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A life of passion and serendipity

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It is a bit embarrassing to have been concerned with the human problem all one's life and find at the end that one has no more to offer by the way of advice than "try to be a little kinder."
Aldous Huxley (1894–1963)

My and my colleagues' 1966 paper entitled "Regional distribution of inspired gas in the lung" [1] became one of the 100 most-cited papers of clinical research from 1961 to 1978 [2]. It inspired many investigations and provided the kernel for understanding regional lung function [3,4]. It also played an important role in propelling me to become one of the 1000 most-cited authors from 1965 to 1978 [5]. Before the 1966 study, my research training in Milan, Liège, and Boston was essentially "programmed" to allow me to formulate concisely the basic factors determining the regional distribution of gas in the lung.

Education

I was born in 1931 in a small village (Sezana, at present in the Republic of Slovenia), which, during my life span has been part of Italy, Germany, the Anglo-American zone of occupation, Yugoslavia, and Slovenia. As a result, I am "a citizen of the world but a foreigner in all countries."

Although my village consisted of only 500 inhabitants (including cows), it provided a stimulating environment. My mother instilled into me a passion in all of my activities (playing, studying, reading, etc.). At home we had many books; as a child I read the novels of Dostoyevsky, Tolstoy, Turgenev, and others at the same time as Mickey Mouse comics. I enjoyed all of them.

One of my elementary school teachers taught me to "look at the stars." She gave praise and awards when deserved, but punished us severely when we misbehaved (e.g., by making us kneel on rice). We were responsible children; hence, we took our punishment as well deserved. After this, only teachers who made me "look at the stars" captivated me.

Because of the havoc caused by the Second World War, my high school teachers were often exceptionally qualified university professors; they taught me to pose questions rather than give superficial answers.

In 1949 I enrolled in the Faculty of Medicine at the University of Milan, Italy. I did so because a family acquaintance had just graduated there and gave me all of his medical books "because he did not need them any longer!" The teaching at the University of Milan ranged from poor to excellent. Surprisingly, however, I also learned a lot from the poor lecturers. My hero, however, was Professor Rodolfo Margaria, who was a world-renowned scientist in exercise physiology. I liked his class, style, and wit, although his lectures were, in general, poorly prepared. After meeting him I decided to pursue a research career with him.

Milan and Liège

In 1956 I carried out research in exercise physiology at the Department of Physiology of the University of Milan, under the guidance of Professor Margaria. My introduction to respiratory mechanics was due to the fact that, in 1957, a very capable Belgian physiologist (Jean-Marie Petit) came, through a misunderstanding, to our Department "in order to learn how to measure esophageal pressure." Such measurements had never been done in Milan, nor was there any suitable equip-

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ment available. Nevertheless, using a water manometer, Petit and I produced an important paper on the measurement of esophageal pressure [6]. Dr. Petit, who was one of the best experimental physiologists that I have ever known, next invited me to join him at his laboratories in Liège, Belgium, which were well equipped for studies in respiratory mechanics. Together, we published a large series of papers in this field. Thus, I became an expert in respiratory mechanics through a fortuitous misunderstanding.

In Liège I learned that "Necessity is the mother of all virtues." In fact, we started measuring the electrical activity of the diaphragm by inserting a long needle through the chest wall into normal human volunteers! Not surprisingly, after a few attempts, we induced a massive pneumothorax in one of our volunteers—the son of the dean of the medical faculty of Liège. After this failure we rapidly developed the esophageal balloon-catheter method to determine the electrical activity of the diaphragm, and this method is still widely used [7].

In Milan, Professor Margaria introduced me to the quantitative analysis of data based on diagrams and mathematics. In those days this approach was not common. As a result, Margaria's pupils were at that time almost a unique breed of investigators.

Boston

In 1960 to 1963 I was a research fellow at the Harvard School of Public Health, Boston, where, in collaboration with Dr. Jere Mead and colleagues, I published two papers dealing with the static volume-pressure relationship of the lung and the topography of pleural surface pressure [8,9].

