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Mechanical Properties of Lungs

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THE FIELD OF RESPIRATORY MECHANICS is both old and young. Donders described its major features in 1849 (90). Rohrer, 70 years later, developed a unifying and quantitative approach to the subject (224, 225, 227) which his pupil, Wirz (257), and his pupil's colleague, Neergaard (196, 197), applied to experiments. These names, plus those of a few contemporaries, would furnish a bibliography encompassing most of the ideas and techniques in this field—but comparatively few measurements. The measurements have come for the most part within the past 15 years, greatly assisted by electrical recording and the acceptance of a simple indirect method for measuring pleural pressure.

GLOSSARY OF SYMBOLS

(Less frequently used symbols are defined as they appear in the text.)

- Measured quantities:
  - V—volume in liters, or milliliters, ml
  - $\dot{V}$—volume rate of change or flow in liters per second, liters/sec
  - $\ddot{V}$—volume acceleration in liters/sec^2
  - P—pressure in cm H_2O, relative to atmospheric, P_B, unless otherwise specified
  - ΔV, ΔP, etc.—change in volume or change in pressure
- Parts of the respiratory system:
  - L—lungs including tissue, air spaces, airways (intrathoracic and extrathoracic), and gas
  - G—gaseous part of L
  - Ti—tissue part of L
  - W—chest wall or thorax, including intrathoracic but extrapulmonary structures, chest wall, diaphragm, abdominal contents, and abdominal wall
- Boundaries of the parts:
  - *ao*—airway opening, i.e. mouth or nose
  - *alv*—terminal air spaces in lung
  - *pl*—pleural space
  - *bs*—body surface
- Derived quantities:
  - P_{el}—elastic component of pressure
  - P_{res}—flow-resistive component of pressure
  - P_{in}—inertial component of pressure
  - C—compliance, the slope of a static volume-pressure curve at a point, or the linear approximation of a nearly straight part of such a curve, expressed in liters/cm H_2O or ml/cm H_2O
  - E—elastance, the inverse of C
  - C_{dyn}—dynamic compliance, the ratio of the tidal volume to the change in pressure between the points of zero flow at the extremes of the tidal volume: $V_T/\Delta P_{el}$, expressed in liters/cm H_2O or ml/cm H_2O
  - R—flow-resistance, the ratio of P_{res} to simultaneous $\dot{V}$, expressed in cm H_2O/liters/sec
  - G_L—conductance, the inverse of R
  - I—inertance, the ratio of P_{in} to simultaneous $\ddot{V}$, expressed in cm H_2O/liters/sec^2

This article reviews just one aspect of respiratory mechanics and even within the limits implied by the title does not attempt to be comprehensive. Instead, specific topics are taken up in detail. Rohrer's method of analysis is the basis for most measurements of respiratory mechanics. It is presented here in an introductory section in order to set it forth in one place along with its assumptions and limitations. This may seem presumptuous and unnecessarily elementary to those already familiar with it and tedious to others. Some may want to skip it and refer to it as necessary. A large share of the remainder deals with the elastic behavior of lungs and the contribution of surface phenomena to it. Major advances have been made in this area over the past 10 years and it seems particularly important to discuss them in detail.

For reviews of the contribution of the thorax, the reader is referred to articles by Fenn (105, 106) and to the monograph by Campbell (55). The bibliography includes articles on the work of breathing and the related topic of mechanical factors in the control of breathing (15, 17–19, 38, 54, 56, 64, 65, 76, 79, 80, 102, 118–121, 159, 163–165, 170, 188–191, 195, 231) that have appeared since Otis' review of this topic (205). Also included are references to more general reviews and to a number of the articles in areas not covered by this review (4, 5, 26, 39, 52, 73, 74, 87, 92, 99, 100, 107, 115, 130, 136, 155, 199, 204, 217, 219, 225, 227, 236, 238, 249).

No common usage of symbols exists in this field. The ones used here represent an effort to select a meaningful set with as little ambiguity as possible. A glossary of these symbols, along with definitions of some frequently recurring terms, is included before the bibliography. In general an attempt has been made to use terms as they are defined by Landowne and Stacy in the monograph *Tissue Elasticity* (152).

THEORY

Mechanical analysis consists of three steps: *1*) description of the motion of a system and its parts; *2*) description of the forces applied to and developed by the system and its parts; *3*) relation of the motion and forces in accordance with physical laws so as to gain understanding of the underlying mechanisms and properties of the system.

Motion of the Respiratory System and Its Parts

For mechanical analysis the respiratory system may be thought of as consisting of three parts: the gas (in the airways and air spaces), the lung structure containing the gas, and the thorax containing the lungs. The result of motion in this system is compression and/or displacement of gas. Since the gas volume is included in, or contained by, each of the parts, the change in volume, ΔV, of each part is identical to that of the other parts. The number of degrees of freedom of a mechanical system is equal to the number of variables required to describe the configuration of the system at any time. The configuration of the respiratory system may be expressed in terms of a single variable, volume.

For practical reasons the gas, airways and lung tissue are frequently considered together. The words lungs or pulmonary and the letter *L* will be used to stand for these, i.e. all parts from the visceral pleura of the lungs to the airway opening. To distinguish the gas and tissue, the first will be referred to by the letter *G* and the second by the letters *Ti*. The words thorax or thoracic and the letter *W* will stand for all of the parts in the wall surrounding the lungs, including the intrathoracic extrapulmonary structures such as the heart and great vessels as well as the chest wall, diaphragm, abdominal contents, and abdominal wall.

Forces Applied to and Developed by the Respiratory System and Its Parts

In a mechanical system where motion is expressed in terms of volume, it is logical to express forces in terms of pressures. A particular restatement of Newton's third law of motion would then be: Any pressure applied to a body is opposed by an equal pressure developed by the body. Let P_G, P_{Ti}, and P_W represent, respectively, the opposing pressures developed by the gas, lung tissue, and thorax; and let P_{ao}, P_{alv}, P_{pl}, and P_{bs} represent the pressures at their 'boundaries' (where *ao* = airway opening; *alv* = alveoli; *pl* = pleural space; *bs* = body surface). The pressure applied to each part is equal to the difference in pressure at the boundaries of the part, and Newton's third law can be expressed as follows for each part.

Part	*Opposing Pressure*	=	*Applied Pressure*
Gas	P_G	=	$P_{ao} - P_{alv}$
Lung tissue	P_{Ti}	=	$P_{alv} - P_{pl}$
Thorax	P_W	=	$P_{pl} - P_{bs}$

During breathing P_{ao} is ordinarily the same as P_{bs}, i.e. barometric or atmospheric pressure, P_B This being the case, if the sum of the opposing pressures is equated to the sum of the applied pressures, the following result is obtained for the total respiratory system:

$$P_G + P_{Ti} + P_W = P_B - P_{alv} + P_{alv} - P_{pl} + P_{pl} - P_B = 0$$

This result expresses D'Alembert's principle (the algebraic sum of forces applied to a body is zero) which is the mechanical equivalent of Kirchhoff's electromotive force law (the algebraic sum of the electromotive forces around a closed circuit is zero). The use of electrical analogs for analysis of mechanical systems depends on this equivalence.

When volume events are measured the measuring apparatus constitutes an additional part of the system. In this case

$$(P_G + P_{Ti} + P_W) + P_{Eq} = 0$$

where P_{Eq} represents the opposing pressure developed by the equipment—valve system, spirometer, body chamber, flow meter, etc. With the exception of pleural pressure, P_{pl}, the methods for measuring pressures and volumes are not discussed in this review. The references listed cover most of the methods used for volume and flow measurements (27, 28, 75, 111, 124, 157, 185, 207, 241, 242, 246, 253).

The following expressions summarize what has been said up to this point about the configuration of the respiratory system and its parts and the forces developed by these parts, *TR* denoting the total respiratory system.

$$\Delta V_{TR} = \Delta V_G = \Delta V_{Ti} = \Delta V_W$$

$$P_{TR} = P_G + P_{Ti} + P_W$$

Mechanical analysis seeks to express the relationship between these two expressions; that is, between the movement of the respiratory system and the forces associated with these movements.

Relationship Between the Motion of the Respiratory System and the Forces Applied to It

Equations expressing relationships between motion of mechanical systems and the forces applied to them are appropriately called 'equations of motion.' For example, the equation of motion of a rectilineal mechanical system with one degree of freedom and with linear elements is $F_a = Kl + Rv + Ma$, (where F_a is the force applied; l, v, and a represent rectilineal distance, velocity, and acceleration; and the coefficients K, R and M are constants representing, respectively, linear elastance, frictional resistance, and inertia). Rectilineal means all the motion can be described as motion along straight lines, hence the appropriate variable expressing motion is linear distance or length. One degree of freedom means that the motion in all of the elements is identical; they all move the same distances, at identical velocities, and accelerations. The sum of the terms on the right-hand side of the equation represents the total force developed by the system in opposition to the applied force; hence the equation is an expression of Newton's third law of motion. These terms represent opposing forces proportional to position, velocity, and acceleration and are attributable, respectively, to specific physical properties of the system: elasticity, frictional resistance, and inertia. Although these properties may be distributed in some unspecified fashion throughout the physical system, they are represented discretely in the equation of motion and may be considered as separate elements. Linear elements means that the coefficients K, R, and M, of the elastic, resistive, and inertial terms, respectively, are constants.

Figure 1 presents a diagrammatic representation of this mechanical system, along with an analogous three-dimensional mechanical system and an analogous electrical system. The three-dimensional mechanical system is presented as a step toward the equation of motion of the respiratory system. The electrical system is presented to point out the analogy between mechanical and electrical systems (201). This analogy has been put to considerable use in studies of mechanical systems for two reasons. First, electrical circuits have been extensively analyzed, and solutions to analogous mechanical problems are frequently more easily found in textbooks of electrical circuit theory than in textbooks on mechanics or mechanical engineering. Second, electrical-circuit diagrams are far easier to draw and to 'think with' than diagrams of mechanical systems.

In most real mechanical systems the elements are nonlinear. The equation of motion of a volume-pressure system with one degree of freedom and nonlinear elements may be written $P_a = \mathfrak{F}1(V) + \mathfrak{F}2(\dot{V}) + \mathfrak{F}3(\ddot{V})$, where P_a is the applied pressure, and where $\mathfrak{F}1(V)$, $\mathfrak{F}2(\dot{V})$, and $\mathfrak{F}3(\ddot{V})$ are unspecified functions of volume (V), volume rate of change, or flow ($\dot{V}$), and volume acceleration ($\ddot{V}$). If we let $P_{el} = \mathfrak{F}1(V)$, $P_{res} = \mathfrak{F}2(\dot{V})$ and $P_{in} = \mathfrak{F}3(\ddot{V})$, where *el* stands for 'elastic,' *res* for 'flow-resistive' and *in* for 'inertial,' we are ready to represent the equation of motion for the total respiratory system and its parts essentially as Rohrer proposed it (224, 225, 227). Before these equations are written, it needs to be pointed out that the gas is treated as being incompressible, and the forces developed by the respiratory muscles are considered as exerting an applied pressure to the respiratory system. This pressure, P_{mus}, is the equivalent of the net effect of respiratory muscle force.

Part	*Applied Pressure*	=	*Opposing Pressure*
Gas	$P_{ao} - P_{alv}$	=	$p_{res\,G} + p_{in\,G}$
Lung tissue	$P_{alv} - P_{pl}$	=	$p_{el\,Ti} + p_{res\,Ti} + p_{in\,Ti}$
Thorax	$P_{pl} - P_{bs} + P_{mus}$	=	$p_{el\,W} + p_{res\,W} + p_{in\,W}$

Summing the applied and also the opposing pressures yields the equation of motion of the total respiratory system:

$$P_{mus} = p_{el_{TR}} + p_{res_{TR}} + p_{in_{TR}}$$

where $p_{el_{TR}} = (p_{el_{Ti}} + p_{el_W})$

$$p_{res_{TR}} = (p_{res_{Ti}} + p_{res_G} + p_{res_W})$$

and $p_{in_{TR}} = (p_{in_{Ti}} + p_{in_G} + p_{in_W})$

The equation of motion for the lungs is obtained by summing equations for the gas and for the lung tissue:

$$P_L = P_{ao} - P_{pl} = p_{el_L} + p_{res_L} + p_{in_L}$$

where $p_{el_L} = p_{el_{Ti}}$

$$p_{res_L} = p_{res_{Ti}} + p_{res_G}$$

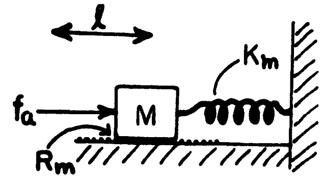
and $p_{in_L} = p_{in_{Ti}} + p_{in_G}$

Put in words, these equations state that the instantaneous pressures applied to the respiratory system or its parts are equally opposed by pressures developed within the respiratory system. These opposing pressures represent the sum of pressures arising from the physical properties of these parts. These properties include elasticity, flow-resistance, and inertia; the opposing pressures related to these properties are unspecified functions, respectively, of volumes, rates of volume change, and volume accelerations.

Further Consideration of the Assumptions Underlying the Analysis

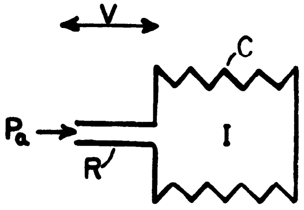
The major part of work in respiratory mechanics may be thought of as describing the 'unspecified functions' in the equations of motion and interpreting them in terms of particular mechanisms. The strengths and shortcomings of this approach become apparent as experimental results are discussed, but at the outset certain of the assumptions underlying the analysis need to be dealt with explicitly.

Assumptions as to volumes. The equations of motion for the respiratory system assume one degree of freedom, as has been pointed out. This is the case for the motion of the respiratory system and the three parts as delineated, i.e. $\Delta V_{TR} = \Delta V_G = \Delta V_{Ti} = \Delta V_W$, but it is not necessarily the case for movements taking place within the parts. Whereas the lungs and thorax may be considered as operating in



Rectilineal Mechanical (length-force; *l-f*)

Elements	*Equations of Motion*
R_m = frictional resistance (linear)	$f_a = K_m l + R_m \dot{l} + M \ddot{l}$
K_m = linear elastance	$f_a = K_m l + R_m v + M a$
M = mass	

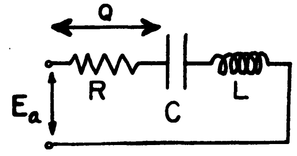


Three Dimensional (volume-pressure; *V-P*)

R = flow-resistance

$$P_a = \frac{1}{C} V + R\dot{V} + I\ddot{V}$$

C = compliance
I = inertance



Electrical (charge-voltage; *q-E*)

R = ohmic resistance

$$E_a = \frac{1}{C} q + R\dot{q} + L\ddot{q}$$

C = capacitance

$$E_a = \frac{1}{C} \int i\,dt + Ri + L\frac{di}{dt}$$

L = inductance

Fig. 1. Three analogous linear systems with one degree of freedom and their respective equations of motion. The rectilineal mechanical system consists of a mass, sliding on a film of oil and attached by means of a spring to a fixed point. The three-dimensional system consists of an elastic bellows and tube containing fluid. The inertance in this case is not discretely represented but is distributed between the moving parts of the fluid and wall of the bellows. The electrical system is a series circuit including ohmic (linear) resistance, capacitance, and inductance.

series in terms of volume change (see fig. 1, electrical analogy), the 'parts' within these parts operate in parallel, e.g. the branched airways, separate lobes and air spaces, and separate motion of the chest and abdominal walls. Parallel systems behave like systems with one degree of freedom only under particular circumstances; namely, when the motion of all of the parts are in fixed proportion to the total motion. In this case a single variable, ΔV, still determines the motion of all parts of the system. It is reasonable to expect that such fixed relationships might prove the exception rather than the rule in the respiratory system.

Assumptions as to pressures. A further implication of the equations of motion is that the pressures at the 'boundaries' of the parts are the same at all points on the respective boundaries. Three of the boundaries have gas on one side normally, i.e. the airway opening, the alveolar surface and the body surface. In these instances the assumption of uniform pressure at the boundary is correct if the gas is in continuity and not flowing. This is the case, or very nearly so, at the body surface all the time, at the airway opening when no gas is flowing, and in the alveoli if all of the airways are patent and all gas flow has stopped. It is very nearly so at the airway opening at all times if the cross section of the flowing air stream is large, and it is apparently true in the alveoli during gas flow under particular circumstances of distribution of lung and airway mechanical properties. The remaining boundary, the pleural surface, normally has tissue on both sides and the distribution of pressure cannot be predicted in any simple way. The degree of uniformity can be observed experimentally, but only when the space is opened, as in open-chest experiments or studies made on excised lungs, is uniformity of pressure, at least at the exposed portions of the pleural surface, assured.

Assumptions as to the physical properties responsible for the terms in the equation of motion. To speak of elastic, flow-resistive, and inertial terms is to imply knowledge as to the responsible physical properties. This is probably justified for the inertial term, since mass inertia is the only likely possibility in this instance. On the other hand, it is not justified for the 'elastic' term. It is safe to say that elasticity of tissues accounts for part of the 'elastic' term, but it is also certain that other properties, e.g. the force of gravity on the abdominal contents and of surface tension in the alveolar lining, which are not elastic in nature, contribute.

PULMONARY STATICS

Mechanical Behavior of the Lungs Under Nearly Static Conditions

Donders (90, 91) was the first to point out that lungs collapse on opening the chest wall because of their own elastic retraction and that this retractive force (measured in terms of airway pressure) increases as the lungs are inflated. At approximately the same time Hutchinson published results obtained on two human lungs immediately post mortem (144). His values furnish the earliest volume-pressure curves for lungs (fig. 2*A*). The linear relationship was not mentioned by Hutchinson and went unnoticed by later workers. Sixty-five years later Cloetta, in a paper which proved to be very influential, obtained a similar result on lungs of dogs, cats, rabbits, and monkeys (71). His measurements were made on living animals by lowering pressure around the lung rather than by raising tracheal pressure. He concluded that under these circumstances the lungs manifest very nearly perfect elasticity both in the quantitative sense, expressed by the linear relationship between volume and pressure, and the qualitative sense, to the extent that they returned completely to their previous volumes when inflating pressures were reversed. Setnikar (236) has presented the fallacies in these conclusions. Linear elasticity of the tissue elements responsible for lung retractive-pressures would not be expected to lead to linearity of volume and pressure. (Volume varies approximately as the cube of the length of tissue elements, whereas pressure has a different and more complex relationship, as will be brought out in the discussion of the roles of surface and tissue forces in pulmonary retraction.) Furthermore, Cloetta's published tracings themselves do not show the complete reversibility he claimed (fig. 2*C*). As to the importance which Cloetta attached to his 'physiological' means of pressure application and to the living state: Hutchinson obtained a similarly linear relationship with dead lungs, inflated by way of the trachea. It has become apparent that the linearity observed depended on two factors: *1*) Inflation was initiated from the

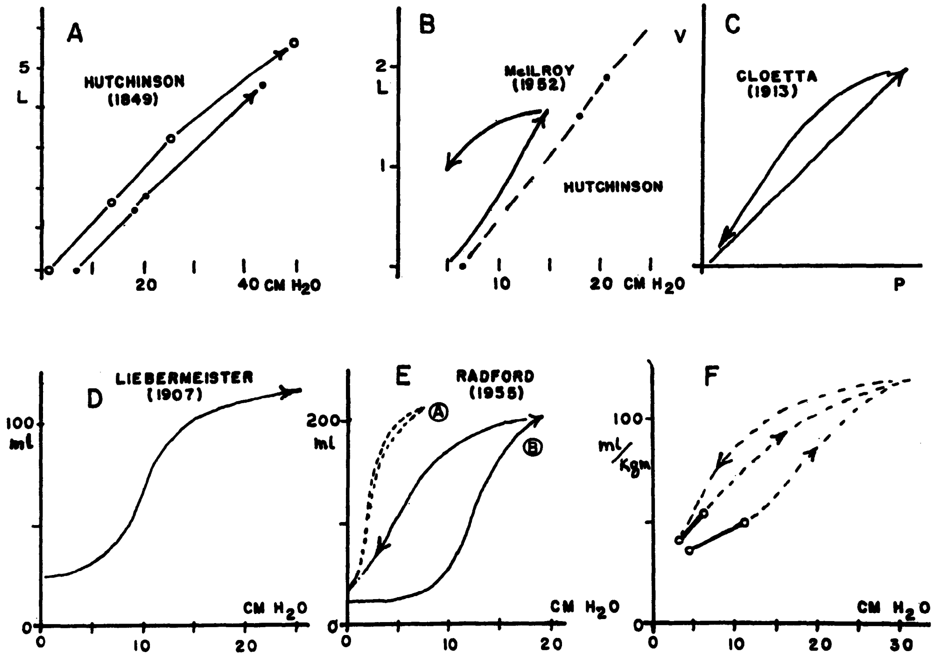


FIG. 2 *A–E*. Static volume-pressure curves obtained on lungs in the open chest or excised. *A*, from data given by Hutchinson (144) for two human lungs studied post mortem (○: 28-year-old female, ht 175 cm; ●: 29-year-old male, wt 56 kg, ht 175 cm). Measurements were made only during inflation. *B*, from volume-pressure tracing given by McIlroy [(160), fig. 3, p. 287] showing deflation as well as inflation and demonstrating static hysteresis. *Dashed line* is from Hutchinson. *C*, from volume-pressure tracing given by Cloetta [(71), fig. 11, p. 354] showing static hysteresis. Scales are linear but arbitrary. *D*, volume-pressure graph obtained by Liebermeister [(154), fig. 1, p. 646] on collapsed right cat lung measured only during inflation. *E*, volume-pressure graph obtained by Radford [(217), fig. 3, p. 185] on excised cat lung showing static hysteresis for air filling. *Dashed line* was obtained on gas-free lung filled with saline and shows very little hysteresis. *F*, composite volume-pressure diagram based on data obtained by Mead and Collier (184) ●——● plus the extended volume-pressure curves obtained by Bernstein (30). Measurements are for lungs in the closed chest.

partially inflated state—care being taken never to allow the lungs to collapse. *2*) Measurements were limited to inflation only.

