Estimation of tissue elasticity of the lung[1,2]

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CARTON, ROBERT W., JOHN W. CLARK, JOHN DAINAUSKAS, AND ARNOLD BARRON. *Estimation of tissue elasticity of the lung.* J. Appl. Physiol. 19(2): 236–242. 1964.—Theoretical work-volume curves for liquid-filled lungs were constructed based on an assumed geometric form and deformation of the terminal air spaces and on the characteristics of single fibers of elastic tissue. These curves were compared with those measured in rats and with one taken from the journal literature in the case of a human lung. The form of the measured curves fitted the theoretical curves. The assumptions necessary were considered in detail. In both species more elastic tissue has been found present in the lung than would be expected theoretically. The action of additional restraining elements was thought necessary at high volume.

pulmonary pressure-volume curves pulmonary work-volume curves lung volume and elastic tissue mass pulmonary elastic tissue tissue elasticity pulmonary mechanics

THE STATIC PRESSURE-VOLUME CURVE of the mammalian lung has been analyzed into two components, ascribable to surface forces and to tissue forces, respectively (8). A variety of tissue sites in the walls of the terminal air spaces has been suggested within which elastic energy could be stored during inspiration, to be released on expiration (11). These included elastic tissue, collagen, reticulin, smooth muscle, and pulmonary blood volume. No clear understanding of the relative contribution of these tissue elements to pulmonary elasticity has emerged.

Mead has reviewed (6) the attempts to interpret pulmonary retraction in terms of the size and shape of the air spaces and the material in their walls. In 1955 Setnikar (13) proposed that the restraining elements within the lung were elastic tissue and collagen acting in parallel, that the elastic tissue obeyed Hooke's law, and that collagen fibers, originally serpentine, became straightened and effective with increasing distention of the organ. He was unable, however, to express theoretical pressure-volume relationships of the lung in absolute terms. To do so would have required knowledge of the geometric characteristics of the terminal air spaces on expansion, of the distribution of restraining elements in their walls, and of the elastic properties of these elements. Recent studies (2) have measured the elastic properties of single elastic fibers from the ligamentum nuchae of the ox. Using this information we (3) have constructed theoretical pulmonary work-volume curves in a model lung and have compared these with those measured experimentally. Such an analysis has estimated the contribution of elastic fibers to pulmonary elastic behavior and has defined the assumptions which underlie a theory of pulmonary tissue elasticity.

THEORY

A model lung can be visualized as consisting of a large number of communicating spaces of equal volume (the alveoli). These spaces can be filled with liquid, and under this condition surface forces will be negligible. Assume that the spaces are hemispheres (Fig. 1*A* and *B*), that they dilate equally and concentrically under a distending pressure, and that their expansion is opposed only by fibers circumferentially distributed in their walls. What work is done as this system expands from one volume to another?

First we shall describe the work of expansion of these hemispheres irrespective of the elastic properties of the restraining bands. We shall then be able to solve our expression by inserting into the general equation of work a specific formula descriptive of the elastic properties of a specific material.

Two hemispheres can be grouped together as one spherule (Fig. 1*C* and *D*). The work of expansion per hemisphere is half that of the spherule; later we shall be able to neglect this factor. The restraining fibers lie along segments of great circles. To calculate work done on expansion, these can be grouped together as a cir-

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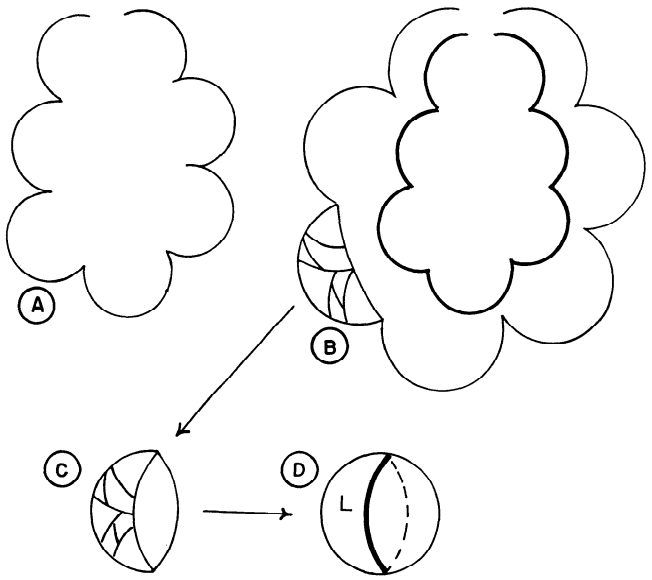


FIG. 1. (*A*): terminal air spaces composed of hemispheres which (*B*) dilate concentrically and are restrained by circumferentially distributed fibers. (*C*): one hemisphere joins with another to form (*D*) a spherule bounded by a circumferential segment of elastic tissue of known diameter and length (*L*).

cumferential band, or as a segment (L) of a circumferential band of known diameter.

