When the twentieth century began, a substantial amount was already known about the mechanics of breathing, and the respiratory muscles. The chest wall had been modeled as a bellows with a bladder inside representing the lung. It was known that the respiratory system was elastic and stored energy on inflation that did the work of expiration. Measurements of transpulmonary pressure had been made and there had been attempts to correlate these with lung volume (1).

However, a century ago we had no framework in which to view measurements. Without a model of how the system behaves, measurements of respiratory mechanics are uninterpretable. In addition, we lacked technology to make measurements. In the past 100 years this has changed: modeling has provided great insights into the system’s behavior and technological advances have permitted measurements that previously were impossible. Sometimes, however, advances are made without new models and new technology because scientists view problems from new perspectives. Such appears to be the case with surface tension, which I discuss separately.

This review is not comprehensive, but focuses on the role of models and technology in the development of new knowledge in the field and on discoveries related to surface tension. Only a limited number of topics are discussed. I apologize to those whose work should be included, but that I fail to discuss.

MODELING

Lung Models

Dixon and Brodie were the first to (implicitly) model the lung as a resistance (the airways) in series with an elastic element (the alveoli) (2). This allowed them to show that the experimental interventions they made changed airway caliber, and not lung elasticity. They showed that bronchoconstriction made ventilation distribution frequency dependent, thus anticipating the work of Otis and coworkers described below (3).

The modeling by Dixon and Brodie allowed measured changes in lung mechanics to be interpreted. However, it was Fritz Rohrer (Figure 1) who provided the conceptual framework underlying today’s studies of the mechanics of breathing. He made a stunning simplification by which the complexities of volumes and pressures of various parts were integrated into the pressures across only the lungs and the chest wall. These operated in series so that the volume changes of each were equal, while the pressure differences were not. He estimated magnitudes of forces developed by muscles, and resistances to motion to obtain a quantitative understanding of both normal and disease states (4, 5). Unfortunately, Rohrer was ahead of his time. His work was largely ignored and forgotten for 30 years until rediscovered by Wallace Fenn and colleagues in 1946 (6).

Rohrer’s simplification implied that pleural pressure was applied to all alveoli, including those embedded deeply in the lung. As a research fellow, I wondered how the pressure around the lung could act on alveoli deep inside. The assumption seemed huge, and unsupported by data. But like everyone else I soon became indoctrinated, took it for granted, and forgot my wonder. Not until Mead and coworkers modeled interdependence of lung units was this issue resolved (7). Mead (Figure 2) realized that stresses were distributed throughout the parenchyma via stretched alveolar walls and suggested that the pressure applied to both the outer surface of intrapulmonary airspaces and the pleural surface was the sum of the forces applied by alveolar walls attached to the surface divided by the surface area over which they acted. If the number of attachments per unit area was equal and each attachment transmitted, on average, the same force the two pressures would be equal. As this appears to be the case, Rohrer’s implicit assumption was shown to be reasonable.

Rohrer did not consider dynamic compression of airways during forced expiration. Fry, Hyatt, and colleagues bridged this gap by making a three-dimensional analysis of lung mechanics with pressure, volume, and flow on the three axes (8, 9). The pressure–volume and pressure–flow relationships were already known, but the flow–volume diagram was not. Thus, they discovered the maximal inspiratory flow–volume curve and they showed that it was independent of effort. To analyze the mechanism of effort independence, they looked at flow resistance in a new way by plotting pressure versus flow at a selected lung volume and created isovolume pressure–flow curves. These curves revealed that during expiration flow increased as driving pressure increased, but when pleural pressure became sufficiently positive, flow reached a maximum so that further increases in pressure resulted in no increase in flow. These maxima decreased systematically with volume. When the flow maxima were plotted as a function of lung volume the maximal expiratory flow–volume curve was reproduced.

These were empirical observations, and although Fry and Hyatt realized that flow limitation resulted from dynamic compression of intrathoracic airways, the parameters that determined flow, and how these were affected by disease, remained unknown. Nevertheless, they pioneered research that has led to a deep understanding of the FEV₁, a measure that has long passed the test of time and that remains as respirology’s commonest and most important test of lung function.