Heynsius used Donder's methods to measure retractive pressures at various volumes and got variable results (140). He noted that if the lungs were allowed to collapse re-expansion was not even and tracheal pressure was greater or smaller according to the number of alveoli open at the same air volume. Liebermeister published volume-pressure curves for excised lobes of cat and human lungs inflated from the collapsed state (154) (fig. 2*D*). As pressure was increased little volume change took place until levels of 8 to 10 cm H_2O were reached, whereupon the lungs filled markedly with only small further increases in pressure. He attributed this to closure of air passages in collapsed lungs which was reversed, re-establishing continuity between the trachea and the air spaces as the pressure was increased.

None of these workers included measurements made during deflation. Had

Liebermeister done so he would have found (as anticipated by Heynsius' observation) smaller pressures during deflation, and the complete volume-pressure cycle from the collapsed state would have been a hysteresis loop.[1] More recent results obtained by Radford with cat lungs (217) and by McIlroy (160) in human lungs demonstrate this hysteresis (fig. 2*E* and 2*B*).

Curves during deflation were published by Neergaard in 1929 in the first investigation of the contribution of surface tension in the alveolar surface to the retractive pressure of the lungs. It has since been shown that surface phenomena are indeed responsible for the major part of the static hysteresis of the lungs. Neergaard did not obtain inflation curves and failed to make this association.

Surface Tension and the Volume-Pressure Behavior of the Lungs

Neergaard first called attention to the contribution of surface tension to the retraction pressure of the lungs some 30 years ago (198). He considered the formation of a bubble on the end of a capillary tube as an analog for the surface geometry within the lungs (fig. 3). Such a bubble would be a segment of a sphere and hence would exert a pressure according to the relationship $P = 2\gamma/r$.[2] As the bubble was formed, r would decrease to a minimum value when the bubble radius equaled the radius of the opening, and then would increase again. The pressure would have a maximum corresponding to the minimum radius of the bubble. (Expressing γ in dynes (d)/cm and the radius in microns, μ, the maximum pressure in cm $H_2O = 20\gamma/r$.) He considered the alveoli as spherical segments which only at maximum inflation approached hemispherical shape and never, except in pathological circumstances, exceeded it (fig. 3, $h < r_b$). With this view, which he supported only indirectly, he had no need to consider such phenomena as opening pressures (3, 133) and the nonstabilizing influence of the surface, which have played a prominent role in more recent work, and which depend on the second region of the curve, where volume and pressure bear a reciprocal relationship.

To measure the contribution of surface tension to the retractive pressure of the lungs, Neergaard compared volume-pressure curves after air filling with those obtained after liquid filling. He used fresh, excised lungs and obtained static deflation curves, having first inflated the lungs nearly maximally. He then removed the gas from the lungs by a vacuum method, filled them and the chamber containing them with a 7% gum-arabic solution, and obtained a stepwise volume-pressure curve during emptying.

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[1] The terms hysteresis and hysteresis loop are used as defined by Landowne and Stacy (152): "Hysteresis is the failure of a system to follow identical paths of response upon application of and withdrawal of a forcing agent. The result of this failure to retrace the same path on withdrawal as on application is the formation of a hysteresis loop."

[2] If r_1 and r_2 are the principal radii of curvature at a point on the surface, the pressure difference 'across' the surface (P), is related to these radii and the tension in the wall, T, by La Place's expression: $P = T\left(\frac{1}{r_1} + \frac{1}{r_2}\right)$. For a spherical segment, $r_1 = r_2 = r$, and $P = \frac{2T}{r}$; for a cylindrical section where $r_1 = \infty$, $P = \frac{T}{r}$. For a 'bubble' with a single surface $T = \gamma$, where γ = surface tension.

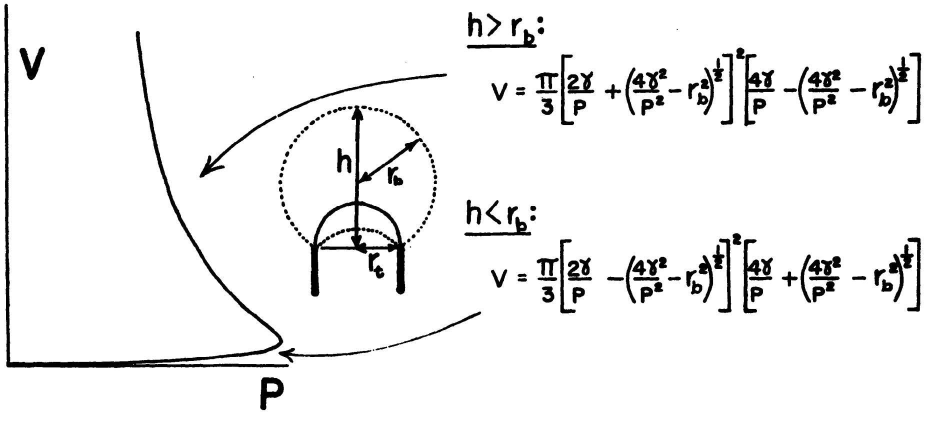

FIG. 3. Volume-pressure diagram for a bubble on a tube. The bubble is regarded as having a single surface; γ stands for its surface tension which is considered to be constant. The equations are given because those published by Neergaard include several typographic errors.

Curves obtained on sheep, pig, and human lungs showed essentially the same relationships: *1*) On the average, surface forces accounted for from ⅔ to ¾ of the total retractive pressure. *2*) In the volume range of normal expiration tissue retraction fell to zero. [Neergaard's finding of zero tissue retractive force at normal end-expiratory levels has not been confirmed, and there is no apparent explanation for this discrepancy (149).] *3*) Surface retractive pressures increased as lung volume was increased. To get some idea of the magnitude of surface tension at the alveolar surface, Neergaard made measurements on lung extracts, reasoning that any surface-active material would according to the Gibbs-Thompson law (23) move to the surface of such extracts, and found values of 35 to 51 d/cm.

To summarize the main features of Neergaard's contributions, he demonstrated that surface phenomena account for a large part of the retractive force exhibited by excised lungs. He proposed the bubble formed on a capillary as a model of the expanding alveolar surface; and he said that the alveoli were, even during maximum inflation, less than hemispheres. In his view the degree of internal curvature of the lung increased with lung volume (i.e. the radius of curvature decreased) and this increased curvature resulted in increased surface retractive pressures as lung volume increased.

Recent work in this area has centered on the magnitude of tension in the alveolar surface, the relationships of this tension to the problem of the stability of the air spaces, and the closely associated phenomena of pulmonary hysteresis.

Magnitude of tension of the alveolar surface. Radford described an ingenious approach to the measurement of surface area of the air spaces from surface energy considerations (214). The total free energy in a surface under constant tension is equal to the product of the surface area and surface tension. The area between fluid and gas volume-pressure curves such as Neergaard obtained represents energy released from the surface. If it is assumed that tissue retractive pressures are the same function of volume in both instances, and if it is further assumed that none of the air spaces closes off during deflation until the lungs have completely emptied, this area represents the total free energy of the gas-liquid surface and one needs only the value of the surface tension in addition to calculate the surface area. Radford chose to use the value of 50 d/cm which is approximately that of serum. By this method he obtained values for rat, cat, and dog lungs, and also made estimates for human lungs, concluding that the true surface area of human lungs lies between 5 and 10 m^2, or approximately one-tenth the values estimated from anatomic measurements. He thought it highly unlikely that this 10-fold difference could be due to error in the assumed surface tension and concluded that the errors were probably on the side of assumptions made in anatomic measurements.

Shortly thereafter, Pattle presented evidence that surface tension in the lungs was considerably less than 1 d/cm (208). This surprising conclusion came from a study of the efficacy of antifoaming agents in the treatment of pulmonary edema, and it is a notable example of a result of far broader significance than the question asked. Pattle found pulmonary edema foam to be highly resistant to the direct application of antifoaming agents in contrast to foams produced by agitation of pulmonary edema fluid or blood serum, which were readily attacked. This suggested that the edema foam formed in the lung brought some stabilizing factor with it from the lung itself. He also obtained stable bubbles by squeezing the cut surface of normal lungs under water. Such foam bubbles remained stable despite repeated washing with water, but lost their resistance to antifoaming agents following incubation with proteolytic enzymes and were destroyed by various protein precipitants. Pattle concluded that the stability was due to a relatively insoluble protein layer lining the bubbles. Assuming a film density appropriate for a protein, he estimated the thickness of the film to be about 50 Angstrom units, a value consistent with that of a monomolecular protein film. Gastric mucus was the only material, other than lung, from which stable foams could be produced. Although this suggested that the film might be mucoprotein in nature, the lining substance differed markedly in its staining reaction from ordinary mucin, and Pattle felt that it should not be described as a mucoprotein.

Pattle attempted to measure the surface tension of the bubbles with two sorts of experiments. He observed size changes of individual bubbles in water saturated with room air; whereas bubbles with appreciable surface tension rapidly disappeared as the gas under pressure within them passed into solution, bubbles from lungs became somewhat smaller and then remained stable for extended periods without further volume decrease. That this was not due to impermeability to gas of the lining layer was suggested by the rapid disappearance of these bubbles in gas-free water. Pattle calculated the upper limit of the surface tension that could account for the observed volume changes to be 0.026 d/cm. He also observed the shape of bubbles trapped in water under glass microscope slides. The buoyancy of the bubble presses it against the glass and distorts it from the spherical shape it would assume if surface tension alone were operating. The ratio of the bubble height to the diameter of a bubble of given size in a liquid of known density is determined by surface tension. Values were again less than 0.1 d/cm. Pattle concluded that the stability of bubbles obtained from the lung is due to a "true surface film which exerts a surface pressure almost equal to the surface tension of the liquid in which they are immersed" thus reducing the surface tension of the bubble almost to zero.

Since blood never formed stable bubbles, Pattle reasoned that the lining substance could not be a blood transudate. Similarly the mucus of the tracheal bronchial tree appeared to be ruled out by the lack of the material in tracheal mucus. He concluded that it was secreted in the "depths of the lungs, below the level at which the ciliated epithelium terminates; for otherwise it would be swept upward and appear in the tracheal mucus." Macklin had postulated a layer of mucus lining the alveoli on histological grounds, and suggested that granular pneumonocytes secreted the substance (168). Pattle proposed that Macklin's mucous layer and the lung-lining substance were one and the same.

As to the functional significance of a lung-lining layer, Pattle emphasized the role of surface tension in influencing the "distribution of liquid between blood and alveoli. This is the effect of surface tension in causing a porous body to soak up liquid." For a surface tension of 55 d/cm, the value of blood serum, the surface of an alveolus of 40 μ diameter would produce a pressure difference across the surface of 41 mm Hg, which would be roughly twice the net pressure for resorption in pulmonary capillaries, and would thus lead to filling of the alveolus with blood transudate. This emphasis on transudation is probably misplaced as will become apparent when the influence of surface tension on the stability of the air spaces is considered.

Brown and Clements were stimulated to resolve the extremes represented by Neergaard and by Radford on the one hand and by Pattle on the other. From entirely different approaches they reached the conclusion that the lung inflates with a high surface tension of approximately the value Neergaard measured, and deflates with a surface tension that falls off rapidly to low values—i.e. the surface exhibits marked area-tension hysteresis—though not so low as Pattle proposed.

Brown measured the volume-pressure relationships of bubbles blown from nasal mucus and several-day-old human pulmonary edema fluid (44, 45) (it should be noted that these were materials which did not give rise to stable bubbles in Pattle's experiments), and demonstrated marked reductions in surface tension during deflation. He also made measurements on excised lungs. By assuming that all surfaces were segments of spheres and that all spatial coordinates changed proportionately, he was able to express changes in lung surface area as proportional to changes in volume to the two-thirds power. He then applied Radford's approach to measurements of fluid- and gas-filled lungs but limited his measurement to the upper portion of the curve, where he assumed γ to be 50 d/cm. From the total area calculated for these levels and the assumed area-volume relationship, he could estimate the area change at lower volumes, and with the associated surface energy changes, estimate the surface tension at any volume. The derived surface and surface-tension relationships were similar to those found for the nasal mucus and pulmonary edema bubbles; the reductions based on an assumed maximum tension of 50 d/cm were to levels between 5 and 10 d/cm.

Clements (67, 68) made direct measurements of the area-tension relationships of lung extracts, principally with a modified Wilhelmy balance. A platinum wire stirrup was raised through the surface until it supported a surface film which exerted a vertical pull on the stirrup. This vertical force developed by the surface film was measured as the area of the extract surface was changed by moving a barrier in the surface. The results were essentially the same for normal saline which had been rinsed in and out of gas-free lungs, for minced whole lung in saline strained through cotton, and for normal saline to which slices of lung tissue had been applied. During expansion of the surface, γ remained nearly constant at values neighboring 40 d/cm, whereas during compression of the surface, γ fell off rapidly at first and then more gradually to values neighboring 10 d/cm.

Possible weaknesses in the work of both Brown and of Clements lie in the assumptions that were necessary. The fact that very different approaches led to similar results lends support, however, as do a number of observations to be taken up in the following two sections.

Stability of the air spaces. Pattle stated: "It is clearly essential to the life of a being with a highly convoluted lung, that the tendency of the air-lung interface to contract should be reduced" (208). Although he saw a high surface tension, and hence a high tendency of the surface to contract, as a threat principally to the dryness of the lung, it has been argued that it poses an even greater threat to the stability of the fine airways and air spaces (68). A soap bubble blown on a tube serves as an example of what is meant by stability in this sense. Such a bubble is stable up to the point where the radius of curvature starts increasing, and unstable beyond this point. In the stable region the volume of the bubble remains steady for a steady applied pressure and shifts with changes in applied pressure so as to produce equal opposing pressures. In the unstable region volume may remain steady for brief intervals if applied pressure is properly adjusted, but such an equilibrium is unstable. Volume changes induced by changes in applied pressure are associated with inappropriate changes in opposing pressure which tend to sustain rather than arrest the change. Volume then increases indefinitely until the bubble bursts or decreases until it attains stability at less than hemispheric shape.

The stable and unstable regions may be distinguished graphically by the slope of the volume-pressure curve (fig. 4*A*). The stable region everywhere has a positive slope ($dv/dp > 0$) and the unstable region a negative slope ($dv/dp < 0$). The conditions determining the sign of the slope may be seen by inspection of the La Place expression for a sphere: $P = \frac{2T}{r}$. A bubble with a constant surface tension can be stable up to the hemispheric shape because r decreases as volume increases. For P to continue to increase beyond this volume, i.e. for dv/dp to remain >0, T must increase and at a relative rate greater than that for r. The following expression defines the necessary condition for stability beyond the hemispheric shape:

$$\frac{dT}{dr} \times \frac{r}{T} > 1.$$

A bubble with constant tension could never be stable by itself beyond the hemispheric stage, no matter what the value of its surface tension. A rubber balloon

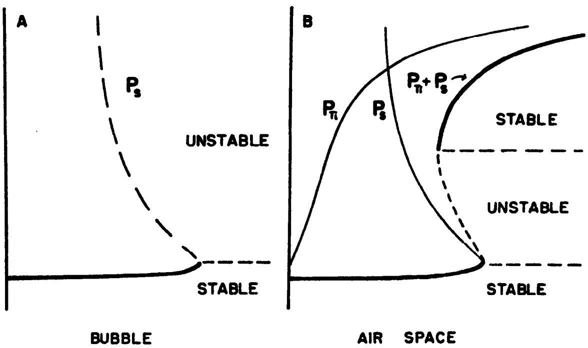

FIG. 4. Volume-pressure diagrams for a 'bubble' *A*, and a hypothetical air space *B* showing how tissue force might confer stability on the air spaces (volume: ordinate; pressure: abscissa). The bubble is unstable at all volumes above the hemispheric shape (fig. 3). For the air space the pressure is the sum of the surface and tissue pressures; the latter increases at higher volumes and confers stability on the air space.

has a wall tension which increases as the balloon is stretched; the expression just given defines how this tension must change if such a balloon is to remain stable.

If one deals with a single balloon or bubble a factitious stability may be established at any volume simply by closing off the airway to prevent volume changes. In this instance the stability resides in the obstruction, not in the balloon or bubble. In the lungs, air spaces are connected to a common airway and cannot remain in a condition of instability except transiently. How are the air spaces stabilized? Three mechanisms have been described; two of them involve the surface and a third the tissue surrounding the surface. The first is the case that Neergaard considered (fig. 3, $h < r_b$) where all surfaces are less than hemispheres and radii of curvature decrease as volume increases. It will be referred to as geometric stability. The second operates beyond the hemispheric shape and involves the change in tension with area discovered by Brown and by Clements. It will be referred to as surface film stability. The third stabilizing influence depends on the tissues surrounding the air spaces. Its operation may be described as follows:

The surface and the tissue elements containing the surface may be thought of as operating in series. That is to say, the net pressure developed by the surface and the tissue is the sum of separate surface and tissue pressures at any volume. Stability demands a positive compliance ($dv/dp > 0$). Its reciprocal, elastance, must also be positive. The elastance of the surface and tissue at any volume, i.e. dp/dv, is the sum of the separate surface and tissue elastances. It follows that any air space can be stable as long as the sum of its surface and tissue elastances is greater than zero. The burden of this formidable series of statements is more easily presented as a graph (fig. 4*B*). If tissue elastance is positive in sign at all volumes and increases with volume (which appears likely from a study of curves of fluid-filled whole lungs), whereas surface elastance is negative in sign and increases in magnitude as volume decreases (which would be the case where radii of curvature decrease with decreasing volume) then, as Clements et al. have said, "It is reasonable to suppose that when the alveoli are extended tissue forces predominate while at moderate to small volumes, surface forces predominate" (68). In such a case stability would be favored at high lung volumes; as lung volumes decreased, instability, with resulting collapse of air spaces, would be expected.

In discussing the influence of the tissue on the stability of the air spaces the influence of neighboring air spaces on one another has been neglected. Indeed, though some such interdependence must exist, nothing is known as to its nature. This unexplored feature which has, among other matters, to do with the distribution of forces within the lung may have an important bearing on air-space stability. We are here forced to limit evaluation to the relative roles of the remaining three influences on stability for which experimental evidence exists.

Role of geometric stability. Neergaard compared air and liquid volume-pressure curves only during emptying and concluded that the increase in surface retraction at high volumes reflected increased curvature of the surface (i.e. reduced radii of curvature) and that radii nowhere increase with volume. In contrast to liquid filling which is continuous and uniform to outward appearance (as is liquid emptying), air filling from the gas-free state is discontinuous and nonuniform (139, 140, 153, 154, 160, 181, 182, 217). Some areas remain gas-free while others 'pop' open. This suggests that the spaces that suddenly fill are passing through unstable states. The presumption is that this instability arises because the radii of curvature in these areas decrease and then increase again, as might be the case for a surface developing within an alveolar duct of greater potential radius than the bronchiole leading to it.

The conclusion that radii of curvature increase at some stage of inflation does not imply that they continue to increase throughout inflation. For example, the filling of alveoli on alveolar ducts presents new opportunities for radii to decrease. It is possible that such alveoli also pass beyond the hemispheric shape and through another unstable state to stability confirmed by the elastance of the alveolar wall. The observations of Radford and McLaughlin of the subpleural air spaces of rat lungs during air filling suggests this train of events (216). With initial filling large spaces appeared, which they interpreted as being alveolar ducts. With further filling the average cross-sectional area of the air spaces decreased as smaller units filled (presumably alveoli). It is not possible from their observations to say whether or not the alveoli fill beyond the hemispheric stage. Moving pictures of the surface of cat lungs show sudden filling of structures of alveolar dimensions, suggesting that the hemispheric shape is exceeded (182). The possibility remains that the conditions for geometric stability may exist in alveoli.