Let L_1 = the resting length of this latter segment and L_2 = the stretched length where the applied force = F. Then (12):

$$(L_2 - L_1)/L_1 = \text{the strain } \epsilon \qquad (1)$$

The work of distending this spherule from relaxed volume to any level of expansion is given by (9):

$$w = \int_{L_1}^{L_2} F\,dL = L_1 \int_0^{\epsilon} F\,d\epsilon \qquad (2, 3)$$

The work of expanding all of the spherules, i.e., the model lung, is given by:

$$W = \Sigma w = (\Sigma L_1) \int_0^{\epsilon} F\,d\epsilon \qquad (4)$$

as long as work per unit L_1 is uniform throughout the lung. This, then, is our general equation of work.

Now for one form of elastic tissue, single fibers from ox ligamentum nuchae 9 μ in diameter, we have previously shown (2) that:

$$\epsilon = \epsilon_m(1 - e^{-bF}) \qquad (5)$$

where ϵ_m and b are known constants; ϵ_m is the limit of stretch (1.3), and b is a coefficient of elasticity (.17). Assuming that elastic tissue does not differ sharply in its properties from species to species and from organ to organ, we can now solve *equation 4* for elastic tissue:

$$W = (\Sigma L_1)\left[(\epsilon F)_0^{\epsilon} - \int_{0,0}^{\epsilon,F} \epsilon\,dF\right] \qquad (6)$$

$$= (\Sigma L_1)\left[\epsilon F - \frac{\epsilon_m}{b}(bF - 1 + e^{-bF})\right] \qquad (7)$$

Also from *equation 5*:

$$F = \frac{1}{b}\log_e \frac{\epsilon_m}{\epsilon_m - \epsilon} \qquad (8)$$

so that work can be given in terms of fiber strain e and total fiber length ΣL_1.

Similarly, changes in lung volume can be expressed (11) in terms of ϵ. For a spherule of volume v_1 (corresponding to circumferential segment L_1), enlarging to v_2 as the segment enlarges to L_2 (Fig. 2):

$$(v_2^{1/3} - v_1^{1/3})/v_1^{1/3} = (L_2 - L_1)/L_1 = \epsilon \qquad (9)$$

If $V = \Sigma v$ = the contained volume of the model lung, then:

$$(V_2^{1/3} - V_1^{1/3})/V_1^{1/3} = \epsilon \qquad (10)$$

$$V_2 = V_1(\epsilon + 1)^3 \qquad (11)$$

Thus, the contained volume of the model lung at any level of expansion can be given in terms of the relaxed volume V_1 (where ϵ = 0) and the fiber strain ϵ. In addition, from *equation 10*, ϵ can be found from the total contained volume, without knowing the number of spherules. Therefore, both the number of "alveoli" and the junction of hemispheres into spherules are automatically allowed for in the calculations and need not be measured separately. Because ϵ is identical both for the microscopic spherule and the whole model lung, the restraining bands can be thought of as one continuous length (ΣL_1) wound round and round V considered as a sphere (Fig. 2).

ΣL_1 in *equation 7* can be evaluated. Let M = the weight of wet elastic tissue in the lung which is effective in this process (effective elastic tissue mass). Let G = specific gravity of elastic tissue, assumed to be 1.2 (the specific gravity of whole ligamentum nuchae), and r = the radius of the grouped fibers in question (4.5 μ).

$$\Sigma L_1 = M/(G\pi r^2) = M/(1.2 \times 3.1416 \times 4.5^2 \times 10^{-8}) \qquad (12)$$

$$= 1.31 \times 10^6\, M \text{ centimeters} \qquad (13)$$

We now have three equations (7, 8, and 11) in which the work of expansion and the lung volume are given in terms of a single parameter, ϵ. In this way, families of theoretical work-volume curves can be constructed for arbitrary values of M and V_1 (Figs. 5 and 8).