My research training in Milan, Liège, and Boston was essentially "programmed" to allow me to formulate concisely the basic factors determining the regional distribution of gas in the lung, which became my main research topic when, in 1963, I arrived in Montreal, Canada.

Montreal

In 1963 I was invited by Dr. David V. Bates to come to McGill University in Montreal. In 1962 his group had introduced a quantitative method for assessing regional pulmonary function, using radioactive xenon [10].

My arrival in Canada was somewhat hectic because I was asked by the Canadian immigration authorities to provide a chest X-ray. This showed that I had overt tuberculosis! Nevertheless, I was allowed to come to Canada on a special minister's permit, thanks to the strenuous efforts made by Drs. D.V. Bates and M. McGregor. I am very grateful because I have spent a most happy time at McGill University. Unknown to me at that time, in view of my previous training, I was ready to make a rapid breakthrough in the area of regional lung function.

I arrived in Montreal in the middle of the summer of 1963, at a time when all the staff were on vacation. I was put in a small office with a single reprint on my desk, that of Ball et al. [10]. I proceeded to read it with interest, particularly as I thought that the studies with radioactive gases were for me a new, rather exotic area of research. On the fourth page of that paper there are two equations which describe the radioactive xenon method which, at first, I could not understand. After a while, however, I realized that the method of Ball et al. was essentially an application of the gas dilution principle with which one could measure the volume in different regions of the lung. In fact, at that moment, I realized the significance of my previous research [6–8] in terms of the regional distribution of gas in the lung; for the first time in my life I was now in full control of a research line, which rapidly led to the development of the "onion skin diagram" (Fig. 1).

Peer review

The manuscript entitled "Regional distribution of inspired gas in the lung" [1] was submitted for publication to the *Journal of Applied Physiology* at the beginning of 1965, together with three companion papers [11–13]. The name of D.V. Bates does not appear with the authors of reference 1, because he told me that, in view of the importance of the study, he wanted to leave all the credit to me! Such generosity is seldom encountered. His name, however, appears in reference 12.

While the three companion papers received favorable reviews, this was not the case with the first manuscript [1], which was rejected! One of the two reviewers concluded the extensive criticism with the following statement: "My comments should be considered merely citations of examples of the faults in this paper rather than an exhaustive catalogue." In spite of the reviewer's adamant rejection of this paper, the section editor of the *Journal of Applied Physiology* (Dr. J. Mead) decided to accept it for publication. In this connection I will add that one of the reviewers of one of the companion papers, entitled "Regional distribution of pulmonary perfusion in erect man" [11], wrote that "While reading the manuscript I felt like listening to the music of Wagner." In his correspondence with us, Dr. Mead stated that he accepted this paper on the "assumption" that the reviewer liked Wagner's music!