Role of surface film stability. Clements was the first to point out that a low coefficient of surface film compressibility (which expresses the sharp drop-off of tension during deflation) would have a stabilizing influence if present in the air spaces (67). At the time this mechanism was proposed the evidence that it operated in the lungs was entirely indirect. Recently Clements has presented more direct evidence supporting his proposal (70). He reports a high degree of correlation between the volume of air remaining in lungs after deflation from full expansion to a pressure of 5 cm H_2O, and the amount of surface activity of extracts made from these lungs. Additional evidence has been presented by Radford (218). He rinsed out lungs with a solution of Tween 20, a nonionic but water-soluble surface-active agent with γ about 45 d/cm in pure solution. Inflation pressures with air were not markedly different from those at similar volumes in untreated lungs, but deflation pressures were considerably increased, and almost all of the air spaces were emptied before pressures had been decreased to 8 cm H_2O. As Clements et al. noted, it is difficult to explain this change on the basis of a high and constant value for alveolar surface tension in normal lungs during deflation (68). Radford and McLaughlin's further observation of the dimensions of air spaces near the surface of the lung along with simultaneous measurement of transpulmonary pressure offers additional support to Clement's thesis (see ref. 68, fig. 9). The mean radius of these spaces at a pressure of 5 cm H_2O during deflation was about 25 μ. Assuming, as an extreme, that the radius of curvature for the cross section at right angles to that observed is infinite (i.e. that the section is cylindrical) and neglecting tissue forces, an upper limit of 13 d/cm for the surface tension can be derived. For a spherical surface the value would be one-half this estimate.

Role of tissue forces in air-space stability. Clements concluded from measurements on lung extracts that surface tension on inflation was approximately 40 d/cm—very nearly the same value as that obtained by Neergaard—and that it changed relatively little as long as surface area increased. The measurements of 'opening pressures' made in lungs are consistent with such a value for surface tension at least initially during inflation. If surface tension changes little (i.e., if the coefficient of surface compressibility is high), and if radii of curvature increase with volume, only tissue restraints remain to explain the stability attained once the air spaces open and while they continue to inflate. This stability would continue during deflation as long as tissue elastance exceeds the negative elastance of the surface. The Tween 20 observations of Radford suggest that instability resulting in air-space collapse occurs at relatively high volumes if the surface tension is fixed at levels near 40 d/cm. It would appear that tissue restraints account for most of the stability of the air spaces while the lung is inflating, and that surface-film stability accounts for much of the range of stability during deflation.

Surface tension and pulmonary hysteresis. There is experimental evidence that most of the hysteresis observed in excised gas-filled lungs is due to surface phenomena. Lungs of adult dogs, cats, and rats, carried through several cycles of liquid filling and emptying, show comparatively little hysteresis, and in the instance of cat lungs, practically none (181, 217) (fig. 2*E*).

Lungs of mature guinea pig, cat, and goat fetuses do show marked hysteresis during liquid filling (3). Based on this observation, Agostoni et al. have reasoned that the similarly marked hysteresis of gas-filled adult lungs is due to tissue properties. The near absence of tissue hysteresis in adult lungs rules out this possibility. Unique and irreversible rearrangements of pulmonary structures accompany the very first instances in which they are appreciably stressed. Tissue hysteresis in fetal lungs must reflect, at least in part, these changes.

Hughes et al. have concluded that tissue stress relaxation (a decrease in stress which takes place in the course of time under constant strain) accounts for a substantial part of pulmonary hysteresis particularly at high lung volumes (143). Their experiments do not permit separation of tissue and surface contributions, but it is true that the time course of tissue stress-relaxation would in general be so short that it could not contribute to hysteresis during fluid filling which has been slow (minutes), but still might account for the considerable drop-off in pressure that occurs at high lung volume following rapid inflation (seconds) (such as illustrated in ref. 49, fig. 6). The time dependence of 'static' hysteresis as well as the dynamic properties of the alveolar surface remain to be worked out. Some findings regarding the former will be taken up in a following section.

The previous section dealing with the stability of the air spaces has indicated two ways in which surface tension might contribute to lung hysteresis. One has to do with differences between inflation and deflation phases in the number of air spaces sharing any given volume (29, 49, 181); the other, with the possible volume-pressure representation of the area-tension hysteresis described by Brown and by Clements. The way in which the quantity of lung inflated might contribute to pulmonary hysteresis has been described as follows (181): During inflation from the gas-free state the total number of air spaces sharing the volume increases progressively. Volume increase of the lungs in this circumstance is partly accompanied by further expansion of air spaces already open and partly by recruitment of new air spaces (30). During deflation the air spaces remain open over much of the volume range. In this way a given volume is shared by a larger number of air spaces at any volume during deflation than during inflation. The larger the number of air spaces sharing the volume, the smaller the stresses on any single air space and the smaller the pressure developed by the lungs. All pressures during inflation would then exceed those at equal volumes during deflation and a volume-pressure cycle would exhibit hysteresis.

Clements has pointed out that area-surface tension hysteresis would contribute to this mechanism to the extent that it extends the range of stable behavior of air spaces during deflation, and that it would be expected to contribute on its own as well by producing volume-pressure hysteresis of the individual air spaces. The relative contribution of the surface hysteresis itself as compared to its influence on the numbers of air spaces open is as yet unknown. The distinction is important since the implication of the two mechanisms on the capillary surface area exposed to gas and on the relative distribution of ventilation and perfusion is altogether different (78, 184). This differentiation is fundamental to an understanding of gas exchange in the lungs and it is a major unsolved problem of pulmonary mechanics.

The existence of a substantial degree of pulmonary hysteresis attributable to surface phenomena plus the observation of greater pressures, in general, during air than during liquid filling of lungs rules out the possibility of lung surface tension being nearly zero as suggested by Pattle. By his methods he could say nothing about surface tension of his bubble 'lining layer' during expansion. Furthermore, it is possible that his stable bubbles had a degree of surface compression and hence surface tension reduction never attained in the lung surface. His contribution was far greater than any controversy as to the precise number to be assigned to alveolar surface tension. The fact remains that he deduced a fundamental property of the lungs simply by observing the properties of bubbles expressed from them.

Role of Tissue Forces in Pulmonary Retraction

Klein was the first to relate retractive pressures of the lung to the length-force characteristics of its tissue elements, and to point to a paradox in these relationships

(150). Donders had observed that retractive pressures became greater with lung inflation (91). Klein proposed to show that retractive pressures arising from the tissues of the lungs might actually decrease as the lungs were stretched. He made volume-pressure measurements on thin-walled rubber balloons and length-tension measurements on strips cut from them. Although tension increased progressively with lengthening, pressure in the balloons rose, and then fell, sometimes to rise again as the balloons were progressively inflated.[3] (The relationship between increases in tension and radius which accounts for these changes has been discussed in the section dealing with the stability of the air spaces.) Klein studied the behavior of balloons connected to a common airway as well, and concluded from his observations that one pressure could be associated with two or more different degrees of filling in the same balloon, and that the same total filling of many interconnected balloons could develop many different pressures. He suggested that rubber-like elastic bands would confer similar behavior on the air spaces which they surround: this might, then, explain the observation by Heynsius (140) that the lungs at the same volume could exert greater or lesser retractive pressures.

It has since been shown that surface phenomena, not 'rubber balloon instability,' can explain Heynsius' observation. When the influence of surface forces is minimized, as in the case of fluid-filled lungs, pressure increases progressively with volume (showing a greater rather than a lesser increase at high lung volumes), and differences at the same volume are small (i.e. long-term volume-pressure hysteresis is of small degree) (181, 217). How then, are the considerations introduced by Klein to be resolved with the observed behavior of the lungs? Setnikar and Meschia have given extensive consideration to this problem (234). They have pointed out that if tissue elements lengthen approximately as the cube root of lung volume, the combined elastic modulus[4] of such elements would have to increase (i.e. linear compliance decrease) with lung volume for retractive pressure to increase progressively with lung volume as well. They suggest collagen fibers as the most probable source of this restraint.

It is useful to summarize very briefly what is known about the elastic properties of elastin and collagen and their respective contributions to the mechanical properties of connective tissues. Elastic fibers are made up of elastin, an amorphous, noncrystalline protein polymer exhibiting rubber-like elasticity (8) (in which stresses are due to heat motion of its molecules) while collagen fibers are made up of collagen, a highly ordered crystalline protein polymer with 'normal body' elasticity (in which stresses are due to stretching and bending of chemical bonds), and an elastic modulus some 400 times greater than that of elastin (46, 47).

With a notable exception (221, 222) these conclusions have depended on measurements made on whole tissues (such as tendons and elastic ligaments) or extracted fibrous networks, rather than on individual fibers (134, 141, 187, 258). The contribution of what Bull aptly called 'nylon-stocking elasticity' (46)—that is to

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[3] Klein mentions a contemporary account describing similar phenomena (169).

[4] Elastic modulus, as defined by Landowne and Stacy (152) is the ratio of the infinitesimal change of stress to a corresponding infinitesimal change in strain. It is essentially rectilineal elastance.

say elasticity having as its 'principal origin the histologic arrangement of the tissue elements'—has been a point at issue. Earlier workers, on the basis of the curls and undulations of fibers seen in histologic sections suggested that so-called 'elastic' fibers had a high elastic modulus and that a mesh of fibers was elastic by virtue of bending of the fibers rather than lengthening (247). Redenz has since presented convincing evidence of the high extensibility (up to 140% of unstretched length) of individual elastic fibers dissected from ox *ligamentum nuchae* (221) and from human aortas (222).

It is undoubtedly true that 'nylon-stocking elasticity' contributes to the behavior of elastic tissues, nevertheless. Hoeve and Flory noted, as have others, that length-tension curves obtained on segments of *ligamentum nuchae* (which contain predominantly elastic fibers) were very nearly linear up to about 70% extensions above resting length (141). This was not to be expected for single fibers of rubber-like polymers, and, the authors suggest, was probably the result of a fortuitous arrangement of elastic fibers which are curled to various degrees in the tissue so that the proportion of fibers contributing to tension increases with lengthening of the tissue. Recently Carton and Dainauskas have obtained length-tension measurements on individual elastic fibers which confirm this view (60).

The jump from the neck ligament of the ox to the lung would appear impossibly large. The stretched elements in the lung include epithelium, endothelium and smooth muscle, as well as the fibrous structures and the intercellular substances in which they are embedded. These form a complex of air passages, air spaces, blood vessels, and surrounding integuments that make the 'nylon stocking' seem a very simple structure indeed by comparison (135, 166, 192). The results of experiments to date suggest that matters may not be as complicated as they at first seem. It would appear that the fibers predominate in determining the retractive pressures developed by the tissues of the lung in a manner quite similar to that observed in elastic ligaments.

First it should be stressed that the over-all static volume-pressure behavior of lung tissue is simpler than that for other hollow structures in the body (7, 223). Once surface phenomena have been minimized, long-term volume-pressure hysteresis of the lungs is practically nil (181, 217). This in itself suggests that smooth muscle does not play an appreciable role, since it typically contributes to hysteresis (7, 223). This conclusion is supported by the studies of Radford and Lefcoe who found in excised, fluid-filled lungs only small changes in retractive pressures following induced contraction and relaxation of the smooth muscle in the tracheobronchial tree (215). [The influence of smooth muscle on retractive pressures in the air-filled lung is quite another matter, as these authors and others have pointed out (198,215).]

There is very little change in lung retraction with temperature between 20° C and 37° C, and with time, at least up to several hours after death (E. P. Radford, Jr. and N. R. Frank, personal communication). Furthermore variations in colloid and total osmolarity of the solution used to fill the lungs, as well as induced capillary transudation of these same fluids, have only small effects (78). The relative 'hardiness' of lung tissue retraction thus demonstrated, along with the small degree

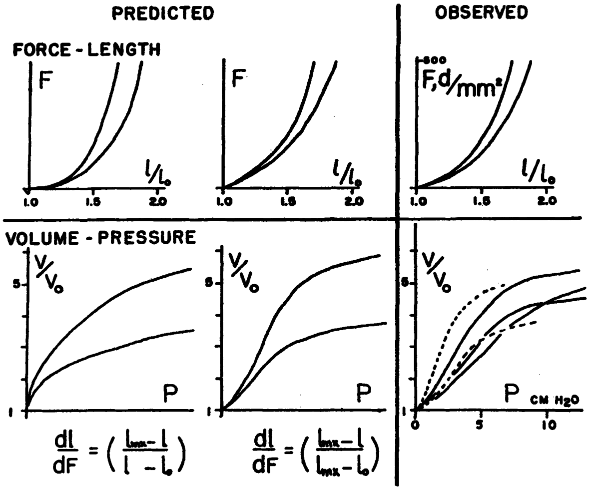

Fig. 5. Predicted and observed force-length and volume-pressure relationships for lung tissue. The predictions are based on models explained in the text. The observations are those of Radford on strips of lung tissue and of Radford, and Mead et al. on saline-filled cat (—) and dog (—) lungs. Lengths and volumes are relative to relaxed volumes. Predicted forces and pressures are plotted on arbitrary linear scales.

of long-term hysteresis, supports the possibility that its retraction depends principally on fibrous elements.

This view is further supported by the length-tension studies performed by Radford on lung tissue slices (217). He found curves of the same shape as these reported for elastic ligaments and aortic rings, structures whose properties depend on tissue fibers, with upper limits in the neighborhood of 80 % extension. Assuming volumes to be proportional to the cube of linear dimensions he calculated a 6:1 ratio for the fully expanded to the relaxed volume which corresponded quite well with observed values.

Setnikar proposed a model for the behavior of elastic and collagenous fibers in lungs (237) which was the same as that suggested by Burton for their combined behavior in blood vessels (47). The two elements are considered to be operating in parallel with each other, the collagen fibers initially somewhat curled and at less than their unstretched length. Setnikar developed a mathematical approximation of this relationship. Taking l_0 as the unstretched length of the combined system of fibers, and l_{mx} as the maximum length (i.e. the length at which all of the collagen fibers are under stretch), he said the linear compliance of the system, dl/dF, could be expressed as a function of the length of the system, l, at any time as follows:

$$\frac{dl}{dF} = B\,\frac{l_{mx} - l}{l - l_0} \qquad (1)$$

where B is the compliance of the fibers with linear elasticity. But this expression does not fit the proposed condition that the compliance of the system be equal to that of the fibers with linear elasticity when the system is unstretched (by expression (*1*) the compliance is infinite at $l = l_0$). The appropriate expression for the proposed condition would be:

$$\frac{dl}{dF} = B\,\frac{l_{mx} - l}{l_{mx} - l_0} \qquad (2)$$

where the linear compliance equals B at $l = l_0$ and zero at $l = l_{mx}$.

Setnikar tested his expression with volume-pressure data obtained on lungs during air deflation and re-expansion, conditions under which surface phenomena must have accounted for a substantial part of the pressures observed. It is of interest to repeat such tests with measurements made under conditions such that surface factors had been minimized. Two such comparisons are presented in figure 5. In the first, predicted length-tension curves are presented, along with Radford's length-tension data on lung strips (217); and in the second, predicted volume-pressure curves are presented, along with observed volume-pressure data on fluid-filled dog and cat lungs[5] (181, 217). The expression which more nearly fits the conditions proposed by Setnikar predicts length-tension and volume-pressure relationships of a general form close to that of the observed relationships.

Vascular distention and lung retraction. Although the contribution of the blood vessels themselves to lung retraction is not known, the influence of vascular distention has been studied quite extensively. In 1887 Basch described two effects (21, 22): congested lungs tended to be stiffer and to contain more gas than uncongested lungs. Both effects have been confirmed. An acute rise in pulmonary capillary pressure of 50 cm H_2O is associated with a fall in pulmonary compliance of about 25% in cat (117), dog (34, 78), and rabbit lungs (142) [and the change is probably no greater in human lungs (31, 32)]. Frank and co-workers have shown that at low lung volumes acute congestion tends to reduce retraction pressure (116, 117) (i.e. to increase lung volume at a given applied pressure). Basch proposed alveolar capillary erection to explain this effect, and others have suggested it as an important mechanism in the initial expansion of the lungs at birth (1, 33, 148). The forces involved appear to be too small for the latter (13), but they may very well play an important role in the stability of the air spaces. It is tempting to speculate that these forces may tip the balance and afford local autoregulation of ventilation and perfusion. For example, the increased depth of breathing in exercise might open air spaces which would then be prevented from closing by their simultaneously increased perfusion. The paradox of reduced compliance in association with reduced pulmonary vascular pressures, accompanying hemorrhagic shock in dogs, may be explained on the basis of air-space closure (12, 131).

Combined Roles of Surface and Tissue Forces in Stability of Lungs—a Summary

The 'static' retractive pressure of the lungs arises from two sources: *1*) the gas-tissue interface and *2*) the tissues themselves. To the extent that the lungs are made up of distensible units in parallel, the potential instability of such systems comes into play. This instability is typified by the behavior of soap bubbles in parallel, in the case of the surface, and by rubber balloons in parallel in the instance of the tissues. The stability of the tissues is indicated by their behavior when freed from

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[5] The expressions for length vs. tension were obtained by integrating (*1*) and (*2*). The volume-pressure predictions were based on the further assumption that volume is proportional to length cubed, and that the linear forces are applied circumferentially, such that $T = \frac{F}{2\pi r}$ and $P = \frac{2T}{r} = \frac{F}{\pi r^2} \backsim \frac{F}{V^{2/3}}$.

surface influences. This stability appears to depend on the high elastic modulus of collagenous fibers. The unstable behavior of the gas-filled lung is manifested by the outward appearance of the lungs during inflation, and, in a certain measure, by their marked volume-pressure hysteresis. A degree of stability is made possible in the gas-filled lungs principally by two factors: *1*) the low compressibility of the surface, discovered by Brown and Clements, and *2*) the high elastic modulus of collagen. The effect of the first is to permit the largest possible number of air spaces to remain open, and of the second to prevent hyperexpansion of some air spaces at the expense of the remainder.

To this point we have discussed the retractive pressure of whole lungs. As to the contribution of its various anatomic divisions into lobes, secondary and primary lobules, very little appears to be known. Martin and Proctor have made volume-pressure measurements on segments of the tracheobronchial tree, but these will be taken up in a later section (175). Frank has reported measurements made on individual lobes of dog lungs (114). A recent conference entitled "The Morphologic Basis of Pulmonary Mechanics"[6] served principally to reawaken pulmonary physiologists and morphologists to their relative isolation. The physiologist speaks of 'airways' and 'air spaces' for want of better knowledge as to the shape of things in the lung during life. It is to be hoped that the classical studies of Macklin and Hartroft on alveolar dimensions of various species will be reported in the open literature (167), and that similar studies in a carefully fixed specimen will be made on the dimensions of alveolar ducts and terminal bronchioles, hopefully as a function of the degree of inflation. Further improvements in the methods of fixation are to be expected as the physical properties of the lungs are taken into account in the techniques used. Certainly, fruitful comparisons of morphologic and chemical attributes of lungs (35, 36, 212, 213) along with their mechanical properties will be made with respect to lung development and growth and aging, with respect to species differences and with respect to pathologic processes.

Measurement of Pleural Pressure (P_{pl})

The measurements discussed up to this point have all been made on 'free lungs,' either excised or in the open chest, and share the advantage of comparatively unambiguous pressure measurement. Before moving on to measurements made on lungs in the intact chest it is necessary to examine the problem of measuring and interpreting pleural pressures. To what extent is it possible to speak of a uniform pressure at the surface of the lungs when they are subjected to external constraints? Two potential sources of local differences in pressure may be anticipated: For excised lungs hanging freely, the force of gravity is equally opposed by elastic forces in the trachea. In the chest, additional forces support the lungs by way of their surfaces. Statically, the net effect of forces applied to the lungs at their surface can be thought of as a vector which is equal and opposite to the vector sum of the force of gravity and the force applied to the lungs by way of the trachea and its hilar attachments. In the upright posture an upward-directed force

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[6] See: Report on the Second Aspen Conference on Research in Emphysema. *Am. Rev. Respirat. Diseases* 81: 734, 1960.

equal to the difference between the weight of the lungs and the force at the hilus must be applied at the lung surface. If the hilar forces were negligible, so that all of the weight of the lungs were supported at the surface, the pressure would be greater at the base than at the apex by perhaps 2 cm H_2O in human subjects (assuming as a rough approximation 1000 g distributed on a 500-cm^2 surface). But hilar support might be appreciable and even approach that for freely hanging lungs; there is, therefore, no necessity for local pressure differences on this basis.