The same relationships can be expressed in terms of pressure and volume (6). From considerations similar

to those given above, the pressure P within the model lung (bottom, Fig. 2) will be identical to that within the spherules (top, Fig. 2) for any given total volume. Consider, then, the situation of the model lung thought of as a sphere. For such a body LaPlace's law states that:

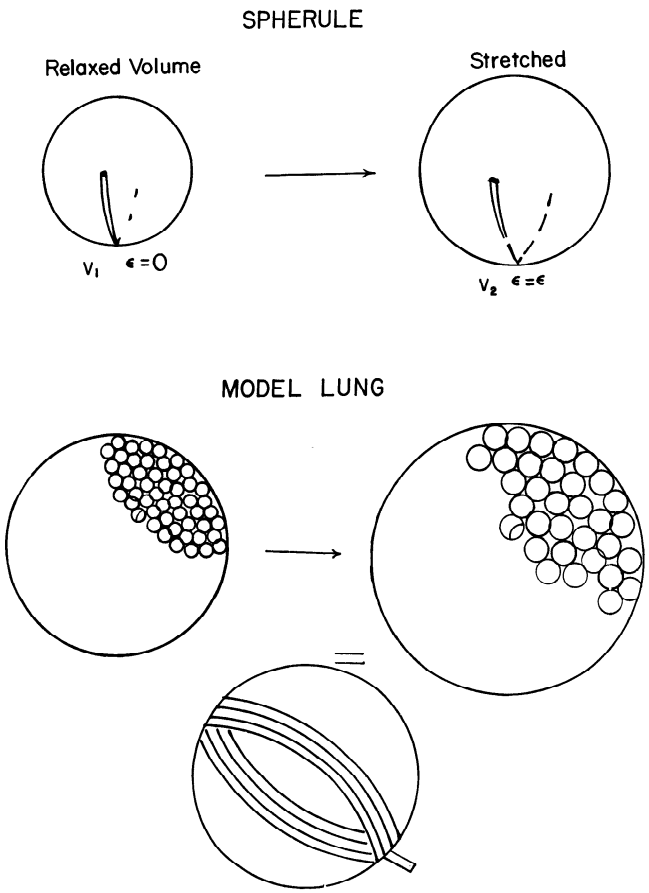


FIG. 2. Relationships between volume and strain on the linear elements in the relaxed and stretched states of the spherule and the model lung.

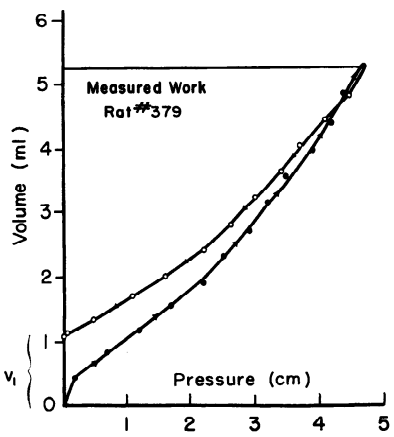


FIG. 3. Pressure-volume curves, *rat 379*, showing relaxed volume V_1. Pressure in cm Ringer-Locke solution. ● First inflation. ○ First deflation. Area between volume axis and deflation curve gives the measured work to any level of volume. Lung weight prior to filling: 1.1 g.

$$P = 2T/R \tag{14}$$

where R is its radius and T the tension in its wall. Let F_T = the total force applied across a circumference of the sphere (to hold it together), and R_1 = the radius of the relaxed sphere, corresponding to V_1 and L_1 above. Then:

$$T = F_T/2\pi R \tag{15}$$

$$F_T = 2F\Sigma L_1/2\pi R_1 \tag{16}$$

$$\therefore P = (\Sigma L_1/R_1\pi^2)(F/R^2) \tag{17}$$

R_1 is easily obtained from V_1. R and F can be expressed in terms of the parameter ϵ, and hence P can be found as a function of lung volume V and elastic tissue mass.

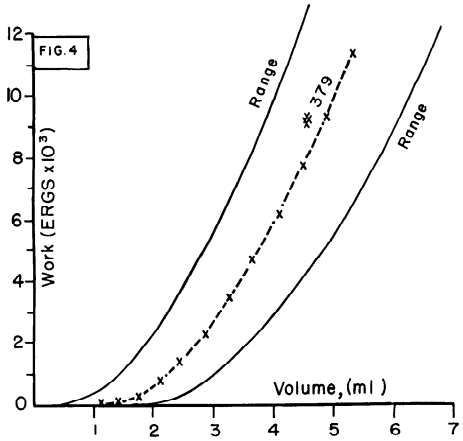
METHODS

Suitable measurements testing the above theory have been made for the rat lung and have been derived from the journal literature in the case of the human lung.

