the pleural space (161; see sect. viiJ). The later formation of alveolar edema could be related a) to the subatmospheric pressure and the compliance of the spaces mentioned above, and b) to the smaller permeability of the alveolar epithelium to electrolytes than to water (52). This lower permeability should produce a transient osmotic pressure difference opposing the filtration of water. Accumulation of liquid in the pleural space should occur after the interstitial edema, both because the visceral pleura provides a further mechanical resistance to the passage of liquid and because the pleural membrane, like the alveolar membrane, is less permeable to electrolytes than to water (136). Since the pressure in the pleural liquid is lower than in the alveoli, one might expect liquid to accumulate in the pleural space before it does in the alveoli. On the other hand, since the resistance to liquid flow through the pleural membrane should be greater than that through the alveolar epithelium, which is thinner, and since the thickness of the pleural liquid does not increase markedly until its pressure is nearly atmospheric (see sect. vF), the thickness of the pleural liquid could still be nearly normal after the onset of the alveolar edema. Experiments on rabbits, intravenously infused with saline solution, suggest that this is the case (E. D’Angelo and E. Agostoni, unpublished observations).

VI. PNEUMOTHORAX

A. Pressure

The volume-pressure relationship of the respiratory system in a closed pneumothorax providing a continuous layer of gas between lung and chest wall has been dealt with above (see sect. ii). In man and in those animals in which the two
pleural spaces are separated, the matter is complicated by the displacement of the mediastinum, which is pulled toward the normal side by the greater recoil of the uncollapsed lung. The pressure in the cavity is higher the greater the volume of gas that entered it. Owing to the compliance of the gas phase between the lung and the chest wall, the movement of the former lags behind that of the latter, the lag being greater the larger the amount of gas. A continuous layer of gas between the lung and the chest wall occurs probably only with a fairly large pneumothorax in the head-up posture. With a small or medium pneumothorax one or more gas cavities form, and part of the lung adheres normally to the chest wall. The pressure in the gas cavity depends essentially on the recoil of the part of lung involved (see sect. viiE).

In an open pneumothorax the volume of the gas in the cavity changes periodically with breathing. Its tidal change is greater the lower the flow resistance of the connection between the ambient and the pleural space relatively to the flow resistance of the respiratory system. If the exit of air from the pleural space is hindered (i.e., if there is a valve-like mechanism in the connection), the pressure in the cavity may increase considerably above atmospheric during expiration.

B. Exchange of Gas

The physiological equilibria of collapsible gas cavities were reviewed by Piiper in 1965 (194) and only the more relevant points are summarized here. Transfer of any particular gas from a cavity into the tissue-blood environment or vice versa is determined by the partial pressure gradient for this gas. The rate of transfer of each gas depends on its partial pressure gradient and its coefficients of diffusion and solubility. In most cases during the process of absorption a condition of constant composition of the gas in the cavity is eventually reached and kept until complete reabsorption has occurred (194, 204).

Owing to the shape of the blood dissociation curves for O2 and CO2 and to the alveolar-arterial O2 gradient, the pressure of the gas in the venous blood is about 70 cm H2O below atmospheric and nearly that much lower than the pressure in a closed pneumothorax (see sect. IIIA). Hence the gas of the cavity is absorbed by blood and the pneumothorax disappears (204).

When air is introduced into the pleural space, CO2, because of its high solubility, enters faster than N2 and O2 leave. Hence, for several minutes there is a slight increase of the volume and pressure of the gas in the cavity in spite of the fact that the total gas pressure of the blood-tissue environment is lower than that inside the cavity (194, 204). During air breathing the condition of constant composition is reached before 60% of the gas is absorbed (194). Under this condition the pressure difference between gas cavity and blood-tissue environment is given mainly by N2, because of its little solubility and diffusibility. The partial pressures of CO2 and O2 in the gas cavity are only slightly higher than those in the surrounding tissues, whereas the partial pressure of N2 is markedly higher, and higher than in the atmosphere (194, 204).

If only N2 instead of air is introduced into the pleural space the initial increase
of volume and pressure of the gas cavity becomes more evident, because both CO₂ and O₂ enter it faster than N₂ leaves it. This phenomenon becomes marked if the synthetic, inert gas sulfur hexafluoride (SF₆) is used. Data obtained in the pneumoperitoneum (234) show that the volume of gas in the cavity after some days is almost doubled because N₂ enters faster than SF₆ leaves it. Then for a while, SF₆ leaves faster than N₂ enters and the volume decreases. The condition of constant composition is eventually reached.

VII. PLEURAL SURFACE PRESSURE

Pleural surface pressure is the force per unit area of pleural surface (see sect. III). It is equal to alveolar pressure minus static transpulmonary pressure (see sect. II). Transpulmonary pressure is taken as positive when the pressure inside the lung is higher than that on its surface. In this review all transpulmonary pressures are static unless otherwise specified. Pleural surface pressure was generally considered to be evenly distributed and equal with opposite sign to the transpulmonary pressure of an excised lung at the same volume. This provides an approximate and analytically useful idea of the overall pressure exerted by the lung on the chest wall (see sect. II). However, since pleural surface pressure should change from region to region because of gravity and the deformation that the lung and the chest wall undergo in fitting each other (76, 154, 207), it is important to know the topography of the pleural surface pressure.

Knowledge of the distribution of pleural surface pressure has been one of the most challenging problems in the physiology of respiration during the last 10 years, both experimentally and theoretically. It therefore seems worthwhile first to discuss the methods of measurement of pleural surface pressure, dividing this matter in two: 1) measurement of overall transpulmonary pressure and 2) measurement of local pleural surface pressure, which in turn may be conveniently grouped into direct and indirect.

The following factors affect the transpulmonary pressure at a given lung volume and they are therefore mentioned first because they apply to all kinds of measurements of pleural surface pressure. The recoil of the lung is affected by the previous volume history (32, 87, 157, 221; see also sect. II). Hence, in order to have comparable data measurements are commonly taken within a short time after a near-maximum inflation of the respiratory system. The recoil of the lung decreases with age (see sect. VII). It has been known since the last century (28, 139) that the pulmonary blood volume may affect the static properties of the lung; Frank (89) showed that an increase of pulmonary blood volume slightly decreases the lung recoil at small lung volumes and increases it slightly at large lung volumes. Contrary to the belief of morphologists of the past (14, 203), the contraction of the bronchial smooth muscle does not alter appreciably the static features of the lung, except to the extent that it might close some airways and decrease the lung volume (199, 200). On the other hand, the contraction of respiratory bronchioli and alveolar ducts increases the lung recoil and decreases the lung compliance (58, 178, 263). Respiratory bronchioli and alveolar ducts are constricted by
histamine, acetylcholine, and serotonin (57, 58) and dilated by epinephrine-like substances (57). According to Olsen et al. (183) vagal stimulation has only a minor effect on the respiratory bronchioles and alveolar ducts. Woolcock et al. (263), however, provided evidence that peripheral airways may be constricted by vagal stimulation, although the differences among dogs were considerable. The increase of lung recoil, resulting from constriction of peripheral airways, did not occur when the vagi were stimulated at high transpulmonary pressure (263). Moreover, Woolcock et al. (262) showed that beta adrenergic blockade caused increase in peripheral airways resistance in all dogs and increase in lung recoil in most. Since the peripheral airways contribute little to the airway flow resistance, their constriction may affect the static properties of the lung without producing a marked increase of airway flow resistance (263). Anesthesia with barbiturate in dogs lowers the tonus of the airway smooth muscles, while that with chloralose and urethane does not [P. T. Macklem, quoted by Wohl et al. (260)]. Marked and prolonged hypoxia with hypercapnia or ventilation with a hypercapnic mixture increases the retraction force of the lung, whereas normocapnic acidosis does not (80). There is a negligible change in lung recoil with temperature between 20 and 37 C [E. P. Radford, Jr. and N. R. Frank, quoted by Mead (154) and Wohl et al. (260)].

A. Methods of Measurement of Overall Transpulmonary Pressure

There are essentially three approaches for the determination of the overall transpulmonary pressure: 1) closure of the airways at any desired lung volume and measure of the airway pressure after a quick and wide opening of the chest wall; 2) closure of the airways at any desired lung volume, opening of the chest wall, and measure of the airway pressure after having isolated the lungs and suspended them from the trachea; 3) measure of the pressure in a relatively large pneumothorax.

In the first approach, when the chest wall is opened in the horizontal postures, the surface of the bottom of the lung undergoes a positive pressure because of the lung weight, and in some postures also because of the heart weight. Hence the overall transpulmonary pressure is slightly overestimated relative to lungs suspended from the trachea. If the chest wall is opened in the head-up posture the lung is supported from the trachea, so that the pressure on all its surface is atmospheric, but the tension exerted by the membranes between the lung and the diaphragm should be eliminated.

In the isolated lung the retractive force of the lung may be altered owing to the changes in the tonus of the smooth muscles of the airways. A small, generally negligible decrease of lung volume during the period taken to isolate the lung may result from cooling of the air within the lung and diffusion of gas out of the lung. Van der Brugh (241), Christie and McIntosh (54), and McIlroy (149) found that the static properties of the lung change soon after death. Mead (154), however, pointed out that most of these changes occur also with changes of the volume history of the lung during life.

A relatively large pneumothorax involves the introduction into the pleural
space of a volume of gas sufficient to separate the lung from the chest wall, except for the supporting surface in the horizontal postures. Since the volume of the lung is reduced, it is necessary to know the gas volume in the pneumothorax and the volume-pressure relationship of the lung and of the chest wall in order to correct for the decrease of lung volume. Furthermore there are problems connected to the lung weight in the horizontal postures and to the pulling of the membranes between lung and diaphragm in the head-up posture, which under this condition are difficult to solve.

It appears from these considerations that the more reliable value of the overall transpulmonary pressure is obtained by the first approach, after correction for the effect of the lung weight. This effect is determined in the isolated lung by measuring the difference in the overall transpulmonary pressure between the lung suspended from the trachea and replaced in situ.

B. Direct Methods of Measurement of Local Pleural Surface Pressure

1) Small pneumothorax (38, 51, 54, 59, 61, 66, 79, 162, 181, 197, 258). A small pneumothorax is a condition under which only a relatively small area of the lung is separated from the chest wall by a gas phase. This approach is probably most deceptive, particularly if the amount of air is very small. Neergaard and Wirz (179, 181) pointed out the artifacts that may occur because of the surface tension at the gas-liquid interface. If a very small amount of air is introduced and the radius of curvature of the bubbles formed is small enough, the retraction force of the lung may be completely balanced by the surface tension and the pressure in the bubbles may be atmospheric (179). If a somewhat larger amount of air is introduced, much of the air may ascend toward the top of the cavity, leaving only one or a few small bubbles around the holes of the needle. Despite the papers of Neergaard and Wirz the problem of surface tension artifact was disregarded until Setnikar et al. (220) again called attention to it. Christie and McIntosh (54) considered this problem insignificant. Farhi et al. (79), who made an accurate study of the dynamics of their transmission system, observed the formation of several small bubbles when less than 1 ml was present in the pleural space of dogs, but overlooked the possibility of surface tension artifacts. They described abrupt changes of pleural pressure for which they had no explanation. These changes occurred even after death, not simultaneously at all points, and without corresponding changes of lung volumes; they were probably caused by changes in the dimension of the gas-liquid menisci, consequent to the division or confluence of bubbles. Besides the surface tension artifact at the air-liquid interface, one must consider that, when the volume of gas around the tip of the cannula is small, the radius of the lung surface deformed by the cannula is small and this may add an appreciable error (see below). In conclusion, most of the measurements done with this approach seem unreliable, with the possible exception of those in which a pneumothorax of a few milliliters was made in the superior part of the chest (38, 162). In order to know what is really measured, the region over and around the tip of the cannula should be cleared of tissues (except at the point where the
cannula was inserted) until the limits of the gas phase may be discerned. It is thus possible to control the conditions of the site of measurement and to know the region of lung involved. The pressure in gas bubbles of 3 ml made in dogs far from the lobar margins and under this control was about 0.3 cm H₂O higher (less sub-atmospheric) than that measured at the same site, before the pneumothorax, with the counterpressure technique (see below) (G. Miserocchi, E. D’Angelo, and E. Agostoni, manuscript in preparation).

2) Pleural balloon (38, 119, 135, 153, 238). Despite the early attempt of Ludwig (143) with a water-filled balloon, this approach has been used comparatively little and only recently. Small, thin-walled latex balloons, containing the minimum volume of air compatible with unstretched wall, are used. The data obtained by Krueger et al. (135) suggest that this method could not yield reliable data unless improved. Turner (238) did not provide values of pressure, but referred only to the vertical gradient of transpulmonary pressure. Hoppin et al. (119) and McMahon et al. (152, 153) tried to solve the problem of the deformation of the lung surface produced by the measuring device.