A second potential source of local difference in pleural pressure has to do with the shape of the lungs. If lungs had precisely the same shape in the chest as when passively inflated at the same volume outside the chest, pressure at all points at the surface of the lungs would be the same. Therefore, local differences in pressure (apart from the supporting pressure already mentioned) can exist only to the extent that the lungs are distorted from their freely inflated shape. It follows from this that any method for measuring pleural pressures which distorts the lung may produce local changes in pressure. But, again, a possibility rather than a necessity is suggested.

Certainly, the outstanding study of local differences in pleural pressure is that of Farhi et al. carried out on dogs (104). These workers took great care in assuring adequate recording characteristics of the two manometer systems and in avoiding leaks of air into the pleural space. Direct inspection of the 13-gauge blunt-type needle tip in the pleural space by means of a nasopharyngoscope revealed a volume of air in the form of small bubbles, estimated to be less than 1 ml. Pressures measured at points between the third and eighth interspace both anteriorly and posteriorly varied from one another by no more than 1.0 cm H_2O and usually by less than 0.5 cm H_2O. On the other hand, pressures measured at the apex were more negative at end-expiration, and less negative at end-inspiration than those measured at intervening points, while the reverse was the case for measurements made from the diaphragmatic sinus near the posterior vertebral gutter. It is possible that the differences between pressures at the apex and base of the lungs reflect local distortions of the lung (by the shape of the chest cavity to which they conform). The possibility exists, as well, that these changes arise from supporting forces. Forces operating in the caudal direction at end-inspiration and cephalad at end-expiration, such as might arise from the lungs' hilar attachments during deep breathing, would produce changes the same in direction as those observed.

Of particular interest from the point of view of the effects of local distortion were the following observations by these workers: "Purposeful measured introductions of small quantities of air produced measurable changes in pressure, even when the amount introduced was only 5 ml. . . . The change in pressure took place not only at the point at which air was introduced but in all parts at which pressure was being measured in the same side of the chest. . . . No air could be recovered from points other than the one at which the air was introduced." They concluded that the observed equal changes in pressure at different points indicated that ". . . the lung behaves as a continuous elastic system so that pressure re-equilibrates by rearrangement of forces within the lung." Here then is direct evidence that under certain circumstances, namely with moderate-sized needles carefully placed, local deformation does not produce local pressure changes.

Unfortunately, equally good data are not available on further questions of the topography of pleural pressure. Evidence presented to the effect that mediastinal pleural pressures and pleural pressures in the region of the heart are less subatmospheric are all open to question in the matter of local artefacts (42, 72, 186, 256). There is great need for better information both as to the surface topography of lung pressure and the distribution of forces and their equivalents in terms of pressure within lungs.

Esophageal pressure and pleural pressure. Wirz gives an excellent critical summary of measurements of pleural pressure prior to 1923 (257). In considerable part recent advances in respiratory mechanics depend on a method which he dismissed as inadequate: the measurement of esophageal pressure (156, 228). Beginning with the studies of Buytendijk (52) 11 years ago this method has received increasing use. Since 1896 when Aron put a needle in the chest of an accommodating 'house servant' and made the first measurements of pleural pressure in a healthy man (10), the total number of direct measurements in subjects with normal lungs has probably been fewer than 10. The reported measurements from the esophageal site over the past decade are well into the hundreds.

The most widely used system for sensing esophageal pressure, first described by Fry et al. (122), consists of a thin-walled rubber balloon about 15 cm long and 2.5 cm in circumference, sealed around a polyethylene catheter. Although details of this method have been adequately described (81, 122, 178, 233), comparatively little has been written as to the factors determining the pressures recorded from such balloons. If the balloon is surrounded by a uniform pressure, the pressure inside the balloon is the same as that outside as long as the intervening rubber wall is unstretched. If the pressure outside the balloon is nonuniform, gas will be displaced from regions where the surrounding pressure is high to parts of the balloon where the surrounding pressure is lower. The pressure inside the balloon will in this circumstance equal the pressure outside the balloon at the points of inflection between the inward and outward stretched regions of the balloon wall. This can be demonstrated when such a balloon is exposed to a hydrostatic gradient by submersion in water. As it is inflated the inflection between the upper more expanded portion and the lower compressed portion moves downward, and the pressure recorded from the balloon at any degree of inflation is equal in cm H_2O to the distance from the surface to the level of the inflection.

It is then apparent that when exposed to a nonuniform pressure the pressure recorded will depend on the degree of inflation of the balloon. At low balloon volumes it will approximate the lowest pressure around the balloon, and as balloon volume is increased, progressively higher pressures, until it equals the highest pressure at any point on its surface. To the extent that there are pressure differences at different points within the esophagus the pressure in the slightly inflated balloon will tend to approximate the lowest of these.

With the balloon in the esophagus the esophageal wall and its adjacent structures become part of the recording system. The esophagus has its own volume-pressure characteristics which are reflected in changes in balloon pressure as a function of volume. A most extensive and useful study of this has been made by Petitnd a Milic-Emili (209). They obtained volume-pressure curves in balloons of various perimeters and lengths and at various positions in the esophagus. Pressure increased approximately linearly with balloon volume in all instances. Above a perimeter of 4.8 cm the rate of increase was constant for balloons of equal length. For such balloons the rise in pressure per ml of volume increase expressed per cm of balloon length was constant over the lower 15 cm of the esophagus in the upright posture. They termed this ratio the 'specific elastance' of the esophagus; in five subjects it averaged 16.0 ± 2.6 cm H_2O/ml/cm and did not change with changes in lung volume. The authors point out that esophageal elastance will lead to errors in recording changes in pleural pressure to the extent that such pressures produce changes in balloon volume (and hence 'transesophageal' pressure). They estimate that the errors from the commonly used balloon (ca. 15 cm long, 25 mm–30 mm perimeter) might be as great as 24% for a measuring system with a volume-pressure coefficient of .04 ml/cm H_2O. Mead et al. present esophageal volume-pressure data with such a balloon showing in nine subjects a mean increase over a 3-ml range of 1.25 cm H_2O/ml, or about one-half that obtained by Petit and Milic-Emili for balloons of this perimeter (178). For the observed value of 1.25 cm H_2O/ml the volume-pressure coefficient for a system permitting a 1% error in recording of pressure variation would be 0.008 ml/cm H_2O. The displacement coefficient of most electrical pressure transducers used for such measurements is much smaller than this, and may be neglected. The volume-pressure coefficient from gas compressibility in ml/cm H_2O is very nearly 10^{-3} times the gas volume in ml. The total gas volume could then be as great as 8 ml and still permit only a 1% error. It appears that errors of the sort described by Petit and Milic-Emili have probably been smaller than they estimate.

Some authors have used water manometers to measure esophageal pressure. Knowles et al. used a U-tube manometer with tubing of 2.5 mm i.d. (151). From the data given it may be estimated that the total gas volume in their system was approximately 7 ml, and the manometer displacement about .045 ml/cm H_2O. The volume-pressure coefficient of ca. 50×10^{-3} ml/cm H_2O would lead to an error in estimating pleural pressure changes of about 6% for such a system if the value of 1.25 cm H_2O/ml for esophageal plus balloon elastance is used. Butler et al. used narrower tubing for the manometer and somewhat larger balloons and must have had smaller errors (48).

Direct comparisons in human subjects of esophageal and pleural pressure have been made by a number of workers (11, 49, 62, 93, 100, 122, 161, 183), the most extensive studies being those of Cherniack et al. in recumbent subjects (62), and by Mead and Gaensler (183). Cherniack et al. reported "extreme variability of the correlation between esophageal and intrapleural pressure." Mead and Gaensler published similar graphs showing considerably less variation, at least in the upright posture. In subjects studied supine as well, esophageal pressure became less subatmospheric than pleural pressure in every instance and the difference between pleural and esophageal pressure changes increased. They concluded that in the supine posture mediastinal structures compressed the esophagus. This conclusion was reached by Knowles et al. (151) and by Ferris et al. (108) in studies of the postural influences on esophageal pressure.

To summarize knowledge as to the pressure at the surface of lungs in the chest:

The best data available suggest that these differences are small over much of the outer surface but there is need for more information on this point and on the general question of the distribution of forces and their pressure equivalents in the lungs. As far as the use of esophageal pressure as a measure of lung surface pressure is concerned, it appears to be about as good as directly measured pleural pressure, at least in the upright posture in human subjects.

Finally, a comment on the venerable question: What holds the lungs against the chest wall? One view, which in the writer's opinion is adequate, is to regard occupancy of the chest cavity as a competition between solids, liquids and gases. The liquids are removed down to a vestige because the capillary pressure in the visceral pleura is considerably lower than its colloid osmotic pressure, a matter first brought forth and beautifully elucidated by Agostoni and co-workers (2). The gases are removed, as Fenn (105) and others have pointed out, because the total gas pressure in venous capillary blood is considerably less than atmospheric due to the relative capacity of the blood for carbon dioxide and oxygen. The lungs, chest wall, and diaphragm are then pressed into service by atmospheric pressure and occupy the space, as it were, by default.

Static Volume-Pressure Behavior of Lungs in the Chest

The sigmoid inflation curve and marked static hysteresis of excised lungs occur when they are inflated from the collapsed state. The exact equivalent is not possible with the lungs in the chest, but it may be approached by producing slow volume cycles over as wide a range of volume change as is practical. Under these conditions lungs in the chest exhibit a similar, but less marked degree of static hysteresis. This has been observed in humans (49, 59, 181), cats and dogs (181, 217) and with pressures measured directly in the pleural space as well as indirectly from the esophagus.

The hysteresis is of smaller degree because it is not possible to collapse the lungs as far or for so long a time with the chest intact. When excised lungs, or living lungs in the open chest, are not allowed to collapse completely, the curves are similar to those obtained with the chest closed (217). In fact, it would appear that live and dead lungs probably behave very much alike in terms of slow volume-pressure behavior. More evidence is needed on this question but certainly the large changes in mechanical properties, said to take place with death, occur with changes in the volume history of the lungs which would in themselves be associated with apparent changes in mechanical properties.

Expression of $p_{el_L} = \mathscr{F}(V)$. For smaller volume cycles in the range of spontaneous breathing, static hysteresis is much reduced and frequently not detectable (49, 181). Furthermore, static pressures change very nearly linearly with volume in the normal tidal range. In this circumstance an explicit expression for $p_{el_L} = \mathscr{F}(V)$ may be given: $p_{el_L} = P_0 + \frac{1}{C}\Delta V$, where P_0 is the static pressure at end-expiration and ΔV is the volume change from this level. The constant, C, is the slope of the volume-pressure relation at P_0 and expresses the compliance of the lungs.

Sources of variability in measurements of pulmonary compliance. It should be apparent at this point in the discussion that no single number will adequately describe the elastic properties of lungs. Measurements of pulmonary compliance (or the inverse relationship, elastance) have gained considerable acceptance in just this sense, however, and the reasons are not hard to find. Cloetta arrived at the generalization that lung volume elasticity is linear (71) just at the time that Rohrer was developing his comprehensive analysis of respiratory mechanics. The convenience of being able to express elastic behavior with a constant must have been attractive to Rohrer and, indeed, it has proved attractive to many investigators since his time.

The first restraint to Cloetta's generalization came with experiments showing that at high lung volumes the relationship was curved in the direction of smaller volume increments for a given change in pressure (176, 245), and hence lower values for *C*. In fact, as Butler has emphasized, the relation is everywhere curved (49) and only approximately linear in the midrange.

A second restraint relates to observations first made by Setnikar et al. (235). These workers ventilated excised dog lungs slowly and at a constant rate with a fixed pattern of applied pressure. After a few cycles a fairly constant volume change was produced. When the amplitude of applied pressure was increased for several cycles (resulting in an increased tidal volume) and then returned to the original levels, tidal volume remained somewhat increased. Stretching of the lungs appeared to increase their 'distensibility.'

A similar sort of behavior has been described for lungs in the chest, in anesthetized paralyzed rabbits by Bernstein (29), in anesthetized dogs by Mead and Collier (184), and in conscious human subjects by Ferris et al. (110). Common to these experiments has been the observation that compliance tends to decrease with time and that these reductions can be reversed by single near-maximal inflations.

Figure 2*F* presents a composite diagram based on the measurements of Mead and Collier and the extended volume-pressure curves of Bernstein. Bernstein proposed that the differences observed reflected the number of alveoli open and participating in ventilation. "The deflation curve from any volume or pressure represents the truly elastic behavior of all those alveoli which have been inflated up to that volume or pressure, but the 'inflation' curves represent the combination of two processes, elastic expansion and recruitment of alveoli, and so change curvature at the point at which the second process starts" (30). The gradual reduction in compliance was attributed to progressive closure of air spaces (29). The finding of areas of atelectasis in the lungs of animals not receiving intermittent forced inflations supports this possibility (94, 184, 250). It does not preclude other contributing factors, such as, for example, lowering of surface compressibility with 'aging' of the alveolar surface (23). As brought out in the discussion of static hysteresis above, the distinction between changes involving the number of air spaces participating in ventilation, in contrast to changes more or less equally shared throughout the lung, is an important one from the standpoint of gas exchange.

Whatever the underlying mechanisms may be, the changes in mechanical behavior are real and substantial. The elastic 'constant,' *C*, that describes the linear and reversible behavior of the lungs for small volume changes is in fact quite variable: It changes with volume, and it can change at the same volume depending on the previous inflation state of the lungs.

Another source of variability in pulmonary compliance is lung size, where size is meant in the sense of the weight or volume of lung tissues. In other systems size is taken into account by expressing deformation in terms of fractional changes from resting (i.e. unstressed) levels. What is the resting volume of the lungs? Slagter and Heemstra (243), on the basis of rises in esophageal pressure at low lung volumes, and Cheng et al. (61), on the basis of increases in flow-resistance, have suggested that human lungs may be collapsed in the elastic sense at residual volume levels. It is doubtful that esophageal pressures can be relied upon at low lung volumes (151), and the resistance changes may well have a dynamic basis (145) (see below). Cloetta used the collapsed volume of the lungs in the open chest as a reference (71), but since gas is then trapped in air spaces (139) this probably exceeds the resting volume. On the other hand the volume of gas-free lungs is probably less than resting volume, since saline-filled cat and dog lungs empty passively to volumes approximately twice their tissue volumes (but still less than the volume of collapsed lungs containing gas).

Neither free collapse nor tissue volume is readily measured in intact animals (58). Furthermore, none of the pulmonary subdivisions is suitable as a measure of lung size since each depends on elastic properties of the lungs and thorax (along with muscle forces) as well as on lung size. (Presumably the correlation between compliance measured in the tidal range and such volumes as the vital capacity and functional residual capacity in normal subjects reflect their common dependence on lung size (77, 113, 174).) At present the best reference is probably lung weight as predicted from body height or weight (88). Static volume-pressure curves obtained during expiration from maximal inspiratory levels (preceded by several maximally deep inflations) based on total lung-gas volumes expressed relative to predicted lung weights or tissue volumes probably would show less variability than other measurements and would be useful for comparisons of elastic retraction of lungs.

Certainly all comparisons of elastic behavior need to be evaluated in terms of the sources of variability that have been described. It would be helpful, whenever possible, if results included information as to body size (or lung size when available), total gas volume as well as changes in volume, the volume history prior to measurement, any changes in volume history during measurement, and, in addition to these—as will be taken up in the next section—the pattern and frequency of breathing.

PULMONARY DYNAMICS

Dynamic Volume-Pressure Hysteresis of Lungs

In breathing, an additional form of volume-pressure hysteresis comes into play due to flow-resistance of the gas and tissues. This flow-resistive hysteresis is seen in pure form when volumes of gas are displaced 'in and out' through a flow-resistive element such as a tube. Bayliss and Robertson pointed out that if the resistance is linear and the volume change sinusoidal the volume-pressure pattern is an ellipse, the major axis being one-half the tidal volume and the minor axis a pressure proportional to the magnitude of the resistance, the tidal volume and the cycling frequency (25). In their classic study of the visco-elastic properties of cat lungs these investigators then used the area of volume-pressure loops obtained on lungs ventilated at constant tidal volumes as a measure of what they termed viscance of the lungs. From measurements at various frequencies using hydrogen as well as air, they concluded that gas viscance could account for only a small part of the total at physiologic frequencies. Essentially the same conclusion was reached by Mount in rat (193) as well as cat lungs (194) and by Dean and Visscher for dog lungs (84). On the other hand, measurements on unanesthetized human subjects suggest that tissue resistance plays a comparatively small role (see below). The explanation of these differences lies in the nature of the hysteresis. Bayliss and Robertson used open-chest preparations with low end-expiratory applied pressures (and consequently small end-expiratory lung volumes) and large tidal volumes (about 3 × spontaneous levels). Essentially the same conditions apply to the studies of Mount and of Dean and Visscher. As has been pointed out, under these conditions the contribution of static hysteresis must have been appreciable.

Flow-resistive hysteresis for a given tidal volume increases with cycling frequency. What can be said as to static hysteresis in these circumstances? There is some evidence suggesting that it changes in the opposite direction, becoming less as the rate of volume change is increased. Mount published graphs of the area of hysteresis loops against frequency (193). As frequencies were increased, loop area decreased slightly before it increased. When hydrogen was used instead of air so as to reduce gas viscance, loop area decreased throughout the frequency range used. Setnikar and Meschia also found decreases in hysteresis with increases in cycling frequency (from 1 to 20 BPM) in dog lungs (work referred to in ref. 236). Setnikar suggested that nonlinear viscosity or thixotropic behavior of the tissues could explain this. Whatever the explanation, frequency sensitivity of tissue flow-resistance might possibly account for the difference in the estimates of its magnitude (see below).

Dynamic Compliance of Lungs (C_{dyn})

How can static and flow-resistive hysteresis be separately studied? One method depends on the assumption that the linearity and reversibility of elastic pressures established for small, slow volume changes are uninfluenced when the volume changes are produced more rapidly. Neergaard and Wirz described the approach which has been used to investigate this question (196). At two points in the respiratory cycle, namely at the instants of zero flow between the phases, all flow-resistive pressures should be zero, and (neglecting inertial pressures) the pressure at these instants should reflect only elastic forces. The question is: Do these pressures bear the same relationship to volume as the pressures measured under static conditions? The dynamic volume-pressure relationship has been measured in terms of what has been called the dynamic compliance (C_{dyn})[7] of the lungs. It is derived as

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[7] Also variously, equivalent compliance, effective compliance, functional compliance and just compliance!

follows: At end-inspiration

$$p_{el_L} = P_0 + \frac{1}{C_{dyn}} V_T.$$

At end-expiration

$$P_{el_L} = P_0.$$

Subtracting,

$$\Delta p_{el_L} = \frac{1}{C_{dyn}} V_T \text{ and}$$

$$C_{dyn} = \frac{V_T}{\Delta p_{el_L}}$$

A number of studies have shown that in most normal lungs C_{dyn} is independent of breathing frequency from 'static' conditions to frequencies in the neighborhood of 60 to 90 BPM (49, 63, 85, 176, 179, 206, 220). The implications of this finding as to the distribution of ventilation within the lungs have been brought out by Otis et al. (206). In a system comprising parallel pathways such as the lungs, C_{dyn} would be independent of the frequency of cycling only if the volume change in each of the pathways to the various parts of the lung remained in fixed proportion to the total volume change of the lungs at all frequencies. (In the section dealing with theory this was indicated as the necessary condition for a parallel system to be regarded as having one degree of freedom.) In an electrical network consisting of separate branches in parallel, the necessary condition for the distribution of current in the branches of the network to be independent of frequency would be that the electrical impedance in each branch change proportionately with frequency. For a system comprised of capacitors and resistors and no inductors (i.e. by analogy, elastic and flow-resistive elements but no inertia) this condition would be met only if the product of the resistance and capacitance in each branch, i.e., the time constant of the branch, was the same. To the extent that the compliance and flow-resistance may be considered to be approximately linear in the lungs the separate pathways may be regarded as having mechanical time constants, and the observation that C_{dyn} is independent of frequency leads to the conclusion that the mechanical time constants of the pathways are the same.

Otis et al. also predicted that if the time constants of separate pathways differed, C_{dyn} (and the 'dynamic resistance' as well) would decrease as breathing frequency increased. The prediction as to C_{dyn} changes has been borne out in normal subjects following induced bronchoconstriction (206), in asthmatic patients (206, 232) (with partial reversal following bronchodilation) and in patients with chronic obstructive emphysema (24, 63, 66, 179, 206). Indeed, in the latter, C_{dyn} even at rest may be markedly reduced from static values.