Rat lung. Sixteen white rats 3 months old and weighing between 201–415 g (average 256) were used. Each rat was ventilated with oxygen for 15 min, the trachea was clamped, the lungs were allowed to collapse, removed, and mounted on a pressure-volume apparatus (7) filled with Ringer-Locke solution at 37 C. Lung volume was changed every 2 min by increments of 0.5 ml and the resulting pressures observed on a manometer filled with the inflating solution. A volume correction was made for liquid diverted to the manometer. Leaks were checked for with methylene blue dye in the inflating solution; occasional tiny leaks were found; no correction was made for these. In addition, the lungs were weighed both before and after inflation.

The relaxed volume (V_1) was taken as that volume at which the descending limb of the first pressure-volume deflation intercepted the volume axis at zero pressure (see Fig. 3). In general the gain in weight after inflation and deflation corresponded to the relaxed volume as given above. The maximum pressures (mean 4.7 cm H_2O) and volumes (mean 5.0) were deliberately kept low because it was important to avoid significant leaks while measuring relaxed volume accurately. The work required to inflate or deflate could easily be calculated by summing the mean pressures times the increments of volume. Work-volume curves for the first descending (expiratory) curve were constructed for each rat and taken as representative of the "tissue" component of the static work of expiration. A second inflation and deflation followed the first descending curve in their pressure-volume behavior.

Subsequently, the trachea and main bronchi were clipped off close to the lungs themselves. The latter were cut, soaked in acetone for 10 min, and then dried to constant weight in vacuum. Following weighing, the lungs were then allowed to soak in an excess of 88%



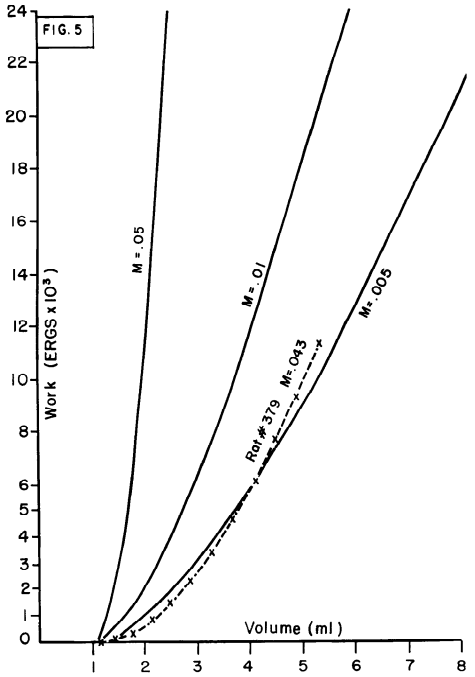


FIG. 4. Work-volume curve of a typical preparation (*rat 379*) (dotted line) and the range for 16 preparations (solid lines). Scale is same as that of Fig. 5.

FIG. 5. Theoretical work-volume curves for V_1 = 1.02 ml and M = .005, .01, and .05 g (solid lines), and the measured work-volume curve of *rat 379*, V_1 = 1.1 ml and M = .043 g (dotted line). Scale is same as that of Fig. 4.

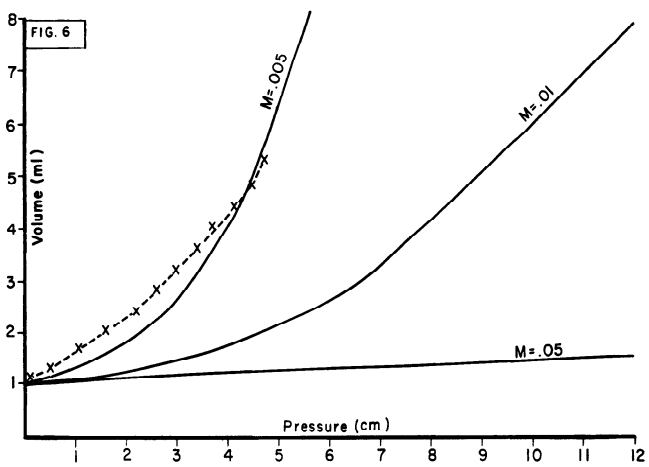
formic acid at 45 C for 45 hr. This process has been shown (5) to dissolve all tissue elements except elastic tissue and slight amounts of bronchial cartilage. The acid-extracted residue was neutralized in running tap water and dried in vacuum to constant weight.

