QUANTITATIVE DIAGNOSIS IN PULMONARY MEDICINE— MAKING VIRTUE OUT OF NECESSITY

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Diffuse lung diseases are of particular concern for occupational medicine; the putative disease-causing agents are generally inhaled and those agents that reach all parts of the lung are capable of inducing disease in fairly simultaneous fashion. The defenses of the respiratory system against inhaled gases and particulates are multiple and complex; thus, the effects of noxious agents may never reach the level of detectibility if one relies on pulmonary function measurements. For example, there is good reason to believe that one can detect alterations in enzyme patterns and increased cell turnover in the alveolar lining cells or the airway epithelial cells long before there are clear cut structural or functional changes. These are changes that are perhaps simply a normal or adaptive reaction to an environmental stress; they probably are real changes and we make no pretense about trying to define them by the use of the usual pulmonary function tests. So, there may be a stage in the development of inhalation disease in which the changes are really not detectable by physiologic testing; these changes will have to be detected by other methods-biochemical, cytological or other.

A tremendous number of factors contribute to the well-known variations of individual response to a particular challenge. The efffect of dose is the first thing that we think of. But apart from the effect of dose, we have to be very aware of the pattern of deposition and uptake when the agent is inhaled into the lung. Agents can deposit at any point along the complex branching system of the lung, depending on particle size, solubility and the rapidity of air flow. There are also genetically determined variables that are important. We know, for example, the significance of a smoker being a heterozygote for alpha-1-antitrypsin deficiency; such people appear to be at a higher risk of developing chronic obstructive lung disease. We are also beginning to realize that there is a tremendous influence of HLA-type on the occurrence of diseases like rheumatoid spondilitis. It may be that research will show that certain people are susceptible to a particular dust-related disease while genetically different individuals are not. Nutritional factors and co-intoxicants may also play a role in whether or not an agent manifests toxic effects on the subject. Cigarette smoke, of course, is the prime example of a co-factor. The patient may have other diseases that interact with the inhaled agent. A nice example of this is Kaplan's syndrome; coal miners with rheumatoid arthritis react to coal dust and present a fairly special clinical picture. And finally, the effects of potentially noxious agents on a pre-existent lung disease have to be considered. Thus, these interactions of many factors make the evaluation of clinical data very difficult.

On the other hand, progress in pulmonary function testing has not stood still. The degree of sophistication and the ability to assign an anatomic locus to a particular abnormality of pulmonary function have been improving. In the past ten years or so, a tremendous amount of attention has been placed on the small airways, which in the adult lung are those airways smaller than approximately 2mm in internal diameter. These airways include the bronchi with cartilage in their walls and also the various

levels of the bronchiolar tree. Because they are very numerous--despite their relatively small individual size—they have a large aggregate cross-sectional area; thus, the rate of air flow in any individual airway is extremely low and air flow resistance is almost negligible—it is very difficult to detect a pressure drop during expiration on the order of a millimeter of water. The major drop in pressure in the normal individual occurs in the large airways, the segmental and lobar, and the main bronchi and trachea. The small airways thus have been called a "silent area", and a lot of disease can exist in these small airways without any clear-cut impairment of the standard parameters of spirometric pulmonary function.

It's been tough to prove this hypothesis of the genesis of chronic obstructive lung disease, but it is accepted by most experts in the field. In most cases the small airways are the locus of the initial attack, which is rather prolonged and insidious. Because these airways are so numerous, one can suffer the loss of many of their numbers before obstructive lung disease becomes apparent. It is not surprising that investigators have looked for ways to detect small airways disease.

While measurement of the FEV_1, particularly as a fraction of the total vital capacity, is still a very useful and relatively sensitive test for the presence of diffuse obstructive lung disease, there appear to be better tests. First of all, efforts have been made to use the maximum mid-expiratory flow rate. This flow rate is determined by looking at the middle half of expiration, starting from total lung capacity and going down to residual volume, dividing that volume into halves and quarters and then looking at the middle-half to see how long it takes to expire that middle-half of the air; the slope of the curve is a rate because it is a change of volume with respect to a change in time and is called the "maximum mid-expiratory flow rate."

The test was touted as a very sensitive and useful one for the detection of small airways disease because the site of flow limitation during expiration seems to displace itself deeper and deeper into the airways of the lung as the lung gets smaller, finally reaching the small airways. It was a reasonable idea and it has been pushed as an important improvement in the interpretation of spirograms. Unfortunately, I don't think it is a very good test. If you look at the variation within a subject on repeated trials, you will see that the maximum mid-expiratory flow rate is difficult to reproduce—even very good laboratories can have a range of 20 to 25%—whereas, vital capacity and the vital forced respiratory volume in one second are reasonably reproducible (within 5% on repeated trials at the same sitting). In addition, the inter-subject variability is very substantial.

Researchers interested in lung mechanics are convinced that we're not extracting all of the useable information from the spirogram. They continue to look for new and better indices with which to analyze these curves. Some of these efforts involve complicated computer procedures—for example, the analysis of moments and slope ratios—to break down the curve into a sum of exponential curves, each of which might reflect the rate of emptying of a certain compartment of the lung. These techniques are not marketable, but they are shown to be of value in the early detection of disease—one that will be in the individual as well as in a group of subjects.