McMahon et al. (152) made a systematic analysis on a model to evaluate the devices introduced into the pleural space for measurement of surface pressure. Since at the edge of any device placed in the pleural space the surface of the lung may have a small radius of curvature and the surface of the lung is under tension, the pressure may be different from that occurring under physiological conditions. Hence it is important that the pressure-sensitive area of the device be far from the edges and that its surface be shaped as that of the lung under physiological conditions. Except for the apex of the lung, the margins of the lobes, and in very small animals, the surface of the lung may be considered nearly flat if the average transpulmonary pressure over a region is to be measured, which is actually what matters from the standpoint of the mechanics of breathing. McMahon et al. (152) concluded that “a thin device with a flat surface and a pressure-sensitive area at some distance from the edge of the device probably offers the best compromise for most purposes.”

Along these lines Hoppin et al. (119) developed the most sophisticated pleural balloon. They used a long flat device with up to seven pressure-sensitive discs surrounded by a wide skirt so that the deformed lung was far from the sensing unit. Since they noticed that the pressure under the ribs was 1-2 cm H₂O higher than that in the intercostal space and related this difference to the curvature produced by the ribs on the lung surface, in most experiments they backed the parietal side of the device with a stiffener made of a sheet of Teflon. The thickness of the measuring device plus the stiffener was 1.3 mm. A flat disc was also used by McMahon et al. (153), but their pressure-sensitive device operated on the principle of a Starling resistor. When the pressure downstream from a Starling resistor is sufficiently lowered, the flow does not increase with further decrease of downstream pressure; under these circumstances flow through the system is extremely sensitive to the surrounding pressure. Hence the air flow through their device was modulated by the pressure acting on the membrane. Both approaches involve a large opening of the chest wall and the relative position of the lung and of the chest wall may be
different from that occurring under physiological conditions. In order to reduce the ensuing pneumothorax, the pleural cavity was washed several times with nitrous oxide after introduction of the device. Most of this gas was then removed by suction and the rest should have been quickly reabsorbed. Occasionally, however, some gas was still found in the pleural space during or at the end of the experiment (119).

3) Counterpressure on exposed surface of lung or of parietal pleura (5, 6, 8, 9, 13, 67, 68). While the Harvard and Johns Hopkins groups were improving the balloon technique, a completely different path was being followed in this laboratory with the aim of measuring pleural surface pressure without introducing a device into the pleural space and without opening the chest wall. This approach (67) stemmed from the same preparation that allowed the pleural liquid pressure to be measured without introducing a device into the pleural space (see sect. vE). In other words, if an incision is made with a minimum of pressure through the endothoracic fascia and the parietal pleura of an apneic animal, no pneumothorax occurs because the surface tension of the air-liquid interface at the rims of the incision prevents the lung and the chest wall from moving apart (3). Since the cut edges of the membrane gape a little, a small area of the lung surface is exposed to atmospheric pressure. Hence this area becomes concave if the lung recoils inward. By sealing a capsule to the region surrounding the incision and lowering the pressure of the air within it, the exposed surface of the lung may be brought back to its normal position. The pressure required for this should be equal to the pleural surface pressure of that region. In order to determine when the lung surface is brought back to its normal position a straight bristle is placed from one rib to the next over the incision and is illuminated in such a way as to cast its shadow on the exposed lung and the surrounding endothoracic fascia. Owing to the relative positions of the light source, the bristle, and the lung, the shadow on the exposed surface of the lung is concave, straight, or convex inward the bristle, according to whether the exposed surface of the lung is concave, flat, or convex—i.e., according to whether the lung exerts a force inward, nil, or outward. The shadow is observed through the Lucite capsule by means of a stereomicroscope. The lung surface is considered to be brought back to its physiological position when the shadow on the exposed surface of the lung is straight (67).

This convenient criterion of reference is based on the following arguments. The shadow of the bristle on the intact endothoracic fascia at FRC is straight or barely concave, and there are no reasons suggesting that, when the endothoracic fascia is exposed, the surface of the lung is markedly displaced relative to physiological conditions. The cut endothoracic fascia moves outward about 0.1 mm when the pressure in the capsule is lowered to straighten the shadow on the exposed sur-

1 While preparing this article I learned that in 1905, to support West's incorrect view that the lung is held against the chest wall by adhesion (see sect. 1), Bruer (37) drew a schema illustrating a preparation with a small incision of the parietal pleura, the lung normally adherent to the parietal pleura in the region surrounding the incision and the exposed surface of the lung concave. It is surprising that nobody thought of taking advantage of this preparation and that it was eventually ignored.
face of the lung. The curvature of the lung surface in the craniocaudal direction should not matter because it is negligible, except at the apical region and in very small animals. In the dorsoventral direction the curvature should not interfere with the measurement since the bristle, and hence its shadow, is placed in the craniocaudal direction, i.e., perpendicular to the dorsoventral curvature. Indeed, when the shadow is straight on the lung it is nearly straight also on the surrounding endothoracic fascia: this may occur only if the latter is in line with the rib in the in-out direction. That is, when the shadow of the bristle is straight, the dorsoventral curvature of the endothoracic fascia and of the exposed surface of the lung should correspond to that of the ribs, as under physiological conditions. Hence, the measurement takes into account the effect of the normal dorsoventral curvature of the lung surface. Moreover, the shadow of the bristle is straight on the exposed surface of the lowermost part of the lung in rabbits and dogs in the lateral and supine postures, where it was shown by a different procedure that the transpulmonary pressure is nil (3, 4; see sect. viiE) and where the balance therefore is obtained by keeping the exposed surface of the lung at atmospheric pressure. In conclusion, the criterion of the straight shadow should involve only a minor error. Since the endothoracic fascia is nearly tangent to the inner surface of the ribs, at least in small- and medium-size animals, the degree of expansion of the lung under the rib should be about the same as that under the intercostal space when the shadow is straight.

This approach made possible a direct determination of the topography of pleural surface pressure over most of the intercostal region without interfering with the physiological apposition between lung and chest wall (5, 8, 9, 67, 68). Its limits are: 1) it can provide only static measurements, 2) it can be applied only to the costal region, and 3) it can be applied only to apneic animals at or above the resting volume of the respiratory system, because breathing movements or deflation break the air-liquid meniscus at the rim of the incision.

The third limit has been overcome by the following modification. A small region of the endothoracic fascia (and probably also of the parietal pleura) is thinned until the region becomes clearly more concave at end inspiration than at end expiration (13); the procedure is then similar to that of the method described above. The results obtained with this approach were in general the same as those obtained with the incision of the parietal pleura. Since this method allows measurements at end expiration and inspiration (provided the breathing frequency is low), it is superior to the previous one, but it is technically more difficult, because it is more difficult to thicken the membrane without breaking it than to make an incision on it without making a pneumothorax. Moreover, when the thinned area is brought back to its physiological position it is essentially flat in the craniocaudal direction, but convex (like the ribs) in the dorsoventral direction (see discussion above on the endothoracic fascia and the exposed surface of the lung). The curvature of the parietal pleura introduces an error because part of the change in pressure required to straighten the shadow is used to overcome the resistance of a structure that does not belong to the lung. The tension of this thin membrane, however, cannot be great and therefore the error introduced should be appreciable only if the radius of curvature is small. This is not the case in the regions investigated unless a very
small animal is used (13). The pressure measured by this approach after having made a small pneumothorax beneath the site of measurement was similar to that measured through a cannula in the gas phase (G. Miscrocci, E. D'Angelo, and E. Agostoni, manuscript in preparation).

C. Indirect Methods of Measurement of Local Pleural Surface Pressure

1) Esophageal pressure. This approach, introduced by Luciani (142) and dismissed as inadequate by Wirz (259), has been widely used since the study of Buytendijk (46). The following references include only the papers concerning the development of the esophageal balloon technique or tending to determine the values of pleural surface pressure and its distribution with this method; they do not include those providing essentially data on changes of pressure with lung volume (20, 42, 45, 51, 64, 66, 78, 86, 93, 131, 154, 158, 159, 162, 170–172, 191, 198, 214, 215, 236, 237, 249, 243, 260). The esophagus and its surrounding structures are part of the recording system (154) and so the esophageal approach is classified here under indirect measurements, although it is not so indirect as those dealt with later. The esophagus at rest is closed at its extremities by sphincters. It is generally relaxed and local spasms or peristaltic waves are easily detected but the effect of a generalized tonus cannot be detected. In man striated muscles are limited to the upper third of the esophagus, whereas in dogs they extend its full length. Although generally collapsed, the esophagus may contain an appreciable amount of air and, under anesthesia, of liquid. It is important to eliminate them because they stretch the esophageal wall (215, 243, 260). The general considerations on surface pressure measurements, which apply to a balloon in the pleural space, apply to a balloon in the esophagus as well. However, since the wall of the esophagus is generally under little tension, deformation artifacts should be small. When the balloon is placed in the esophagus, balloon pressure increases with balloon volume because of the distention of the esophageal wall and the surrounding structures (159, 191); this effect increases at the extremes of lung volume (171). Hence the balloon must be such as to operate with a very small amount of air (0.2–0.3 ml in man) or measurements must be done at various balloon volumes in order to extrapolate to zero volume (171). If the pressure outside the balloon is not uniform the gas within the balloon is displaced to where the surrounding pressure is lower. Hence the pressure recorded by a relatively long balloon approximates the lowest pressure on its surface (154). In the upper third of the esophagus displacements of the trachea may stretch the esophagus and produce artifacts (170). In the supine posture the esophageal pressure is affected by the weight of the mediastinum (86, 131, 158). In the head-up and prone postures the pressure measured in the middle third and the cranial part of the lower third of the esophagus should be close to pleural surface pressure in the same region, provided that there is no tonus of the esophagus. The heartbeat artifacts, however, make reading the record difficult. A systematic study of these artifacts was made by Trop et al. (236). The dynamic response of the esophageal balloon-catheter system was studied by Fry et al. (93). The optimal internal diameter of the catheter was found to be about 1.8 mm: the frequency-re-
response curve of such a system containing air was flat up to frequencies of about 7 cycles/sec. The flat response is extended to higher frequencies if the system is filled with helium because of its lower density. The changes of esophageal pressure followed those of alveolar pressure up to high breathing frequencies.

Several direct comparisons between esophageal pressure measured with the balloon and pleural pressure in a small or medium pneumothorax have been done in man (20, 45, 51, 66, 70, 93, 158) and animals (162, 260). In some of these studies the methods were inadequate for the measurement or the comparison of absolute values of pressure, in most cases the studies having been done only to compare the changes of pressure. In fact esophageal pressure measurement generally has been intended only to provide data on changes of pleural surface pressure with lung volume under static or dynamic conditions (12, 154, 156, 160). The changes of esophageal pressure generally have been found similar to those in the pneumothorax. Recently measurements of esophageal pressure in dogs were done simultaneously with measurements of pleural surface pressure with the counterpressure technique (see above); the average tidal changes of esophageal pressure both in the supine and head-up postures were not significantly different from those of pleural surface pressure both in the superior and in the inferior parts, but individual differences were found (13).

Using short balloons (2–3 cm long) Milic-Emili et al. (170) and Bryan et al. (42) studied the distribution of esophageal pressure in man and Trop et al. (237) in dogs. With the same aim, Proctor et al. (198) measured flow through a Starling resistor placed in the esophagus of dogs. Trop et al. pointed out that the artifacts caused by mediastinal structures may render unreliable the determination of the distribution of the pleural surface pressure from esophageal pressure measurements.

In conclusion, the measurement of esophageal pressure with adequate balloons has provided useful data about changes of pleural surface pressure and has allowed the determination in living man of the static and dynamic volume-pressure relationship of the lung and of the chest wall (see sect. II). It has also provided to some extent data on the absolute value of pleural surface pressure. Hence this method has greatly contributed to the progress of the mechanics of breathing. On the other hand, its contribution to the knowledge of the topography of pleural surface pressure is small. In fact: 1) even data obtained with adequate techniques (42, 170, 198, 237) must be taken with reservation, owing to the possible artifacts introduced by the esophagus and surrounding structures; and 2) only a limited region of the pleural surface may be scanned from the esophagus and only in some postures. At present, however, the esophageal balloon technique is the most direct way to provide some data on the distribution of pleural surface pressure in healthy man.

Measurements of esophageal pressure with air-filled open-tip catheters (76) are affected by artifacts due to the surface tension of the air-liquid interface at the holes of the catheter or within the catheter itself. Moreover, they do not measure real surface pressure (152). Liquid-filled open-tip catheters (26, 27, 72, 150) measure liquid pressure, not surface pressure (189; see sect. IIIB and vE). However, they may be used to measure tidal changes since liquid and surface pressure should change nearly equally in the esophagus.
2) Regional lung volume (23, 42, 128, 168, 233). Studies with lobar spirometry (146, 147) and particularly with radioactive gas dilution techniques (24, 41, 253) showed that ventilation is not even and that its distribution changes with posture. Since the regional distribution of gas in the lung is not determined mainly by regional differences in flow resistance (41), it must be due mainly either to regional differences in compliance of the lung or to regional differences in static transpulmonary pressure. Since the former are small (90), the regional differences of volume distribution must be mainly related to regional differences in static transpulmonary pressure (41). Recent work, however, showed that the regional distribution of ventilation is altered at high flow rates (29, 175, 206).