Previous experiments have shown that the dried rat lung weighs 17.8% (SD ± .85) of the weight of the freshly removed (wet) lung. The dried elastic tissue residues were reconverted to wet weight by multiplication by 100/17.8 to give the measured elastic tissue mass for each rat. It would have been preferable to have used a conversion factor for elastic tissue itself. No such values are currently available, because of the difficulty of extracting elastic tissue in the same state of hydration as that in which it exists in the body. The elastic tissue residue was found to constitute 3.36% (SD ± 0.42) of total dried lung weight.

We now had measured values for M (elastic tissue mass), V_1 (relaxed volume), and $W = f(V)$ (work of inflation or deflation as a function of volume). These were compared with the theoretical values.

Human lung. Human pulmonary work-volume curves and corresponding values for relaxed volume and measured elastic tissue mass were taken from the literature.

Pressure-volume measurements of the human lung filled with Ringer-Locke solution are not as reliable as measurements made on the rat, cat, and dog lung because fluid filling the human lung tends to leak through the pleura. This process is even more evident in the ox lung and renders measurements of ox pressure-volume curves by this technique impossible. However, Clements et al. (4) have published the results of inflation of a human lung, and from their graph work-volume curves can be calculated in a fashion similar to that indicated above for the rat. Pierce and Hocott (10) measured the



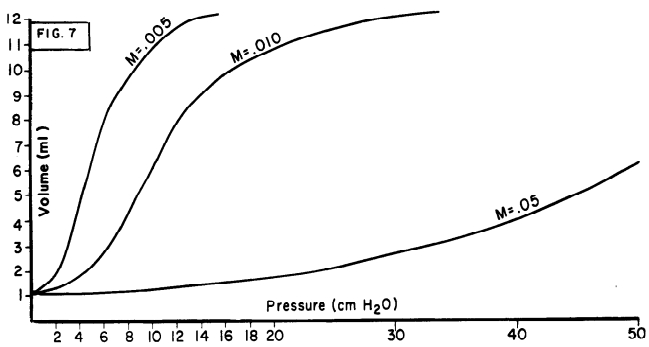


FIG. 6. Theoretical pressure-volume curves for V_1 = 1.02 ml and M = .005, .01, and .05 g (solid lines), and the measured pressure-volume curve on deflation of *rat 379*, V_1 = 1.1 ml and M = .043 g (dotted line). Pressures in centimeters water and Ringer-Locke solution, respectively.

FIG. 7. Theoretical pressure-volume curves for V_1 = 1.016 ml and M = .005, .01, and .05 g. These curves represent an extension of the theoretical curves in Fig. 6 (rat lungs). Those for M = .005 and .01 are drawn to ϵ = 1.29. (ϵ_m = 1.3).

elastin content of the right middle lobes of 48 human subjects using a modification of the Lowry alkaline-extraction method. From their figures the measured elastic tissue mass in humans could be estimated. Calculations from these two sources allowed us to extend our analysis to a second species.

RESULTS

Rat lung. The curve shown in Fig. 3 reflects the liquid-filled pressure-volume behavior of *rat lung 379*. The pressure-volume and work-volume behavior of this preparation was typical of that of the group of 16 rat lungs (see Fig. 4). In this pressure-volume curve, the first descending limb cut the volume axis at $V_1 = 1.14$ ml. The average relaxed volume for the group as a whole

