The Challenge of Pulmonary Emphysema*

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I feel very privileged to be invited to be your Stoneburner Lecturer for this year. When I came to consider what I really wanted to say and what might interest people in widely different areas of medicine, there really was little choice. I perhaps can claim to be able to talk about emphysema from a rather broader standpoint than some other physicians. Not because I suffer from it, which is sometimes a good reason for talking about a disease, but because I have been trained both in England and in America, and the outlook on this disease has differed in Europe and in the States.

I started work on emphysema under the guidance of Dr. Christie in 1948, and in 1948 no one was much interested in the disease. I worked in Philadelphia in 1952, and there I gave a lecture on emphysema which was so controversial that it was disbelieved. The climate is different now, and I am talking about something of which most of you already know a fair amount. I have selected it as a topic because, whether you are a public health administrator, an internist, an allergist, an anesthetist, a surgeon, or even just a cigarette smoker, you should be interested in this condition.

One reason for contemporary concern about this disease is the considerable increase in the standardized mortality in the United States since 1945, for what physicians call on the death certificate "emphysema and fibrosis." The rate of increase of lung cancer has been similar, but since 1955 the diseases categorized as "emphysema" have been increasing more rapidly than has lung cancer. Over the same period, of course, mortality from tuberculosis has dipped. But the puzzle of nomenclature can be seen from the fact that bronchitis, as certified in the United States, has apparently *not* increased at all as a cause of mortality. If I were to show you a comparable graph from Europe, bronchitis would appear to have been the main cause of the increased mortality, and emphysema to a much smaller extent. I think we now realize that this is purely a semantic matter. Differences are not great between different industrialized communities in any of these diseases. It has been largely a matter of what the physician has called the condition he has looked at.

Certified causes of death at best are enigmatic and subject to shifting classification. The autopsy incidence of morphological emphysema as found in 138 random autopsies of inflated right lungs at the Massachusetts General Hospital in Boston has been reported by Dr. Thurlbeck. With reference to men only, and by dividing the autopsy population into 12 decades of age, the incidence of quite obvious morphological emphysema, excluding the little bits of emphysema at the apices and other minor forms, is striking. Once men are in the fifth and sixth decades, half of the random autopsy population shows considerable

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morphological emphysema. The same data in identical form are found in my own hospital in Montreal. So Montreal and Boston have a virtually identical autopsy incidence. Many pathologists have emphasized that the true incidence of emphysema can only be evaluated if the lungs are inflated. If they are fixed when collapsed, he will underestimate the incidence of this condition by at least half; and second, he will not be in a position to see, as I will show you in a few moments, its most damaging form. When the Massachusetts General Hospital group is broken down into categories, the male-female incidence is very different. In 59 females, 45 had no detectable morphological emphysema. In 79 males, only 25 had no emphysema. This reflects the 4:1 prevalence of emphysema in men.

There is another reason why this group of diseases has become very important. You will recall the major episode of smog in London in 1952, but you may have forgotten that this episode killed 4,000 people in 6 days. The smog lasted from December 2 until 14, approximately. London is so large that it took the Registrar General's figures 3 weeks to catch up on the surplus mortality of 4,000 people. So this is another reason why this disease has become important.

The First Challenge

The first of emphysema's three challenges is to understand not what the acute episode can do, which we know very well in a population with some lung disease, but to understand what lesser degrees of atmospheric pollution do, not over 6 days but over 20 years. I fancy it will be a long time before we understand the interrelationship between the acute sensational phenomenon and the chronic unsensational mortality.

I grew up in an era when chronic bronchitis did not have a respectable pathology. In *Boyd's Pathology* for 1947, chronic bronchitis was not a respectable disease. It was mainly an important complication of tuberculosis, or it was sometimes a nuisance in people with heart disease, but as a primary pathological entity it was little regarded. It is worth reminding you that now it has a highly respectable and extremely carefully quantified pathological existence, depending on hypertrophy of the bronchial mucous glands.