From measurements of the distribution of regional lung volume, obtained by dilution of $^{133}$Xe during inspiration, and from measurements of esophageal pressure Milic-Emili et al. (168) calculated the transpulmonary pressure as a function of lung height in the seated man. They determined: a) the relationship between regional lung volume and height of the lung during stepwise inspiration from residual volume to total lung capacity; b) the relationship between regional lung volume and overall lung volume at various lung heights, establishing the height at which the relative change of regional lung volume is equal to that of the overall lung volume (isovolume point); and c) the esophageal pressure at this height and its relationship with the regional lung volume at the same height over the vital capacity range. From these data, assuming that the static volume-pressure relationship of the lung is equal at various heights and that the esophageal pressure equals pleural surface pressure at the isovolume point, they calculated the relationship between transpulmonary pressure and lung height over all the vital capacity range. This approach has been extended by Kaneko et al. (128) to man in the lateral, prone, and supine postures and by Bryan et al. (42) to seated man under headward accelerations of 1, 2, and 3 g.

This approach should involve a progressive underestimation of the values of the overall vertical gradient of transpulmonary pressure below total lung capacity. In fact all the measurements of the distribution of regional lung volume have been done at total lung capacity and have been referred to the vertical distance between top and bottom counter, but the vertical distance between the parts of the lung that at TLC are at the height of the top and bottom counter, respectively, becomes smaller as the lung volume decreases. Taking into account the changes of the height of the lung occurring between TLC and FRC in the head-up posture one can roughly estimate that the value of the overall vertical gradient of transpulmonary pressure at FRC should have been underestimated by 10–20%. In the lateral posture, owing to the small change of the lung height over the inspiratory capacity (about 1 cm), the error at FRC should be negligible. The assumption of equal static volume-pressure relationship of the various regions of the human lung is supported by the findings of Sutherland et al. (233), but not by those of Bake et al. (23) in man and of Frank (90) and Faridy et al. (81) in dogs. In this connection it must be considered that a small difference in the static properties of the lobes may affect appreciably the calculated value of overall vertical gradient of transpulmonary pressure, particularly at large lung volume (E. D'Angelo, personal com-
munication). In conclusion, this ingenious approach is quite indirect and requires a sophisticated technique, but in turn it is the only one enabling systematic measurements on man.

3) Alveolar size (102). The topography of pleural surface pressure could be calculated from regional measurements of the alveolar size in situ and from the relationship between alveolar size and transpulmonary pressure of isolated lung lobes. This approach, however, is valid only if the regional size of the alveoli is uniquely related to the regional transpulmonary pressure when the volume history of the lung has been the same and the surface properties have not been altered. This implies that, for a given volume, the shape of the alveoli in situ must be equal to that of the alveoli in the excised lung. An additional problem with this approach is the difficulty of measuring alveolar size with sufficient precision. Glazier et al. (102) froze excised and in situ dog lungs, measured alveolar size by morphometric techniques, and calculated the regional volume of the alveoli. Few data, however, are provided, because they made measurements in the isolated lung only at 2 values of transpulmonary pressure. In the analysis of Glazier et al. (102) it was important that the shape of the alveoli did not change at various lung volumes. Evidence of this was provided by Glazier et al. (102) in the lung in situ, by Storey and Staub (229) in open-chest cats, by Dunnill (74) in excised dog lungs, and by Forrest (88) in open-chest guinea pigs. Macklin (145) and Frazer et al. (92), however, concluded that the shape of the alveoli changes with lung volume. According to Klingele and Staub (130) the shape of the alveoli in isolated lower lobes of cats is approximately constant from 50 to 100% lung volume, but changes at lower volumes.

4) Weight/area hypothesis (102). The finding of a marked decrease of alveolar volume from top to bottom in the head-up posture and of a homogenous volume in the head-down posture led Glazier et al. (102) to apply the weight/area hypothesis to their frozen lungs in order to calculate the vertical distribution of pleural surface pressure. This hypothesis stemmed from Mead’s suggestion of considering the lung as a spring suspended from the top (102, 168, 198), a comparison useful to illustrate but not to explain the difference of alveolar volume from top to bottom. According to the weight/area hypothesis, as reported by Glazier et al., if the lung hangs by the chest wall and the supporting force of the hilum is small, pleural surface pressure at a given height should be given by the weight of the lung below that height divided by the cross-sectional area of the lung at that height. Since the lung is roughly conical in shape, pleural surface pressure and alveolar size should decrease markedly from top to bottom in the head-up posture, whereas they should be about the same in the head-down posture. However, the weight/area hypothesis is inconsistent because the lung is considered as if it were suspended from a single zone, which implies that pleural surface pressure beneath this zone is homogenous, yet this hypothesis has been used to explain the vertical gradient of transpulmonary pressure (36, F. Hoppin, personal communication). In an isolated lung suspended from the apex, regional lung expansion is uniform and pleural surface pressure nil, except where it is clamped (129).

5) Lung density (115). Hogg and Nepszy (115) measured the distribution of lung density both in intact dogs in the head-up posture and in excised lungs by sawing out blocks of frozen lung tissue of known volume and weighing those that
did not contain large airways. The volume of air per unit lung weight was calculated by subtracting the specific volume (1/density) of the gas-free lung tissue from the specific volume of these blocks. The volume of air per unit lung weight was also determined in excised lungs at various transpulmonary pressures and a volume-pressure curve was constructed. From the latter and the volume of air per unit lung weight at various heights in situ, the transpulmonary pressure at various heights in the lung in situ may be calculated. This approach, however, is not so straightforward as it may appear, because the values of regional air volume per unit lung weight of each animal must be expressed as percent of the value at TLC owing to the variance of the lung density. To calculate the regional lung volume Hogg and Nepszy divided the frozen thorax into slices 2 cm thick and computed the volume of each slice of lung from the areas of the top and bottom of the slice using the prismoidal formula. From the volume of a slice and the density of the block taken from it they obtained the weight of the slice and hence the volume of air per unit of weight, as indicated above. To express the regional air volume per unit of lung weight as percent of that at TLC, they measured TLC in the living animal in the prone posture and divided this value by the weight of the lung obtained in the exsanguinated, frozen animals in the head-up posture. The exsanguination was necessary to avoid differences in blood contents and hence in lung density between excised and in situ lungs. From the data of regional volume at various heights and a volume-pressure curve of the excised lung (in which volume was also expressed as % TLC), they calculated the transpulmonary pressure at various heights. In comparison to the measurements of alveolar size this approach offers the advantage that it is less time consuming than morphometry and its avoids any assumption concerning the alveolar shape to obtain the regional lung volume. On the other hand, in order to calculate the local transpulmonary pressure the assumption must be made that the shape of the alveoli at a given volume is the same in excised and in situ lungs. Moreover the computation of the regional volume as percent TLC may introduce an appreciable error because the conditions during TLC measurements were markedly different from those during measurements of regional volume and lung weight. In this connection it must be considered that, as in all cases in which the transpulmonary pressure is calculated from regional lung volume, a small error in the measurement of lung volume involves a large error in the value of transpulmonary pressure at large lung volume owing to the low compliance. Since this method involves an appreciable error in the measurement of regional lung volume expressed as percent TLC, it appears rather unreliable to determine the transpulmonary pressure in the superior part in the head-up posture, since the lung is relatively expanded in this region.

**D. Overall Transpulmonary Pressure**

Surprisingly there are only a few measurements of the overall transpulmonary pressure in which the essential conditions for the measurement are satisfactorily stated. Table 3 summarizes the data obtained at the resting volume of the respiratory system in various postures and species with the first approach described in
TABLE 3. Transpulmonary pressure, lung volume, and lung weight of isolated lungs at resting volume of respiratory system

<table>
<thead>
<tr>
<th>Posture</th>
<th>Species</th>
<th>No.</th>
<th>Body Wt, kg</th>
<th>Lung Wt, g</th>
<th>Lung Vol, ml</th>
<th>Transpulmonary Pressure, cm H2O</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left lateral</td>
<td>Rat</td>
<td>5</td>
<td>0.26±0.02</td>
<td>2.3±0.1</td>
<td>4.5±0.2</td>
<td>1.52±0.08</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>5</td>
<td>0.96±0.09</td>
<td>16.2±1.9</td>
<td>39.3±3.1</td>
<td>1.8±0.08</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>3</td>
<td>6.66±1.05</td>
<td>70.3±3.6</td>
<td>251.0±7.9</td>
<td>2.4±0.06</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>3</td>
<td>15.07±0.78</td>
<td>92.0±4.9</td>
<td>340.0±15.4</td>
<td>2.4±0.06</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>3</td>
<td>28.50±0.77</td>
<td>241.2±6.5</td>
<td>808.5±23.7</td>
<td>2.6±0.06</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Ram</td>
<td>5</td>
<td>75.8±0.34</td>
<td>1088.0±31.1</td>
<td>3864.3±55.9</td>
<td>2.8±0.08</td>
<td>5</td>
</tr>
<tr>
<td>Supine</td>
<td>Rabbit</td>
<td>23</td>
<td>2.07±0.05</td>
<td>16.5±0.4</td>
<td>31.2±1.4</td>
<td>1.9±0.04</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>3</td>
<td>17.00±3.3</td>
<td>70.3±3.6</td>
<td>251.0±7.9</td>
<td>2.5±0.10</td>
<td>67</td>
</tr>
<tr>
<td>Prone</td>
<td>Rabbit</td>
<td>13</td>
<td>1.98±0.05</td>
<td>13.5±1.0</td>
<td>36.7±2.5</td>
<td>3.2±0.06</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>8</td>
<td>11.90±1.90</td>
<td>37.0±1.3</td>
<td>110.0±3.4</td>
<td>2.5±0.14</td>
<td>67</td>
</tr>
<tr>
<td>Prone suspended</td>
<td>Rabbit</td>
<td>4</td>
<td>2.10±0.09</td>
<td>13.5±1.0</td>
<td>36.7±2.5</td>
<td>3.2±0.06</td>
<td>8</td>
</tr>
<tr>
<td>Head-up</td>
<td>Rabbit</td>
<td>14</td>
<td>2.09±0.09</td>
<td>10.7±0.6</td>
<td>49.7±1.4</td>
<td>4.7±0.15</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>6</td>
<td>9.07±0.58</td>
<td>10.7±0.6</td>
<td>49.7±1.4</td>
<td>5.0±0.11</td>
<td>67</td>
</tr>
</tbody>
</table>

\( a \) Data on transpulmonary pressure were obtained in living animals anesthetized with sodium pentobarbital (or in rabbits with a mixture of urethane and sodium pentobarbital) and paralyzed with succinylcholine-chloride. Before measurements, respiratory system was expanded to about 30 cm H2O. Tracheal pressure was measured after a wide opening of chest wall; value recorded was corrected for effect of lung weight, i.e., for difference in tracheal pressure between isolated lungs suspended from trachea and lungs replaced in situ. Lungs were isolated after having tied vessels at hila in order to avoid blood losses. \( b \) unpublished data referring to the same animals. \( c \) unpublished data referring to the same animals. \( d \) From Agostoni et al. (8): body wt 2.13 ± 0.03, 2.22 ± 0.06, and 2.20 ± 0.08 kg in lateral, supine, and head-up postures, respectively; No. was 3, 4, and 3, respectively. \( e \) This refers to only 2 of 3 dogs: body wt 7.4, 14.9, and 29 kg for small, medium, and large size, respectively. \( f \) Plus unpublished observations.

The overall transpulmonary pressure at FRC in the lateral posture increases almost twofold from rats to rams, whereas it is essentially the same in small and large dogs [this feature also appears in the data of Heynsius (114)]. The differences between postures are related to differences in lung volume produced by gravity, mainly through the abdomen; in the lateral, supine, and prone postures the abdomen has mainly an expiratory effect, whereas in the prone suspended and head-up postures it has an inspiratory effect. Moreover, in the head-up posture the lung volume is increased owing to the reduction of the volume of the intrathoracic extrapulmonary blood. The implications and significance of these data in connection with the topography of pleural surface pressure are dealt with in section VII F.

E. Topography of Pleural Surface Pressure

The data on the distribution of pleural surface pressure are divided into two groups. The first refers to the data of studies in which the height of the site of meas-
urement was not systematically indicated, as well as to scattered data found in studies that were not concerned with the distribution of pleural surface pressure. The second refers to the data of studies in which the height of the site of measurement was systematically taken into account. Despite the great interest raised during the last 10 years on the vertical distribution of pleural surface pressure, there are only a few studies in which the height of the site of measurement is precisely indicated.

1) Data with no systematic reference to height of site of measurement. Brookhart and Boyd (38) measured about -5 cm H$_2$O in a small pneumothorax made beneath the caudal part of the sternum in a supine dog. They also made measurements with small balloons and in the region around the heart, where a higher (less subatmospheric) pressure was found, but no information is given about the height of the site of these measurements. Besides, they did not give information about the size of the pneumothorax when they made measurements around the heart and when they introduced the balloon. Wiggers et al. (258) made measurements in dogs in various parts of the costal region and between lobes after introduction of less than 1 ml of air. They found some regional difference of pressure but they did not indicate the height of the sites of measurement, and owing to the very small pneumothorax their data are likely to have been affected by artifacts (see sect. VIIB). Mead and Whittemberger (162) measured -4 and -7 cm H$_2$O in a small pneumothorax made beneath the sternum at the 4th intercostal space in a supine cat and in a supine dog, respectively.

