Dr. Mack: Chronic cor pulmonale or pulmonary heart disease has become increasingly important recently. We are recognizing many more cases now than in the past not only because of better diagnostic methods, but because we are acquiring an increasing population of patients with marked reduction in pulmonary reserve who do not succumb to the first severe respiratory infection they encounter, but can survive repeated infection with the aid of modern therapy. Thus, they can live on to develop changes in the pulmonary circulation and the right ventricle we recognize as chronic cor pulmonale. This includes particularly patients with severe diffuse obstructive emphysema and patients who have survived chronic destructive pulmonary disease or resectional surgery. There is considerable disagreement about many of the aspects of chronic cor pulmonale and as you will see, even the definition is subject to some controversy. Chronic cor pulmonale may be defined as right ventricular hypertrophy due to disordered structure and/or function of the lungs or the pulmonary vessels. This excludes left ventricular failure, acquired valvular heart disease, and congenital heart disease. A classification of the various etiologies of cor pulmonale is not an academic matter, but is of practical importance since the success of therapy will depend upon the recognition, reversibility and treatment of the cause. A functional classification which I would like to present here groups the pulmonary conditions which may lead to the development of chronic cor pulmonale into three main categories:

1. The largest and the most important group includes those pulmonary diseases where severe diffuse obstructive emphysema has developed: chronic bronchitis, pulmonary tuberculosis (often complicated by extensive fibrosis, resectional or collapse surgery), fibrocystic disease of the pancreas, silicosis, and some types of diffuse sarcoidosis.

2. The second category includes those conditions where the main abnormality is chronic alveolar hypoventilation and where the changes in the lungs and the pulmonary vessels are minor or secondary. In chronic diffuse obstructive emphysema, chronic alveolar hypoventilation is also very important, but extensive anatomic changes in the lung are present. The chronic alveolar hypoventilation syndromes are usually due to severe and chronic defective function of the chest bellows and include: (a) massive bilateral pleural thickening; (b) such chronic neuromuscular disorders as severe residual respiratory paralysis following poliomyelitis, the muscular dystrophies, myasthenia gravis, and amyotrophic lateral sclerosis; (c) kyphoscoliosis; and (d) the cardiopulmonary syndrome associated with obesity (Pickwickian syndrome). Patients have also been described who demonstrate chronic alveolar hypoventilation, but who have normal chest bellows and normal lungs. They suffer from a diminished ventilatory drive from a damaged respiratory center and demonstrate a poor ventilatory response to exercise and inspired carbon dioxide. They develop hypoxemia, hypercapnia, secondary polycythemia, right ventricular hypertrophy and eventually failure.

3. The third category comprises those pulmonary diseases where the pathologic changes are localized mainly in or about the pulmonary vessels. Intraluminal processes include multiple recurrent small pulmonary emboli, thrombosis of the major pulmonary arteries, primary pulmonary hypertension, sickle cell anemia, pulmonary schistosomiasis, and diffuse pulmonary vasculitis. Extraluminal or perivascular involvement occurs in diseases associated with severe diffuse interstitial infiltration of the lungs with fibrous tissue, inflammatory cells, or neoplastic tissue: this includes Hamman-Rich syndrome, scleroderma, asbestosis, sarcoidosis, beryllium disease, histiocytosis-X, radiation fibrosis, diffuse interstitial fibrosis due to chronic obstruction of the pulmonary veins, endolymphatic carcinomatosis, etc. This is by no means a complete list of the causes of chronic cor pulmonale, but it demonstrates the type of functional classification of etiology which is most useful.