Now it is time we took up some practical examples of the kind of patient you deal with, and we deal with. I am not going out of my way to speak of the only case I have seen in 5 years that represented so and such. I am talking about things that I believe are extremely common. The first patient was a 66-year-old man who worked all his life with the Canadian Pacific Railway, largely an office job, and gave a rather clear history of some breath shortness for 2 years, some chronic cough for perhaps 15 years, not very much sputum, and an occasional episode of respiratory infection. He had dyspnea for 1 year. The function tests were done when he had one such episode while in another hospital. He had left that hospital diagnosed as having arteriosclerotic heart disease. They found an abnormal EKG, swollen ankles, liver two fingers-breadth's enlarged, and a normal chest film. When he was studied in the function lab in November, 1958, the findings were: a vital capacity about half of what it should be, a lung volume much bigger than it ought to be—gross over-inflation, and markedly uneven gas distribution. The F.E.V. (forced expiratory volume) should have been 70 L per minute, but was only 19 L per minute. His airflow rate should have been 3 L per second, but was only 0.2 L per second; therefore, he had terrible ventilatory obstruction. The transport of carbon monoxide, or the diffusing capacity, should have been about 14 and was 7 ml per minute per mm of Hg. This tells us either he had very uneven ventilation/perfusion distribution in the lung, which is commonly found, or he had a reduced surface area for gas exchange, or a thickened alveolar membrane. His arterial CO_2 tension was 56 mm of Hg, and the pH 7.4. You know, therefore, this was a chronic situation because he had brought his bicarbonate up to adjust the pH. The oxygen saturation was a little down. About 9 months after these tests were done he came to the hospital with a very severe pneumonia, and he died as a tracheotomy was being done. The whole lung section of this man showed black areas which look at a distance like currants. These are holes which

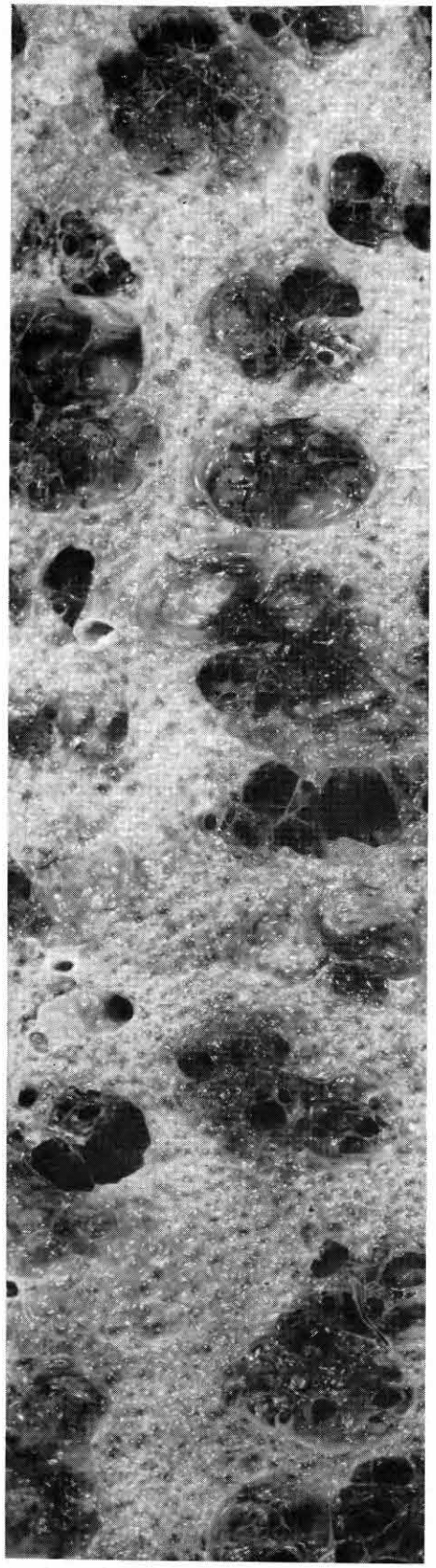


FIG. 1—Whole lung section from patient with centrilobular emphysema. Barium added for clearer demarcation.