Early attempts to understand the physiologic factors that determined maximal flow focused on parameters that governed flow through segments of the tracheobronchial tree. Mead and colleagues (10) realized that once maximal expiratory flow was reached on an isovolume pressure–flow curve, there were three constant parameters: flow, volume, and lung elastic recoil pressure.
They pointed out that once expiratory flow becomes limited, the airways at the alveoli are distended whereas at the trachea they are compressed. Thus there had to be points between the trachea and alveoli where the airways were neither compressed nor distended. Such points (called equal pressure points, EPPs) where the pressure inside an airway had to equal the pressure outside, separated the airways into distended and compressed segments. As the pressure outside EPPs was pleural pressure, the pressure inside also had to be pleural pressure and the pressure drop between alveoli and an EPP (the upstream segment) had to be lung elastic recoil pressure. Thus at maximal flow on an isovolume pressure–flow curve, both the driving pressure and flow were constant in the upstream segment. The ratio of these quantities (the resistance of this segment) was also constant, strongly suggesting that its geometry was constant too. To account for this, the position of an EPP had to be fixed once flow was maximal. Thus Mead and coworkers modeled maximal expiratory flow at a given lung volume as a fixed resistor (the upstream segment) in series with a variable resistor downstream from EPPs, which contained the flow-limiting segments (10). This work revealed the importance of lung elastic recoil as a determinant of maximal expiratory flow. Because lung recoil decreases systematically with lung volume, it had to be an important contributor to the decrease in maximal expiratory flow with lung volume.

In an analysis similar to that of Mead and colleagues, Pride and coworkers attempted to explain the mechanism of flow limitation by modeling the lung as a resistance between the alveoli and a point downstream from EPPs, where the transmural pressure reached a critical value (Ptm’) sufficient to limit flow. This segment was in series with airways downstream from this critical point and lung recoil pressure was an important component of the pressure drop to Ptm’ (11). Their analogy was to a waterfall, where the flow is independent of the height of the falls, just as maximal expiratory flow is independent of the total driving pressure between alveoli and the mouth. In addition to revealing the importance of lung elastic recoil and the resistance of airways between the alveoli and Ptm’, this analysis underscored the importance of the mechanical properties of the flow-limiting segments.

This was a period of great intellectual ferment for those interested in the mechanics of breathing. The main protagonists were Don Fry, Bob Hyatt, Jere Mead, Sol Permutt, and Dick Riley. They and their friends met from time to time in a series of informal, unstructured, open-ended, no-holds-barred meetings that came to be known as the Flow–Volume Underworld. Arguments (but never quarrels) between Jere and Sol that continued well into the night have become legendary. At the dinners, usually held in someone’s home, the liquids that flowed as freely as the arguments, undoubtedly contributed to loquaciousness, if not to logic. But in contrast to other scientific controversies, the Flow–Volume Underworld solidified friendships and trust. The no-holds-barred nature meant that everything was on the table. There were no secrets, nor were there any concerns that others would steal ideas or fail to give appropriate credit to another. I learned an awful lot from the Flow–Volume Underworld, but most importantly, I learned how to conduct oneself in a scientific controversy. My life, and the lives of all the participants in the Flow–Volume Underworld, were immeasurably enriched by these unforgettable meetings, which, by the way, are still being held.

Although the ideas of Jere Mead and Sol Permutt provided insight into parameters that determined maximal expiratory flow, they were essentially descriptors. Explanation awaited Dawson and Elliott’s work (12) showing that maximal expiratory flow occurred when the linear velocity of gas at the flow-limiting segments (now called choke points) became equal to the speed at which a pressure wave travels along the airways to the alveoli. This high linear velocity prevents transmission of downstream pressure through choke points, so that flow becomes independent of pressure. Incidentally, the fluid dynamics of waterfalls are similar.

**Chest Wall Models**

The modern era of the mechanics of breathing was ushered in when Rahn, Otis, Chadwick, and Fenn presented the pressure–volume diagrams of the lungs and thorax (6). The most important of these was the relaxation pressure–volume curve; that is, the
plot of respiratory system volume against the pressure difference across it when all respiratory muscles are completely relaxed. If this is known, the pressures developed by respiratory muscles can be quantified by measuring displacements away from the relaxation curve. Thus for the first time one could measure the pressures developed by respiratory muscles to breathe. This knowledge was essential for the intelligent use of mechanical ventilators. Rahn and coworkers also measured maximal pressures that the muscles could develop. This knowledge was crucial for understanding mechanisms of hypercapnic respiratory failure, and fatigue. Because the area contained by a pressure–volume curve has the units of work, these diagrams developed the field of respiratory energetics by which work, power, and efficiency could be quantified. By modeling breathing as sinusoidal, Otis was able to calculate the work performed by the respiratory muscles (13). When these measurements were combined with the O₂ cost of breathing, the efficiency of the respiratory muscles could be calculated (14).