What is the pathogenesis of the right ventricular hypertrophy in the various pulmonary disorders? In category 1 (chronic diffuse obstructive emphysema) increased work of the right ventricle results from two major abnormalities: (1) an increased resistance to flow through the pulmonary circuit, and (2) an increase in cardiac output (inconstantly present). The increased resistance to flow in the pulmonary circuit results from an actual reduction in the size and distensibility of the pulmonary vascular bed, increased viscosity of the blood (if polycythemia is present), and possibly the development of intrapulmonary vascular shunts. Of great importance is the effect of hypoxia in increasing pulmonary vascular resistance by causing reversible vasoconstriction. Cardiac output may be increased, and in the face of an increased pulmonary resistance, throws a particularly heavy load on the right ventricle. In the group of conditions where chronic alveolar hypoventilation occurs because of defective chest bellows or an insensitive respiratory center, the lung is usually normal, although in some instances, as in kyphoscoliosis, there may be some restriction of the pulmonary vascular bed; the major abnormality is chronic alveolar hypoventilation with the production of hypoxia, hypercapnia, polycythemia, pulmonary hypertension, right ventricular hypertrophy and eventually cardiac failure. In the third category (pulmonary disease where the pathologic changes are predominantly vascular) the pathogenesis is somewhat more simple. There is a marked decrease in the size of the pulmonary vascular bed and a tremendous increase in resistance. The cardiac output cannot increase with exercise and is often lower than normal even at rest. Many of the clinical manifestations in this group are the result of a low or restricted cardiac output. You will note that it is in
categories 1 and 2 (chronic diffuse obstructive emphysema and the chronic alveolar hypoventilation syndromes) that hypoxemia and hypercapnia play an important role in pathogenesis; it is in these two groups that polycythemia frequently develops and where an increased cardiac output may be present. In these two groups, pulmonary arterial pressures are elevated, but usually not to very high levels. Oxygen therapy may be required in these two categories, but always with caution because of the danger of respiratory depression; mechanical respiratory aids may be necessary. In the third category (pulmonary disease where the pathologic changes are predominantly vascular), there is a high output load on the right ventricle. This is the group (especially where the processes are intraluminal) where the pulmonary arterial pressure may reach a very high level, often approaching the systemic arterial pressure. These patients often demonstrate very little hypoxia or hypercapnia at rest, although this may develop upon exercise. In this group, oxygen may be administered freely whenever necessary without fear of respiratory depression and carbon dioxide narcosis. While this outline will serve as an introduction, it may also help to demonstrate areas in which there is not complete agreement. Dr. Mattingly, how do you feel about the definition of chronic cor pulmonale, or the term itself?