go from the bottom to the top. They can be better shown if you outline the normal lung with barium (fig. 1). You are now close to what killed him, an example of severe widespread *centrilobular emphysema.* Each of these holes is roughly in the center of the lobule, and around it is an area of remaining normal alveoli. Virtually no lobule anywhere in either lung is spared. When this lung was allowed to collapse and sectioned in the normal way, it was reported as being normal. This lesion is exceedingly hard to see if you allow the lung to collapse. When these holes collapse, they approximate; the alveoli in between are normal, and the pathologist, by allowing the lung to collapse, has put himself in the worst possible position to see the lesion responsible for the disease. It was Gough in Cardiff who separated out this form of emphysema from others. He called it centrilobular emphysema. It is a good name and it was the first step forward in differentiating the pathology of this disease. One of the mysteries of emphysema is why this is such a lethal condition. The man I showed you had normal coronary arteries. His right ventricle was hypertrophied and not his left. (He had no arteriosclerotic heart disease although this had been diagnosed.) The only thing he died of was his severe CO_2 retention, which came upon him when he got pneumonia. However, he had had hypercapnia chronically for several years. The mystery is why this lesion, which can be quite minimal and unspectacular, so often gives rise to such severe blood gas disturbance.

The Second Challenge

This brings me to challenge number two; that is, to understand much more fully than we do at the moment the interrelationship between the structural changes, which the pathologist can picture, and the functional derangement responsible for the patient getting to the pathologist at all. This is something which many people are working on, and I can only present you with the problem and stimulate you to this extent: that there probably is no disease of an organ as big as the lung in which 75% of the alveoli can be intact, and yet in which you die from its consequences. There must be something then about the situation of this lesion in the middle of the lobule at the end of the bronchiole which is particularly harmful. It is remarkable that you cannot get along with 25% of your lung gone, if it happens that this destruction has occurred at the end of each terminal bronchiole. There was a period in which people used to chat about the tremendous reserve of the lung. They said you could take one lung out of a man and he could walk upstairs. That is fine. He can, but you punch out the center of each lobule and he has a very limited prognosis.

My second example is of a man about the same age as the previous man, to illustrate the clues you can get in life that the lesion is centrilobular emphysema. This man's pulmonary function tests were similar to those of the first patient, also showing severe ventilatory defect and hypercapnia (table 1). This man happens to still be alive. But I wanted to mention him because of his chest x-rays (fig. 2*a*). In the close-up of a carefully taken bronchogram, where plenty of time was allowed for the material to get into the pools, the major bronchi are fairly normal, but when it gets to the periphery it fills the pools. Simon and Reid have called these the "Lily of the Valley" sign, as the total picture is rather like a lily of the valley (fig. 2*b*). If you will take a lung with centrilobular emphysema and inject it in the autopsy room, you get a very similar picture. There is a hole, and furthermore there is considerable distortion of bronchi. The pool is filled at the end. So you can get a clue from bronchography. As I will show you in a moment, there is quite a different sort of emphysema which clinically may be almost indistinguishable from this one.

I am not going to talk in this lecture about details of technique of study, because these are of interest only to people working in this field. I am going to take a jump, however, to describe briefly a technique, because I want to show you what you may learn with it. I am not going into great detail. The point I want you to get is the result. The research group with whom I work has been busy for 4 years working on what may be learned by studying how the lung handles radioactive xenon. Xenon is a radioactive gas that you can breathe in very

safely, and measure from outside the chest what the lung is doing with it (fig. 3). A subject having such a study has behind him six scintillation counters, positioned in particular places in relation to the chest x-ray, three on one side and three on the other. With this method, you can get an idea of what each bit of the lung is doing; sometimes, as I will show you, with very surprising results. Then you can use it another way. You can dissolve xenon in saline and put it in the arm vein, and watch its clearance into lung alveoli. Of what gets to an alveolus, 95% will be cleared into the gas phase. I think it is quite obvious, without a lot of mathematics, that in this way you can quantify the ventilation which each lung zone is getting, and its blood distribution, as shown by this study. A complete examination of the kind I have very briefly described gives you rather less than one-half the radiation of a single chest film, so there is no serious radiation hazard in the use of this particular isotope.

Now I am going to show you what happens if you do this very simple experiment. It takes a few minutes of the patient's time and a lot of instrumentation, but you can learn a lot from it. Figure 4 shows the three counter positions on each side—six rings where the counters were positioned on this patient. The patient is a 46-year-old woman who had been com-

TABLE 1

Pulmonary function report of Mr. A. H. M., age 61, who had minimal sputum for 10 years (<10 cc per day) and dyspnea on exercise for 5 years.