The seminal work of Wallace Fenn and colleagues was followed by Moran Campbell’s separation of lung and chest wall pressure–volume curves (15), by which the elastic and flow-resistive work performed on the lung and chest wall by the muscles could be partitioned, positive and negative work could be quantified, and work performed by storing elastic energy in the lung and chest wall separately measured.

The Campbell diagram did not allow work to be partitioned among individual respiratory muscle groups. Duomarco and Rimini provided a framework by which this problem could be approached (16). Their analysis gave remarkable insight into respiratory muscle action simply by measuring abdominal pressure and displacement. They modeled the abdomen as a liquid-filled sac with a hydrostatic gradient (although nonhydrostatic gradients occur [17]). They pointed out that if one breathed with the diaphragm alone, abdominal pressure rose during inspiration and the abdomen moved outward; if one breathed with inspiratory rib cage muscles, abdominal pressure fell and the abdomen moved inward during inspiration; a breath taken by abdominal muscles started with an expiration that increased abdominal pressure accompanied by inward abdominal displacement, followed by a fall in abdominal pressure with outward abdominal displacement during inspiration. These contributions provided the basis for analyzing actions of specific respiratory muscle groups, but more modeling was needed.

The next advance came from Konno and Mead (18), who modeled the rib cage and abdomen as two compartments in such a way that the motion of a single point on each compartment served as a quantitative measure of its volume change. Because abdominal pressure drove the relaxed abdominal wall, Konno and Mead constructed relaxation pressure–volume curves of the abdomen, and so were able to quantify pressures developed by abdominal muscles from dynamic abdominal pressure–volume loops (19). Agostoni and Rahn had already measured transdiaphragmatic pressure as the pressure difference across the diaphragm measured with esophageal and gastric balloons (20). The problem of quantifying the agencies acting on the rib cage remained.

Goldman and Mead had shown that abdominal pressure was an important agency driving the relaxed rib cage (21). As a result, Mead recognized the importance of the area of apposition of the diaphragm to the inner surface of the rib cage (22) through which abdominal pressure was transmitted to act on the rib cage. The forces developed by the diaphragm fibers attached at the costal margin also acted on the rib cage. This force was modeled by Loring and Mead (23) as a fraction of the total transdiaphragmatic pressure (the insertional component). The parallel and serial arrangements of the costal and crural parts of the diaphragm, the abdominal muscles, and the nondiaphragmatic inspiratory muscles were defined (24). Finally, Ward and coworkers developed a two-compartment rib cage model that allowed quantification of rib cage muscle action (25). Thus the pressures developed by the diaphragm, abdominal muscles, and both inspiratory and expiratory rib cage muscles could now be measured. Shortening, and shortening velocities, could be estimated by motions of compartments they displaced. Thus pressures, relative velocities of shortening, and power are now known for each of the major respiratory muscle groups during quiet breathing and exercise (26).

TECHNOLOGICAL ADVANCES

Esophageal Pressure
The most important new technology for the mechanics of breathing was unquestionably the introduction of esophageal pressure as a measure of pleural and therefore transpulmonary pressure, by Buytendijk (27). This, along with the introduction of the pneumotachograph by Fleisch as discussed by Otis (28) allowed detailed measurements of lung mechanics in both health and disease in human subjects. The statics and dynamics of the lungs were rapidly quantified as summarized in Mead’s superb review (29). Investigation of lung mechanical abnormalities in disease became possible, resulting in a rapid increase in knowledge of the pathophysiology of chest disorders.

A most important contribution was the demonstration of the importance of time constants (the product of the resistance and compliance) of parallel lung units in determining the distribution of ventilation. These determined how rapidly air flowed in and out of airspaces. If time constants were different for different units, ventilation distribution would change with breathing frequency; the tidal volume of slow units would fall as breathing became faster and lag behind their faster neighbors, leading to asynchrony (3). This was measured as frequency dependence of compliance (3). Normal lungs were not frequency dependent, implying that the time constants of parallel airspaces were equal. In airway obstruction, however, compliance was frequency dependent, implying asynchronous airspaces and abnormal ventilation distribution.