Dr. Mattingly: Perhaps I will do nothing more than just confuse the issue, but since you ask for differences of opinion, I shall state that I have long ceased to use the term cor pulmonale in medical records and writings except to put it in parentheses. I admit that this is, in part, a campaign in teaching graduate and undergraduate medical students to be specific in terms they use and to get away from the teaching of syndrome medicine which I detest in many respects. So my desire to drop the term cor pulmonale may be just a personal whim. Secondly, I also like to spell things in good English rather than in Latin as we used to practice in writing prescriptions. These are some of the minor reasons, although they may not be good ones. I shall now state more specific reasons for using other definitions and other classifications. Before we can discuss this, we have to agree that we are dealing with the same groups of patients, that is, individuals with diseases or abnormalities that originate in the lungs or involve the lungs and which in turn produce myocardial insufficiency by virtue of these lesions which do not start primarily in the heart. On this, I think we agree. Unless we do agree on this basic concept, we are talking about two different groups of conditions. For instance: if we just "lump" into this group all conditions which involve the pulmonary system and the cardiovascular system, we would include all cardiovascular diseases. Yet, certainly a lesion such as mitral stenosis, in which the symptomatology is primarily pulmonary, is certainly a basic cardiac disease and not one that would be classified as cor pulmonale. To discuss this group, we will have to discuss those conditions that begin with lesions in the pulmonary system and secondarily affect the heart. If I speak about the same group, then in what different way may I decide to define or classify these? Well, it would be better to classify them on the basis of some common etiologic factor, some common type of pathogenesis or on the basis of similar abnormalities. It has already been stated, and I agree, that the etiology, the pathogenesis, as well as the manifestations of these pulmonary diseases cover a very wide spectrum and therefore, no one term could certainly cover them from the standpoint of etiology or pathogenesis. However, there are certain manifestations and objective findings that occur common to all these numerous conditions. One of these findings is that of right ventricular hypertrophy and I think the common factor which precedes right ventricular hypertrophy in every instance is pulmonary hypertension. The pattern of that hypertension, its characteristics or severity, would differ in chronic emphysema with complicating pulmonary heart
disease where you are primarily dealing with one type of pulmonary parenchymal disease from that in obstructive vascular lesions where it has a more malignant form. However, I do not think we can mention any of these pulmonary conditions which result in so-called cor pulmonale in which there is not an abnormality of the pulmonary artery pressure either at rest or with exercise or both. This seems to be the common objective finding that is present in all. Secondly, we, as practitioners of medicine, and our medical students today thoroughly understand the concept of systemic hypertension where we have patients with easily recognizable persistent hypertension who do not as yet have left ventricular hypertrophy or myocardial insufficiency. We classify these individuals as having hypertensive vascular disease. Now, when they progress and develop left ventricular hypertrophy and then symptoms of myocardial insufficiency, we call them hypertensive cardiovascular disease. Why can’t we apply the same terminology and definition to those diseases in which pulmonary hypertension is the problem? Using this, we would then simply have two conditions: (1) *pulmonary hypertensive vascular disease*, to identify those conditions in which pulmonary hypertension exists as a result of some disease or abnormality in the pulmonary system which includes all the ones we mentioned which have not yet progressed to the point where it has produced right ventricular hypertrophy or dilatation and failure; we like and use the second term: (2) *pulmonary hypertensive cardiovascular disease* when it progresses further with right ventricular hypertrophy and failure. Each of these in turn may be divided into primary and secondary types. Contrary to systemic hypertension where primary hypertension constitutes the largest bulk in the pulmonary group, primary is the smaller and the secondary types are the larger. I have a better understanding of the problem when these terms are used. For example, when we say a patient has emphysema with secondary pulmonary hypertensive or pulmonary hypertensive cardiovascular disease, I know then his pulmonary disease has gone to the point of producing pulmonary hypertension and/or right ventricular hypertrophy and failure. Likewise, the present situation in which one uses the term “cor pulmonale” to refer to all cardiac failures due to pulmonary diseases is somewhat similar to that of previous years when the term “Bright’s Disease” was used to identify all patients found to have left ventricular enlargement, heart failure and proteinuria. Sir Clifford Albutt was one of the first clinicians to point out to us that there were some patients with accentuation of the second aortic sound, big hearts without proteinuria. He designated this condition “essential hyperpiesis or hypertension.” Following the development of the use of a blood pressure apparatus for measuring systemic blood pressure, clinicians ceased to pay attention to accentuation of the second aortic sound, but recognize systemic hypertension by simply taking the blood pressure. Today, without a simple clinical method of quickly measuring the pulmonary blood pressure, we are in the same predicament with respect to recognition of pulmonary hypertension resulting from pulmonary disease.

Dr. Mack: Thank you, Dr. Mattingly. Dr. Anderson, would you like to add something to the discussion of the definition?

Dr. Anderson: I have no argument with the term cor pulmonale other than to agree that it lacks specificity. It is a pleasant term to say. I don’t think what we say here today is going to eliminate its general usage. I agree with Dr. Mattingly that the comparison of pulmonary hypertension to systemic hypertension is an excellent one, but it is probably going to be difficult to convert the whole medical profession to this concept. One point which should be emphasized, however, is that chronic cor pulmonale is not a disease entity. It’s really a symptom complex. We are not saying much more when we use this term than when we say right heart failure. Consequently, when we use this term we must
include other descriptive words, at least in our written diagnoses. It has been proposed that in addition to using the term, "chronic cor pulmonale," we should include with it our concept of the etiologic factors, the functional factors, and also the structural changes that are pertinent in the individual case. I'd like to make a plea for the inclusion of these pertinent descriptive additions when we use the term cor pulmonale rather than merely presenting cor pulmonale as one disease process. This emphasizes what has already been pointed out by Dr. Mack that cor pulmonale is not a single type of illness, but is one which has many facets in etiology and one in which, because of these facets, the clinical syndrome which develops in the course of these patients' illness may be quite different even though the end result may be quite similar.

