CONSIDERABLE UNCERTAINTY existed regarding the magnitude of pulmonary dead space in the immediate post-World War II era. The dead space concept was originated by Bohr (2), who viewed total ventilation as composed of two distinct, but homogeneous, components—alveolar ventilation that participated fully in gas exchange and dead space ventilation in which no respiratory exchange occurred. With knowledge of the composition of inspired air, Bohr used a mass balance approach to calculate dead space from measurements of tidal volume and mixed and expired alveolar gas compositions. The validity of the latter variable was at the root of discrepancies in dead space values reported in the literature before Fowler’s work (4). Multiple methods for sampling alveolar gas (6) had been used, and the choice of alveolar sample led to discrepant estimates of dead space. Douglas and Haldane (3) used the Haldane-Priestley method to measure alveolar carbon dioxide fraction and reported a fourfold increase in resting dead space when tidal volume increased with exercise. These findings were criticized by Krogh and Lindhard (8), who employed hydrogen as a tracer and a better means of alveolar sampling. The latter authors concluded that dead space varied relatively little—less than 100 ml despite widely differing respiratory maneuvers. Although subsequent reports supported their conclusion, the issues still were not clearly defined when Fowler began his studies. Values of dead space were important because at that time alveolar ventilation was calculated from total ventilation and an assumed or empiric value for dead space.

An interesting series of events intersected to improve conceptual and quantitative understanding of dead space. In 1946, Julius Comroe accepted the Chairmanship of the Department of Physiology and Pharmacology of the Graduate School of Medicine at the University of Pennsylvania (7). Comroe developed a coordinated program to investigate pulmonary function in health and disease. He recruited a number of now-eminent scientists, one of whom was Ward S. Fowler. At the same time, John C. Lilly (10) in the Johnson Foundation at the University of Pennsylvania, together with J. P. Hevesy, was developing a rapidly responding nitrogen meter (response rate of 0.02 s) for the Air Force to test for leakage in respiratory masks. Lilly and colleagues (9) earlier had invented a sensitive capacitance manometer. Lilly (11) constructed a flowmeter consisting of a laminar resistor that produced small changes in pressure proportional to flow. The combination of the manometer and laminar resistor allowed continuous measurements of airflow throughout the respiratory cycle. Hence, Fowler was in an excellent position to investigate the respiratory dead space with the instrumentation from the Johnson Foundation and the "advice and encouragement" of Julius Comroe (4). Unlike previous investigators, Fowler did not need to rely on analysis of a single aliquot of expired air to estimate alveolar composition, but he could choose an appropriate value from the continuous recordings of nitrogen concentration and expired airflow. The latter signal was laboriously integrated over time to provide a record of cumulative expired volume.

Fowler (4) used a tidal breath of pure oxygen that completely filled the dead space and mixed with alveolar gas downstream of the dead space. He described three phases in the subsequent expired nitrogen-volume recording. The initial portion of the expired gas (I) contained no nitrogen, and the last phase (III) contained a "relatively constant" nitrogen concentration representing the dilution of the pre-existing alveolar nitrogen by the inspired oxygen. The short intermediate second phase (II) of the experimental plot was characterized by a transient increase in nitrogen concentration from the initial dead space to final alveolar values. Fowler recognized that a square wave change in nitrogen concentration would not be

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Fig. 1. Ward S. Fowler. Photograph from Mayo Clinic College of Medicine, courtesy of Gary C. Sieck.

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observed as dead space was cleared during expiration because of the presence of different path lengths of dead space between the mouth and alveoli, the lack of a uniform velocity across the cross section of the tracheobronchial tree, and the effect of diffusion on gas concentrations at the boundary between the dead space and alveolar volumes. In his calculations, Fowler used the plateau in phase III to represent alveolar nitrogen concentration and divided the integrated nitrogen-volume curve by expired volume to obtain mixed expired nitrogen concentration. Together with the measurement of total expired volume, he calculated the dead space volume with Bohr’s formula. He noted that the nitrogen-volume recording was “rectilinear” in almost all cases, most likely the result of the normal health of his subjects. If there was a slight slope to phase III, the nitrogen concentration was extrapolated backward to the point where phase II ended to determine an alveolar concentration. Because the entire procedure of integration by hand was time consuming, he analyzed most records with a graphic method. He assumed that expiratory flow was constant, avoiding the integration of flow to obtain expired volume. Using a squared transparency, the mean flow-weighted nitrogen transient in phase II was estimated to obtain the volume of the dead space. Although less exact, this methodology produced essentially the same results as the more laborious integration and calculation using Bohr’s equation.

In this initial paper, Fowler (4) referred to dead space measured in this manner as “physiological dead space.” However, this measurement more closely approximates “anatomic” or “series” dead space according to current concepts (1). As he extended his studies beyond healthy subjects, Fowler (5) incorporated the concepts of nonuniformity of respiratory variables in the lung into his interpretation of the single breath washout technique.

Fowler (4) obtained a mean dead space during resting ventilation of 156 ml in 45 males (mean weight 161.5 lb.) and 104 ml in four females (mean weight 120 lb.). These values are quite close to the current rule of thumb numerically equating resting dead space (ml) to ideal body weight (pounds). Fowler also demonstrated that dead space increased modestly with increasing tidal volume and correlated the increase in dead space with increased end-inspiratory lung volume. This report also included investigation of the role of diffusion on measured dead space. A 20-s breath hold at end inspiration reduced measured dead space by 40%, “presumably because the peripheral boundary of pure inspired gas had receded up the bronchial tree” (4). Although clearly supporting Krogh and Lindhard’s (8) conclusion that dead space varied only moderately with respiratory variation, Fowler concluded that assuming a normal value for calculations would not be a sound practice because patterns of ventilation can vary appreciably.

When Fowler (5) extended his studies to include patients with lung disease, it clearly indicated that the alveolar “plateau” was not a truly constant value. He demonstrated that nitrogen concentration in phase III increases progressively with expired volume even in normal individuals when a full vital capacity maneuver is used rather than a tidal breath. Fowler used the slope of phase III to characterize nonuniformity of ventilation in patients. Of the considered causes of nonuniformity, he dismissed stratification of gas concentrations from the dead space to alveoli as unlikely in view of the large effect of diffusion on the gas boundary demonstrated in his earlier experiments. He concluded that regional nonuniformity of ventilation/lung volume was the most important factor. Fowler also suggested that temporal nonuniformity of alveolar expansion resulting from a first-in, last-out sequence also could be responsible for sloping of the alveolar plateau.

Other studies have extended the complexities of dead space ventilation to include nonuniform distribution of gas in the dead space at the start of inspiration, gas mixing secondary to cardiac oscillations, and the variance of measured dead space observed using tracer gases of differing solubility (1). The concept of dead space has evolved extensively in the last half century since Fowler’s original work (4), but his initial and subsequent studies led to the development of many current concepts of dead space and the means to evaluate the functional effects of respiratory illnesses.

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REFERENCES