Vital capacity	2.1 L
Functional residual capacity	5.4 L
Mixing efficiency	37%
Forced expiratory volume	19 L/min
Maximum midexpiratory flow rate	0.24 L/sec
Arterial	
pCO_2	58 mm Hg
pH	7.4
HCO'_3	34.5 mM/L
Resting CO diffusion	5.3 ml CO/min × mm Hg

FIG. 2—Chest x-ray (a) and bronchogram (b) of patient A. H. M.

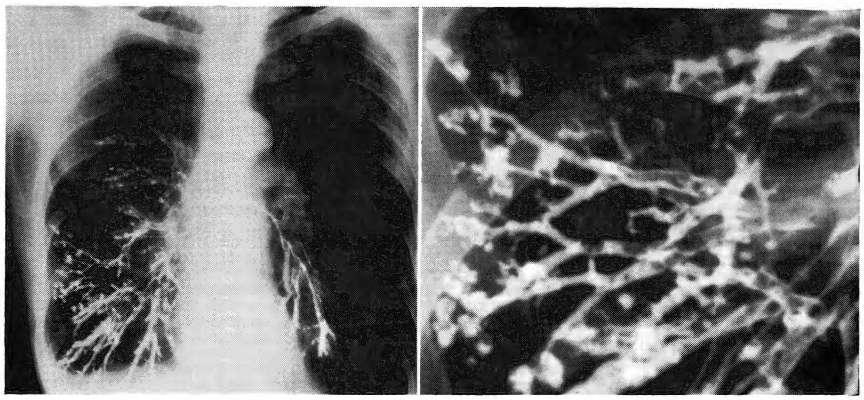


FIG. 4—Location of xenon counters in relation to chest film.

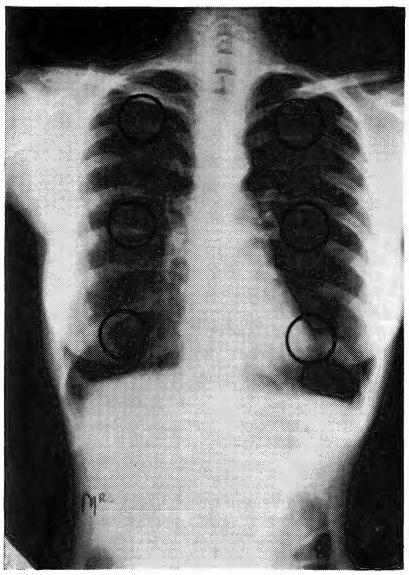
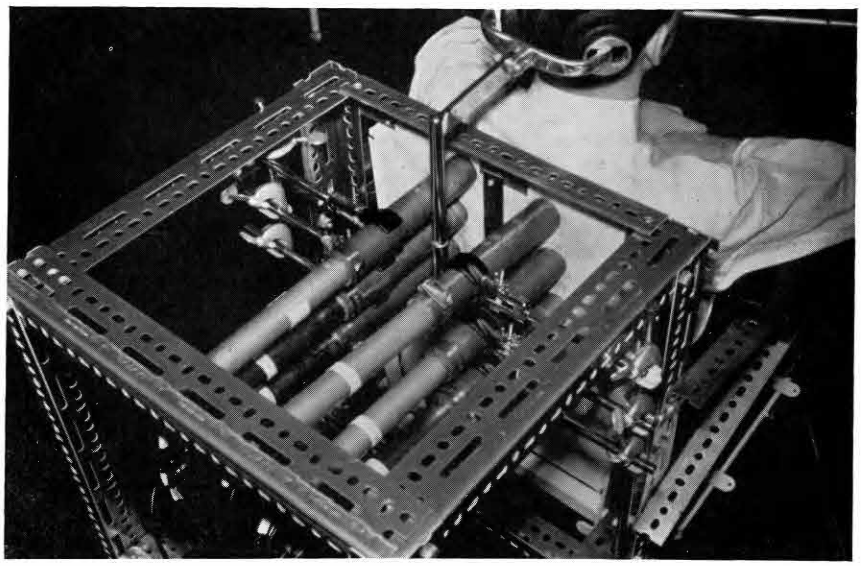


FIG. 3—Xenon scintillation counters in position.



plaining of breathlessness for 2 years. She had never smoked more than two cigarettes a day, and she never had any sputum, not even enough for a specimen. When she became dyspneic, no one really would believe her. The chest film was thought to be normal; physical examination of the heart was normal; the electrocardiogram was normal, and the blood pressure was normal. The only thing was her repeated statement that she was short of breath. The physical signs of the lungs were minimal. I think the only thing to make you suspicious was that the breath sounds were a little hard to hear in someone who was quite thin, as she weighed only about 105 pounds; she had lost a bit of weight. She was so incapacitated with dyspnea that she could cook standing up at the stove only with difficulty. Of course, the consequence of the combination of these findings is that you get referred to psychiatry. This she had for 6 months without noticeable benefits, except that her own views on psychiatrists became much better defined than they had been in the past!