Partitioning of Pulmonary Resistance
The use of the retrograde catheter allowed the resistance of the tracheobronchial tree to be partitioned (30, 31). The demonstration that the small airways were low-resistance pathways, but were the site of airway obstruction in chronic obstructive pulmonary disease (32), led to the concept that the small airways could be the site of substantial airway obstruction with few symptoms and little effect on mechanics of breathing but with abnormal ventilation distribution and gas exchange (32). Tests of this hypothesis confirmed its validity (33–36), and also demonstrated that collateral ventilation played a major role in determining the pathophysiological effects of airway obstruction (33, 34, 36).

The low resistance of peripheral airways clarified why alveoli were synchronous in health (3). This was obviously desirable but difficult to construct with large differences in pathway length between the carina and the alveoli (37). When peripheral resistance is low, time constants of peripheral units are small, permitting differences between parallel units with little effect on synchrony at physiological breathing frequencies (30).

Two other factors promote synchrony in the lung: interdependence (7) and collateral ventilation (33). The latter permits ventilation of airspaces beyond an obstructed peripheral airway (but not with fresh air [36, 38]) while if asynchrony develops the forces of interdependence amplify the pressures to slow units increasing collateral flow (7). Thus, three factors converge to promote syn-
chronous behavior of airspaces in the normal lung: low resistance of peripheral airways, forces of interdependence, and collateral ventilation (33).

**Whole Body Plethysmography**

Variable-pressure whole body plethysmography was introduced in 1956 by DuBois and coworkers (39) and rapidly became the method of choice for measurements of the subdivisions of lung volume (40) and airway resistance (39). The linear relationship between airway conductance and lung volume was demonstrated (41), providing the physiologic basis for the current interest in deep inspirations in asthma. Subsequently, Mead introduced volume displacement whole body plethysmography (42), which measured volume changes due to gas compression and decompression. Gas compression was shown to lead to large artifacts in the measurement of flow–volume curves in chronic obstructive pulmonary disease (43, 44) that are usually ignored today. Jaeger and Otis showed that the work of gas compression and decompression was substantial (45).

**Radioactive Gases**

The introduction of radioactive gases to study lung function led rapidly to quantification of regional distribution of gas within the lung. Knipping and colleagues were the first to study regional distribution of 133Xe (46), but it was Ball and coworkers who made the measurements quantitative (47). Although scintillation counters could detect regional differences in counts arising from radioactive gases in the lung, it was unclear whether these differences were due to differences in concentration, in amount of lung tissue seen by a counter, or in geometry or absorption by chest wall tissue. Ball and coworkers devised an equilibration procedure, so that the concentration of 133Xe measured at the mouth was identical to that throughout the lung. Thus counts recorded by each counter over each lung region were calibrated in terms of concentration. This breakthrough allowed quantification of regional alveolar concentrations of 133Xe and the estimation of regional lung volumes.

It was soon observed that superior lung regions were more expanded than dependent lung regions (48). This was in the direction of gravity and thus alveolar size distribution changed systematically with posture (49). Increased gravitational forces increased the magnitude of the gradient (50). A gradient in alveolar size suggested a gradient in distending pressures, with pleural pressure more negative over superior regions than over dependent regions. Milic-Emili and colleagues assumed that the elastic properties of the normal lung were uniform so that each region had identical surface area (58). Independently, Clements measured lung extracts with a Langmuir–Wilhelmy balance and showed that surface tension was constant, which, 3 years later, Clements showed was not the case (58).

In the meantime Pattle (Figure 3) discovered that lung tissue extracts stabilized bubbles in water and postulated that there was an alveolar lining layer with very low surface tension. Independently, Clements measured lung extracts with a Langmuir–Wilhelmy balance and showed that surface tension fell to low levels of about 1 dyn/cm. Compressed films, “rich in...lung surfactant,” as Goerke and Clements state, “lose mate-