A test that seems to have a place in the detection of early disease is the single breath nitrogen test devised by Ward Fowler at the Mayo Clinic about 30 years ago. It consists of the subject taking a full breath of oxygen then continuously measuring the concentration of nitrogen at the mouth while he is slowly expiring. There is a rapid rise in N_2 concentration, which proceeds to a plateau as he continues to breathe out.

Fowler focused on the slope of the plateau, concluding that a slope greater than a certain amount indicated diseased lungs and a maldistribution of air. His conclusions are still valid today. More recently, it has been found that a reproducible rise in nitrogen concentration takes place toward the end of the expiration; the lung volume at which this rise occurred was termed the "closing volume"--this is seemingly the volume of the lung at which airways closure begins. When you reach the residual volume, all your airways are theoretically closed. However, the airways do not close all at once but rather in a staggered sequence, starting with the bases and moving up to the apexes. There is general agreement that if the volume at which airways closure first becomes manifest is higher than it should be for that particular patient, then there is an abnormality or disease in the small airways. In other words, the small airways are closing prematurely at a higher lung volume, giving rise to an elevated closing volume.

Another study—it's new to us but it's been done in Europe for a number of years--is very interesting and of particular interest to occupational medicine. In this study you don't just look at the pulmonary function of a subject sitting in the pulmonary function lab. Instead, you attempt to provoke abnormalities in a subject by exposing him to increasing concentrations of a bronchoconstrictive aerosol—histamine, methacholine and carbachol are most commonly used—and observe the effect of the agent and its concentration on his pulmonary mechanics. The asthmatic displays hyperactivity to the bronchoconstrictor; no one knows what gives the asthmatic that particular proclivity, but we do know that it is possible to induce temporary airway hyperreactivty by histamine challenge.

One drug that is noted for this phenomenon is toluene diisocyanate (TDI); it induces an asthma-like disease in persons who have no asthma history. It would be interesting to know if these subjects had normal histamine reactivity prior to their TDI exposure; in other words, is theirs truly acquired or does TDI bring out a latent tendency. On the other hand, if TDI exposure is discontinued, will these subjects return to a state of normal histamine reactivity? I don't know.

Woodworkers—ie, those exposed to red cedar dust in particular, possibly due to the plicatic acid in the wood—develop enhanced responsiveness to histamine as well as wheezing. After a fairly prolonged withdrawal from exposure, the histamine reactivity returns to normal. In this particular case an industrial exposure can engender a rather prolonged, yet potentially reversible, bronchoconstrictive activity. It might be very interesting to carry out such studies in cotton workers. This is a new approach to pulmonary function—airways function in particular—to quantitate response to provocative tests; I think it's an area that should be of great interest to industrial and occupational physicians who have these kinds of patients.

In the case of cigarette smoking, there is evidence that continued smoking will lead to the progression of abnormal pulmonary function at a more rapid rate than that associated solely with aging. Sir Charles Fletcher in England has led a team of epidemiologists and physicians who have pretty well established that the relationship between cigarette smoking and the development of obstructive lung disease is probably correct. He has further shown that if a cigarette smoker with well-established obstructive lung disease stops smoking, the rate of decline of his pulmonary function reverts to the normal slope; he may, therefore, prolong his useful working life out to age 60 or 65 before there is severe symptomatology and disability. I don't know if there is similar evidence for other potentially toxic agents. For instance, does it make any difference to stop exposure if you have pneumoconiosis with micronodulation and hardly any detectable change in pulmonary function? Again, I'm not sure. The whole field of

epidemiology requires cooperative studies and complicated methodology, which should be of interest to occupational physicians who have access to patients with chemical exposure.

In addition to its manifest advantages, exercise imposes an automatic drive to the respiratory and circulatory systems, which overrides psychologic factors that are so frequently confusing at rest. Exercise testing also provides useful information on the cardiovascular system as well as the respiratory system. And finally, it will indicate the limiting factor of the gas transport system.

In normal individuals the cardiovascular system limits the amount of oxygen that is circulated; thus, exercise in ordinary individuals improves the maximum oxygen consumption by increasing the stroke volume. The respiratory system is not a limiting factor for the ordinary individual; there is normally a nice linear relationship between ventilation and oxygen consumption, with a ratio of about 25:1. At rest the expired ventilation might be 6 liters per minute and the oxygen consumption 0.25 liter per minute thus ventilation:consumption = 24:1. At very heavy exercise, oxygen consumption may rise to 4 liters per minute whereas ventilation will be on the order of 100 liters per minute (again, a ratio of 25:1). The limiting factor is how much blood the heart can pump.

For the patient with obstructive lung disease, the situation is entirely different. These patients have a large fraction of their ventilation devoted to the non-gas exchanging parts of the lungs—ie, dead space ventilation; therefore, they have ratios that are closer to 40:1 or even 50:1. So the best that a poor devil can get out of his 40 liters a minute (ie, 40 breaths per minute at 1 L/breath—pretty good for a patient with obstructive lung disease) is 1 liter per minute of oxygen consumption. Mind you, walking at a normal pace on a level surface requires about 1 liter per minute of oxygen consumption. This man might, therefore, function as a bank president or a professor of medicine, but he certainly will not be able to function in a job where he has to move around, climb steps, etc.

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