Comparing predicted values for a woman of this size and age, as we have in three series of studies (table 2), you can see how consistent the pulmonary function findings were. Her vital capacity finally came down to 900 ml. The lung volume initially was not big, but became bigger. The total lung capacity was about correct. The gas distribution was very poor. Her ventilation was appalling, maximum midexpiratory flow rate, unaffected by bronchodilators, very bad indeed. The resting diffusing capacity was one-third normal, and on hyperventilation we managed to get a reading of 5.6. This told us that something was very badly wrong with distribution and gas exchange. However, there was no CO_2 retention, and the oxygen saturation was not strikingly abnormal. This is the kind of case one should show all residents from the start, since the arterial blood can be a bad indicator of pulmonary abnormality. You can be incapacitated for years and have normal arterial blood. It is often misused in practice by people who have not had enough experience with these diseases who place too much reliance on this as a test of function. It is very important to know it, but it is very important not to place too much dependence

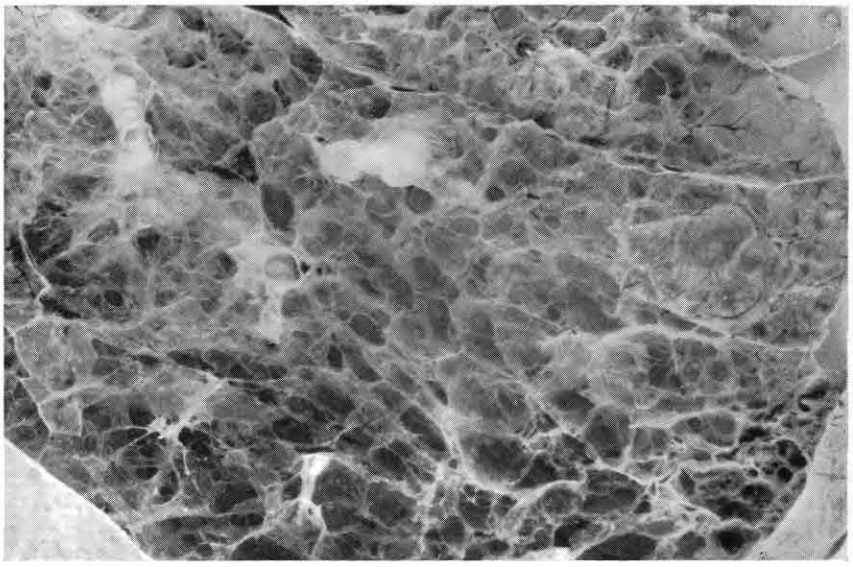


FIG. 5—Section of right lower lobe from patient L. B., showing panlobular emphysema.

TABLE 2

Pulmonary function report of Mrs. L. B., age 46. See Fig. 4 for x-ray.

	Predicted	April, 1958	May, 1960	April, 1961
Vital capacity (L)	2.8	1.3	1.1	0.9
Functional residual capacity (L)	2.6	2.6	3.1	3.5
Total lung capacity (L)	4.2	3.4	3.8	4.1
Mixing efficiency (%)	60	22	37	17
Forced expiratory volume$_{0.75}$ × 40 (indirect maximum breathing capacity) (L/min)	76	13	15	11
Maximum midexpiratory flow rate (L/sec)	3.7	0.17	0.20	0.15
Resting CO diffusion (ml/mm Hg × min)	14.0	4.6	4.3	4.4
Arterial blood				
pH	7.4	7.42	7.41	7.37
pCO_2 (mm Hg)	40	40	43	40
O_2 Hb saturation (%)	94	90	95	91

TABLE 3

Xenon^{133} distribution indices of Mrs. L. B.