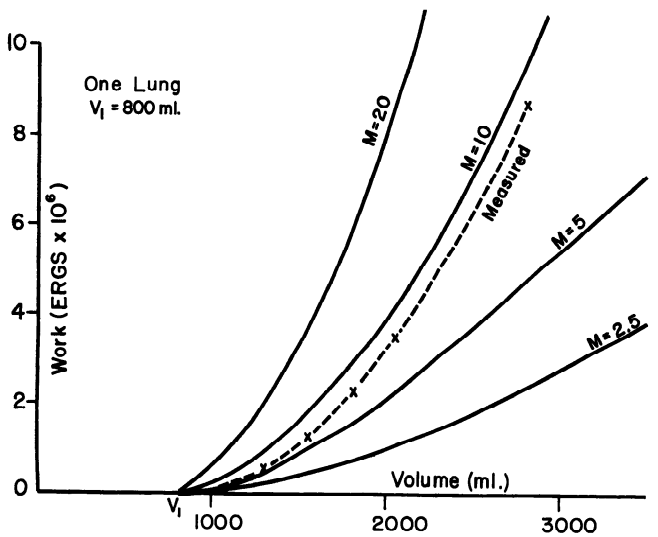


FIG. 8. Solid lines represent theoretical work-volume curves calculated for effective pulmonary elastic tissue masses of 2.5, 5, 10, and 20 g. Dotted line represents measured values derived from the literature (4, 10). (Human lung.)

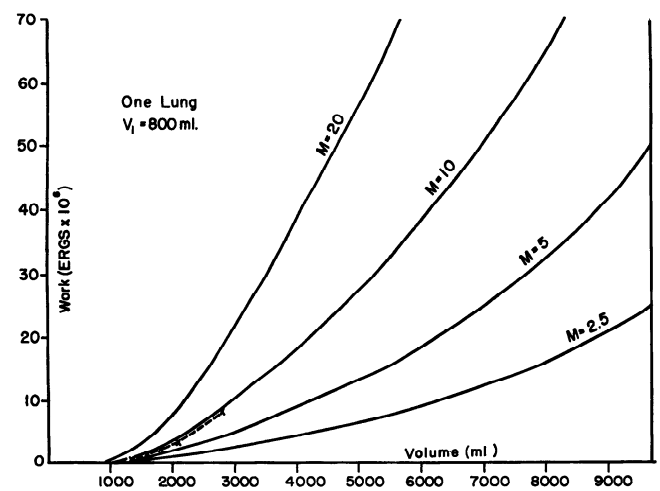


FIG. 9. An extension of Fig. 8 showing two of the theoretical work-volume curves drawn to their limit at $\epsilon = \epsilon_m = 1.3$, corresponding to $V = 9734$ ml. (Human lung.)

was $V_1 = 1.02$ (SE $\pm$ .08). The measured work to any desired level of volume is the area between the first descending limb and the volume axis. There is no simple way in which this work can be represented by a single number, but it is possible to construct work-volume curves, which show the work performed to any volume plotted against that volume. In Fig. 4 the work-volume curve for *rat 379* is shown, as well as the range of measured work-volume curves for all 16 rat lung preparations.

This typical measured work-volume curve can now be compared with the theoretical curves calculated for $V_1 = 1.02$ ml and for varying elastic tissue masses (Fig. 5). The shape of the measured curve fitted the shapes of the theoretical curves. The mean wet elastic tissue mass of these 16 rats was .054 (SE $\pm$ .004) g, obviously greater than that to be expected theoretically, but surprisingly close in view of the distant assumptions with which we started.

Figures 6 and 7 show the same phenomena in the form of pressure-volume curves, as indicated in the section on theory.

Human lung. A similar line of reasoning was followed for the human lung. Only a single human lung was considered, as opposed to the use of paired right and left rat lungs. In Fig. 8 are drawn the theoretical work-volume curves corresponding to a relaxed volume $V_1 =$ 800 ml and to effective elastic tissue masses of 2.5, 5, 10, and 20 g. The work-volume curve for a single human lung calculated from data given by Clements et al. (4) is shown as a dotted line, and has associated with it a measured elastic tissue mass of some 25 g. This latter figure was obtained as follows: Pierce and Hocott (10) showed that the average total dry elastin of the right middle lobe amounted to .55 g, that the dry weight of the lung is 16.7% of the wet weight, and that the right middle lobe comprises about 6.5% of the total weight of both lungs. Thus for one lung:

$$(.55 \times 100 \times 100)/(6.5 \times 16.7 \times 2) = 25.3 \text{ g}$$

As in the case of the rat lung, the human measured work-volume curve approximated in shape the theoretical curves. It lay in an area which corresponded to a theoretical effective elastic tissue mass of 9 g.