Coleridge and Linden (59) made measurements in supine dogs in the costal and mediastinal pleural space without introducing air purposefully. Hence, if no leakages occurred, the only air in the space should have been that coming from the measuring device because of the expansion of the gas contained in it. As discussed above, this condition is deceptive. They reached the pleural space alongside the right atrium by thrusting a rigid cannula through the right wall of the trachea. From their schema the tip of the cannula appears to be at about half the lung height. They found an end-expiratory pressure in the costal region of about -6 cm H$_2$O, while that in the mediastinal region was about -3 cm H$_2$O. The tidal changes of pressure were a little smaller in the mediastinal region than in the costal one. After the introduction of 5–10 ml of air in each site, the pressure in the costal region increased more than in the mediastinal one and the pressure in the two sites became almost equal. It is difficult to accept these results as real differences in pleural surface pressure. It seems likely that more air leaked in around the cannula introduced through the trachea than around the cannula introduced through the intercostal space. If this was the case, the cannula in the costal region, with very little air around its tip, was probably sensing something related to the deformation of the lung surface produced by the cannula, or something close to pleural liquid pressure (see sect. VIIB). On the other hand, the cannula in the mediastinal region, surrounded by an appreciable amount of air, was probably sensing something close to pleural surface pressure. This situation would explain the effect obtained with the introduction of 5–10 ml of air in each site.
Farhi et al. (79) studied supine dogs with less than 1 ml of air around the cannula, a condition in which surface tension and deformation artifacts are appreciable. They stated that between the 3rd and 8th intercostal space the end-expiratory pressure did not vary more than 1 cm H$_2$O, while in the 1st and 2nd interspace it was lower (more subatmospheric) and the tidal changes were smaller. Actually these differences are not statistically significant. Only the end-expiratory values found in the dorsal region (i.e., at a lower site) of the 10th and 11th interspace are significantly higher than those measured in the other regions. They found that the introduction of a small amount of air produced equal increases of pressure at the points at which air was introduced and in other parts of the same side, from which no air could be removed. They concluded that “the lung behaves as a continuous elastic system so that pressure reequilibrates by rearrangement of forces within the lung.” This important point should be investigated again with a more adequate technique (see sect. VI$\alpha$).

Konar et al. (132a) made measurements in the fourth intercostal space in the anterior axillary line of 23 males with normal respiratory apparatus in the supine posture. Measurements were made through a needle connected with a water manometer and a recording capsule. The average value ($\pm$SE) was $-5.43 \pm 0.37$ cm H$_2$O on the right side and $-3.26 \pm 0.25$ cm H$_2$O on the left side.

In 15 prone dogs, medium and large size, with a 10- to 20-ml pneumothorax, Cook et al. (61) found an average end-expiratory pressure of $-3.4 \pm 0.99$ (sd) cm H$_2$O. The site of measurement was 4–5 cm below the vertebral column at the 8–10th intercostal space; i.e., it should correspond to the upper third of the lung. From the tracing of Wohl et al. (260) it appears that the end-expiratory pressure in the esophagus of prone dogs of medium size was $-2.5$ to $-3$ cm H$_2$O. In comparing the above data it must be considered that, except for the last two works (61, 260) in which the respiratory system was inflated to 30 cm H$_2$O a short time before the measurements, in the others the volume history of the lung was not taken into account.

2) Data with systematic reference to height of site of measurement. Parodi (187) found that the pressure in a small pneumothorax in head-up and supine dogs, as well as in standing and sitting patients, increased from top to bottom, whereas it did not change appreciably from the cranial to the caudal region at a given height in supine dogs. Unfortunately he did not provide values. Prinzmetal and Kountz (197) measured in patients the pressure in a small pneumothorax at the 5th intercostal space on the midaxillary line and found that, in the lateral posture, it was 3–5 cm H$_2$O lower in the superior than in the inferior part. Duomarco et al. (76) studied esophageal pressure with an open-tip catheter and the pressure in a small pneumothorax at various heights in head-up dogs. They concluded that there was no appreciable difference between top and bottom. However, their approaches were rather inadequate, for reasons discussed in section VI$\alpha$.

Krueger et al. (135) made measurements with a balloon in the pleural space of head-up dogs and found a significant overall vertical gradient of transpulmonary pressure: 0.22 cm H$_2$O/cm above and 0.56 cm H$_2$O/cm below the diaphragmatic dome. The variance of their data was large, the individual overall
vertical pressure gradient ranging from 0.009 to 0.48 above the diaphragmatic
dome and from 0.13 to 1.4 below it. In the only case where the value of the pres-
sure recorded is given, the end-expiratory pressure at the top was about \(-1.5 \text{ cm H}_2\text{O}\) and 6 cm below the top it was zero. These pressures are too high, because if
they were true the lower half of the lung would have been collapsed at end ex-
piration. Hence the method of Krueger et al. could provide only a rough measure
of the vertical change of pleural surface pressure. Their work, however, called
attention to this matter. With a similar technique Turner (238) found in head-up
dogs a vertical pressure gradient roughly comparable to that found by Krueger,
but it was more marked at the top than at the bottom. Moreover, Turner found
that the gradient did not change with increasing lung volume and that in the head-
down posture pleural surface pressure was lower in the caudal part, the overall
vertical gradient being about the same as in the head-up posture.

Daly and Bondurant (66) measured the pressure in a 1- to 2-ml pneumo-
thorax in healthy seated men. The average pressure was \(-3.3 \text{ cm H}_2\text{O}\) in the
3rd intercostal space ventrally, \(-4.2 \text{ cm H}_2\text{O}\) in the 5th intercostal space on the
anterior axillary line, and \(-1.8 \text{ cm H}_2\text{O}\) in the 8th intercostal space dorsally. These
data suggest the existence of a vertical gradient, but the positive value in the
lower region, as well as some values near atmospheric in the superior or middle
region, suggests the presence of surface tension artifacts.

Milic-Emili et al. (170) found with a short balloon that the vertical pressure
gradient over the middle third of the intrathoracic esophagus was about 0.2 cm
\(\text{H}_2\text{O/cm}\) in the standing man. As in Turner's experiments, the gradient did not
change with increase of the lung volume. It is not clear, however, whether the
gradient was significant. In the head-down posture (72° from the horizontal)
the pressure in the superior part was lower, but not significantly lower. Bryan et
al. (42) made similar experiments and reported an average vertical pressure gradi-
ent of 0.25 cm \(\text{H}_2\text{O/cm}\) (range 0.02-0.44 cm \(\text{H}_2\text{O/cm}\)), which doubled at 2 g.
During increased acceleration the pressure in the upper balloon decreased,
whereas that in the lower balloon increased. Since the resting volume of the res-
piratory system in a seated man at 2 g should increase also in its dependent part,
owing to the increased pull of the abdomen, the finding of an increased pressure
in the lower part at 2 g suggests that under these conditions the abdominal muscles
were contracted at FRC. Glaister (98) found an average vertical pressure gradi-
ent of about 0.4 cm \(\text{H}_2\text{O/cm per g}\) only over 5 cm of the lower esophagus. Trop
et al. (237) found in head-up dogs an average vertical pressure gradient of 0.28
\(\text{cm H}_2\text{O/cm}\) (range 0-0.85).

By measuring the flow through a Starling resistor placed in the esophagus of
dogs, Proctor et al. (198) determined the distribution of the esophageal pressure
in various postures. In the head-up dog the pressure in the superior part of the
intrathoracic esophagus was \(-6 \text{ to } -15 \text{ cm H}_2\text{O}\). The vertical pressure gradient
was about 0.2 cm \(\text{H}_2\text{O/cm}\) over the lower two-thirds, while it increased in the
upper third of the intrathoracic esophagus. In the supine posture the pressure
was about the same over the caudal and middle part of the intrathoracic esophagus
and a few to several centimeters \(\text{H}_2\text{O}\) lower in the cranial part. Proctor et al.
maintained that the lower pressure found in the cranial part of the intrathoracic esophagus in the supine posture was not caused by artifacts due to the traction of the trachea on the esophagus, as suggested by Milic-Emili et al. (170), because they could not alter the values by manipulating the cervical trachea. In the head-down posture they found that the pressure in the caudal part was about $-3 \text{ cm H}_2\text{O}$, and that this value was only a little lower than or similar to that in the cranial part.

From measurement of regional lung volume obtained by dilution of $^{133}\text{Xe}$ and from values of esophageal pressure, Milic-Emili et al. (168) calculated the transpulmonary pressure as a function of lung height in the seated man. They found an almost linear relationship between lung height and transpulmonary pressure. This latter was about $8.5 \text{ cm H}_2\text{O}$ at the top and $3 \text{ cm H}_2\text{O}$ at the bottom of the lung at FRC. The vertical pressure gradient was about $0.2 \text{ cm H}_2\text{O}/\text{cm}$ and did not change with lung volume. Taking into account that their method should progressively underestimate the overall vertical gradient below TLC (see sect. VII), the value at FRC could have been roughly $0.22 \text{ cm H}_2\text{O}/\text{cm}$. Milic-Emili et al. (168) showed that near RV the lowermost part of the lung is not ventilated and suggested that the lowermost airways are collapsed at RV. That some airways are collapsed at RV was shown by Burger and Macklem (43). To the extent that alveoli and airways resist collapse (50), pleural surface pressure should become positive before collapse occurs. At RV, pleural surface pressure on the lowermost part should be positive, as suggested by Milic-Emili et al. (see direct evidence below).

Kaneko et al. (128), with the same technique as Milic-Emili et al., found an almost linear relationship between the change of transpulmonary pressure and the height of the lung in man in the lateral posture at volumes above 50% of the VC and in the supine and prone postures at volumes above 40% of the VC. The vertical pressure gradient was about $0.18 \text{ cm H}_2\text{O}/\text{cm}$ in the lateral and supine postures and about $0.16 \text{ cm H}_2\text{O}/\text{cm}$ in the prone posture. With the same technique Bryan et al. (42) found that the vertical gradient of transpulmonary pressure increased proportionally to the increase of headward acceleration, the gradient becoming nil if the data were extrapolated to 0 g. During increased acceleration, the transpulmonary pressure at the top increased, whereas that at the bottom decreased. Hence the gradient rotated around an isopressure point, which corresponded to the isovolume point, i.e., to the place where the relative changes of regional lung volume were equal to those of the overall lung volume. Similarly, from data of regional lung emptying, Jones et al. (127) found that the lower part of the lung during 3 g acceleration was less expanded than at 1 g. As noted above with regard to esophageal pressure during increased acceleration, the finding of Bryan et al. and Jones et al. of a reduced expansion of the lower part of the lung may be explained only if, during increased headward acceleration, the abdominal muscles were contracted at FRC. Indeed, if during increased headward acceleration the abdominal wall yields little, the pleural surface pressure in the lower part of the lung could become positive at a lung volume corresponding to the FRC of seated man at 1 g. Studying the washin of $^{133}\text{Xe}$ Glaister (99) found that in head-up
and head-down subjects the lower region was more ventilated than the upper one, suggesting that the lower part of the lung was less expanded than the upper one.

From measurements of alveolar size in dog lungs frozen in situ, Glazier et al. (102) found that at FRC in the head-up posture, the volume of apical alveoli was about 4 times that of the basal ones, most of the change occurring over the upper 10 cm of lung. No difference was found between peripheral and hilar regions and between dorsal and ventral regions at a given height. In the horizontal postures alveolar volume at a given height was the same in both cranial and caudal parts. The volume of the upper alveoli was about twice that of the dependent ones in the supine posture, this difference being a little less in the lateral and prone postures. In the head-down posture and in the isolated lung the volume of the alveoli was uniform over the whole height. In the head-up posture the volume of the alveoli at the top was about the same as that in an isolated lung expanded to 23 cm H2O, while the volume of the alveoli at midheight was about the same as that of the alveoli of an isolated lung expanded to 10 cm H2O. According to these data the overall transpulmonary pressure of the lung at FRC in the head-up dog should be about 10 cm H2O, which seems too high (see sect. VIII D). Furthermore there are some discrepancies. When the dog was exposed to 3-g headward acceleration without abdominal binder, the volume of the alveoli was similar to that at 1 g throughout the whole height in spite of the increase of lung volume presumably produced by the caudal displacement of the abdomen under the acceleration. The volume of the alveoli at the top of the lung in the lateral posture was significantly smaller than that at the bottom of the lung in the head-up posture. In the head-up dog with the respiratory system inflated at an alveolar pressure of 5 cm H2O, the volume of the alveoli was similar to that at PAlv = 0 throughout the whole height in spite of the increase of lung volume. These discrepancies of the alveolar volume probably depend on differences in the alveolar dimension among animals and on the error involved in the computation of the alveolar volume. Glazier et al. found that the vertical gradient of alveolar size of head-up dogs decreased and disappeared when the respiratory system was inflated to 10 and 30 cm H2O, respectively. Moreover, they found that the apical alveoli of head-up dogs with the respiratory system inflated to 10 or 30 cm H2O were smaller than at FRC. Hogg and Nepsky maintained that this finding was probably due to a pneumothorax occurring during the freezing process. It seems more likely, however, that this finding depended on the deformation of the apical alveoli occurring in the head-up posture at FRC (E. D'Angelo, manuscript in preparation). Glazier and Hughes (101) in dogs exposed to 5-g forward acceleration found that the volume of the ventral alveoli increased more than twofold relative to the volume of ventral alveoli of supine dogs at 1 g; most of the dorsal alveoli were collapsed.