	Right			Left		
	Upper	Mid	Lower	Upper	Mid	Lower
Tidal breath	139	33*	12*	88*	29*	106*
Predicted	58	70	87	57	70	91
Perfusion	249	69	61	278	79	86
Predicted	38	70	137	42	67	129

* Abnormally slow clearance observed from these sites.

on it. I will show you why this woman's arterial blood was normal, because it is quite clear when you see where the ventilation and perfusion were going, that they were fairly accurately matched. It is worth stressing that you can be in a desperate situation from a ventilation point of view for years, without any change in the arterial blood. This is another part of the challenge of relating structure to function.

(Table 3) Now, the xenon technique I showed you ends up as a series of numbers, and I am not going into the derivation of these numbers; we call them distribution indices. Their magnitude is not very important, but they tell us the amount of ventilation going into different portions of one lung and the other. What I want you to notice is that, on simple tidal breathing, instead of there being slightly more ventilation in the lower than the upper, on the right side there is a 10-fold difference, and perfusion distribution on the right side is also reduced. Almost all the perfusion is going through the upper part of the right lung, and much less in the lower. As you sit there, upright, which is the position she was studied in, you have about four times as much perfusion through the lower as the upper, so that in normal subjects the upper zone counter is about 60, and in her it was about 150. There is much better ventilation in the left lower zone. It is much better, in fact, than the left upper. However, we have the same imbalance of blood distribution, so that we now know what we never would have guessed from the chest film, let alone from the stethoscope, that the right lower zone has grossly impaired ventilation and perfusion. Presumably this is one of the main areas that has been destroyed. With these people who have been almost entirely incapacitated for years who are below the age of 50, we have on occasion taken out lobes that are doing nothing. Figure 5 shows what her right lower lobe looked like. This was a completely destroyed lobe. It was destroyed this time not in the centrilobular fashion showed in the first patient, but generally destroyed. This often is referred to as *panacinar or panlobular emphysema.* Already, therefore, we have made a differentiation. This is a youngish woman with very little smoking history, virtually no bronchitis, and at least one lobe of her lung, and probably the left lower as well, has been destroyed. At operation, the right upper looked normal, but I do not believe it was completely normal. We got marginal improvement in function by taking out the lower lobe. She was just able to go out and walk around the block. She is still alive. The blood gases are exactly as they always were. To return to that point about the blood gases, when one lobe, in her case the right upper, is getting most of the ventilation and most of the perfusion, there is no imbalance. The lung manages to keep the arterial blood normal, but half the right thorax is occupied by a lobe which is idle in terms of ventilation and perfusion. It was because we believed then, as we do now, that this destroyed lobe in some circumstances can interfere with the ventilation of the more normal lobe on the same side that the lobectomy was performed.

I wanted to show you a similar situation in a man of about the same age. If you study chest x-rays and tomograms carefully, by looking very carefully at the vasculature, you can get some idea where the blood is going. Figure 6 shows the angiogram of a patient in whom radioactive xenon studies were performed. These showed that the left upper zone was getting about five-sixths of both ventilation and perfusion. It was all he had to live on. He had been incapacitated for 4 years. The angiogram shows clearly the predominant perfusion of the left upper zone. If the pathological differentiation were as clear-cut as I have just made it, we would be on very good ground. But that isn't so. Often these two lesions occur together in the same lung. This is a commonplace finding when you look at autopsy material. Before one gets fancy about differential etiology, it is important to remember that whatever theory you construct may have to explain the simultaneous incidence of the two lesions in the same lung.

One of the points of the radioactive xenon technique is to see whether it can tell us not only what one lobe, or zone, is doing in relation to others, which is an interesting thing to know, but also whether, by some refinement or trick, it can tell us anything about the distribution of blood and gas oc-

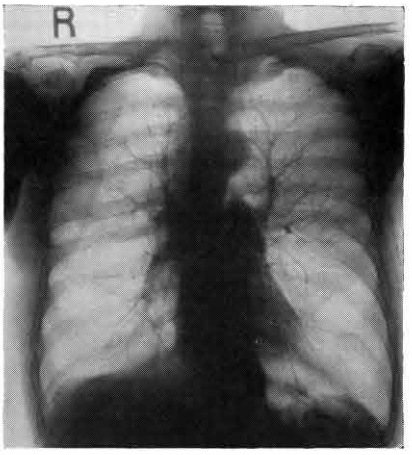


FIG. 6—Angiogram of patient with panlobular emphysema. The upper lobes are relatively spared.