**Dr. Mack:** Thank you, Dr. Anderson. In the pathogenesis of chronic cor pulmonale, particularly the type associated with chronic diffuse obstructive emphysema, there have been varying reports as to the magnitude of the cardiac output in these patients. What happens to the cardiac output during a period of marked deterioration in the presence of acute infection when the patient is critically ill, and what happens to the cardiac output after satisfactory treatment? Dr. Goldberg, would you tell us about the various factors influencing the cardiac output in chronic cor pulmonale?

**Dr. Goldberg:** The cardiac output in chronic pulmonary disease, particularly chronic pulmonary emphysema, has been the subject of much study and controversy. The cardiac output, I might say at the outset, has been reported in all ranges from elevated above to below normal. I think that a consideration of the factors concerned with the cardiac output in chronic pulmonary disease is essential for an understanding of this variability. First, it has been shown that the cardiac output is elevated in patients with chronic pulmonary emphysema of the obstructive type in which there is hypoxia. It has been pointed out that the cardiac output is increased in these people and perhaps implied that polycythemia and increased blood volume have a part to play. Hence, we see there are at least two factors that are concerned with the increase in the cardiac output in patients with pulmonary emphysema - hypoxia and polycythemia. Increased work of breathing, frequently present, places a further demand for oxygen consumption and hence an increase in cardiac output. Exercise causes an increase in cardiac output. It is true that the rise in cardiac output may be limited in these people, i.e., less than would be expected in normal individuals, but the output still goes up in the absence of failure. When these patients develop infections with fever, this again adds another factor demanding an increased blood supply, and hence an increase in the cardiac output. I would like to point out that there have been other studies which show that the cardiac output may be normal or below normal in chronic pulmonary emphysema, despite the presence of rather severe hypoxia. I think it's important to know in which stage of the disease we find the patient. If the patient has mild pulmonary emphysema with little or no hypoxia, he may have a normal cardiac output. If he is in the end stages of his disease with congestive failure, he will have a low cardiac output. If the individual is in between and he has hypoxia with polycythemia, the cardiac output may be high. He may maintain this high output even in congestive failure in the early stages. The level of cardiac output prior to the time when failure supervenes will determine the level it will be at the time of failure. Hence, it may be either above or below the normal values in congestive failure. We can see, therefore, there is quite a bit of variability in the cardiac output in patients with chronic pulmonary disease.

**Dr. Mack:** To summarize briefly: if we consider all of those factors which tend to produce an increase in the cardiac output in patients with severe diffuse obstructive emphysema in one column and the factors that tend to reduce cardiac output in the
other, we can then see how these factors interact to produce the cardiac output measured in a particular patient at a particular time in a particular stage of his disease. This explains well the apparent discrepancies in the reported studies. Now, turning to some of the more clinical aspects of the problem of chronic cor pulmonale: how does one make a diagnosis of chronic cor pulmonale? It is very difficult to recognize the presence of early right ventricular hypertrophy in the absence of dilatation. Nevertheless, there are certain findings that are helpful; some will permit us to suspect the presence of right ventricular hypertrophy, others will make us certain of its presence. How often will we need machines to evaluate this problem? Dr. Mattingly, I wonder if you could discuss some of the clinical manifestations of chronic cor pulmonale.