Agostoni and D'Angelo (3) showed that the transpulmonary pressure at the bottom of the lung of dogs, cats, and rabbits at FRC in the lateral posture is about nil. They made a small incision on the parietal pleura and eliminated the surface tension of the air-liquid meniscus at the rims of the incision by keeping a thin layer of isotonic saline solution on the incision. When the incision was made at the bottom, the lung did not retract or protrude; when the incision was made a
few millimeters above the bottom or at a higher level, the lung retracted. This finding was confirmed with another approach on the same kind of preparation (see below) in dogs and rabbits in the lateral and supine postures (67) and in rams in the lateral posture (5).

From measurements of regional lung density both in intact exsanguinated dogs and in excised exsanguinated lungs at various transpulmonary pressure, Hogg and Nepszy (115) estimated that in the head-up dog at FRC the transpulmonary pressure at the top ranged from 10 to 15 cm H$_2$O and dropped to about 6 cm H$_2$O 5 cm below the top. The vertical gradient of transpulmonary pressure over the rest was about 0.2 cm H$_2$O/cm. If, however, one calculates the values of the volume of air per unit lung weight as percent of that at TLC, from the data of lung weight and cross-sectional area at the various heights provided in the paper, one finds that most data in the upper region are markedly different from those reported in the paper. Hence, most data of transpulmonary pressure in the upper regions obtained in this way are markedly different from those published in the paper (E. D’Angelo, personal communication).

McMahon et al. (153) made measurements by means of two Starling resistors placed in the pleural space at the 3rd and 6th left intercostal space on the mid-axillary line of large dogs. The average end-expiratory transpulmonary pressure in the supine posture was about 1.4 cm H$_2$O both in the 3rd and 6th space; in the lateral posture it was 1.5 cm H$_2$O in the 3rd space and 3 cm H$_2$O in the 6th space. In the head-up posture it was 4.2 cm H$_2$O in the 3rd space and 2.8 cm H$_2$O in the 6th space; in the head-down posture it was −0.4 cm H$_2$O in the 3rd space and 1.8 in 6th space. These values seem too low if one considers the overall transpulmonary pressure of the isolated lung at a corresponding volume. The low values of transpulmonary pressure are probably due to the thickness of the sensing device, although the effects of bubbles of gas cannot be ruled out. The vertical gradient of transpulmonary pressure between the two points investigated was 0.20 cm H$_2$O/cm in the head-up posture and 0.31 cm H$_2$O/cm in the head-down posture. Unfortunately no information is given on the height of the lung in the various postures and of the relative height of the sites of measurement.

Hoppin et al. (119), using the skirted, multiple, stiffened balloon, studied the distribution of pleural surface pressure in dogs in various postures and at various lung volumes. At FRC in the head-up posture the average transpulmonary pressure was about 7.5 cm H$_2$O 3 cm below the apex and about 2.2 cm H$_2$O 21 cm below the apex, the overall vertical gradient being about 0.3 cm H$_2$O/cm. In the supine posture the transpulmonary pressure at about midheight was about 4 cm H$_2$O in the apical region and 2 cm H$_2$O in the caudal region. In the head-down posture the transpulmonary pressure 21 cm above the apex was about 4 cm H$_2$O and 3 cm above the apex 1 cm H$_2$O, the overall vertical gradient being about 0.15 cm H$_2$O/cm. In the lateral posture the vertical pressure gradient was 0.3–0.4 cm H$_2$O/cm. Hoppin et al. maintained that the vertical pressure gradient was unaffected when the respiratory system was expanded by increasing the alveolar pressure. If, however, in the head-up posture the value of the apical region (about which the authors are not confident because it is a “cramped region”)
is disregarded, a significant decrease of the vertical gradient with increasing lung volume is found; moreover, the vertical gradient at Palv = 20 cm H2O is not significant (9). Hoppin et al. found that at low lung volume the transpulmonary pressure at the bottom became negative even in the head-up posture. The upper level at which the transpulmonary pressure became negative increased with the decrease of lung volume. Finally, they noticed that the transpulmonary pressure was greater over the interlobar fissures.

The most systematic studies on the topography of pleural surface pressure have been undertaken with the technique of the counterpressure on the exposed surface of the lung or of the parietal pleura (5, 8, 9, 13, 67). Most of the right intercostal region of apneic rabbits and dogs at the resting volume of the respiratory system in the lateral, supine, prone, head up, and head down postures was scanned. Measurements done on the left side gave values similar to those obtained

![Graph showing the relationship between lung height and pleural surface pressure in various postures.](http://physrev.physiology.org/...)

**Fig. 7.** Percentage of lung height against pleural surface pressure in right intercostal region of rabbits at resting volume of respiratory system in various postures. Numbers near symbols indicate references. Best-fit equations relating pressure (P) to height (H) are: supine $P = -0.06H - 5.47 + 2.53H^2$; lateral $P = -0.13H - 4.99 + 6.09H^2 - 4.61H^3$; prone $P = -0.27H - 4.89 + 2.2H^2$; prone suspended $P = -1.89 - 4.25H + 1.70H^2$; head-up $P = -2.27 - 8.63H + 4.01H^2$. Asterisk indicates that origin is not significantly different from zero. Points at zero height refer to two measurements. These expressions are purely descriptive; no physical meaning is attributed to the constants. Broken line in lateral posture partitions upper from lower hemithorax.
FIG. 8. Percentage of lung height against pleural surface pressure in right intercostal region of dogs at resting volume of respiratory system in various postures. Numbers near symbols indicate references; crosses refer to unpublished data of G. Miserocchi obtained with technique of counterpressure on exposed parietal pleura. Best-fit equations relating pressure (P) to height (H) are: supine \( P = -0.22H + 0.16 H^2 - 8.20 H^3 \); lateral \( P = -0.03H - 7.31 H^2 + 11.9H^3 \); prone \( P = -0.72 - 5.97 H + 3.40 H^2 \); head-up \( P = -1.74 - 6.43 H \). Asterisk indicates that origin is not significantly different from zero. Points at zero height refer to two measurements. These expressions are purely descriptive; no physical meaning is attributed to the constants. Broken line in lateral posture partitions upper from lower hemithorax.

on the right side, but the left side has not been thoroughly scanned. No systematic or marked differences of pleural surface pressure were found at a given height and in a given posture in the craniocaudal or dorsoventral directions. The relationships between lung height and pleural surface pressure are illustrated in Figures 7 and 8. The mean of the local transpulmonary pressure integrated over the lung height agreed with the overall transpulmonary pressure of the lungs isolated at FRC in the corresponding posture (67). The value of this comparison, however, is limited because of the lack of information on the local transpulmonary pressure in regions other than the intercostal one. The data obtained at the resting volume of the respiratory system in apneic animals have been confirmed in breathing animals with the counterpressure on the parietal pleura (13; Figs. 7 and 8). D'Angelo et al. (67) pointed out that, for a given species and posture, pleural surface pressure was uniquely related to the percentage of the lung height. If pleural surface pressure in dogs of different size was plotted against the absolute height of the lung a family of curves was obtained. Their data indicated that the
difference of transpulmonary pressure between top and bottom within a given species was essentially the same in spite of the size and that this difference increased relatively little with size even between species. On the basis of these data and of a comparison with those indirectly obtained in man by Milic-Emili et al. (168), they suggested that the overall vertical gradient of transpulmonary pressure should decrease with increasing size, contrary to the current view of a fairly constant vertical gradient, which probably originated from the findings of a roughly similar vertical gradient in man and dogs (see above). The marked decrease of the overall vertical gradient of transpulmonary pressure with increasing size (Figs. 9 and 10, Table 4) was shown by Agostoni and D’Angelo (5), who made measurements in rats, rabbits, dogs of small, medium, and large size, and rams in the lateral posture. They found that the difference of transpulmonary pressure between top and bottom increased only about 2 times from rats to rams in spite of an increase of nearly 8 times in lung height. Hence the overall vertical gradient of transpulmonary pressure decreased almost 4 times from rats to rams. That the overall vertical gradient of transpulmonary pressure should decrease with the increase of size could have been inferred without measurements of local transpulmonary pressure simply by measuring the transpulmonary pressure of isolated lungs at the resting volume of the respiratory system. Indeed, since it does not seem likely that under normal conditions pleural surface pressure in the lowermost regions at FRC is positive, the transpulmonary pressure of isolated lung at FRC should increase several times with size if the vertical gradient of transpulmonary pressure were about the same in animal of different size. Instead the transpulmonary pressure at FRC increases less than 2 times from rats to rams (Table 3). Moreover, the transpulmonary pressure at the top of the lung in the lateral posture increased from rats to small dogs, but leveled off from small dogs to rams. Although these findings should be confirmed in other species in order to evaluate their physiological significance, they support the view that the respiratory system is designed in such a way as to prevent a marked increase of transpulmonary pressure at the top with increasing size (5; see sect. VIII).

When the relaxed respiratory system was artificially expanded by increasing
alveolar pressure relative to body surface pressure, the transpulmonary pressure increased more at the bottom than at the top both in the supine and head-up postures. The vertical gradient of transpulmonary pressure decreased and eventually became nil when pleural surface pressure was higher than body surface pressure both in the supine and head-up postures (9, 13). On the other hand, when the respiratory system was expanded by the action of its muscles, the vertical gradient of transpulmonary pressure at end inspiration was not significantly different from that at end expiration both in the supine and head-up postures, at least up to a transpulmonary pressure of about 12 cm H₂O. The tidal changes of transpulmonary pressure were therefore similar in the superior and inferior parts of the lung (13). For both kinds of expansion of the lung no marked or systematic differences of transpulmonary pressure were found at a given height and in a given posture in the craniocaudal or dorsoventral direction. When the relaxed respiratory system was brought below its resting volume by lowering the pressure in the airways, the transpulmonary pressure became negative from the bottom up. When the airway pressure was -10 cm H₂O, the transpulmonary pressure was negative over most of the lung height in supine dogs but only in the lower part in head-up dogs. However, since the airways close when the transpulmonary pressure becomes negative, the significance of the transpulmonary pressure under these conditions is limited (13).

Morphometric measurements of in situ subpleural and inner alveoli, performed in rabbits under several conditions under which the topography of pleura.

**FIG. 10.** Lung height against overall vertical gradient of transpulmonary pressure in various species in head-up posture at resting volume of respiratory system. Transpulmonary pressure was not measured at very top and bottom of lung, but 1–3 cm below or above, respectively. Overall vertical pressure gradient was therefore obtained dividing difference between these pressures by vertical distance between corresponding points. Values on ordinate refer to whole height of lung. Only D’Angelo et al. (67) and Agostoni and Miserocchi (13), however, provided measurements of lung heights; other data were obtained indirectly. Values of vertical pressure gradient and lung height of Milic-Emili et al. (168) were approximately corrected for lung height at FRC, since only lung height at TLC was given. Values of lung height of McMahon et al. (153), Hoppin et al. (119), and Trop et al. (237) were calculated from a relationship between lung height (at FRC in head-up posture) and body weight.