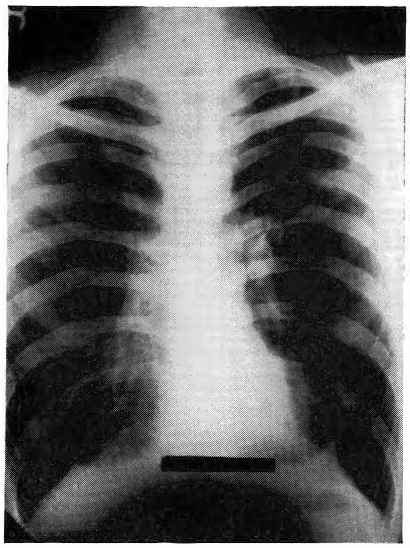


FIG. 7—Chest film of a young asthmatic. X-ray alone could lead to a mistaken diagnosis of emphysema.

curring within a specific zone. Although we have gone only a little way with this kind of differentiation, it is worth mentioning. We are trying to develop means of measuring effective ventilation within zones or counter fields, in the hope that differences may reflect varying pathological types of emphysema. We think this may become very important because it seems to us that the pattern of centrilobular emphysema usually has this kind of imbalance. This is the first clue we have had in 10 years of work that might get us closer to the differential function of these different types of emphysema.

The Third Challenge

Now, my third challenge in emphysema is, of course, to the clinician. It is to challenge him to be able to differentiate in life between bronchitis, asthma, and emphysema. It is really a challenge to get close to the morphology of the lung of the patient he is treating. In other words, how can he find out what the morphology was like, not merely afterward when we have the lung to look at, but during life? Most physicians would agree that this is very difficult. It is very difficult in the lung because the x-rays are, with some exceptions, of rather little value. The physical examination is almost worthless and is as often misleading in terms of differentiation as it is helpful. By that I mean, that if the chest is barrel-shaped, I still don't know what's happening to the lung underneath. Not only do I not know, but I know that *you* don't know, and no amount of talking on the chest contour in relation to lung morphology will convince me that you can do very well with a tape measure, or standing and looking at the plain x-ray film. The better pathologists you have, the worse you will find you are doing. One kind of x-ray is often diagnosed in x-ray departments as indicating emphysema. The one in figure 7 belongs to a radio weather forecaster, so that if I listen to the weather forecast in the morning at half-past seven, I can hear whether he's wheezing. He's a young man of 28. He has a clear history of allergy in the family, suffers from hay fever, and is an asthmatic; never very severe but never completely free of bronchospasm. The plain film could easily deceive a radiologist into thinking this might be destroyed lung. On examination in the pulmonary laboratory (table 4), he had an impaired vital capacity. His lung was somewhat over inflated, as the residual volume is a 1,300 ml too big. The ratio of residual volume to total lung volume, which some people like to think of as a measure of emphysema, was elevated. The gas distribution was poor, the ventilation was diminished, and the maximum midexpiratory flow rate was quite considerably down. The resting diffusing capacity, however, was above normal. When you see this phenomenon of a normal diffusing capacity by a steady-state method, you can go out on a limb and say you *never* have that kind of diffusing capacity when your lung parenchyma is destroyed. That is the only way you can really use it. When it's like this, regardless of how bad the ventilation is, regardless of how

TABLE 4

Pulmonary function report of Mr. F. E., age 28, who had spasmodic asthma. Blood gas tensions were normal. Xenon studies: slight prolongation of washin and washout in all zones; normal indices of perfusion and ventilation distribution; no disparity between clearance of "ventilated" and "perfused" lung.