Measurement of Flow-Resistive Pressures (p_{res_L})

We have now completed the list of known circumstances under which compliance measured in the tidal range may change in the same lungs simply on the basis of the breathing pattern. The list includes changes with lung volume per se, with the volume history of the lungs prior to measurement, and with the frequency of breathing. For normal lungs undergoing small volume changes over a considerable range of frequencies, compliance may be regarded as constant for a given tidal volume. Within these limits the following expressions can be used to solve for the opposing pressures developed by the lungs and gas other than those relating to elastic forces.

The equation of motion for the lungs and gas contained, as developed in the section on theory, is $P_L = p_{el_L} + p_{res_L} + p_{in_L}$. Under the stated conditions, $p_{el_L} = P_0 + \frac{1}{C_{dyn}} (\Delta V)$, we may re-express the equation of motion for the lungs as follows:

$$p_{res_L} + p_{in_L} = P_L - \left[P_0 + \frac{1}{C_{dyn}} (\Delta V) \right].$$

In practical circumstances inertial pressures are very small (see below) and have been neglected. In this case

$$p_{res_L} = P_L - \left[P_0 + \frac{1}{C_{dyn}} (\Delta V) \right].$$

The solution of this expression has been accomplished in a variety of ways. Neergaard and Wirz, the first to suggest this approach (196, 257), made graphic solutions from time plots. Others have used volume-pressure graphs directly recorded by a variety of means (9, 95, 176, 200). The underlying principles and limitations remain the same.

In the other commonly used method for measuring p_{res_L}, the solution is accomplished mechanically. If the airway opening is suddenly closed, e.g. by a valve in the mouthpiece, the pressure difference between the airway and the pleural surface changes abruptly by an amount equal to the flow-resistive pressure existing at the instant of interruption.

Before interruption (again neglecting inertia)

$$P_{L_1} = p_{el_L} + p_{res_L}$$

After interruption

$$P_{L_2} = p_{el_L}$$

Thus, $p_{res_L} = P_{L_1} - P_{L_2}$. This method was first used by Vuilleumier (251, 252) and has been extensively applied by Fry et al. (123). It has the advantage of being uninfluenced by the shape of the volume-elastic pressure function or the degree of static hysteresis. In circumstances such that C_{dyn} changes with respiratory frequency its meaning is ambiguous.

Pulmonary Flow-Resistance $[p_{res_L} = \mathfrak{F}(\dot{V})]$

From measurements of flow-resistive pressures and the rates of volume change associated with them (hereafter referred to simply as flow), the function $p_{res_L} =$

$\mathfrak{F}(\dot{V})$ can be obtained empirically. Investigations of this relationship have been in three areas: *1*) the shape of the function $p_{res_L} = \mathfrak{F}(\dot{V})$ and the mechanisms responsible for this shape; *2*) the partitioning of flow-resistive pressures, both between tissues and gas, and between the various air passages; *3*) the influence of static and dynamic changes in the dimensions of the air passages on flow-resistance. Measurements of the relative contributions of gas and tissue flow-resistance will be discussed first since the remaining points concern only the gas component.

Separation of total pulmonary flow-resistance into gas and tissue components. This separation can be accomplished by measuring the flow-resistive pressure applied to the gas and subtracting it from the total ($p_{res_{Ti}} = p_{res_L} - p_{res_G}$). The pressure applied to the gas is equal to the difference in pressure between the airway opening and the alveoli ($P_G = P_{ao} - P_{alv}$). Neergaard and Wirz described a method for measuring alveolar pressure (197) that has also been used by Vuilleumier (252) and by Otis and Proctor (203). They reasoned that because of the large alveolar volume relative to that in the airways, the pressure in the airway following interruption of the stream should equilibrate in a very short time to a value very near to the one that existed in the alveoli prior to interruption. It has since been estimated that alveolar pressure would have changed substantially prior to such equilibration (137, 177), and that the pressure should more nearly approximate the total flow-resistive pressure, including any tissue component. This conclusion is supported by the finding that flow-resistance by this method is actually slightly greater rather than less than total pulmonary resistance (69, 177). [The interrupter technique as ingeniously modified by Ainsworth (6) and by Clements (69) continues in use as a method for estimating total pulmonary resistance (61, 240).]

A second approach has been to change the physical properties of the gas, thus altering gas flow-resistance while leaving tissue resistance unchanged. Bayliss and Robertson used hydrogen for this purpose (25). They found comparatively small changes and concluded that most of lung viscance is in the tissues, which, as discussed above, was probably the case under the conditions of the experiments. Fry et al. came to the opposite conclusion in measurements on human subjects breathing argon-oxygen mixtures (123). McIlroy et al. pointed out that these previous studies had underestimated the effects of changes in the gas properties on Reynold's number and hence in the distribution of turbulence in the airways (162). They used gas mixtures of equal kinematic viscosity (the kinematic viscosity is the ratio of viscosity to density) in order to assure similar distribution of turbulence within the airways at a given flow. For such mixtures the pressure necessary to produce a given flow is proportional to either the density or the viscosity of the flowing gas. Knowing these quantities it was possible to solve for tissue resistive pressures from measurements made with any two such mixtures of differing viscosity. These authors estimated tissue resistance to be approximately linear and to be on the average 30 to 40 % of total pulmonary resistance.

The third and most versatile approach has been to measure alveolar pressure indirectly from measurements of alveolar gas compression and expansion. The method was proposed and attempted by Sonne (244), but its first practical application was made by DuBois et al. who overcame the problems of measurement with great ingenuity (97). A subject in a closed chamber produces changes in chamber pressure to the extent that he changes the temperature, the number of molecules, or the volume of some part of the gas. Synchronously with inspiration he does all three—warming and adding water vapor to the inspired gas[8] as well as expanding it to the extent that alveolar pressure is less than chamber pressure. If chamber gas is saturated at body temperature the temperature and water vapor effects could be removed, but this is not a convenient solution (16, 20). Instead DuBois et al. magnified the effects of alveolar gas compression and expansion and minimized the other changes by having the subject pant shallowly through a flowmeter. They then calibrated the fluctuations in chamber pressure in terms of alveolar pressure by closing off the airway and having the subject continue panting efforts. With flow stopped, airway pressure equalled alveolar pressure. The relationship between alveolar and chamber pressure was thereby established and could be applied to the measurements prior to airway closure. The relationship between airway and chamber pressure during obstruction could also be used to measure total intrathoracic gas volume by Boyle's law (96). [Again a method long known in principle but here first put to practical use (128, 210).] Pulmonary tissue resistance was estimated (by subtracting gas flow-resistance from total pulmonary flow-resistance simultaneously measured) to be about 20% of the total, or approximately one-half that estimated by McIlroy et al. (172).

In the experiments of McIlroy et al. subjects inspired a total volume of about one liter in about 0.5 seconds, or at a frequency equivalent to 60 to 100 BPM. In the method of DuBois et al. the tidal volume is 100 to 200 ml delivered at a frequency somewhere between 120 to 200 BPM. It is possible that the differences in estimated tissue resistance relate to these differences in breathing pattern. (As mentioned in connection with the static volume-pressure hysteresis seen in lungs in open-chest preparations, there is evidence that it decreases with frequency.) Whatever the explanation of the differing estimates it is clear that lung tissue resistance has been estimated only under conditions that differ appreciably from spontaneous breathing.

Shape of the flow-resistance function [$p_{res_L} = \mathfrak{F}(\dot{V})$]. Rohrer thought direct measurement of the gas flow-resistance so remote a possibility he undertook the formidable task of estimating it by applying laws governing the flow of gas through tubes to post-mortem measurements of the dimensions of the air passages (224). To this day the theory of flow through highly branched systems is fragmentary and for distensible branched systems virtually nonexistent. Furthermore, morbid dimensions of the air passages bear a largely unknown relationship to dimensions in life. Rohrer's study is nevertheless of great value quite apart from the accuracy of his predictions.

Rohrer distinguished two sources of gas flow-resistance. One he called 'tubular' such as occurs in cylindrical tubes. The other he referred to as 'additional' and by this he meant resistance due to sudden changes in cross section or to bends in the passages. He calculated, incorrectly, that all tubular flow would be laminar in character even during rapid breathing. According to the Hagen-Poiseuille law,

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[8] The additional changes due to the respiratory quotient are here neglected.

tubular flow-resistive pressures would then be directly proportional to flow; the pressures due to 'additional' resistances would be proportional to flow squared, and total flow-resistive pressure could be expressed as follows:

$$p_{res_G} = K_1(\dot{V}) + K_2(\dot{V})^2$$

$K_1(V)$ is the laminar flow term with K_1 containing the viscosity of the gas and the tubular geometry. $K_2(\dot{V})^2$ is the 'additional resistance' term, where K_2 includes the density of the gas and the cross section and bend geometry.

As was pointed out by Gaensler and Maloney (129), Rohrer made an arithmetical mistake in calculating Reynold's numbers leading to a tenfold overestimation of the velocity at which the transition from laminar to turbulent flow would occur Rohrer's assumption that all tubular flow would be laminar was correct only for quiet breathing (254) (see table 1).

For turbulent flow, pressures are approximately proportional to flow squared. In this case an expression such as Rohrer's might still give a reasonable fit to flow-pressure relationships, but as McIlroy et al. (162) and others (171) have pointed out the 'constants' have altogether different meanings from the ones Rohrer intended. The results obtained by McIlroy et al. on subjects breathing gas mixtures of differing viscosities and densities show that K_1 and K_2 should not be referred to as 'laminar' and 'turbulent' constants as has been done. Helium, which saturated at body temperature is about one-fifth as dense as air and slightly more viscous, would be expected to cause changes in K_2 and a slight increase in K_1. In fact, it produced substantial changes in both. Ethane, about one-sixth more dense

TABLE 1

	DIAMETER mm	LINEAR VELOCITY RELATIVE TO THAT IN TRACHEA	REYNOLDS' NUMBER, R_e*		
			$\dot{V}$ = .33 liter/sec	$\dot{V}$ = 3.33 liters/sec	$\dot{V}$ = 10 liters/sec
Nasal canal	5	1.4	400	4,000	12,000
Pharynx	12	1.1	800	8,000	24,000
Glottis	8	3.4	1600	16,000	48,000
Trachea	21	1.0	1250	12,500	37,500
Bronchi	17	0.9	910	9,100	27,300
	9	1.3	700	7,000	21,000
	6	1.6	570	5,700	17,100
	4	0.8	190	1,900	5,700
	2.5	0.5	74	740	2,220
	1	0.6	35	350	1,050
Lobular bronchioles	.4	0.1	2	20	60

Reynolds' numbers at various points in the airways at flows corresponding to peak levels during quiet breathing ($\dot{V}$ = .33 liter/sec), moderate hyperventilation ($\dot{V}$ = 3.3 liters/sec, minute volume about 60 liters), and maximal efforts ($\dot{V}$ = 10 liters/sec) as based on airway dimensions given by Rohrer (224). Critical Reynolds' number = 2000.

* $R_e = \dfrac{\rho v d}{\eta}$: η = viscosity; ρ = density; v = linear velocity; d = diameter.

and half as viscous as air would be expected to influence K_1 considerably and K_2 moderately. In fact, it had little discernible effect on either. The finding with ethane seems particularly remarkable and serves to underline the inadequacy of present knowledge as to the aerodynamics of the respiratory passages.

Partitioning of airway resistance. Rohrer predicted that nasal resistance would account for 50% of the total during quiet breathing (224). Butler found nasal resistance to be from 50 to 75% of total gas flow-resistance (51). From Rohrer's data it may be estimated that upper airway resistance including that of the glottis would account for about 25% of the total during quiet mouth breathing (224). Opie et al. measured intratracheal pressure from needles passed through the cricothyroid membrane in the normal subjects during mouth breathing and found that resistance above that point averaged 28% of total pulmonary resistance (202). In similar experiments Hyatt and Wilcox found a value of about 20% (147). Rohrer predicted that most of the 'additional resistance' ($K_2(\dot{V})$) would be above the trachea and that lower airway resistance would be nearly linear. Ferris et al. found that lower airway resistance was linear at least up to flow rates of 1.2 liters/sec (109).

Rohrer estimated that more than 70% of lower airway resistance would be in bronchi 1 mm and smaller, i.e. from lobular bronchioles. There is no objective measurement testing this prediction. It is probable Rohrer underestimated the diameters of the small bronchi. This follows from the finding by Martin and Proctor of increasing distensibility of small as compared to larger bronchi. At end-expiration it can be estimated from their data that radii of the trachea, 5 mm and 2 mm bronchi are, respectively, 102%, 145%, and 200% of resting (i.e. undistended) values (175).

Rohrer was the first to consider in detail the influence of local mechanical factors on the distribution of ventilation (224, 226). Fowler (112), seeking explanations for the unequal distribution of ventilation in normal human lungs, has referred to Rohrer's conclusion that air passages leading to centrally located air spaces, i.e. those near the hilus, have less flow-resistance than those serving more peripheral regions. If Otis et al. (206) are correct in inferring from the dynamic behavior of normal lungs that pathway time constants (the product of flow-resistance and compliance) are everywhere the same, then central regions with low flow-resistance would have to be more compliant than peripheral regions. These regions would then be better ventilated than peripheral ones. In normal lungs this spatial inequality would be independent of the breathing pattern. As Otis et al. have indicated, in the case of unequal time constants for the separate pathways the degree of inequality would change with breathing frequency and even during the breathing cycle. Single-breath gas analysis supports this prediction. (As pointed out by Otis et al. (206) and recently re-emphasized by DeFares and Donleben (85), inequality or equality of pathway time constants have implications as to possible changes in the distribution of ventilation with respiratory frequency. They do not in themselves determine distribution.)

Ross found no evidence of regional differences in flow-resistance from measurements of bronchial dimensions made on casts of dried dog lungs (230). He dis-

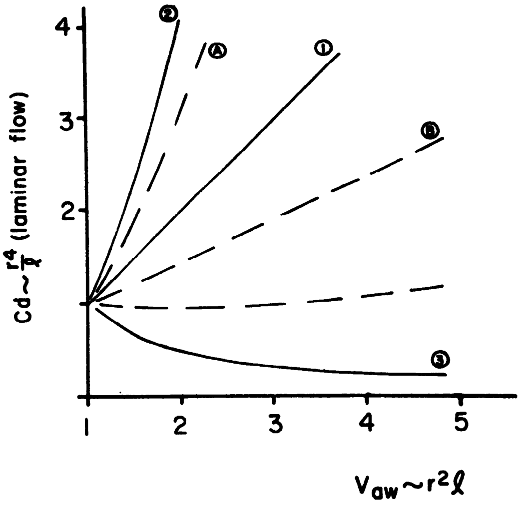

FIG. 6. Airway conductance (*Cd*) changes with airway volume (V_{aw}) for regular changes in radius and length. ①$\Delta r = \Delta l$; ②$\Delta l = 0$; ③$\Delta r = 0$; Ⓐ$\Delta l = 0.25\Delta r$ [small dog bronchi (175)]; Ⓑ$\Delta l = 2\Delta r$ [dog trachea (175)]; *unnumbered curve* $\Delta l = 5\Delta r$.

cussed a variety of applications of bronchial geometry on gas exchange. There is need for extension of studies such as those of Rohrer and Ross, hopefully with better information as to in vivo dimensions.

In summary, nasal flow-resistance makes up a substantial part of total gas flow-resistance. During mouth breathing, upper airway resistance accounts for about one-quarter of the total and probably nearly all of the nonlinearity of flow-resistance. The distribution of flow-resistance along and between the unequally branching pathway from trachea to the air spaces is unknown. Whatever may be the particular distribution of flow-resistance to various parts of the lung, it appears to relate to the volume-elastic characteristics of the separate pathways so as to permit a distribution of ventilation which is independent of the breathing pattern in normal lungs.

Airway conductance and volume of the lungs. Within a given species differences in the volume of the lungs (the volume of the gas and tissue) can be accounted for in terms of growth, individual variation, and degree of inflation. Airway resistance has been shown to be inversely related to volume in all three instances: in children as compared to adults (37, 77), in adults of various sizes (37, 77, 174), and in an individual breathing at different lung volumes (37, 50, 123, 176). This section examines the extent to which observed relationships between airway resistance and lung volume reflect particular changes in the dimensions of the airway. This is done by applying concepts developed by Rohrer to actual measurements made in human subjects, principally those of Briscoe and DuBois who measured airway resistance in children and adults at various degrees of lung volume (37).

Rohrer predicted changes in total airway resistance that would accompany regular changes in the dimensions of the airways (224). The solid lines in figure 6 illustrate some of the cases he considered. Conductance ($1/R$) is used rather than its inverse because the correlation is then positive in most instances. Considering all flow to be laminar, when changes in radius and length are equal, the relationship between conductance and airway volume is linear (*curve 1*). *Curves 2* and *3* are the limiting case for unequal changes in radius and length. Martin and Proctor observed radius changes to be greater than length changes in dog bronchi during passive distention, while the reverse was true for the trachea (175). *Curves A* and *B* are based on their data.

The relationships for turbulent flow in tubes, and for 'additional resistance' can also be represented. In the first case all conductances are increased by the factor Δr. For example, *curve 1* becomes transposed to *curve 2*. For 'additional resistance' conductance is proportional to Δr^4 and length does not enter in, hence *curve 2* applies.

To make the step from airway to lung volume the relative changes of these two must be known. If it is assumed that lung volume changes in direct proportion to airway volume, the relationships in figure 6 would hold for lung volume as well. Disproportionate increases in conductance relative to lung volume could then arise from one or a combination of three factors: *1*) greater changes in radius relative to length; *2*) turbulent tubular flow; and *3*) the contribution of changes in 'additional' resistances. Disproportionate increases in volume relative to conductance would result only from greater changes in length relative to radius.

If airway volume increased (or decreased) out of proportion to lung volume, since conductance and airway volume are positively correlated in the majority of cases (fig. 6), it would be expected that airway conductance would also increase (or decrease) out of proportion to lung volume.

For adults of similar age but different lung size, all linear dimensions of the lungs and airways probably change nearly equally, with the possible exception of the smallest air spaces and airways. It follows that lung volume and conductance

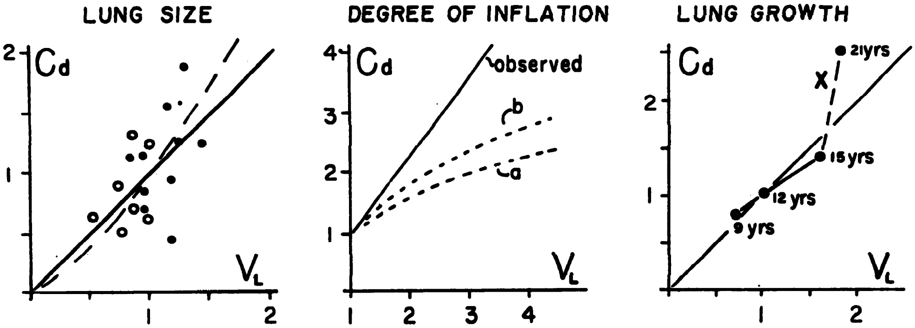

Fig. 7. Observed and predicted changes in airway conductance (*Cd*) for changes in lung volume (V_L) relating to size, degree of inflation, and growth. Changes with lung size are expressed relative to average values for the group (ref. 37); *open circles* are females, *dots* are males. Changes with degree of lung inflation are expressed relative to the smallest volumes obtained. The *solid line* represents the average observed relationship (ref. 37). The *dashed lines* are predictions based on a fixed upper airway resistance equalling 25% of the total at resting FRC. *Line a* is for equal changes in length and radius and laminar flow (fig. 6, *line 1*). *Line b* is for equal changes in length and radius and turbulent flow (fig. 6, *line 2*). Changes with lung growth are expressed relative to the value for the 12-year-olds. *Dots* represent data from ref. 77. The X is from ref. 37 and is average adult data relative to that observed in eight children of average age: 9 years.

should increase together, with a somewhat disproportionate increase in conductance to the extent that 'additional' resistances and turbulent tubular flow contribute. Figure 7 shows data of Briscoe and DuBois for 6 females and 10 male adults (37). In view of the scatter of points a larger group, hopefully with greater size differences, is needed before the correspondence with the predicted relationships can be tested. A comparison of jockeys and basketball players would probably suffice.

For changes in lung volume caused by lung inflation and deflation the relationship to airway conductance is better established. Briscoe and DuBois found that in every instance lung volume and airway conductance were nearly linearly related (37). The average relationship in 11 male adult subjects producing volume changes from minimum levels that ranged from 1.6 to 4-fold is shown in figure 7 (the somewhat greater changes in conductance relative to volume reflects the observation that the regression line intercepted the volume axis at a positive value). They noted that if changes in length and radius are equal in the airways responsible for the conductance changes, the observed linear relationship means that the airways and air spaces must be equally compliant (239). (Rohrer's predictions also lead to this conclusion.) This consideration assumes the major part of airway resistance to be in the smaller airways. If the upper airways account for 25 % of the total resistance at a flow of 0.5 liter/sec, which appears to be a reasonable estimate, and if upper airway conductance did not change with lung inflation, the predicted relationship shown by the *dashed lines* in figure 7 would hold. The discrepancy between the observed and predicted curves could be explained if upper airway conductance were negligible, or increased with lung inflation, and to some extent if radius changes in radius of the lower airways were disproportionate to changes in length. The findings of Martin and Proctor (fig. 6) suggest the possibility that changes in radius may predominate in small airways (175). Measurements of upper airway conductance at different lung volumes have not been reported.