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**EMILIO AGOSTONI**

*Volume 52*
TABLE 4. Transpulmonary pressure (Pl) at top and bottom of lung, lung height, and overall vertical gradient of Pl at resting volume of respiratory system

<table>
<thead>
<tr>
<th>Posture</th>
<th>Species</th>
<th>Pl, cm H₂O</th>
<th>Lung Height, cm</th>
<th>Overall Vertical Gradient of Pl, cm H₂O/cm</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Top</td>
<td>Bottom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lateral</td>
<td>Rat</td>
<td>2.50±0.06*</td>
<td>0</td>
<td>2.87±0.36</td>
<td>0.88±0.06</td>
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<tr>
<td></td>
<td>Rabbit</td>
<td>3.59±0.09</td>
<td>0</td>
<td>4.88±0.13</td>
<td>0.73±0.02</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>3.7</td>
<td>0</td>
<td>5.05</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>Small dog</td>
<td>5.66±0.12</td>
<td>0</td>
<td>6.93±0.18</td>
<td>0.82±0.002</td>
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<td></td>
<td>Medium dog</td>
<td>5.71±0.16</td>
<td>0</td>
<td>9.00±0.33</td>
<td>0.63±0.012</td>
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<td></td>
<td>Large dog</td>
<td>5.76±0.07</td>
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<td>12.20±0.30</td>
<td>0.47±0.017</td>
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<td></td>
<td>Dog</td>
<td>6</td>
<td>0</td>
<td>8.8</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>Ram</td>
<td>5.29±0.02</td>
<td>0</td>
<td>22.02±0.39</td>
<td>0.29±0.001</td>
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<td>Supine</td>
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<td>3.2</td>
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<td>0</td>
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</tr>
<tr>
<td></td>
<td>Dog</td>
<td>4</td>
<td>0</td>
<td>10.0</td>
<td>0.40</td>
</tr>
<tr>
<td>Prone</td>
<td>Rabbit</td>
<td>3</td>
<td>0</td>
<td>4.9</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
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<td>2.8</td>
<td>0</td>
<td>4.9</td>
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<tr>
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<td>3.2</td>
<td>0</td>
<td>9.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Prone suspended</td>
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<td>4.3</td>
<td>1.4</td>
<td>5.7</td>
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<td>Head-up</td>
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<tr>
<td></td>
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<td>1.5</td>
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</tr>
<tr>
<td></td>
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<td>1.5</td>
<td>16.0</td>
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<tr>
<td>Head-down</td>
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<td>-2</td>
<td>6.2</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>4.5</td>
<td>-0.7</td>
<td>13.2</td>
<td>0.39</td>
</tr>
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</table>

* SE.
increasing size: in the lateral posture it goes from about 0.9 cm H₂O/cm in rats to about 0.2 cm H₂O/cm in man. In some postures the vertical gradient changes markedly over the lung height. Above FRC the data from different sources are controversial. This depends in part on the different means of expansion of the respiratory system. When the relaxed respiratory system is artificially expanded by increasing alveolar pressure relative to body surface pressure, transpulmonary pressure increases more at the bottom than at the top. Hence, the vertical gradient of transpulmonary pressure decreases and eventually disappears. When the respiratory system is expanded by action of its muscles the vertical gradient does not change significantly, at least up to moderate expansions. When a subject expires below FRC, pleural surface pressure increases and becomes positive from the bottom up; as a result, the airways close. This begins just below FRC in the supine posture and near RV in the head-up posture.

All the more reliable measurements of the topography of pleural surface pressure obtained so far refer to static or nearly static conditions. Although Schilder et al. (213) reported that during maximum voluntary ventilation the pattern of esophageal pressure changes was the same at various heights, it appears that the topography of pleural surface pressure under dynamic conditions is still to be investigated.

F. Nature of Vertical Gradient of Transpulmonary Pressure

Wirz (259) and Rohrer (207) pointed out that the weight of the lung could cause a difference of transpulmonary pressure between top and bottom. From the density and the height of the lung they calculated that the difference of transpulmonary pressure between top and bottom in a standing man should be 1.5-2 cm H₂O provided that the lungs were not supported by the hila. Since they believed that the lungs were in part supported by the hila they concluded that the difference of transpulmonary pressure between top and bottom due to the lung weight should be smaller.

Parodi (187) maintained that the transpulmonary pressure decreases from top to bottom because of the weight of the lung. According to him the transpulmonary pressure at FRC is essentially produced by the weight of the lung: the higher the density of the lung the greater the transpulmonary pressure at the top and, for a given density, the larger the size the greater the transpulmonary pressure at the top because of the greater ratio between lung volume and supporting area. Apparently Parodi believed that the difference of transpulmonary pressure between top and bottom due to the lung weight could be several centimeters H₂O. He supported his view by the finding that the transpulmonary pressure of the superior part was some centimeters H₂O higher than normal when the density of the lung was increased by a disease. It is not clear, however, why his data of lung density, both normal and pathological, are so high.

Rohrer (206a), Duomarco et al. (76), and Mead (154) felt that the different shape of the lung and of the chest wall, besides lung weight, could cause local differences in transpulmonary pressure. Assuming, as a rough approximation, a lung
weight of 1000 g distributed on a 500-cm² surface (it is not clear how this area was inferred), Mead (154) estimated that the difference in transpulmonary pressure between top and bottom due to the lung weight in absence of hilar support should be about 2 cm H₂O. He added, however, that the hilar support might be considerable.

Having found that the value of lung density (0.22 g/ml) was similar to that of the overall vertical gradient of transpulmonary pressure above the diaphragmatic dome in head-up dogs at FRC, Krueger et al. (135) suggested that the lung behaves as a homogeneous fluid of the same mean density. Their suggestion had a relatively great influence although: a) they stated that the agreement between lung density and vertical gradient could have been coincidental, b) the reliability of this comparison is questionable in the absence of information regarding whether the trachea was closed in the head-up posture and whether losses of blood from the lung were prevented when the lungs were excised to measure their density, and c) the data of the pleural surface pressure were too high and their variance great (see sect. VII).

Turner (238) proposed that the vertical pressure gradient depends on differences in the supporting forces, rather than on fluid-like behavior of the lung tissue, because he found that the vertical gradient of transpulmonary pressure did not decrease with increasing lung volume, and hence decreasing lung density.

Wood et al. (261) pointed out that because of the effect of gravity on the thoracic contents the alveoli at the top should be more expanded than those at the bottom. They considered that under an acceleration of a few g in the ventral direction the superior alveoli should be markedly expanded, whereas the dependent ones should be compressed.

Having found that the value of the vertical gradient of transpulmonary pressure in the head-up and horizontal postures was similar to that of the lung density given by Krueger et al. (135), and particularly that it increased proportionally to acceleration, Milic-Emili and his associates (49, 198, 168, 169) clung to the hypothesis of Krueger et al. of the fluid-like behavior of the lung. Although they noticed that the vertical pressure gradient did not decrease with increasing lung volume, as it should have if it depended on the lung density, they concluded that the vertical pressure gradient is “gravity dependent, i.e. related to the lung weight.” Actually, the finding that the vertical pressure gradient increases proportionally to the acceleration does not prove that it depends on the lung weight; it proves only that it depends on gravity, and gravity may affect the vertical pressure gradient more through its action on the chest wall than on the lung (see below). Moreover, their finding that the vertical pressure gradient in the head-up posture was similar to that in the horizontal postures does not fit the fluid-like hypothesis, because in the horizontal postures the density of the lung is higher than in the head-up posture, owing to the smaller lung volume and the greater amount of blood. Glaister (98-100) also believed that the uneven distribution of ventilation in the gravity direction depended on the effect of the lung weight. Proctor et al. (198) interpreted their data with the spring analogy and therefore they too believed that the vertical gradient of transpulmonary pressure is mainly related to the effect of gravity on the lung.
By comparing the X-ray profile of a lung of a head-up monkey with that of the excised lung suspended only by the hilum, West (251) concluded that the hilar support in the head-up posture is small. Still, we do not know how much the hilar support is and whether it changes with the posture and the lung volume.

In commenting on their findings of transpulmonary pressure at the bottom in the horizontal and head-up postures as well as on some findings of distribution of the alveolar size of Glazier et al. (102), Agostoni and D’Angelo (3) pointed out the importance of the weight of the upper part of the abdomen in determining pleural surface pressure in the head-up posture. Indeed, in the head-up posture at FRC the pressure of the upper part of the abdomen is subatmospheric and the diaphragm not distended; hence the weight of the upper part of the abdomen pulls on the lung (16, 75). Hogg and Nepszy (115), to provide an alternative to the spring and fluid analogies, attempted an indirect analysis of the abdomen effect by utilizing their data of transpulmonary pressure and of pleural surface area of horizontal slices of lung of head-up dogs. They subtracted from the transpulmonary pressure at each height a constant value corresponding to the transpulmonary pressure of the lungs at FRC. According to them this difference at each height should be the transpulmonary pressure due to gravity. Multiplying this transpulmonary pressure at a given height by the area of the pleural surface of the corresponding horizontal slice, they estimated the component of the weight normal to this area of pleural surface. In order to obtain the actual weight supported by the pleural surface of each slice they multiplied this force by the cosine of the angle between the vertical and a line normal to the pleural surface. The whole weight supported by the pleural surface was obtained by summing the values of each slice; it exceeded the lung weight by about 2 kg. Hogg and Hepszy (115) inferred that this was the weight of the abdomen supported by the pleural surface and concluded that it should be a major determinant of the regional pleural surface pressure. Their conclusion is correct, but their procedure, for the reasons given below, does not seem able to add a contribution to the notion that, in the head-up posture at FRC, the abdomen pulls on the lung with a pressure of about 4 cm H$_2$O at the level of the diaphragmatic dome (see above). 1) The data of transpulmonary pressure in the superior part seem unreliable as previously discussed (see sect. vitC,E). 2) The transpulmonary pressure of the lungs at FRC does not reflect a weightless equilibrium between the lung and the chest wall, because the expansion (and hence the recoil) of the lung is determined also by the weight of part of the abdomen. 3) According to their data the “isovolume” level should be above the diaphragmatic dome and the gravity-dependent fraction of pleural surface pressure should be positive below this level, in spite of the pull due to the weight of the upper part of the abdomen. 4) In order to obtain the weight supported by the pleural surface of each slice the component force normal to the pleural surface should be divided (not multiplied) by the cosine of the angle between the vertical and a line normal to the pleural surface; it is not clear, however, what they really did since neither the values of the angles nor the weights supported by the pleural surface of each slice are given in the paper.

McMahon et al. (153) maintained that the weight of the mediastinal struc-
ture affects pleural surface pressure in the costal region. They found that pleural surface pressure in the right-side-down posture was lower in the 6th than in 3rd left intercostal space and interpreted this as due to the pull of the heart weight on the more caudal region of the lung. It is not clear, however, whether the height of the 3rd intercostal space corresponded to that of the 6th. Moreover, records from several places are necessary to support this view. Neither Hoppin et al. (119) nor D’Angelo et al. (67) found evidence of this in the left-side-down posture when the height of the sites of measurement was carefully taken into account. A finding suggesting that in rabbits the mediastinal structures do not affect pleural surface pressure in the costal region through a direct action on the lung is reported below (8).

Hoppin et al. (119), by compressing the abdomen of head-up dogs, changed the shape of the chest wall in such a way as to simulate roughly that in the supine posture at the same lung volume. They either did not find appreciable changes in transpulmonary pressure or the changes were opposite to those expected. Hence they inferred that at FRC the vertical gradient of transpulmonary pressure may be relatively independent of the chest wall shape and that the gravity effect on the pressure gradient is not due to the associated shape changes. Considering this finding together with those obtained at large lung volume and in the head-down posture (see sect. viiE), Hoppin et al. (119) and Mead (155) were led to conclude that their results confirmed a paradox, in the sense that the lung appeared to behave as a liquid and as a solid. According to them, at low and middle volume the lung behaves almost as a liquid; some of the departures from the liquid-like behavior could depend on extreme deformations such as those involving small radii of curvature or great change of the overall shape. At large volume the resistance to shear could become marked and hence the behavior would be less liquid-like. Their view on the nature of the vertical gradient of transpulmonary pressure is best summarized by their own words: “Whatever the precise distribution of pleural pressure, one would expect the underlying principle to show through: that the distribution of pressure should reflect the intervening weight of the lung. Therefore when the magnitude of the overall pressure gradient deviates markedly from the density of the lung, it is probable either that support of the lung is being influenced by the hilar structures, or, more likely, that a significant different pressure distribution pertains over surfaces of the lung which are not being measured” (119). Some evidence against the fluid-like behavior of the lung and the spring analogy was provided by data of D’Angelo et al. (67) on the local pleural surface pressure in various postures and by the findings of Katsura et al. (129) that in excised dog lobes supported from the apex or the base the alveolar expansion was uniform except in close proximity to the sites of support.

Since the vertical gradient of transpulmonary pressure is gravity dependent (see above), the abdomen is more dense and fluid-like than the lung, and the diaphragm is not rigid, the abdomen in the horizontal postures should be important in originating this gradient (8). In order to quantitate the effect that the vertical pressure gradient of the abdomen produces, through the diaphragm, on the vertical gradient of transpulmonary pressure, Agostoni et al. (8) determined the
topography of pleural surface pressure in the costal region and the lung density after evisceration and compared these data with those obtained under normal conditions. Both in rabbits and dogs (see ref 5 for dogs in the lateral posture) the vertical gradient of transpulmonary pressure decreased markedly after evisceration, the transpulmonary pressure changing according to the changes of lung expansion produced at various heights by the evisceration. In rabbits in the supine and lateral postures, the overall vertical gradient after evisceration decreased about 2 and 3 times, respectively, whereas the lung density decreased only 1.5 times. In the prone rabbit suspended from the vertebral column, in which the abdomen has an inspiratory effect, the vertical gradient after evisceration decreased about 2 times, whereas the lung density increased significantly. These results showed that in these species the vertical gradient of transpulmonary pressure does not depend essentially on the lung weight and that, in the horizontal postures, it depends markedly on the vertical gradient of abdominal pressure (8). Of course they also showed that the lung does not behave in this respect as a fluid. After evisceration the relationship between lung height and pleural surface pressure in the lateral posture became similar to those in the supine and prone postures. Hence the S-shaped relationship found under normal conditions in the lateral posture (Figs. 7 and 8) is due to the effect of the abdomen. The similarity of the relationship in the three postures indicates that in these postures pleural surface pressure in the costal region is not affected by a direct action of the mediastinum on the lung, at least in rabbits (8).