**Dr. Mattingly:** As you have stated, the symptomatology is rather difficult to evaluate and although you have spoken of the use of machines, some of these machines or laboratory procedures are not simple and one cannot routinely catheterize every patient to determine his pulmonary pressure. Therefore, the means for getting answers are not such that can be applied with reasonable ease. First, a word about symptoms. One of the difficult problems of evaluating symptoms is one that occurs in mitral stenosis. Here, the lesion is primarily cardiac, yet the symptomatology is pulmonary and again you have pulmonary conditions that eventually end in cardiac failure with cardiac symptoms predominating. There is a mixture of the symptoms that is not easy to differentiate one from the other. I think if we do pay attention to symptoms, we have to pay attention to them with certain degrees of suspicion. For example, fatigue is a symptom that is common to the type of heart failure we see secondary to pulmonary diseases, yet fatigue is a manifestation of pulmonary disease itself, especially chronic emphysema. So this will have a different meaning when we are evaluating a patient who has no symptoms of emphysema or pulmonary insufficiency, but who otherwise may be developing early right heart failure from vascular lesions in the lung. Also, fatigue may be very important in the early diagnosis of primary pulmonary hypertension or some of the other vascular lesions without the parenchymal lesions and without the problems of pulmonary insufficiency being manifested through ordinary tests. Other symptoms that are helpful, but which are present in both is respiratory distress and here we have one feature that can help us. Let us evaluate a patient who has chronic pulmonary disease due to emphysema. His distress occurs with exercise and when he is quiet he may lie flat without orthopnea and distress in spite of the fact that he has severe pulmonary difficulties, yet once he starts to develop right heart failure, he may now get his orthopnea and his respiratory distress at rest. This often gives us one of the early clues of the development of frank failure. While dyspnea is usually a common symptom, it is different in its characteristics when cardiac involvement intervenes. There are certain other symptoms that may help us, one of which has been mentioned here where there are lesions that involve cardiac output, that is, the ones where high pulmonary resistance is present, that interfere with the development of increasing cardiac output under exertion to the extent that these patients develop dizziness and syncope from cerebral ischemia as the result of an insufficient cardiac output on demand. On the other hand, reduced cardiac output may be related to arrhythmias that develop in these patients on the basis of myocardial ischemia associated with interference with coronary circulation secondary to a reduced and fixed cardiac output in the latter stages from either occlusive vascular lesions or from chronic parenchymal pulmonary lesions. As far as objective findings are concerned, we have mentioned two of the most persistently found abnormalities—that of elevation of the pulmonary artery pressure and right ventricular hypertrophy. **If we**
could put a blood pressure cuff around the hilum of a lung with the same ease with which we can put a blood pressure cuff around the arm, we would have no difficulty in recognizing early pulmonary hypertension. Remember, the present situation is exactly where we were in recognizing systemic hypertension prior to the time of the development of the blood pressure cuff. We had to depend on the presence of an accentuated second aortic sound and evidence of left ventricular hypertrophy as evidence of hypertension. Otherwise, we had to guess that a patient had elevated systemic pressure unless we used Hale's method of putting a cannula in a big artery. Now, can we recognize pulmonary hypertension in its early stages by means other than the catheter? In certain types of pulmonary lesions we can. If the individual does not have a distorted thoracic cage from emphysema, kyphoscoliosis of the spine or other abnormality, one can usually detect an abnormal accentuation of the second heart sound as heard or palpated at the pulmonary valve area. This is an important clue to the possibility of pulmonary hypertension. In addition to this, in those with an essentially normal chest one can often detect early right ventricular hypertrophy by a systolic lift along the second, third or fourth left parasternal borders due to the hypertrophy of the right ventricle. You can make these two observations during the routine examination of the patient. The presence of severe emphysema may deter us from using these methods of simple examination to the fullest extent, but other procedures are helpful. The radiologic demonstration of right ventricular enlargement which has been discussed by others is very difficult until you begin to get dilatation along with hypertrophy. It is aided, however, by taking lateral views as well as PA views in the routine cardiac roentgenograms. The electrocardiogram is most helpful in identifying early right ventricular hypertrophy. For example, in performing annual physical examinations of military personnel, we have had the opportunity to pick up several individuals each year who were suspected of having pulmonary hypertension by paying attention to auscultatory characteristics of the second pulmonary sound and by the electrocardiographic abnormalities. Subsequent right heart catheterizations and careful evaluations of the screened suspects resulted in the recognition of a sizable group of primary and secondary types of pulmonary hypertension prior to the development of heart failure. Thus, simple screening procedures are helpful in the recognition of pulmonary hypertension.