Although Briscoe and DuBois studied children and found smaller conductance values than in adults, they did not comment on the relative changes in lung volume and conductance between these groups. Taking their average data, adult conductance is increased disproportionately as compared to lung volume. A similar relationship is found in the data presented by Cook et al. between total pulmonary conductance and lung volume (77). These workers quote average measurements for some 85 children and adolescents between the ages of 6 and 16 (138). Average data for three age groups along with data on young adults are presented in figure 7 relative to the values obtained in the 12-year-old children. The average data of Briscoe and Dubois are included. Among the children and adolescents, lung volume increases disproportionately compared to conductance.

One is tempted to conjecture from these results that as the lung grows at least from age 8 through 14, the size and/or number of individual air spaces increases out of proportion to the size of the airways; and that this is followed by a period of further growth when the airways (through radius increases including those in the larynx) more than catch up. Available anatomic data are not good enough to test this possibility (14, 103). One approach might be to measure, by gas-dilution methods, and compare the growth of dead space and alveolar volumes.

Dynamic changes in airway resistance. In a paper published in 1892 (101), Einthoven theorized about the influence intrathoracic pressures might have on the widths of the various parts of the tracheobronchial tree. Under static conditions, when there is no flow, airway pressures are atmospheric throughout. Since pleural pressure is less than atmospheric, to the extent that the outer walls of the airways are exposed to this pressure, there is a tendency for the airways to be widened. This tendency increases at greater degrees of lung inflation as pleural pressure becomes more subatmospheric.

Under dynamic conditions additional pressures are applied to the walls of the tracheobronchial tree. During inspiration pleural pressures become more negative and the widening tendency is increased. But airway pressures are no longer everywhere equal; because of the flow-resistance of the airways, pressures are most negative in the alveoli, less so in the bronchi, and closest to atmospheric in the trachea. As a result the increased widening tendency associated with flow is distributed along the tracheobronchial tree, being greatest in the large airways and least in the small ones.

During expiration, with reversal of flow, pleural pressure rises decreasing the widening tendency. Indeed if flow becomes high enough so that pleural pressure rises above atmospheric, the pressure outside some of the airways may even be greater than the internal pressures, and widening will be replaced by narrowing. Again these dynamic effects are distributed along the tracheobronchial tree, and again they would be most marked in the large airways where intraluminal pressures are nearest to atmospheric.

Sixty years intervened before Einthoven's theories were confirmed by experiment. His predictions have been supported in detail both by roentgenographic observations and measurements of flow resistance. Indeed, it has been shown that dynamic increases in airway resistance during expiration set the limit on the ventilatory capacity of the respiratory system in normal and diseased lungs alike and are perhaps the most common cause of ventilatory disability.

Dayman in a paper that is a classic among writings on the pathophysiology of the lungs (82), demonstrated very marked rises in resistance during expiration in patients with pulmonary emphysema. He independently proposed the same mechanisms as Einthoven and added another. He suggested that radial forces directly applied by tissue elements to the walls of small airways might be of importance in protecting them from dynamic narrowing. In effect, then, lung elastic retraction might make distinct contributions to the 'widening tendency,' one indirectly through its influence on pleural pressure, and the other directly by way of local tissue forces. In pulmonary emphysema Dayman suggests that high expiratory resistance probably represents various combinations of three predisposing factors: intrinsic narrowing of peripheral airways, loss of radial support of airways by tissue elements, and decrease in the over-all retractive force of the lungs (with attendant rises toward atmospheric of the 'static' component of pleural pressure).

Since these same widening and narrowing tendencies operate in normal lungs, it is not surprising that increases in expiratory flow-resistance are found during rapid expiratory efforts and that these increases are more readily produced at low than at high lung volumes (53, 57, 123, 176). Dekker et al. have concluded from direct measurements of intrabronchial pressures at various levels that at least in normal subjects the increased resistance occurs predominantly in the large bronchi (86). On the other hand, Martin and Proctor found progressively smaller pressures required to collapse dog tracheas, 5 and 2 mm bronchi (175). It would appear that the larger airways which bear the brunt of these dynamic pressures are to some extent mechanically protected or, as Dayman has expressed it, are "armored against collapse by cartilage" (82). Whittenberger et al. (255) and Ross et al. (229) have pointed out that partial collapse of the large bronchi and the trachea may be an important part of the cough mechanism, assuring high stream velocities necessary for effective expectoration (229).

No comparable decreases in airway resistance occur during rapid inspiration when, according to Einthoven, dynamic widening of the airways might be expected. It has been suggested that the discrepancy between the phases is explainable on the basis that the increase in expiratory resistance is self-augmenting (with airway narrowing leading to increased resistance which in turn leads to increased narrowing downstream), while decreases in resistance during inspiration would be self-canceling (widening leading to smaller flow-resistive pressures and hence less widening) (176).

A particularly useful view of dynamic changes in resistance has been taken by Fry and his co-workers (125–127, 145, 146) [and a similar one by Dayman (83)]. Over a considerable portion of an expired vital capacity the maximum flow attainable is limited not by muscular effort but by dynamic increases in airway resistance. These flow maxima decrease with lung volume, presumably as the 'widening tendency' provided by elastic retraction diminishes. Hyatt et al. have described a simple way of recording this important relationship by plotting flow against volume during a moderately forced expiratory vital capacity (145). Roughly the lower two-thirds of such curves is found to be reproducible, relatively uninfluenced by upper airway or external resistance and largely independent of effort.

Fry has developed a mathematical model in an attempt at interpreting these curves in terms of properties of the lungs, airways, and flowing gas (125). Apart from the promise this approach gives toward specific interpretation, more general implications of the flow-volume curves are already clear (127). Tests of ventilatory capacity (such as the maximum breathing capacity and the various timed expiratory vital capacities) test principally the degree of dynamic narrowing occurring in the intrathoracic airways. Their usefulness is greatly enhanced because results depend only to a minor degree on muscular effort (158). The patient with pulmonary emphysema even at rest may be expiring along his maximum flow-volume line. His only means of increasing minute ventilation are to spend less time breathing in and to breathe at a higher lung volume. Einthoven's prediction for asthmatic patients holds equally well here: "expiration would have to be superficial and of little power to avoid airway narrowing. In these circumstances a powerful expiration would be useless and a waste of energy" (101).

In closing this section on dynamic changes in airway resistance a further point about airway pressures needs mention. Part of the change of pressure at the inside wall of an airway has nothing to do with the flow-resistance (i.e. pressures related to energy losses in laminar and turbulent flow) but is the result of the Bernoulli effect (89). This pressure relates to the kinetic energy of the air stream, and hence to the density of the gas, ρ, and the square of its linear velocity, v^2. Taking both the Bernoulli effect and flow-resistance into account, the pressure, p, at the inner wall of an airway differs from atmospheric, P_B, as follows:

$$p = P_B \pm p_{res} - \frac{\rho v^2}{2g}$$

p_{res}, the pressure loss due to flow-resistance of the airways through which gas flows between the point in question and the ambient air, adds or subtracts according to the direction of flow. The pressure due to the Bernoulli effect, $\frac{\rho v^2}{2g}$, (g being the acceleration of gravity) is always negative and hence in the direction to produce airway narrowing. Its magnitude in cm H_2O, assuming the density to be near that of ambient air may be calculated from the following:

$$P = \frac{0.56(\dot{V})^2}{(A)^2}$$

with $\dot{V}$ in liters/sec and A, the cross-sectional area in cm^2.

This pressure is small under ordinary circumstances (less than $-.05$ cm H_2O in the trachea during quiet breathing and about -5 cm H_2O during a maximally rapid inspiration) but may become large and contribute significantly to narrowing during forced expirations when linear velocities in narrowed airways must be high.

The Bernoulli effect is mentioned here in some detail because it needs to be taken into account in the measurement of flow-resistive pressures. Failure to do so can lead to appreciable errors when, for example, mouth pressure is sampled from a side tap in a mouthpiece of small cross section. At least part of reported differences in resistance between the respiratory phases relates to this factor (123).

Pulmonary Inertance $[p_{in_L} = I(\ddot{V})]$

The most extensive measurements of the inertial properties of the respiratory system have been made by DuBois, Brody, and co-workers (40, 41, 98). Comparatively few measurements have been made in the lungs. Mead estimated the inertial component of esophageal pressure fluctuations during voluntary panting (180) at points of zero flow between the phases by assuming that p_{el_L} was unchanged at these frequencies and that therefore:

$$p_{in_L} = P_L - \left[\frac{1}{C_{dyn}}(\Delta V)\right], \text{ at } \dot{V} = 0$$

The ratio of this pressure to simultaneous volume acceleration appeared to be linear and expressed the inertance of the lung tissue and gas. By making measurements at increasing ambient pressures he found that inertance increased approxi-

TABLE 2. APPROXIMATE VALUES FOR COEFFICIENTS IN EQUATION OF MOTION FOR ADULT HUMAN LUNGS (AT RESTING FRC IN THE UPRIGHT POSTURE)

Equations of motion:

$$P_L = P_0 + \frac{1}{C_{dyn}}\Delta V + K_1(\dot{V}) + K_2(\dot{V}): + I(\ddot{V})$$

$$\cong P_0 + \frac{1}{C_{dyn}}\Delta V + R\dot{V}$$

P_0 at FRC	5 cm H_2O	(43, 59, 115, 151, 178, 183, 245)
at TLC	25 cm H_2O	(43, 59, 115, 151, 179, 245)
at RV	± ?	(61, 243)
C_{dyn}	200 ml/cm H_2O	(11, 43, 49, 52, 113, 174, 176, 245)
K_1	1.6 cm H_2O/liter/sec	(63, 123, 176)
K_2	0.4 cm H_2O/(liter/sec)^2	
R quiet breathing	2.0 cm H_2O/liter/sec	(11, 63, 115, 123, 145, 176)
rapid inspiration	7.0 cm H_2O/liter/sec	
rapid expiration	10–30 + cm H_2O/liter/sec	
$R_L = R_G + R_{Ti}$ with R_G =	60–85% of total	(97, 152, 172)
I	0.01 cm H_2O/liter/sec^2	
$I_L = I_G + I_{Ti}$ with I_G =	ca. 100% of total	(180)

Numbers in parentheses are references.

mately in direct proportion to gas density, and he concluded from the observed relationship that tissue inertance was negligible. During quiet breathing the amplitude of p_{in_L} was estimated to be about 0.02 cm H_2O or some 0.5% of the total applied to the lungs. During heavy exercise p_{in_L} might increase 100-fold but would contribute less than 5% of the total pressure fluctuation.

COMMENT ON THE EQUATION OF MOTION FOR THE LUNGS AND A FURTHER LIMITATION IN ITS USE

The various relationships that have been discussed may be combined in a single expression.

$$P_L = P_{ao} - P_{pl} = \left[p_0 + \frac{1}{C_{dyn}}\Delta V\right] + \left[K_1(\dot{V}) + K_2(\dot{V})^2\right] + \left[I\ddot{V}\right]$$

The bracketed quantities are the elastic, flow-resistive, and inertial terms. During quiet breathing, flow-resistance is nearly linear and inertial pressures are negligible; the expression then simplifies to the following:

$$P_L = P_{ao} - P_{pl} = P_0 + \frac{1}{C_{dyn}}\Delta V + R\dot{V}$$

This article has attempted to discuss in detail the restrictions placed on the quantities and terms in these expressions. Comparatively few values have been given for the various coefficients. The reader is referred to original articles for these. Approximate values for some of the coefficients are given in table 2.

In closing, a further restriction on the use of the equations of motion needs to be discussed. One of the conditions necessary for the development of the equation of motion is that all motion be accountable in terms of a single variable. The observation that C_{dyn} does not change with respiratory frequency is an indication that in normal lungs distribution of volume is also independent of frequency. In this case lung configuration and motion are determined by a single variable and application of the equation of motion is uncomplicated. What of the case where C_{dyn} changes with frequency? This is a common finding in abnormal lungs and, as has been discussed, probably reflects changes in the distribution of volume with changes in respiratory frequency. The equation of motion is still meaningful in such a case, but an additional restriction is imposed. For a fixed frequency (at a particular average volume and volume history) the distribution of volume change is also fixed. The terms and coefficients in the equation of motion then pertain to the lungs at that particular frequency only. Clearly confusion can arise if measurements made at different frequencies are compared without bearing this in mind.

The measurement of p_{res_L} by airway interruption serves as an example of this, as Cherniack has indicated (63). At the instant before interruption, P_L is appropriate to the frequency content of the breath at that time. After interruption, gas within the lungs redistributes to static conditions, and the pressure corresponds to a frequency of zero. The pressure change corresponds to no single frequency and in instances where C_{dyn} is frequency dependent its meaning is ambiguous.

Interpretation of airway resistance measured by the gas compression method of DuBois et al. (97) also is complicated in these circumstances. Estimation of the pressure in the air spaces becomes dependent on the distribution of volume among the air spaces when differences in air-space pressures exist. Such differences are to be expected when time constants of the pathways differ, particularly during the panting maneuver used for the measurement. The pressure in the air spaces with large volumes would then have a greater influence on the pressure measured than those with small volumes, quite apart from the distribution of volume change. There is no reason to believe that esophageal pressures would be similarly weighted. It is doubtful that valid estimates of lung tissue resistance based on these measurements can be made in patients with asthma or emphysema, where substantial changes in C_{dyn} with frequency exist and where in all probability considerable differences in the volume of air spaces occur (173).

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REFERENCES

1. ADAMS, F. H., P. KARLBERG, AND J. LIND. Possible role of capillary erection as a cause for lung expansion in the newborn infant. *Clin. Research* 6: 111, 1958.
2. AGOSTONI, E., A. TAGLIETTI, AND I. SETNIKAR. Absorption force of the capillaries of the visceral pleura in determination of the intrapleural pressure. *Am. J. Physiol.* 191: 277, 1957.
3. AGOSTONI, E., A. TAGLIETTI, A. FERRARIO AGOSTONI, AND I. SETNIKAR. Mechanical aspects of the first breath. *J. Appl. Physiol.* 13: 344, 1958.
4. AGOSTONI, E., F. F. THIMM, AND W. O. FENN. Comparative features of the mechanics of breathing. *J. Appl. Physiol.* 14: 679, 1959.
5. AGOSTONI, E. Volume-pressure relationships of the thorax and lung in the newborn. *J. Appl. Physiol.* 14: 909, 1959.
6. AINSWORTH, M. AND J. W. EVELEIGH. A method of estimating lung resistance in humans. *Ministry of Supply, C.D.E.E. Porton Tech. Paper* 320, 1952.
7. ALEXANDER, R. S. Elasticity of muscular organs. In: *Tissue Elasticity*, J. W. Remington (editor).

Washington, D. C.: American Physiological Society, 1957, pp. 111–122.

8. ALFREY, T. JR. *Mechanical Behavior of High Polymers.* New York: Interscience, 1948.
9. ARNOTT, W. M., J. BUTLER, AND A. C. PINCOCK. A pressure-volume diagram recorder for respiration in man. *J. Physiol. (London)* 124: 6P, 1954.
10. ARON, E. Der intrapleurale Druck beim lebenden, gesunden Menschen. *Arch. pathol. Anat. u. Physiol.* 160: 226, 1900.
11. ATTINGER, E. O., R. G. MONROE, AND M. S. SEGAL. Mechanics of breathing in different body positions. I. In normal subjects. *J. Clin. Invest.* 35: 904, 1956.
12. ATTINGER, E. O. Pulmonary mechanics and hemodynamics during changes in ventilation and blood volume. *J. Appl. Physiol.* 15: 429, 1960.
13. AVERY, M. E., N. R. FRANK, AND I. GRIBETZ. Inflationary force produced by pulmonary vascular distention in excised lungs. Possible relation of this force to that needed to inflate the lungs at birth. *J. Clin. Invest.* 38: 456, 1959.
14. AVERY, M. E. Some effects of age and size on pulmonary mechanics. Normal and abnormal respiration in children. 37th Ross Conference of Pediatric Research, Kansas City, 1960. In press.
15. BADER, R. A., M. E. BADER, AND D. J. ROSE. Oxygen cost of breathing in dyspnoeic subjects as studied in normal pregnant women. *Clin. Sci.* 18: 223, 1959.
16. BARGETON, D., G. BARRÈS, R. LEFEBVRE DES NOETTES, AND P. GAUGE. Mesure de la résistance des voies aériennes de l'Homme dans la respiration normale. *J. physiol. (Paris)* 49: 37, 1957.
17. BARTLETT, R. G. JR., H. F. BRUBACH, AND H. SPECHT. Oxygen cost of forced breathing in the submerged resting subject. *J. Appl. Physiol.* 11: 377, 1957.
18. BARTLETT, R. G. JR., H. F. BRUBACH, AND H. SPECHT. Oxygen cost of breathing. *J. Appl. Physiol.* 12: 413, 1958.
19. BARTLETT, R. G. JR., H. F. BRUBACH, R. C. TRIMBLE, AND H. SPECHT. Relation of increased airway resistance to breathing work and breath velocity and acceleration patterns with maximum and near maximum breathing effort. *J. Appl. Physiol.* 13: 194, 1958.
20. BARTLETT, R. G. JR., H. F. BRUBACH, R. C. TRIMBLE, AND H. SPECHT. Airway resistance measurement during any breathing pattern in man. *J. Appl. Physiol.* 14: 89, 1959.
21. BASCH, v. S. Ueber eine Function des Capillardruckes in den Lungenalveolen. *Wiener Med. Blatter* 10: 466, 1887.
22. BASCH, v. S. *Klinische und experimentelle Studien. I. Band. Beiträge zur Pathologie des Kreislaufs. Lungenödem. Cardiale Dyspnoe.* Berlin: August Hirschwald, 1891.
23. BATEMAN, J. B. Some properties of films and membranes. In: *Physical Chemistry of Cells and Tissues*, R. Höber (editor). Philadelphia: Blakiston, 1945, pp. 187–216.
24. BATES, D., A. P. FISHMAN, W. S. FOWLER, P. C. PRATT, AND R. V. EBERT. Report of Committee on definition of emphysema. *Am. Rev. Respirat. Diseases* 80: 114, 1959.
25. BAYLISS, L. E. AND G. W. ROBERTSON. Visco-elastic properties of the lungs. *Quart. J. Exptl. Physiol.* 29: 27, 1939.
26. BERNOULLI, E. Zur Mechanik der Atembewegungen. *Arch. exptl. Pathol. Pharmakol.* 66: 313, 1911.
27. BERNSTEIN, L. AND D. MENDEL. Accuracy of spirographic recording at high respiratory rates. *Thorax* 6: 297, 1951.
28. BERNSTEIN, L., J. L. D'SILVA, AND D. MENDEL. Effect of the rate of breathing on the maximum breathing capacity determined with a new spirometer. *Thorax* 7: 255, 1952.
29. BERNSTEIN, L. Elastic pressure-volume curves of the lungs and thorax of the living rabbit. *J. Physiol. (London)* 138: 473, 1957.
30. BERNSTEIN, L. Indications of quantal behavior in the inflation and deflation of rabbit lungs. *Am. Rev. Respirat. Diseases* 81: 744, 1960.
31. BONDURANT, S., J. B. HICKAM, AND J. K. ISLEY. Pulmonary and circulatory effects of acute pulmonary vascular engorgement in normal subjects. *J. Clin. Invest.* 36: 59, 1957.
32. BONDURANT, S., J. MEAD, AND C. D. COOK. A re-evaluation of effects of acute central congestion on pulmonary compliance in normal subjects. *J. Appl. Physiol.* 15: 875, 1960.
33. BONHAM CARTER, R. E. Architectural function of pulmonary capillaries. *Lancet* 1: 1292, 1957.
34. BORST, H. G., E. BERGLUND, J. L. WHITTENBERGER, J. MEAD, M. McGREGOR, AND C. COLLIER. Effect of pulmonary vascular pressures on the mechanical properties of the lungs of anesthetized dogs. *J. Clin. Invest.* 36: 1708, 1957.
35. BRISCOE, A. M. AND W. E. LORING. Elastin content of the human lung. *Proc. Soc. Exptl. Biol. Med.* 99: 162, 1958.
36. BRISCOE, A. M., W. E. LORING, AND J. H. McCLEMENT. Changes in human lung collagen and lipids with age. *Proc. Soc. Exptl. Biol. Med.* 102: 71, 1959.
37. BRISCOE, W. A. AND A. B. DUBOIS. Relationship between airway resistance, airway conductance, and lung volume in subjects of different age and body size. *J. Clin. Invest.* 37: 1279, 1958.
38. BRODOVSKY, D., J. A. MACDONELL, AND R. M. CHERNIACK. Respiratory response to carbon dioxide in health and in emphysema. *J. Clin. Invest.* 39: 724, 1960.
39. BRODY, A. W. Mechanical compliance and resistance of the lung-thorax calculated from the flow recorded during passive expiration. *Am. J. Physiol.* 178: 189, 1954.
40. BRODY, A. W., A. B. DUBOIS, O. I. NISELL, AND J. ENGELBERG. Natural frequency, damping factor and inertance of the chest-lung system in cats. *Am. J. Physiol.* 186: 142, 1956.
41. BRODY, A. W., J. J. CONNOLLY, JR., AND H. J. WANDER. Influence of abdominal muscles, mesenteric viscera and liver on respiratory mechanics. *J. Appl. Physiol.* 14: 121, 1959.
42. BROOKHART, J. M. AND T. E. BOYD. Local differences in intrathoracic pressure and their relation to cardiac filling pressure in the dog. *Am. J. Physiol.* 148: 434, 1947.
43. BROWN, C. C. JR., D. L. FRY, AND R. V. EBERT. Mechanics of pulmonary ventilation in patients with heart disease. *Am. J. Med.* 17: 438, 1954.
44. BROWN, E. S. Lung area from surface tension effects. *Proc. Soc. Exptl. Biol. Med.* 95: 168, 1957.