In head-up rabbits the difference of transpulmonary pressure between top and bottom decreased by about 60-70% after evisceration, whereas the lung density increased significantly. These experiments, however, are difficult to interpret because the lung height changes markedly after evisceration and the part of the lung below the dome of the diaphragm is affected by the vertical gradient of the abdominal pressure before evisceration. The values of the overall vertical gradient in eviscerated head-up rabbits were almost the same as those in eviscerated rabbits in the horizontal postures, whereas the lung density was only 2/3. This suggested that the overall vertical gradient does not depend essentially on lung density even after evisceration (8).

Further insights into the nature of the vertical gradient of transpulmonary pressure may be stimulated by a tentative interpretation of the behavior of the vertical pressure gradient above the resting volume of the respiratory system of rabbits and dogs (9, 13). The decrease of the vertical pressure gradient found when the relaxed respiratory system was artificially expanded by increasing the alveolar pressure (Palv) relative to body surface pressure (Pbs) has been interpreted with the following mechanisms. The first one is based on the differences of the regional compliance (C) of the lung (l) and of the chest wall (w). When Cw is small relative to Cl, the change of transpulmonary pressure (ΔPl) is a small fraction of the change of alveolar pressure (ΔPalv), whereas when Cw is large relative to Cl, ΔPl is a large fraction of ΔPalv. If Cw is smaller than Cl at the top and greater at the bottom, the change of transpulmonary pressure for a given increase of Palv will be small at the top and large at the bottom, and therefore the vertical gradient of transpulmonary pressure will decrease. Considering the regional values of pleural
surface pressure at FRC and assuming that the specific static features of a horizontal slice of the lung, or of the relaxed chest wall, are similar to that of the whole lung or chest wall, respectively, the above requirements would be met over a small volume above FRC (Fig. 1). Particularly because of this assumption as it relates to the chest wall, this analysis must be taken with reservation; the quantitative treatment made by the authors was intended only to illustrate a possible mechanism. The changes of $P_l$ and $P_w$ at various heights were calculated using the compliances as specific regional compliances: $\Delta P_l = \Delta P_{alv}C_w/(C_l + C_w)$, and $\Delta P_w = \Delta P_{alv}C_l/(C_l + C_w)$. The computation showed that this mechanism could account for most of the decrease of $\Delta P_l$ between top and bottom observed just above FRC in the horizontal postures and that its effect decreased progressively and reversed when $P_{alv}$ was roughly higher than 5 cm H$_2$O. In the head-up posture this analysis could not be performed, but this mechanism could be operating.

The second mechanism is provided by the decrease of intrapulmonary and extrapulmonary blood volume produced by the inflation of the lung. It should produce a further slight decrease of the difference of $P_l$ between top and bottom (68; see below), enhancing the effect of the first mechanism.

The third mechanism is based on the conditions reducing the effect of the lung weight on the vertical gradient of transpulmonary pressure. When the respiratory system is expanded the effect of the lung weight should decrease slightly because of the decrease of the lung weight per unit supporting area. Moreover, the vertical gradient could decrease because of the increased rigidity of the lung tissue. It might be that hilar support becomes greater as the lung volume increases and/or that most of the support is provided by small areas, producing pressure difference at the surface only over limited regions and therefore not affecting the general distribution of lung expansion. However, these conditions are uncertain because the vertical gradient does not decrease when the respiratory system is expanded by the action of its muscles (see below). A condition that could reduce and essentially eliminate the vertical gradient of transpulmonary pressure due to the lung weight was suggested by the finding that in all postures and conditions studied the vertical gradient of transpulmonary pressure became nil when $P_{pl}$ exceeded $P_{bs}$ over the whole height of the lung, in spite of the different degree of lung expansion. When $P_{pl}$ exceeds $P_{bs}$ (i.e., when the lung no longer pulls on the chest wall, but pushes on it) static friction should be increased. The increased static friction could prevent the sliding of the pleural membranes under the action of the lung weight. That the external surface of the lung may be supported under this condition is suggested by the fact that an excised lung, moderately expanded until most of its outer surface pushes against the vertical wall of a cylindrical wet glass container, does not slide down when the hilar support is removed. Moreover, it is conceivable that, when each lung unit pushes on the next one, static friction is important within the lung as well as at the surface. An increase in internal static friction could prevent any sag related to the sliding between units. If the rigidity of lung tissue relative to its weight were such as to minimize the sag related to elastic deformation, the horizontal slices, held at their lateral surface...
by static friction, would become nearly self-supporting. The vertical gradient due to lung weight could thus disappear. Since this is mere speculation it might be that other factors intervene when $P_{pl}$ exceeds $P_{bs}$. Finally, it must be considered that at the degree of lung expansion at which the vertical gradient is nil, the first mechanism, which would tend to increase the vertical gradient, can no longer operate, because at this stage the lung and the chest wall are represented at all heights by the same point on the corresponding volume-pressure curves, and therefore the value of the compliance of the lung, or, respectively, of the chest wall, is the same at all heights of the lung (9).

When the respiratory system is expanded by the action of its muscles the condition is different from the case of the relaxed respiratory system being expanded by an increase in $P_{alv}$. First, the expanding force is not evenly distributed on the respiratory system and therefore the effect of mechanism 1 may be masked. Second, pleural surface pressure decreases, and hence mechanism 2 is reversed owing to the increase of intrathoracic blood volume. Third, $P_{pl}$ does not become higher than $P_{bs}$. Under this condition the vertical pressure gradient did not decrease at least up to a transpulmonary pressure of about 12 cm H$_2$O. (9, 13). When the respiratory system is brought below its resting volume by lowering the alveolar pressure the vertical pressure gradient should increase according to the mechanisms illustrated above, provided that closure of the airways does not occur. Under these conditions the vertical gradient increased in head-up rabbits (E. D’Angelo, unpublished observations) but decreased in head-up dogs (13).

In order to partition the factors contributing to the vertical gradient of transpulmonary pressure, D’Angelo et al. (68) measured pleural surface pressure at various heights in the costal region of supine rabbits after change of the lung weight and evisceration with diaphragm removal. After exsanguination followed by restoration of the intrathoracic extrapulmonary blood, the lung weight decreased significantly, but the vertical gradient did not, suggesting that the contribution of the lung weight and of the gravity-dependent distribution of pulmonary blood to the vertical pressure gradient is small under normal conditions. After the diaphragm had been removed in such a way as to avoid lung collapse, the lung weight remained the same as after evisceration, while the vertical gradient decreased by 35–40% of normal, still being significant. Since the lung weight was unchanged, the decrease of the vertical gradient produced by the diaphragm removal should have been due to removal of an interaction between diaphragm and rib cage. Since the relationship between lung height and pleural surface pressure in eviscerated rabbits was found to be similar in the supine and prone suspended postures (8; see above), the diaphragm-rib cage interaction cannot be related to a gravity-independent shape effect (i.e., an intrinsic difference between shape of the lung and of the chest wall). Hence the fraction of the vertical gradient eliminated by diaphragm removal should depend on the gravity effect on the interaction between diaphragm and rib cage. It seems unlikely, however, that gravity may produce such an effect by acting on the diaphragm, owing to its small mass. The matter is not clear and D’Angelo et al. (68) suggested that part of the action of gravity on the mediastinum could be transmitted to the diaphragm through the ligaments. In this sense the
mediastinum could indirectly affect the vertical gradient; a direct effect had been previously ruled out (8; see above). To ascertain whether the vertical gradient of transpulmonary pressure left over after removal of the diaphragm was essentially related to the lung weight, D'Angelo et al. (68) did the same experiment in the prone suspended posture. If the vertical gradient left over after removal of the diaphragm were related to a shape effect independent of gravity, the vertical gradient in the prone suspended posture should be the reverse of that in the supine posture, whereas if it were related to gravity it should remain about the same. In the latter case it should depend on the effect of gravity on the lung, because the shape of the rib cage should be little affected by gravity in both postures. The vertical gradient in the prone suspended posture was similar to that in the supine posture. Hence, the vertical gradient left over after diaphragm removal in these postures should be essentially related to the lung weight. These experiments showed that the lung weight and the gravity-dependent distribution of pulmonary blood should contribute 20–25% of the vertical gradient in normal rabbits in these postures. Similar conclusions were drawn from experiments in which the range of lung weight change was increased by placing tungsten beads in the airways, although these experiments should be taken with reservations (68).

In conclusion, in supine and prone suspended rabbits at FRC about 40% of the vertical gradient of transpulmonary pressure should be due to the abdomen (8), 35–40% to the effect of gravity on a hypothetical diaphragm-rib cage interaction, and 25–20% to the lung weight and the gravity-dependent distribution of the pulmonary blood (68). In head-up rabbits at FRC the contribution of the abdomen to the difference of transpulmonary pressure between top and bottom should be about 60% (8), that of the diaphragm-rib cage interaction about 25%, and that of the lung weight less than 15%, because in this posture a little could also be contributed by a gravity-dependent shape effect of the rib cage (68). Only in head-down rabbits at FRC, owing to the great amount of intrathoracic blood, the vertical pressure gradient should be considerably affected by the lung weight and the gravity-dependent distribution of intrapulmonary blood (67; see below). The above partitioning of the factors contributing to the vertical pressure gradient could be different in man.

The vertical gradient of transpulmonary pressure under normal conditions therefore seems to be mainly determined by the effect of gravity on the chest wall. If this is the case, it should be possible to produce marked differences of pleural surface pressure at a given height by applying to the chest wall uneven stresses normal to the gravitational field. Agostoni and D'Angelo (6) decreased the pressure over the caudal part of the abdomen of supine rabbits and dogs at FRC and found that the pleural surface pressure in the cranial region decreased more than in the caudal one at the same height, i.e., a craniocaudal gradient was produced. When the abdominal pressure was decreased to such an extent as to increase the lung volume as in the head-up posture at FRC (about 67 and 60% TLC in rabbits and dogs, respectively), the craniocaudal gradient of transpulmonary pressure was similar to that in the head up posture at FRC. By further lowering the abdominal pressure the craniocaudal gradient of transpulmonary pressure became
greater than that in the head-up posture at FRC. This effect was not due to the increase of lung volume, because it had been previously shown that after inflation of the relaxed respiratory system or at end inspiration the pleural surface pressure at a given height was not markedly or systematically different in the craniocaudal direction (9, 13; see sect. viiE). Hence, these results showed that: 1) under special conditions pleural surface pressure in the costal region may be markedly different at a given height and in a given posture; 2) deformation may change the distribution of pleural surface pressure, as shown by the evisceration experiments (8; see above); and 3) a craniocaudal gradient of transpulmonary pressure in the supine posture may be obtained by simulating the effect of gravity on the chest wall in the head-up posture. Besides their interest for the study of the nature of the vertical gradient of transpulmonary pressure, these and other experiments on deformation may contribute to the understanding of the transmission of forces within the lung.

From the results obtained by lowering the abdominal pressure in the supine posture and the idea that the vertical gradient of transpulmonary pressure is mainly determined by the effect of gravity on the chest wall, Agostoni and D’Angelo (6) inferred that by lowering the abdominal pressure in the head-down posture to such an extent as to overcome the gravity effect it should be possible to reverse the vertical gradient of transpulmonary pressure. When the abdominal pressure of head-down rabbits was decreased to such an extent as to increase the lung volume as in the head-up posture at FRC, the vertical gradient was reversed and it became nearly equal to that in the head-up posture at FRC. The small difference between the two gradients should be due to the effect of gravity on the lung, which in this comparison intervenes twice. By further lowering the abdominal pressure the vertical gradient became greater than that in the head-up posture at FRC. Finally, when the abdominal pressure in head-up rabbits was increased until the lung volume was equal to that in the head-down posture at FRC, the vertical pressure gradient disappeared but did not reverse, owing to the considerable effect of the action of gravity on the lung due to the large amount of blood and the small volume of air. Indeed, under this condition the vertical pressure gradient reversed only in exsanguinated rabbits (6).

These experiments showed that, except when the lung is engorged with blood, the distribution of transpulmonary pressure in the species studied is essentially related to the regional expansion that the lung undergoes in fitting the chest wall, whose shape in turn is mainly determined by the action of gravity on its parts, particularly the abdomen-diaphragm (6).