In Fig. 9 we have drawn the human theoretical curves to their limits at $V_2 = 800\ (\epsilon_m + 1)^3 = 9734$ ml and compared them with the measured human values. Note that the theoretical work-volume curves of both rat and human lungs extend well beyond their known total capacities. In other words, elastic tissue behavior as interpreted here would allow a degree of stretch of the lung far beyond that observed (3,000 to 4,000 ml in the case of a human lung). At the upper limit of lung expansion we must, therefore, postulate other forces added to those attributed to elastic tissue. It may be that in this area collagen and reticulin (less stretchable elements) here become fully extended and exert restraining forces.

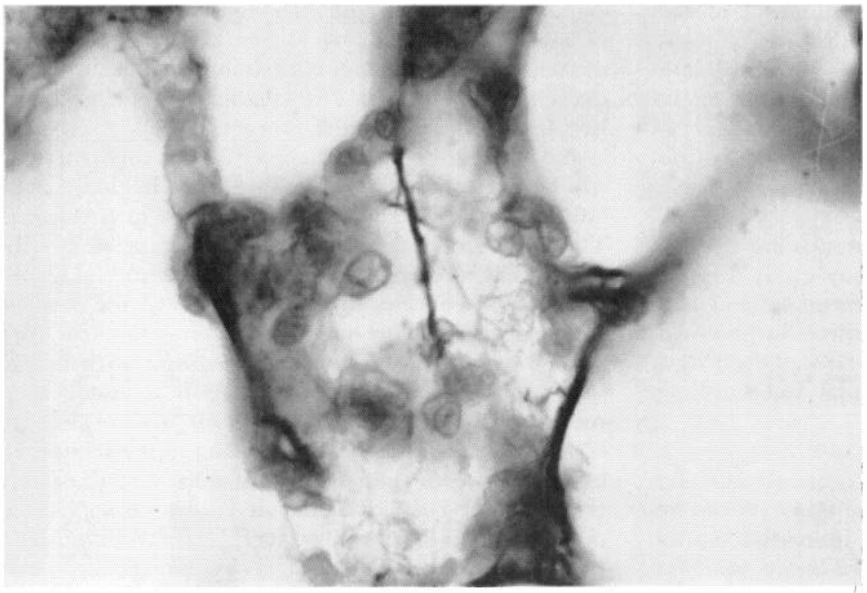


FIG. 10. An alveolar wall of a normal rat lung, stained to show elastic fibers. Other fibers above and below the plane of the section join those shown. 10 μ section at 1,100 X. Weigert's resorcin-fuchsin stain.