45. BROWN, E. S., R. P. JOHNSON, AND J. A. CLEMENTS. Pulmonary surface tension. *J. Appl. Physiol.* 14: 717, 1959.
46. BULL, H. B. Protein structure and elasticity. In: *Tissue Elasticity*, J. W. Remington (editor). Washington, D. C.: American Physiological Society, 1957, pp. 33-42.
47. BURTON, A. C. Relation of structure to function of the tissues of the wall of blood vessels. *Physiol. Revs.* 34: 619, 1954.
48. BUTLER, J. AND B. H. SMITH. Pressure-volume relationships of the chest in the completely relaxed anesthetized patients. *Clin. Sci.* 16: 125, 1957.
49. BUTLER, J., H. C. WHITE, AND W. M. ARNOTT. Pulmonary compliance in normal subjects. *Clin. Sci.* 16: 709, 1957.
50. BUTLER, J., C. G. CARO, R. ALCALA, AND A. B. DUBOIS. Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease. *J. Clin. Invest.* 39: 584, 1960.
51. BUTLER, J. Work of breathing through the nose. *Clin. Sci.* 19: 55, 1960.
52. BUYTENDIJK, H. J. Oesophagusdruck en longelasticiteit. Dissertatie, Groningen, 1949.
53. CAMPBELL, E. J. M., H. B. MARTIN, AND R. L. RILEY. Mechanisms of airway obstruction. *Bull. Johns Hopkins Hosp.* 101: 329, 1957.
54. CAMPBELL, E. J. M., E. K. WESTLAKE, AND R. M. CHERNIACK. Simple methods of estimating oxygen consumption and efficiency of the muscles of breathing. *J. Appl. Physiol.* 11: 303, 1957.
55. CAMPBELL, E. J. M. Respiratory Muscles and the Mechanics of Breathing. London: Lloyd-Luke, 1958.
56. CAMPBELL, E. J. M., E. K. WESTLAKE, AND R. M. CHERNIACK. Oxygen consumption and efficiency of the respiratory muscles of young male subject. *Clin. Sci.* 18: 55, 1959.
57. CAMPBELL, E. J. M. Volume-pressure diagram of the lungs and transmural pressure of the airways. *J. Appl. Physiol.* 14: 153, 1959.
58. CANDER, L. AND R. E. FORSTER. Determination of pulmonary parenchymal tissue volume and pulmonary capillary blood flow in man. *J. Appl. Physiol.* 14: 541, 1959.
59. CARO, C. G., J. BUTLER, AND A. B. DUBOIS. Some effects of restriction of chest cage expansion on pulmonary function in man; an experimental study. *J. Clin. Invest.* 39: 573, 1960.
60. CARTON, R. W. AND J. DAINAUSKAS. Isolation and physical properties of single elastic fibers. *Federation Proc.* 19: 383, 1960.
61. CHENG, T. O., M. P. GODFREY, AND R. H. SHEPARD. Pulmonary resistance and state of inflation of lungs in normal subjects and in patients with airway obstruction. *J. Appl. Physiol.* 14: 727, 1959.
62. CHERNIACK, R. M., L. E. FARHI, B. W. ARMSTRONG, AND D. F. PROCTOR. A comparison of esophageal and intrapleural pressure in man. *J. Appl. Physiol.* 8: 203, 1955.
63. CHERNIACK, R. M. Physical properties of the lung in chronic obstructive pulmonary emphysema. *J. Clin. Invest.* 35: 394, 1956.
64. CHERNIACK, R. M. AND D. P. SNIDAL. Effect of obstruction to breathing on the ventilatory response to CO2. *J. Clin. Invest.* 35: 1286, 1956.
65. CHERNIACK, R. M. Oxygen consumption and efficiency of the respiratory muscles in health and emphysema. *J. Clin. Invest.* 38: 494, 1959.
66. CHRISTIE, R. V. Elastic properties of the emphysematous lung and their clinical significance. *J. Clin. Invest.* 13: 295, 1934.
67. CLEMENTS, J. A. Surface tension of lung extracts. *Proc. Soc. Exptl. Biol. Med.* 95: 170, 1957.
68. CLEMENTS, J. A., E. S. BROWN, AND R. P. JOHNSON. Pulmonary surface tension and the mucus lining of the lungs: some theoretical considerations. *J. Appl. Physiol.* 12: 262, 1958.
69. CLEMENTS, J. A., J. T. SHARP, R. P. JOHNSON, AND J. O. ELAM. Estimation of pulmonary resistance by repetitive interruption of airflow. *J. Clin. Invest.* 38: 1262, 1959.
70. CLEMENTS, J. A. Pulmonary alveolar stability. *Federation Proc.* 19: 378, 1960.
71. CLOETTA, M. Untersuchungen über die Elastizität der Lunge und deren Bedeutung für die Zirkulation. *Arch. ges. Physiol.* 152: 339, 1913.
72. COLERIDGE, J. C. G. AND R. J. LINDEN. Measurement of effective atrial pressure. *J. Physiol.* (London) 126: 304, 1954.
73. COLVILLE, P., C. SHUGG, AND B. G. FERRIS, JR. Effects of body tilting on respiratory mechanics. *J. Appl. Physiol.* 9: 19, 1956.
74. COMROE, J. H. JR., R. E. FORSTER II, A. B. DUBOIS, W. A. BRISCOE, AND E. CARLSEN. *The Lung. Clinical Physiology and Pulmonary Function Tests.* Chicago: Yr. Bk. Pub., 1955.
75. COMROE, J. H. JR., S. Y. BOTELHO, AND A. B. DUBOIS. Design of a body plethysmograph for studying cardiopulmonary physiology. *J. Appl. Physiol.* 14: 439, 1959.
76. COOK, C. D., J. M. SUTHERLAND, S. SEGAL, R. B. CHERRY, J. MEAD, M. B. McILROY, AND C. A. SMITH. Studies on respiratory physiology in the newborn infant. III. Measurements of mechanics of respiration. *J. Clin. Invest.* 36: 440, 1957.
77. COOK, C. D., P. J. HELLIESEN, AND S. AGATHON. Relation between mechanics of respiration, lung size and body size from birth to young adulthood. *J. Appl. Physiol.* 13: 349, 1958.
78. COOK, C. D., J. MEAD, G. L. SCHREINER, N. R. FRANK, AND J. M. CRAIG. Pulmonary mechanics during induced pulmonary edema in anesthetized dogs. *J. Appl. Physiol.* 14: 177, 1959.
79. COOPER, E. A. A comparison of the respiratory work done against an external resistance by man and by a sine-wave pump. *Quart. J. Exptl. Physiol.* 45: 179, 1960.
80. COURNAND, A., D. W. RICHARDS, R. A. BADER, M. E. BADER, AND A. P. FISHMAN. Oxygen cost of breathing. *Trans. Assoc. Am. Physicians* 67: 162, 1954.
81. CRANE, M. G., D. A. HAMILTON, AND J. E. AFFELDT. A plastic balloon for recording intraesophageal pressures. *J. Appl. Physiol.* 8: 585, 1956.
82. DAYMAN, H. Mechanics of airflow in health and in emphysema. *J. Clin. Invest.* 30: 1175, 1951.
83. DAYMAN, H. Mechanics of breathing. In: *Pulmonary Emphysema*, A. L. Barach and H. A. Bickerman (editors). Baltimore: Williams & Wilkins, 1956, pp. 251-289.
84. DEAN, R. B AND M. B. VISSCHER. Kinetics of lung ventilation. An evaluation of the viscous and elastic resistance to lung ventilation with particular reference

to the effects of turbulence and the therapeutic use of helium. *Am. J. Physiol.* 134: 450, 1941.

85. DEFARES, J. G. AND P. G. DONLEBEN. Relationship between frequency-dependent compliance and unequal ventilation. *J. Appl. Physiol.* 15: 166, 1960.
86. DEKKER, E., J. G. DEFARES, AND H. HEEMSTRA. Direct measurement of intrabronchial pressure. Its application to the location of the check-valve mechanism. *J. Appl. Physiol.* 13: 35, 1958.
87. DEKKER, E. De invloed van de intrathoracale druk op de wijdte en stromingsweerstand van de luchtwegen bij normale proefpersonen en buj patiënten met asthma en emphyseem. Thesis, Rotterdam: La-Noble and Bronder, 1958.
88. DITTMER, D. S. AND R. M. GREBE (editors). *Handbook of Respiration.* Philadelphia: Saunders, 1958.
89. DODGE, R. A. AND M. J. THOMPSON. *Fluid Mechanics.* New York: McGraw-Hill, 1937.
90. DONDERS, F. C. Bijdrage tot het mechanisme van ademhaling en bloedsomloop in den gezonden en zieken toestand. *Ned. Lancet* 5: 333, 1849.
91. DONDERS, F. C. Beiträge zum Mechanismus der Respiration und Circulation im gesunden und kranken Zustande. *Ztschr. Rat. Med.* 3: 287, 1853.
92. DONLEBEN, P. G. *Studies on Lung Mechanics.* Thesis, Leyden: Drukkerij Romijn-Apeldoorn, 1959.
93. DORNHORST, A. C. AND G. L. LEATHART. A method of assessing the mechanical properties of lungs and air-passages. *Lancet* 263: 109, 1952.
94. DRINKER, C. K. AND E. HARDENBERGH. Effects of the supine position upon the ventilation of the lungs of dogs. *Surgery* 24: 113, 1948.
95. DUBOIS, A. B. AND B. B. ROSS. A new method for studying mechanics of breathing using cathode ray oscillograph. *Proc. Soc. Exptl. Biol. Med.* 78: 546, 1951.
96. DUBOIS, A. B., S. Y. BOTELHO, G. N. BEDELL, R. MARSHALL, AND J. H. COMROE, JR. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J. Clin. Invest.* 35: 322, 1956.
97. DUBOIS, A. B., S. Y. BOTELHO, AND J. H. COMROE, JR. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. *J. Clin. Invest.* 35: 327, 1956.
98. DUBOIS, A. B., A. W. BRODY, D. H. LEWIS, AND B. F. BURGESS, JR. Oscillation mechanics of lungs and chest in man. *J. Appl. Physiol.* 8: 587, 1956.
99. DUOMARCO, J. L. AND R. RIMINI. La presion intraabdominal en el hombre en condiciones normales y patologicas. Buenos Aires: 'El Ateneo,' 1947.
100. EHRNER, L. Lung compliance and respiratory resistance determined from time-marked esophageal pressure-tidal volume curves and their relation to some other tests of lung function. A clinical and pathophysiological study of 148 cases with various chest diseases. *Acta Med. Scand.* Suppl. 353, 1960.
101. EINTHOVEN, W. Ueber die Wirkung der Bronchialmuskeln, nach einer neuen Methode untersucht, und über Asthma nervosum. *Arch. ges. Physiol.* 51: 367, 1892.
102. ELDRIDGE, F. AND J. M. DAVIS. Effect of mechanical factors on respiratory work and ventilatory responses to CO_2. *J. Appl. Physiol.* 14: 721, 1959.
103. ENGEL, S. *The Child's Lung: Developmental Anatomy, Physiology, and Pathology.* London: Arnold, 1947.
104. FARHI, L., A. B. OTIS, AND D. F. PROCTOR. Measurement of intrapleural pressure at different points in the chest of the dog. *J. Appl. Physiol.* 10: 15, 1957.
105. FENN, W. O. Mechanics of respiration. *Am. J. Med.* 10: 77, 1951.
106. FENN, W. O. Pressure volume diagram of the breathing mechanism. *Handbook of Respirat. Physiol.* W. M. Boothby (editor). Randolph Field, Texas: USAF School of Aviation Med., 1954.
107. FENN, W. O. Mechanism of breathing. *Sci. Am.* 202(1): 138, Jan. 1960.
108. FERRIS, B. G. JR., J. MEAD, AND N. R. FRANK. Effect of body position on esophageal pressure and measurement of pulmonary compliance. *J. Appl. Physiol.* 14: 521, 1959.
109. FERRIS, B. G. JR., L. OPIE, AND J. MEAD. Partitioning of respiratory resistance in man. *Federation Proc.* 19: 377, 1960.
110. FERRIS, B. G. JR AND D. S. POLLARD. Effect of deep and quiet breathing on pulmonary compliance in man. *J. Clin. Invest.* 39: 143, 1960.
111. FLEISCH, A. Der Pneumotachograph, ein Apparat zur Geschwindigkeitsregistrierung der Atemluft. *Arch. ges. Physiol.* 209: 713, 1925.
112. FOWLER, W. S. Intrapulmonary distribution of inspired gas. *Physiol. Revs.* 32: 1, 1952.
113. FRANK, N. R., J. MEAD, A. A. SIEBENS, AND C. F. STOREY. Measurements of pulmonary compliance in seventy healthy young adults. *J. Appl. Physiol.* 9: 38, 1956.
114. FRANK, N. R. Static volume-pressure characteristics of excised lobes of dogs' lungs. *Federation Proc.* 16: 40, 1957.
115. FRANK, N. R., J. MEAD, AND B. G. FERRIS, JR. Mechanical behavior of the lungs in healthy elderly persons. *J. Clin. Invest.* 36: 1680, 1957.
116. FRANK, N. R., E. P. RADFORD, JR., AND J. L. WHITTENBERGER. Static volume-pressure interrelations of the lungs and pulmonary blood vessels in excised cats' lungs. *J. Appl. Physiol.* 14: 167, 1959.
117. FRANK, N. R. Influence of acute pulmonary vascular congestion on recoiling force of excised cats' lung. *J. Appl. Physiol.* 14: 905, 1959.
118. FRITTS, H. W. JR., A. P. FISHMAN, A. COURNAND, AND D. W. RICHARDS, JR. Efficiency of ventilation during voluntary hyperpnea. *Federation Proc.* 14: 51, 1955.
119. FRITTS, H. W. JR. AND A. COURNAND. Effect of chronic obstructive emphysema on the efficiency of ventilation during voluntary hyperpnoea. Abstr. XX Intern. Physiol. Congr., Brussels, 315, 1956.
120. FRITTS, H. W. JR. Energy cost and control of breathing in patients with chronic pulmonary emphysema. *Am. Rev. Respirat. Diseases* 80: 131, 1959.
121. FRITTS, H. W. JR., J. FILLER, A. P. FISHMAN, AND A. COURAND. Efficiency of ventilation during voluntary hyperpnea: Studies in normal subjects and in dyspneic patients with either chronic pulmonary emphysema or obesity. *J. Clin. Invest.* 38: 1339, 1959.
122. FRY, D. L., W. W. STEAD, R. V. EBERT, R. I. LUBIN, AND H. S. WELLS. Measurement of intraesophageal pressure and its relationship to intrathoracic pressure. *J. Lab. Clin. Med.* 40: 664, 1952.
123. FRY, D. L., R. V. EBERT, W. W. STEAD, AND C. C. BROWN. Mechanics of pulmonary ventilation

in normal subjects and in patients with emphysema. *Am. J. Med.* 16: 80, 1954.

124. FRY, D. L., R. E. HYATT, C. B. McCALL, AND A. J. MALLOS. Evaluation of three types of respiratory flowmeters. *J. Appl. Physiol.* 10: 210, 1957.

125. FRY, D. L. Theoretical considerations of the bronchial pressure-flow-volume relationships with particular reference to the maximum expiratory flow volume curve. *Phys. in Med. Biol.* 3: 174, 1958.

126. FRY, D. L. Physics of air flow in emphysema. *Am. Rev. Respirat. Diseases* 80: 123, 1959.

127. FRY, D. L. AND R. E. HYATT. Pulmonary mechanics: A comprehensive graphic analysis of the relationship between pressure, volume, and airflow in the lungs of normal and diseased human subjects. *Am. J. Med.* 29: 672, 1960.

128. GAD, C. Ueber Grösse und Bedeutung des Residualluftraumes. *Tagebl. Versamml. Deutsch. Naturf. Aerzte* 54: 117, 1881.

129. GAENSLER, E. A., J. V. MALONEY, JR., AND V. O. BJÖRK. Bronchospirometry. II. Experimental observations and theoretical considerations of resistance breathing. *J. Lab. Clin. Med.* 39: 935, 1952.

130. GAENSLER, E. A. AND I. LINDGREN. Mechanics of breathing. *Progr. in Cardiov. Diseases* 1: 397, 1959.

131. GERST, P. H., C. RATTENBORG, AND D. A. HOLADAY. Effects of hemorrhage on pulmonary circulation and respiratory gas exchange. *J. Clin. Invest.* 38: 524, 1959.

132. GILBERT, R., R. H. EICH, AND J. H. AUCHINCLOSS, JR. Application of Hooke's law to the elastic properties of the lung. *Am. Rev. Tuberc. Pulmonary Diseases* 77: 863, 1958.

133. GRUENWALD, P. Surface tension as a factor in the resistance of neonatal lungs to aeration. *Am. J. Obstet. Gynecol.* 53: 996, 1947.

134. HASS, G. M. Method for the isolation of elastic tissues. *Arch. Pathol.* 34: 807, 1942.

135. HAYEK, H. v. *Die Menschliche Lunge.* Berlin: Springer, 1953.

136. HEAF, P. J. D. AND F. J. PRIME. Compliance of the thorax in normal human subjects. *Clin. Sci.* 15: 319, 1956.

137. HEEMSTRA, H. AND B. SLAGTER. Interpretation of oesophageal pressure and of 'alveolar' pressure obtained by the interruption method. *Acta Physiol. et Pharmacol. Neerl.* 4: 421, 1955.

138. HELLIESEN, P. J., C. D. COOK, L. FRIEDLANDER, AND S. AGATHON. Studies of respiratory physiology in children. 1. Mechanics of respiration and lung volumes in 85 normal children 5 to 17 years of age. *Pediatrics* 22: 80, 1958.

139. HERMANN, L. Ueber den atelectatischen Zustand der Lungen und dessen Aufhören bei der Geburt. *Arch. ges. Physiol.* 20: 365, 1879.

140. HEYNSIUS, A. Ueber die Grösse des negativen Drucks im Thorax beim ruhigen Athmen. *Arch. ges. Physiol.* 29: 265, 1882.

141. HOEVE, C. A. J. AND P. J. FLORY. Elastic properties of elastin. *J. Am. Chem. Soc.* 80: 6523, 1958.

142. HUGHES, R., A. J. MAY, AND J. G. WIDDICOMBE. Effect of pulmonary congestion and oedema on lung compliance. *J. Physiol.* (London) 142: 306, 1958.

143. HUGHES, R., A. J. MAY, AND J. G. WIDDICOMBE. Stress relaxation in rabbits' lungs. *J. Physiol.* (London) 146: 85, 1959.

144. HUTCHINSON, J. Article: *Thorax. Todd Encyclop. Anat. & Physiol.* 1849–1852, 1059.

145. HYATT, R. E., D. P. SCHILDER, AND D. L. FRY. Relationship between maximum expiratory flow and degree of lung inflation. *J. Appl. Physiol.* 131 331, 1958.

146. HYATT, R. E. Pressure-flow-volume interrelationships in man. *Am. Rev. Respirat. Diseases* 80: 138, 1959.

147. HYATT, R. E. AND R. E. WILCOX. Partition of pulmonary flow resistance into upper and lower airway components. *Federation Proc.* 19: 376, 1960.