Dr. Mack: Thank you, Dr. Mattingly. You have demonstrated the difficulties of the early clinical recognition of chronic cor pulmonale. Coming back to the use of various mechanical aids, I wonder if Dr. Anderson would tell us about the use of chest fluoroscopy, roentgenograms, and the electrocardiogram in the diagnosis of chronic cor pulmonale.

Dr. Anderson: I would first like to comment on a few points of diagnosis by clinical means along the lines that Dr. Mattingly has described and then perhaps enlarge a bit on the value of the x-ray and the electrocardiogram. I feel that one of the more important phases of clinical management and clinical diagnosis of chronic cor pulmonale is the role of preventive medicine and preventive treatment. These are patients who usually are not consulting the physician for the first time when they have developed their right ventricular failure. They are people who have been frequenting our offices for months and years with pulmonary symptoms. In many cases, I think we should be very careful in our observation of these patients to be aware of the subtle findings that Dr. Mattingly has pointed out which may indicate we are not doing a good enough job if we are to prevent them from developing congestive heart failure. At times, we can recognize in the examining room the phase with increased cardiac output. Characteristically in the stage when the emphysematous patient has increased cardiac output, we can be aware
of a bounding pulse, and that his hands are warm in contrast to the patient who has incipient left ventricular failure. If his chest isn’t too malformed by virtue of his emphysema, we can quite often be aware of hyperactivity of the precordium. This obviously isn’t possible in a big barrel-chested individual. Sometimes when a patient presents with chronic dyspnea and complains of orthopnea, we’re in a dilemma because some patients with pulmonary emphysema have orthopnea without actually having developed symptoms of congestive failure. As a consequence of bronchospasm, they will often sit up at night and wheeze a bit and cough up a mucus plug and thus may be suspected of having left ventricular failure. There’s a difficulty, at least on my part, in being able to recognize which is the predominant factor in many of these patients because they are in an older age group and may have systemic hypertension. I find that at times one of the best devices to determine whether congestive failure is entering into the picture is to institute a trial of cardiac therapy which often will help resolve the question as to whether they are basically suffering with their pulmonary emphysematous and bronchitic disease or whether they are in truth having symptoms of left ventricular failure.

The roentgenographic diagnosis of chronic cor pulmonale also presents difficulties. One point which should be emphasized at the outset is that it is rare for the patient with pulmonary emphysema to have the usual evidence of cardiac enlargement on his chest x-ray film. Frequently because the thoracic cage is large, the heart shadow appears quite small. Here the importance of having serial x-ray examinations is an obvious advantage. The availability of films on patients six months or a year before to serve as controls when one sees widening of the cardiac silhouette will be of tremendous help. As Dr. Mattingly pointed out, the first x-ray evidence of pulmonary hypertension often is an enlargement of the main pulmonary artery and its immediate branches. This is best observed in the right anterior oblique position or in the lateral rather than in the straight PA position. Relatively clear peripheral lung fields in the presence of increased size of the central pulmonary vessels is also evidence of pulmonary hypertension in these patients just as it is for the patient who has a congenital cardiac defect and who has developed severe pulmonary hypertension. The electrocardiogram has not been very helpful to me in diagnosing the occurrence of pulmonary hypertension in the patient who has pulmonary emphysema with incipient cor pulmonale because the changes which we so often see are often seen over a period of years before we have evidence of the onset of cor pulmonale. These changes include the development of the so-called P-pulmonale pattern made up of rather tall P waves in leads 2 and 3 and AVF, a clockwise rotation of the heart on its longitudinal axis so that there is a production of right axis deviation, and also a shift of the transition zone to the left in the precordial leads with persistence of an S wave in V5 and V6. I think, as Dr. Mattingly has already suggested, that the electrocardiogram is of much greater diagnostic value in the group of patients who have primarily pulmonary vascular disease, that is, pulmonary arterial obstructive disease. Here one is more likely to find the pattern of pressure overloading developing over the right ventricle with the development of a QR deflection or a tall R deflection in the right precordial leads together often with secondary T wave inversions in the right precordial leads. These findings suggest to us that we are getting into a situation where the right ventricle may be going to fail.