G. Functional Implications of Vertical Gradient of Transpulmonary Pressure

The static features of the various lobes of the lung are nearly the same (81, 90, 268) and also at the sublobar level the differences should be small (229). Hence, the decrease of transpulmonary pressure from top to bottom implies that the lung is more expanded in the superior region than in the inferior one. Direct evidence of this was provided by in situ measurements of alveolar size (102; E. D’Angelo, manuscript in preparation) and of lung density (115). Hence, if the tidal volume
per alveolus were the same in the superior and inferior regions, the latter should have a more rapid turnover of gas because of the smaller volume of gas in the alveoli at FRC. Moreover, the smaller volume of the inferior region implies that at or above FRC in the head-up posture the lower region operates on a steeper (more compliant) part of the volume-pressure curve (Fig. 1) than the upper region. Because of this, for a given change of pleural surface pressure above FRC, the lower region of the lung undergoes a volume change that is nearly twice that undergone by the upper one (168, 169, 250). The tidal changes of pleural surface pressure at slow flow rates are nearly the same in the superior and inferior regions (13, 168). Hence, the combination of the vertical distribution of lung expansion and of the shape of the volume-pressure curve of the lung explains most of the distribution of ventilation occurring during breathing with a slow flow rate. The distribution of ventilation above FRC is independent of the magnitude of the tidal volume (168). Although the data of Kaneko et al. (128) indicate a similar behavior in the horizontal postures, this might not really be the case for a small tidal volume inspired from FRC. Indeed, if in man, as in animals at FRC in the horizontal postures, the transpulmonary pressure at the bottom of the lung is about nil, then the lowermost region of the lung should be ventilated less for a small tidal volume than the middle or superior regions, because the compliance of the lung at a transpulmonary pressure near zero is small.

A relatively high ventilation of the lower region is important for the efficiency of the respiratory gas exchange since the lower region is also more perfused by blood. The change of blood flow with distance down the lung under normal conditions is, however, 3 times greater than the change of ventilation (250). During inflation of the relaxed respiratory system the tidal changes of transpulmonary pressure are greater at the bottom than at the top, particularly just above FRC (see sect. vnF); hence, the difference of ventilation between lower and upper regions should be even greater than that during spontaneous breathing.

Owing to the greater expansion of the upper region of the lung, the upper airways should be more distended, unless their passive ciststance or the tonus of their smooth muscles is greater than in the lower region. The lower region of the lung should then have a greater flow resistance in addition to a greater compliance, i.e., a longer time constant. This would favor airflow in the upper region and thus tend to make the distribution of ventilation more uniform. According to Mead (155), however, this is immaterial, because the time constant of the normal lung is so short compared to the period of a breathing cycle that the longer time constant of the lower region is still too short to influence the distribution of ventilation, at least at normal breathing frequencies. Moreover, at normal breathing frequencies, the distribution of ventilation depends mainly on the regional compliance of the lung because the mechanical impedance (i.e., the ratio of applied pressure to produced flow) of separate pathways within the lung stems mainly from the regional compliance (155). At high flow rates, however, the difference of flow resistance between superior and inferior regions affects the distribution of ventilation (29, 126, 175, 206, 267). The distribution above FRC becomes more uniform during fast expiration (175) than during fast inspiration (206). Whether the in-
crease in uniformity achieved during fast expiration depends also on a decrease of the vertical gradient of transpulmonary pressure is at present only a matter of speculation (175).

Below FRC in the horizontal postures and near RV in the upright posture, pleural surface pressure in the lowermost region is positive (13, 168; see sect. viiE) and the lowermost airways should be closed. Hence, when a small breath is taken, no air enters the lowermost region of the lung until pleural surface pressure reaches the critical value at which the lowermost airways open. Besides, when pleural surface pressure is near atmospheric, the lowermost region of the lung operates on a rather flat portion of the volume-pressure curve. Under these conditions, therefore, the superior region is more ventilated than the inferior one (168, 169). This implies an impairment of the regional ventilation/perfusion distribution.

Since at low flow rates the distribution of ventilation seems mainly related to the vertical gradient of transpulmonary pressure (41, 168), and since the distribution of transpulmonary pressure in rabbits and dogs may be changed by changing the abdominal pressure (6; see sect. viiF), it should be possible to change the distribution of ventilation by changing the abdominal pressure. This could be a way to change the distribution of ventilation independently of the gravitational field and hence to some extent independently of the distribution of circulation (6).

Glaister (99), to check whether the differences in the distribution of ventilation between the erect and supine postures at FRC were related to the lung volume, lowered the pressure on the caudal part of the abdomen of supine men until the lung volume was increased by about 2.5 liters and did not find a change in the distribution of ventilation between cranial and middle regions. His finding may appear to disagree with the above considerations based on rabbit and dog data. Apart from species differences, this could depend on changes of the breathing movements of the chest wall in such a way as to mask the effect of the altered distribution of transpulmonary pressure. In order to check whether it is possible to change in man the distribution of transpulmonary pressure by lowering the abdominal pressure, the regional distribution of ventilation should be determined during the increase of lung volume produced in a supine relaxed subject by lowering the abdominal pressure.

The effect of the vertical gradient of transpulmonary pressure on the pulmonary circulation has not been studied. Something could be inferred by applying to the various levels the information on the relationships between degree of lung expansion and pulmonary hemodynamics (163). The effects of the vertical distribution of lung expansion on the vagal receptors and on a hypothetical topographical control of airway muscle tone are unknown.

H. Changes of Pleural Surface Pressure with Age and Under Special Conditions

In the mature fetus the resting volume of the chest wall corresponds to that of the lung and pleural surface pressure is not subatmospheric (1, 21, 31, 259). This condition has a functional significance: if the chest wall recoiled outward, there would be a considerable amount of liquid in the lung or in the pleural space that
might compromise breathing (12). No information is available on the distribution of the pleural surface pressure in the newborn before or after the first breath. Before the onset of breathing there is liquid in the lung; hence the pressure in the lower air spaces is higher than in the upper ones. How much of this hydrostatic pressure is balanced by the lung tissues or by the chest wall is not known. Since the specific compliance of the chest wall in the newborn is high (12) one may expect that the lower airspaces are more expanded than the upper ones. After the onset of breathing, the substitution of air for liquid provides some retraction force to the lung because of the surface tension of the air-liquid interface. The inward recoil of the aerated lung is opposed by the chest wall; this opposition increases progressively as the resting volume of the chest wall increases. These events originate the opposing recoil of the lung and of the chest wall and hence the subatmospheric pressure on the pleural surface (1, 12).

The retractive pressure of the lung for a given volume decreases with age (56, 91, 177, 193, 239): at 50% TLC it decreases about 2 cm H₂O from age 20 to 60 years, while the lung compliance over the tidal range increases (239). Over the same age range FRC increases by about 8% TLC because of the concomitant change of the mechanical properties of the chest wall, while TLC remains essentially the same. As a result transpulmonary pressure at FRC should be slightly decreased (239). No information is available on the change of the topography of the pleural surface pressure with age. Since at FRC in the horizontal postures the pleural surface pressure at the bottom is about atmospheric, in old subjects it should be above atmospheric. Indeed, in the supine posture above about 44 years of age the lowermost region of the lung at FRC is not ventilated (137), suggesting a positive pressure on the lower region of the pleural surface. In the sitting posture this occurs in subjects older than about 65 years (116, 137).

A positive value of pleural surface pressure at the bottom of the lung occurs also in obese subjects because of the decrease of FRC (117). The same thing should occur during swimming because of the reduction of FRC produced by the immersion (11, 118, 125). The changes of pleural surface pressure produced by the acceleration have been dealt with above (see sect. VILE) because of their interest in the study of the nature of the vertical gradient of transpulmonary pressure.

After the introduction of a small amount of air in the superior part of the pleural space of supine rabbits and dogs (up to 5 and 30 ml, respectively) or of liquid in supine rabbits and cats (up to 6 and 10 ml, respectively) pleural surface pressure in the regions where the lung fitted the rib cage normally was essentially unchanged (G. Miserocchi, E. D'Angelo, and E. Agostoni, manuscript in preparation), contrary to previous findings (79; see sect. VILE). The effect on the topography of the pleural surface pressure of the substitution of liquid for air or of atelectasis in part of a lung remains to be studied.

I. Maximum Range of Pressure on Pleural Surface

The maximum range of pleural surface pressure is from about -120 cm H₂O during maximum static inspiratory efforts at low lung volume to about 200
cm H₂O during maximum static expiratory efforts at large lung volume (12). Thus during maximum inspiratory efforts pleural surface pressure may become about 50 cm H₂O lower than the sum of the partial pressures of gases in the interstitial liquid or tissues (see sect. vIa). However, no gas bubbles form because a condition of supersaturation can be maintained in the liquids and tissues even for greater decompressions, unless the cavitation process is favored (182).

On the other hand, the maximum range of transpulmonary pressure is from about 40 cm H₂O in the upper part at the end of maximum inspiration to minus a few centimeters H₂O in the lower part at the end of a maximum expiration (see sect. II and VIIE).

J. Surface Pressure of Peribronchial and Perivascular Spaces

The peribronchial and perivascular spaces within the lung are to some extent analogous to the pleural space (113). Generally the surface pressure of these spaces has been considered equal to pleural surface pressure for lack of knowledge, although it was felt that this was an oversimplification. Howell et al. (120) and Permutt et al. (190) showed that intravascular pressure during lung inflation changed more than could be accounted for if the perivascular surface pressure equaled pleural surface pressure. On the other hand, Hyatt and Flath (123) noted that the differences between in situ and excised pressure-diameter curves for dog bronchi were small and concluded that peribronchial surface pressure in situ probably did not differ from pleural surface pressure. Recently Mead et al. (161) with a theoretical and a model analysis of the stress distribution in the lungs provided an elegant demonstration that the surface pressure in these spaces may be lower (more subatmospheric) than pleural surface pressure, the difference increasing with the lung volume and from the periphery toward the hilum. Mead et al. showed that, although in a uniformly expanded lung the local stresses equal the transpulmonary pressure, in a nonuniformly expanded lung the local stresses differ from the transpulmonary pressure in such a way as to reduce the nonuniformity. To the extent that a bronchus is less distensible than the surrounding parenchyma, the stress at the outer surface of the limiting membrane would be greater than that elsewhere, and this difference should increase as the lung volume increases. Hence the surface pressure in the peribronchial space would be lower than pleural surface pressure: this difference should be small at FRC, but marked at large lung volume. Since the specific compliance of the small bronchi is greater (and hence closer to that of the lung parenchyma) than that of the large bronchi, the surface pressure in the peribronchial space should become lower from the periphery to the hilum. The bronchi and the vessels share a common space and therefore they probably share a common surface pressure, which should be influenced by their respective compliance. The gradient of surface pressure from the periphery to the hilum could play a role in lymph drainage along the peribronchial space (161; see sect. vG).

In line with the analysis of Mead et al., Hyatt et al. (124), from measurements of transpulmonary pressure and linear dimensions of the bronchi in isolated dog lobes, inferred that at pressures above 5 cm H₂O the transmural pressure of bronchi
with diameter greater than 1.3 mm should be higher than the transpulmonary pressure and that this difference should increase with the size of the intrapulmonary bronchi. From their diagrams it can also be inferred that the transmural pressure of bronchi 1 mm or less in diameter should be lower than the transpulmonary pressure. This should imply that the bronchioli are more distensible than the parenchyma, at least in the excised lung. By placing small pressure transducers in the intrapulmonary vessels of isolated lobes Pratt (196) attempted to quantitate the difference between the transmural pressure of the intrapulmonary bronchi and the transpulmonary pressure. It is doubtful, however, whether his approach is adequate for this purpose, because of the distortion that may be produced by the vessel wall.

VIII. COMPARISON BETWEEN PRESSURE AT VARIOUS PLEURAL SURFACE PRESSURE AND PLEURAL LIQUID PRESSURE AT VARIOUS LUNG HEIGHTS AND VOLUMES

At FRC pleural liquid pressure is lower (more subatmospheric) than pleural surface pressure (see sect. iii). Direct measurements have shown that this difference is only 1–3 cm H₂O at the bottom and generally increases with the height (67). Since pleural surface pressure at the top decreases little with the increase of the animal size, whereas pleural liquid pressure decreases by 1 cm H₂O/cm of the lung height (at least up to medium sizes), the difference between pleural surface and pleural liquid pressure at the top increases markedly with the animal size. In two rams in the lateral posture pleural liquid pressure at the top was about −24 cm H₂O and about −1 cm H₂O at the bottom (E. Agostoni and E. D’Angelo, unpublished observations). Since pleural surface pressure at the top was about −5.5 cm H₂O (5), the difference at the top was 18.5 cm H₂O. At the margin of the lobes the surface pressure should be lower than elsewhere and should be equal to the pressure of the pleural liquid. The thickness of the pleural liquid at the margin of the lobes is in fact much larger than elsewhere and no contacts should occur over these regions (see sect. vD).

Simultaneous measurements of pleural surface and pleural liquid pressure at the same height in supine rabbits showed that the tidal changes of pleural liquid pressure were about 2 times greater than those of pleural surface pressure (13): i.e., the difference between pleural surface and pleural liquid pressure is greater at end inspiration than at end expiration. Hence, over this volume range, the pressure elicited by the deformation forces increases with the increase of lung volume (see sect. iii).

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PLEURAL SPACE MECHANICS


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124

EMILIO AGOSTONI

Volume 52


January 1972

PLEURAL SPACE MECHANICS


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