148. JÄYKKÄ, S. Capillary erection and lung expansion. *Acta Paediat.* 46, Suppl. 112, 1957.

149. KILCHES, R. Zur Frage der Retraktionskräfte der Lunge. *Klin. Wochschr.* 19: 695, 1940.

150. KLEIN, F. Ueber das Verhältniss zwischen Druck und Füllung bei Hohlorganen (Lungen und Herz) und dessen Ableitung aus der Längsdehnung. *Z. Biol.* 33: 219, 1896.

151. KNOWLES, J. H., S. K. HONG, AND H. RAHN. Possible errors using esophageal balloon in determination of pressure-volume characteristics of the lung and thoracic cage. *J. Appl. Physiol.* 14: 525, 1959.

152. LANDOWNE, M. AND R. W. STACY. Glossary of terms. In: *Tissue Elasticity*, J. W. Remington (editor). Washington, D. C.: American Physiological Society, 1957, pp. 191–201.

153. LAWTON, R. W. AND D. JOSLIN. Measurements on the elasticity of the isolated rat lung. *Am. J. Physiol.* 167: 111, 1951.

154. LIEBERMEISTER, G. Zur normalen und pathologischen Physiologie der Atmungsorgane. I. Ueber das Verhältnis zwischen Lungendehnung und Lungenvolumen. *Zentr. allgem. Pathol.* 18: 644, 1907.

155. LILJESTRAND, G. Untersuchungen über die Atmungsarbeit. *Skand. Arch. Physiol.* 35: 199, 1918.

156. LUCIANI, L. Delle oscillazioni della pressione intratoracica e intraddominale. *Arch. Sci. Med.* (*Tor.*) 2: 177, 1878.

157. McCALL, C. B., R. E. HYATT, F. W. NOBLE, AND D. L. FRY. Harmonic content of certain respiratory flow phenomena of normal individuals. *J. Appl. Physiol.* 10: 215, 1957.

158. McGREGOR, M. Value of an index of maximal expiratory force in the interpretation of tests of maximal ventilatory capacity. *Am. Rev. Tuberc.* 78: 692, 1958.

159. McGREGOR, M. AND M. R. BECKLAKE. Oxygen cost of breathing. Estimates based on respiratory muscle force. *Federation Proc.* 19: 375, 1960.

160. McILROY, M. B. Physical properties of normal lungs removed after death. *Thorax* 7: 285, 1952.

161. McILROY, M. B., R. MARSHALL, AND R. V. CHRISTIE. Work of breathing in normal subjects. *Clin. Sci.* 13: 127, 1954.

162. McILROY, M. B., J. MEAD, N. J. SELVERSTONE, AND E. P. RADFORD, JR. Measurement of lung tissue viscous resistance using gases of equal kinematic viscosity. *J. Appl. Physiol.* 7: 485, 1955.

163. McILROY, M. B. AND F. L. ELDRIDGE. Measurement of the mechanical properties of the lungs by simplified methods. *Clin. Sci.* 15: 329, 1956.

164. McILROY, M. B. Dyspnea and the work of breathing in diseases of the heart and lungs. *Progr. in Cardiov. Diseases* 1: 284, 1959.

165. McKERROW, C. B. AND A. B. OTIS. Oxygen cost of hyperventilation. *J. Appl. Physiol.* 9: 375, 1956.

166. MACKLIN, C, C. Musculature of the bronchi and lungs. *Physiol. Revs.* 9:1, 1929.
167. MACKLIN, C. C. AND W. S. HARTROFT. Report to the subcommittee on physiological aspects of chemical warfare, Canadian Defense Research Board, Ottawa, 1943.
168. MACKLIN, C. C. Pulmonary alveolar mucoid film and the pneumonocytes. *Lancet* 266: 1099, 1954.
169. MALLOCK, A. Note on the instability of India-rubber tubes and balloons distended by fluid pressure. *Proc. Roy. Soc.* 49: 458, 1891.
170. MARGARIA, R., G. MILIC-EMILI, J. M. PETIT, AND G. CAVAGNA. Mechanical work of breathing during muscular exercise. *J. Appl. Physiol.* 15: 354, 1960.
171. MARSHALL, R., E. H. LANPHIER, AND A. B. DUBOIS. Resistance to breathing in normal subjects during simulated dives. *J. Appl. Physiol.* 9: 5, 1956.
172. MARSHALL, R. AND A. B. DUBOIS. Measurement of the viscous resistance of the lung tissues in normal man. *Clin. Sci.* 15: 161, 1956.
173. MARSHALL, R. AND A. B. DUBOIS. Viscous resistance of lung tissue in patients with pulmonary disease. *Clin. Sci.* 15: 473, 1956.
174. MARSHALL, R. Physical properties of the lungs in relation to the subdivisions of lung volume. *Clin. Sci.* 16: 507, 1957.
175. MARTIN, H. B. AND D. F. PROCTOR. Pressure-volume measurements on dog bronchi. *J. Appl. Physiol.* 13: 337, 1958.
176. MEAD, J. AND J. L. WHITTENBERGER. Physical properties of human lungs measured during spontaneous respiration. *J. Appl. Physiol.* 5: 779, 1953.
177. MEAD, J. AND J. L. WHITTENBERGER. Evaluation of airway interruption technique as a method for measuring pulmonary air-flow resistance. *J. Appl. Physiol.* 6: 408, 1954.
178. MEAD, J., M. B. McILROY, N. J. SELVERSTONE, AND B. C. KRIETE. Measurement of intraesophageal pressure. *J. Appl. Physiol.* 7: 491, 1955.
179. MEAD, J., I. LINDGREN, AND E. A. GAENSLER. Mechanical properties of the lungs in emphysema. *J. Clin. Invest.* 34: 1005, 1955.
180. MEAD, J. Measurement of inertia of the lungs at increased ambient pressure. *J. Appl. Physiol.* 9: 208, 1956.
181. MEAD, J., J. L. WHITTENBERGER, AND E. P. RADFORD, JR. Surface tension as a factor in pulmonary volume-pressure hysteresis. *J. Appl. Physiol.* 10: 191, 1957.
182. MEAD, J., E. P. RADFORD, JR., B. G. FERRIS, JR., AND J. L. WHITTENBERGER. Principles of respiratory mechanics, Part II. (Moving picture). New York: National Foundation for Infantile Paralysis, 1955.
183. MEAD, J. AND E. A. GAENSLER. Esophageal and pleural pressures in man, upright and supine. *J. Appl. Physiol.* 14: 81, 1959.
184. MEAD, J. AND C. COLLIER. Relation of volume history of lungs to respiratory mechanics in anesthetized dogs. *J. Appl. Physiol.* 14: 669, 1959.
185. MEAD, J. Volume displacement body plethysmograph for respiratory measurements in human subjects. *J. Appl. Physiol.* 15: 736, 1960.
186. MELTZER, S. J. On the respiratory changes of the intrathoracic pressure, measured in the mediastinum posterior. *J. Physiol. (London)* 13: 218, 1892.
187. MEYER, K. H. AND C. FERRI. Die elastischen Eigenschaften der elastischen und der kollagenen Fasern und ihre molekulare Deutung. *Arch ges Physiol.* 238: 78, 1936.
188. MILIC-EMILI, G., J. M. PETIT, AND L. DELHEZ. Les relations entre le travail mécanique ventilatoire pendant l'exercise musculaire et la capacité pulmonaire totale chez l'individu sain. *Arch. intern. physiol. et biochem.* 67: 417, 1959.
189. MILIC-EMILI, G. AND J. M. PETIT. Il lavoro meccanico respiratorio durante la massima ventilazione polmonare voluntaria. *Boll. soc. ital. biol. sper.* 35: 431, 1959.
190. MILIC-EMILI, G., J. M. PETIT, AND R. KOCH. Il lavoro meccanico della respirazione durante l'esercizio muscolare negli insufficienti cardiorespiratori. *Med. Lavoro* 50: 108, 1959.
191. MILIC-EMILI, G. AND J. M. PETIT. Mechanical efficiency of breathing. *J. Appl. Physiol.* 15: 359, 1960.
192. MILLER, W. S. *The Lung*. Springfield, Ill.: Thomas, 1937.
193. MOUNT, L. E. Ventilation flow-resistance and compliance of rat lungs. *J. Physiol. (London)* 127: 157, 1955.
194. MOUNT, L. E. Variations in the components of the ventilation hindrance of cat lungs. *J. Physiol. (London)* 131: 393, 1956.
195. MURRAY, J. F. Oxygen cost of voluntary hyperventilation. *J. Appl. Physiol.* 14: 187, 1959.
196. NEERGAARD, K. v. AND K. WIRZ. Über eine Methode zur Messung der Lungenelastizität am lebenden Menschen, insbesondere beim Emphysem. *Z. klin. Med.* 105: 35, 1927.
197. NEERGAARD, K. v. AND K. WIRZ. Dis Messung der Strömungswiderstände in den Atemwegen des Menschen, insbesondere bei Asthma und Emphysem. *Z. klin. Med.* 105: 51, 1927.
198. NEERGAARD, K. v. Neue Auffassungen über einen Grundbegriff der Atemmechanik. Die Retraktionskraft der Lunge, abhängig von der Oberflächenspannung in den Alveolen. *Z. ges. exptl. Med.* 66: 373, 1929.
199. NIMS, R. G., E. H. CONNER, AND J. H. COMROE, JR. Compliance of the human thorax in anesthetized patients. *J. Clin. Invest.* 34: 744, 1955.
200. NISELL, O. I. AND L. S. G. EHRNER. A simple apparatus for measurement of pressure volume relationship in respiration. *J. Appl. Physiol.* 8: 565, 1956.
201. OLSON, H. F. *Dynamical Analogies*. Princeton: D. van Nostrand, 1958.
202. OPIE, L. H., A. C. SMITH, AND J. M. K. SPALDING. Conscious appreciation of the effects produced by independent changes of ventilation volume and of end-tidal pCO₂ in paralyzed patients. *J. Physiol. (London)* 149: 494, 1959.
203. OTIS, A. B. AND D. F. PROCTOR. Measurement of alveolar pressure in human subjects. *Am. J. Physiol.* 152: 106, 1948.
204. OTIS, A. B., W. O. FENN, AND H. RAHN. Mechanics of breathing in man. *J. Appl. Physiol.* 2: 592, 1950.
205. OTIS, A. B. Work of breathing. *Physiol. Revs.* 34: 449, 1954.
206. OTIS, A. B., C. B. McKERROW, R. A. BARTLETT, J. MEAD, M. B. McILROY, N. J. SELVERSTONE, AND E. P. RADFORD, JR. Mechanical factors in distribution of pulmonary ventilation. *J. Appl. Physiol.* 8: 427, 1956.

207. OTIS, A. B. Some physical techniques used in the study of external respiration. *Physical Techniques in Biological Research.* New York: Acad. Press. To be published.
208. PATTLE, R. E. Properties, function, and origin of the alveolar lining layer. *Proc. Roy. Soc. (London) B* 148: 217, 1958.
209. PETIT, J. M. AND G. MILIC-EMILI. Measurement of endoesophageal pressure. *J. Appl. Physiol.* 13: 481, 1958.
210. PFLÜGER, E. Das Pneumonometer. *Arch. ges. Physiol.* 29: 244, 1882.
211. PIERCE, J. A. AND R. V. EBERT. Elastic properties of the lungs in the aged. *J. Lab. Clin. Med.* 51: 63, 1958.
212. PIERCE, J. A., J. B. HOCOTT, AND R. V. EBERT. Studies of lung collagen and elastin. *Am. Rev. Respirat. Diseases* 80: 45, 1959.
213. PIERCE, J. A. AND J. B. HOCOTT. Studies on the collagen and elastin content of the human lung. *J. Clin. Invest.* 39: 8, 1960.
214. RADFORD, E. P. JR. Method for estimating respiratory surface area of mammalian lungs from their physical characteristics. *Proc. Soc. Exptl. Biol. Med.* 87: 58, 1954.
215. RADFORD, E. P. JR. AND N. M. LEFCOE. Effects of bronchoconstriction on elastic properties of excised lungs and bronchi. *Am. J. Physiol.* 180: 479, 1955.
216. RADFORD, E. P. JR. AND M. McLAUGHLIN. Dependence of lung mechanical properties on anatomic relationships within terminal lung units. *Federation Proc.* 15: 147, 1956.
217. RADFORD, E. P. JR. Recent studies of mechanical properties of mammalian lungs. In: *Tissue Elasticity,* J. W. Remington (editor). Washington, D. C.: American Physiological Society, 1957.
218. RADFORD, E. P. JR. Symposium on emphysema and the 'chronic bronchitis' syndrome. General discussion. *Am. Rev. Respirat. Diseases* 80: 42, 1959.
219. RAHN, H., A. B. OTIS, L. E. CHADWICK, AND W. O. FENN. Pressure-volume diagram of the thorax and lung. *Am. J. Physiol.* 146: 161, 1946.
220. RAU, G., H. BEHN, W. GEBHARDT, P. H. ROSSIER, AND A. BÜHLMANN. Atemmechanische Untersuchungen am Lungenmodell, bei Lungengesunden und bei Patienten mit obstructivem Emphysem. *Schweiz. med. Wochschr.* 87: 374, 1957.
221. REDENZ, E. Untersuchungen über die elastische Faser. I. Untersuchung der isolierten elastischen Faser des Nackenbandes mit dem Mikromanipulator. *Beitr. pathol. Anat. u. allgem. Pathol.* 76: 226, 1927.
222. REDENZ, E. Untersuchungen über die elastische Faser. II. Dehnung der elastischen Fasern und Platten der Aortenwand mit dem Mikromanipulator. *Z. Zellforsch.* 4: 611, 1926.
223. REMINGTON, J. W. Extensibility behavior and hysteresis phenomena in smooth muscle tissues. In: *Tissue Elasticity,* J. W. Remington (editor). Washington, D. C.: American Physiological Society, 1957, pp. 138–153.
224. ROHRER, F. Der Strömungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmässigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken. *Arch. ges. Physiol.* 162: 225, 1915.
225. ROHRER, F. Der Zusammenhang der Atemkräfte und ihre Abhängigkeit vom Dehnungszustand der Atmungsorgane. *Arch. ges. Physiol.* 165: 419, 1916.
226. ROHRER, F. Uber die topographische Verteilung der Luftströmungsverhältnisse in der Lunge. *Schweiz. med. Wochschr.* 51: 765, 1921.
227. ROHRER, F., K. NAKASONE, AND K. WIRZ. Physiologie der Atembewegung Handbuch der normalen und pathologischen Physiologie, II, pp. 70–127. Berlin: Springer, 1925.
228. ROSENTHAL, I. Die Wirkung der elektrischen Vagusreizung auf die Atembewegungen. I. *Archiv. Physiol. Bois-Reymond* (Suppl. Ed.), 1880, p. 34.
229. ROSS, B. B., R. GRAMIAK, AND H. RAHN. Physical dynamics of the cough mechanism. *J. Appl. Physiol.* 8: 264, 1955.
230. ROSS, B. B. Influence of bronchial tree structure on ventilation in the dog's lung as inferred from measurements of a plastic cast. *J. Appl. Physiol.* 10: 1, 1957.
231. ROSSIER, P. H. AND A. BÜHLMANN. Dyspnoe und Atemarbeit. Atemmechanische Untersuchungen während Hyperventilation und grosser korperlicher Arbeit. *Schweiz. med. Wochschr.* 89: 543, 1959.
232. SCHERRER, M., A. KOSTYAL, H. WIERZEJEWSKI, F. SCHMIDT, AND H. A. v. GEUNS. Zur Pathophysiologie des provozierten bronchialasthmatischen Anfalls. *Intern. Arch. Allergy Appl. Immunol.* 9: 65, 1956.
233. SCHILDER, D. P., R. E. HYATT, AND D. L. FRY. An improved balloon system for measuring intraesophageal pressure. *J. Appl. Physiol.* 14: 1057, 1959.
234. SETNIKAR, I. AND G. MESCHIA. Proprietà elastiche del polmone e di modelli meccanici. *Arch. fisiol.* 52: 288, 1952.
235. SETNIKAR, I., G. MESCHIA, AND E. MILLA. Variazioni delle proprietà elastiche del polmone in seguito alla distensione. *Boll. soc. ital. biol. sper.* 28: 636, 1952.
236. SETNIKAR, I. *Meccanica Respiratoria.* Estratto dal volume N.3 degli Aggiornamenti di Fisiologia. Dott. Luigi Macri, ed. P4, Firenze, 1955.
237. SETNIKAR, I. Origine e significato della proprietà meccaniche del polmone. *Arch. fisiol.* 55: 349, 1955.
238. SHARP, J. T., G. T. GRIFFITH, I. L. BUNNELL, AND D. G. GREENE. Ventilatory mechanics in pulmonary edema in man. *J. Clin. Invest.* 37: 111, 1958.
239. SHEPARD, R. H., E. J. M. CAMPBELL, H. B. MARTIN, AND T. ENNS. Factors affecting the pulmonary dead space as determined by single breath analysis. *J. Appl. Physiol.* 11: 241, 1957.
240. SHEPHARD, R. J. Timed airway resistance. *J. Physiol. (London)* 145: 459, 1959.
241. SILVERMAN, L. AND J. L. WHITTENBERGER. Clinical pneumotachograph. *Methods in Med. Research* 2: 104, 1950.
242. SILVERMAN, L. AND J. L. WHITTENBERGER. Instantaneous air flow measurements. *Methods in Med. Research* 2: 215, 1950.
243. SLAGTER, B. AND H. HEEMSTRA. Limiting factors of expiration in normal subjects. *Acta Physiol. et Pharmacol. Neerl.* 4: 419, 1955.
244. SONNE, C. Untersuchungen über die relative Weite der Bronchiolen bei der verschiedenen Luftspannung der Lungen. Beitrag zur Kenntnis der Pathogenese des Bronchialasthmas. *Acta Med. Scand.* 58: 313, 1923.
245. STEAD, W. W., D. L. FRY, AND R. V. EBERT. Elastic properties of the lung in normal men and in

patients with chronic pulmonary emphysema. *J. Lab. Clin. Med.* 40: 674, 1952.

246. STEAD, W. W., H. S. WELLS, N. L. GAULT, AND J. OGNANOVICH. Inaccuracy of the conventional water-filled spirometer for recording rapid breathing. *J. Appl. Physiol.* 14: 448, 1959.
247. STERNBERG, C. Über die elastischen Fasern. *Arch. pathol. Anat. u. Physiol., Virchow's* 254: 656, 1925.
248. STORSTEIN, O., A. S. FIELD, JR., R. MASSUMI, AND F. D. GRAY, JR. Airway resistance and lung compliance. Effects of histamine and hyperventilation in normal subjects and patients with chronic lung disease. *Yale J. Biol. and Med.* 31: 387, 1959.
249. VERSTRAETEN, J. M. Klinische en experimentele onderzoekingen over de 'elastance' van de longen. Thesis, Gent, 1956.
250. VERZAR, F. AND L. JEKER. Die physiologischen Atelektasen der Lunge. *Arch. ges. Physiol.* 238: 379, 1936.
251. VUILLEUMIER, P. La signification de las depression pleurale. Etude a l'aide d'enregistrements optiques. *Schweiz. med. Wochschr.* 69: 697, 1939.
252. VUILLEUMIER, P. Über eine Methode zur Messung des intraalveolären Druckes und der Strömungswiderstände in dem Atemwegen des Menschen. *Z. klin. Med.* 143: 698, 1944.
253. WELLS, H. S., W. W. STEAD, T. D. ROSSING, AND J. OGNANOVICH. Accuracy of an improved spirometer for recording of fast breathing. *J. Appl. Physiol.* 14: 451, 1959.
254. WEST, J. B. AND P. HUGH-JONES. Patterns of gas flow in the upper bronchial tree. *J. Appl. Physiol.* 14: 753, 1959.
255. WHITTENBERGER, J. L. AND J. MEAD. Research in tuberculosis and related subjects. Respiratory dynamics during cough. *Trans. 48th Meeting Natl. Tuberc. Assoc.*, New York, 1952, p. 414.
256. WIGGERS, C. J., M. N. LEVY, AND G. GRAHAM. Regional intrathoracic pressures and their bearing on calculation of effective venous pressures. *Am. J. Physiol.* 151: 1, 1947.
257. WIRZ, K. Das Verhalten des Druckes im Pleuraraum bei der Atmung und die Ursachen seiner Veränderlichkeit. *Arch. ges. Physiol.* 199: 1, 1923.
258. WOHLISCH, E. Statistisch-kinetische Theorie, Thermodynamik und biologische Bedeutung der kautschukartigen Elastizität. *Kolloid Z.* 89: 239, 1939.