**SURFACE TENSION**

The first hint that surface tension at the alveolar air–liquid interface might be important came from Dixon and Brodie, who pointed out that airspaces might be unstable in the same way that two soap bubbles blown at the ends of a Y-tube are (2). Unfortunately, they did no experiments, and no investigators considered the role of surface tension in lung mechanics until von Neergaard, 26 years later. He measured lung elastic recoil pressures in air- and liquid-filled lungs and correctly attributed the difference to surface tension (56). He thereby showed that surface forces were an important determinant of lung elasticity. Another 25 years passed before Radford repeated von Neergaard’s experiments. Radford’s ingenious idea was that the hysteresis area of the air-filled pressure–volume curve that was eliminated in saline-filled curves was the work performed by surface tension. Therefore by solving the equation \[ P \cdot dV = \gamma \cdot dA \] (where the left-hand term is the area of hysteresis removed by saline filling, \( \gamma \) is surface tension at the alveolar air–liquid interface, an assumed constant, and \( A \) is the alveolar surface area) he could estimate the surface area of the air–tissue interface in the lung (57). Sadly, his estimates were incorrect, both because he used incorrect values of alveolar dimensions and assumed that \( \gamma \) was constant, which, 3 years later, Clements showed was not the case (58).

In the meantime Pattle (Figure 3) discovered that lung tissue extracts stabilized bubbles in water and postulated that there was an alveolar lining layer with very low \( \gamma \) (59). Independently, Clements measured lung extracts with a Langmuir–Wilhelmy balance and showed that \( \gamma \) changed with surface area (58). On expansion (corresponding to inspiration) \( \gamma \) increased to about 25 dyn/cm. With compression (corresponding to expiration) it fell to low levels of about 1 dyn/cm. Compressed films, “rich in...lung surfactant,” as Goerke and Clements state, “lose mate-

![Figure 3. Mary Ellen Avery and Richard Pattle (1918–1980) at a Ciba symposium.](image-url)
rial [i.e., surfactant molecules leave the surface resulting in an increase in $\gamma$] so slowly that surface tension remains as low as 1 dyne/cm for hours. This striking metastability of overcompressed lung surfactant films makes breathing easy for the individual and theoretical interpretations difficult for the surface chemist” (60).

Following the pioneering and seminal studies of Patte and Clements, progress was rapid. The lining material was identified as dipalmitoyl phosphatidylcholine (61), and the physiologic role of surfactant in maintaining the lungs free of pulmonary edema and in stabilizing alveoli was discovered (62–65). Of particular importance was the discovery by Avery (Figure 4) and Mead that the alveolar lining layer was deficient in the respiratory distress syndrome of infancy (66). The high $\gamma$ at the alveolar air–liquid interface in infants with this disease made alveoli unstable and atelectatic, while creating a large pressure difference across the surface causing pulmonary edema.

**IMPACT ON CLINICAL PRACTICE OF MECHANICS OF BREATHING RESEARCH**

The discovery of surfactant, its physiological role, and its absence in the neonatal respiratory distress syndrome have resulted in an extraordinary reduction in infant mortality from neonatal respiratory distress syndrome in the United States, from 270 deaths per 100,000 live births in 1972 to only 20 deaths per 100,000 live births in 2000. This success story was due to improved modes of mechanical ventilation resulting from mechanics research as well as from corticosteroids, and surfactant replacement. As a result, neonatal respiratory distress syndrome is no longer the most important cause of neonatal death in developed countries. If one evaluates therapeutic benefit by the number of useful years of life saved as well as by reduction in mortality, this stunning success must rank as one of medicine’s greatest achievements ever.

Knowledge of mechanics of breathing made intelligent use of mechanical ventilators possible, and therefore paralysis during anesthesia. Respiratory intensive care, particularly for hypoxic and hypercapnic respiratory failure, would not be possible without knowledge of mechanics. Volume reduction surgery works because it improves the mechanics of breathing. Respiratory mechanics research has defined the abnormalities in obstructive sleep apnea and discovered its successful treatment by nasal continuous positive airway pressure. The mechanics of continuous positive airway pressure have been shown to benefit the failing left ventricle by reducing its afterload. The contributions that a century of research in the mechanics of breathing have made to clinical practice is convincing evidence that research dollars invested have paid handsome dividends.

**Conflict of Interest Statement:** P.F.M. holds patents for measuring ventilation and its parameters noninvasively, for measuring variability of airway impedance as a prognostic indicator in asthma, for dynamic measurement of individual cell volume and shape, and for lung morphometry by ultrasound.

**References**


**Figure 4.** John Clements and Mary Ellen Avery. Evidently, John has just said something outrageous (for which he is famous) and Mel, while appropriately embarrassed, cannot stop herself from laughing.