	Predicted	Observed
Vital capacity (L)	5.6	3.4
Functional residual capacity (L)	4.2	3.8
Residual volume	2.0	3.3
Residual volume/total lung capacity (%)	26	49.5
Mixing efficiency (%)	65	34
Forced expiratory volume$_{0.75}$ × 40, (indirect maximum breathing capacity) (L/min)	140	83
Maximum midexpiratory flow rate (L/sec)	4.50	1.30
Resting CO diffusion (ml/min × mm Hg)	23.5	33.0

bad the gas distribution is, you'll never lose your money if you bet on a normal parenchyma. Of course such patients rarely get to pathology, so you don't win much because these asthmatics do not tend to die. But this tells you his lung parenchyma must be intact, regardless of what the x-ray department thinks. When you study such a man with a single breath of inspired xenon, you find that his regional gas distribution is normal. He has no gross change in perfusion distribution either. But when you study him on a steady state experiment, you find in this particular man that the right upper and lower zones have a very considerably impaired ventilation. I show him because I don't know why his asthma is not a uniform phenomenon. I don't know why it has singled out two zones, but this appears to be a common feature in asthmatics. It is important to stress that spasmodic asthma does not *of itself* give rise to emphysema. They are utterly and completely distinct phenomena. In terms of xenon distribution, asthma does not appear to cause the kind of gross upset of perfusion distribution you commonly see with a destroyed lobe, nor does it cause the imbalance between ventilation and perfusion clearance you may see in centrilobular emphysema. What it does cause is regional ventilation impairment without much change of perfusion. There is an upset of ventilation-perfusion distribution, but it is a consequence of the ventilation change, the perfusion being very much as normal.

In this differentiation between emphysema and asthma, there is one important bit of evidence I have not dwelt on or shown you anything about. That is, in emphysema, at a certain lung volume, which we'll say is 4.5 L, the transpulmonary pressure, or the pressure between the esophagus and the mouth, is much less negative than in normal people. Asthmatics, however, whether over or under 20, follow more or less the normal curve for lung recoil. If you destroy alveoli, you cut down the normal recoil of the lung, which is quite a useful way of knowing whether you are looking at an asthmatic lung with a normal recoil, or whether you're looking at one which has destroyed alveoli. This simple test is not used anything like enough, and we have evidence that it very rarely lets you down.

There must be 15 theories of the etiology in emphysema and you are quite entitled to take your pick among these. It is probably as good as anyone else's pick. But that is not really the question we can yet ask. We have to be sure we are looking at one condition. We have to be sure that we have refined our understanding of the relationship between the structural change, which the pathologists can show us, and the function defect, as far as we can. Only then can we talk meaningfully about differentiations in this disease in life. And when the practicing physician is faced with a man of 45 with a chronic cough and a good deal of dyspnea, he is challenged to predict what the lung is like. Until he seriously tries to do this, it's extraordinarily hard to realize how bad the methods are at his disposal to make any differentiation between bronchitis with airway obstruction, asthma with spasmodic airway obstruction, often chronic (both of those having an intact lung parenchyma), and the differing kinds of emphysema. Only if he is worrying about the vascular pattern of the lung, only if, with the support of the function lab, he is moving a little closer to excluding people from one or another category, can he really get a perception in his own mind of how good or bad he is at making this kind of clinical differentiation. This distinction is not merely of academic interest. It is absolutely cardinal in understanding the interrelationships of these diseases and guessing intelligently at their etiology. There is never any excuse for sloppy clinical thinking; there is surely every reason to encourage people to sharpen it to the maximum. The first thing you learn when you try to predict accurately the morphology of the lung in people, and follow them over a long period of time, is that in this main endeavor, we have hardly yet begun.

"It is surprising, perhaps, to realize how many people at one time or another exert some sort of medical function. The old-world grandmother who nursed a dozen cases of measles in her own children does not hesitate to make a diagnosis on her young grandchild, nor to tell her daughter precisely what to do. The arthritic may sing the praises of flannel cloths and goose-fat; the newspaper editor may freely recommend a "reducing diet," and the pharmacist a sleeping-pill or headache remedy. Laymen who give such advice are relying on experience. Often the advice seems to work, perhaps not perfectly, but at least to a gratifying degree.

"Many laymen have been extremely skilled in diagnosis and have achieved considerable therapeutic success. However, giving appropriate advice is only part of medical skill—an important practical part, to be sure, but still only a part. The layman can learn from experience what to do, but the physician must also know *why* he does what he does. He must know it in a manner quite detailed, clear and rational, organized and logical. It is this knowledge which sets off the physician from the layman . . . Aristotle made the distinction quite explicit, that almost anyone can learn procedure empirically, through rule of thumb, but whoever lays claim to scientific knowledge must know the reasons and the general principles."

Lester S. King, *The Growth of Medical Thought*. Chicago: The University of Chicago Press, 1963, pp. 1–2.