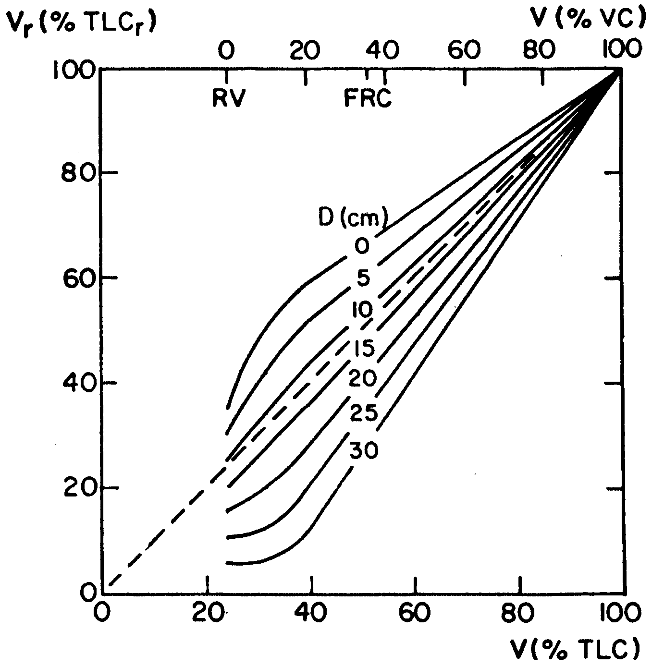

Fig. 1. *Ordinate*: Regional lung volume (*Vr*), expressed as percent regional total lung capacity (*TLCr*). *Abscissa*: Overall lung volume (*V*), expressed as percent TLC (*bottom*) and as percent vital capacity (*VC*) (*top*). The *broken line* (line of identity) indicates percentile degree of expansion of the regions equal to that for the entire lungs. The vertical distance (*D*) from top of lungs (in centimeters) is indicated on each curve. From reference 1, with permission

What was discovered

The 1966 paper [1] provides a quantitative description of the factors governing the regional distribution of gas within the lung. Furthermore, it introduced the "onion skin diagram", depicted in Fig. 1. This diagram was obtained in a normal seated young man by having him inhale air labeled with radioactive xenon, and then measuring the regional count rates over different parts of the chest, using 12 scintillation counters.

Progress in physiology is often marked by the development of diagrams, which provide a concise formulation of basic aspects. In respiratory physiology there are many such examples, e.g., the O_2–CO_2 diagram of Rahn and Fenn [14]. Our study also provided such a diagram. For upright humans, Fig. 1 indicates a number of things: (a) the alveoli in the upper lung regions are more expanded than those in the lower lung zones at all lung volumes, except at full inflation (100% total lung capacity [TLC]); (b) above the functional residual capacity (FRC), there is non-sequential lung gas filling, as reflected by the linear relationships between regional and overall lung volume, but the ventilation per alveolus is higher in the lower lung zones, as reflected by the steeper slopes of the lines; (c) below the FRC, lung gas emptying is sequential, reflecting progressive small airway closure in the dependent lung zones as residual volume is approached; and (d) lung regions empty progressively with decreasing lung volume until a minimal limiting volume is reached. This volume reflects gas trapping behind closed small airways. These findings led to the concept and measurement of the closing volume [15].

After publication, our paper [1] immediately became very popular, stimulating a vast number of physiologic and clinical investigations, which have been extensively reviewed elsewhere [3,4,16,17]. Furthermore, our findings are now described in most textbooks of respiratory physiology, and, hence, have become part of the physiologic heritage. It is axiomatic, however, that scientific diagrams, such as that in Fig. 1, have limitations in view of the complexity of the respiratory system and the "scientific" approach on which they are based.

Broadly speaking, the approach to a given topic can be "mystic" or "scientific": perception of the whole versus selection of parts. Because "scientific" accounts are, by definition, selective, they provide only a partial story. As a result, "scientific" accounts have limitations because they are necessarily based on simplifying assumptions.

Useful considerations for young investigators

My research has characteristically consisted of the development of new methods to study different aspects of respiratory physiology. In fact, apart from introducing the esophageal electrodes to assess the electrical activity of the diaphragm [7] and refining the esophageal method to determine pleural pressure [8,9], with my colleagues I introduced the mouth occlusion method [18] and detailed assessment of breathing pattern [19] in studies of the control of breathing. In addition, we introduced the measurement of closing volume [15] and assessment of respiratory mechanics in intensive care unit (ICU) patients [20]. New methodology is essential for the discovery of new findings, and I strongly recommend to young investigators that they closely evaluate the available methods and attempt to provide new methodology or, at least, improved techniques. I worked in many areas of respiratory physiology, and I found that, almost invariably, this task could be accomplished if approached with passion. In most instances, however, the achievements were also due in good part to serendipity.

Postscript

The 1966 article [1], although written in a clear and concise fashion, is not easy to read, as it requires considerable knowledge of both respiratory mechanics and gas exchange. It still represents, however, the essential synthesis of the factors that govern the regional distribution of gas in the lung. In preparing the present manuscript, however, I found that, at this time in my life, the names and memories of my coauthors have become more important to me than the scientific content of my papers.

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