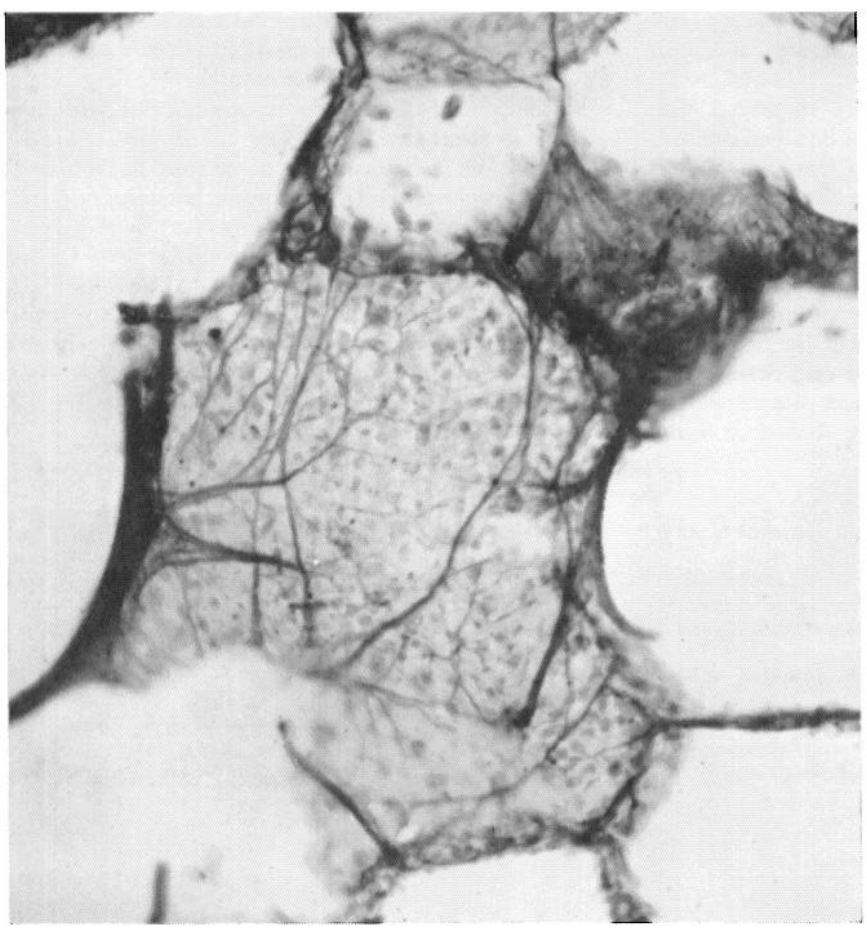


FIG. 11. An alveolar wall of a normal human lung, stained to show elastic fibers. 20 μ section at 430 X. Weigert's resorcin-fuchsin stain.

DISCUSSION

Comparisons of the theoretical and the measured pulmonary liquid-filled work-volume curves in both man and the rat show certain constant features. The measured curves approximate the theoretical curves in shape. In both species the measured curves reach an upper limit long before the theoretical curves, implying the presence of additional restraining elements. In both, the measured elastic tissue mass is somewhat greater than the theoretical effective elastic tissue mass. This can be ration-

alized to some extent: A considerable amount of the lung's elastic tissue content, especially that in the walls of large bronchi and blood vessels, will be ineffective in a process such as is described above. Roughly one might estimate 50% of the pulmonary elastic tissue as inoperative in this fashion, and hence the measured figures given above for the human are surprisingly close to the theoretical (9 g to 12.5 g).

The rat theoretical elastic tissue content is not as close to the adjusted measured (.005 g to .027 g). It is interesting that a relation between elastic tissue content and static tissue work persists over a three-hundredfold change in animal size. This could also be explained by a relatively fixed relation between animal weight, lung weight, and lung work.

We must recognize that such an analysis as is given above is loaded with assumptions and is chiefly of value as it *a*) points out how pulmonary tissue elasticity can be carried back to the basic properties of individual tissues and *b*) brings to attention the need for more concrete information about our assumptions. Consider some of these individually. *1*) The terminal air spaces are hemispheres and expand concentrically. Actually the reasoning leading to *equation 11* is valid for any isotropic dilation of the terminal air spaces, and not only for hemispheric alveoli. Weibel and Gomez (15) have suggested the alveoli as polygons with a minimal ratio between surface and volume, i.e., closely approximating the geometry of a hemisphere. In addition they have shown that the "average alveolar diameter" is a linear function of the cube root of lung volume. This is compatible with isotropic behavior. As they have pointed out, however, further experimental work is necessary in this area. *2*) Volume expansion in alveolar ducts can be treated as though it occurs in hemispheres. Storey and Staub (14) have shown in the cat that the diameters of alveoli and alveolar ducts enlarge proportionately during volume expansion of the lung but that the degree of lengthening of alveolar ducts is not known. Nor has the precise method of application of restraining elements to alveolar ducts been worked out. Our treatment of them as equivalent to hemispheres must be regarded as a simplifying assumption. *3*) Volume changes in the conductive zone can be neglected. The volume of the conductive zone is estimated (15) as making up 10% of the lung volume. *4*) The stress-strain properties of pulmonary elastic tissue correspond to those measured in fibers from ox ligamentum nuchae. Species differences between the elastic behavior of elastic tissue have not been investigated. We are assuming that this is a simple material without much species variation and are exploring the consequences of such an assumption. Measurements of the long-range elasticity of elastic fibers in the lung also have not been made. Nor have there been any studies of the physical properties of chemically isolated lung elastica such as those made on the aorta by Ayer, Hass, and Philpott (1). *5*) Elastic tissue in the alveoli is circumferential in its distribution in man and the rat. Repeated microscopic observations (Figs. 10 and 11) suggest this as the case in both species. *6*) Collagen and reticulin, as well as other rigid tissues, do not come "on the stretch" until the volume is close to total capacity. Setnikar has suggested (13) that the action of collagen is necessary to explain the nonlinear stress-strain behavior of alveolar restraining elements. We feel that elastic tissue itself has a nonlinear stress-strain pattern (2), but agree that a more rigid behavior than that of elastic tissue is operative in the walls of the terminal air spaces at high volume.

This study indicates that there is an adequate elastic tissue mass distributed through the respiratory zone to account for the lung's tissue elasticity through the major part of the breathing range, but that the action of other less-stretchable elements must be invoked as the upper limit of lung stretch is approached.

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