Dr. Mack: Thank you, Dr. Anderson. As you can see, the modalities of examination as described give us evidence of cor pulmonale only when it is rather far advanced. It should be emphasized that a high index of suspicion in a patient being followed with chronic pulmonary disease in any of the categories described will permit us to make the diagnosis earlier. Availability of previous x-ray films, the compari-
son of serial electrocardiograms with the development of certain positional changes even in absence of a typical ventricular hypertrophy pattern may all be very helpful. The development of blood-gas abnormalities often indicates impending right heart failure. A rising hematocrit may be a very simple and very useful way of predicting congestive heart failure; when a patient with chronic pulmonary disease develops polycythemia, right ventricular hypertrophy is almost always present. Dr. Goldberg has made some observations that may afford us the earliest evidence in a living patient that chronic cor pulmonale is present. This involves the use of the intracardiac catheter.

**Dr. Goldberg:** You have heard that the physical findings, electrocardiograms and x-ray films of the chest provide us with a certain amount of suspicion that a patient may have cor pulmonale. I think we have to get back to the definition and realize that the crux of this diagnosis rests upon the demonstration of right ventricular hypertrophy or dilatation or both. As you have heard, these people may have long-standing hypertension in the pulmonary circuit with very little change in the heart size and with no specific changes on the electrocardiogram. I think that if we agree that cor pulmonale is heart disease secondary to lung disease, then, as Dr. Mattingly said earlier, the forerunner of hypertrophy of the right heart is pulmonary hypertension. It has been shown that the important load leading to hypertrophy of the ventricles is a pressure load. The right heart is notoriously adapted for volume loads. As you know, in atrial septal defect, the pressure in the pulmonary circuit and right heart doesn’t rise until late in the disease. Although the output of the right heart is three or four times normal, we may not demonstrate any hypertrophy of this chamber. When the pulmonary artery pressure rises, however, this chamber hypertrophies. It is felt that hypertrophy results from increased work, particularly pressure load. Hence, it becomes important to try to demonstrate pulmonary hypertension, as Dr. Mattingly said, and the only way you can do it is to place a catheter into the pulmonary artery. Unfortunately, not everybody can have a pulmonary artery catheterization, but certainly we can screen out patients and suspect the condition from our clinical findings that have been just alluded to. I think the most important statement we heard today was made by Dr. Anderson who said that it is much more satisfying to prevent this condition than to treat it, and I think that if we keep our eyes open and appreciate that some of the things we see in these patients with chronic pulmonary disease can produce cor pulmonale, that we make every effort to prevent it. I would like to point out one thing and that is in the normal individual the pulmonary artery pressure changes vary little with an increase in oxygen consumption. In the patient with chronic pulmonary disease, the pulmonary circuit may respond to exercise in several ways. He may have such minimal disease that there is no change in his pulmonary artery pressure with exercise. On the other hand, the patient with pulmonary hypertension at rest probably has some degree of right ventricular hypertrophy. Yet, I wonder if we use that same analogy with the systemic circuit. Do we consider every patient that has essential hypertension as having hypertensive heart disease? I think they probably have some left ventricular hypertrophy. Do we refer to those asymptomatic patients who have normal sized hearts and normal electrocardiograms with systemic hypertension as having hypertensive heart disease? I would like to hear Dr. Mattingly on this. Certainly it is reasonable to assume that if the pulmonary hypertension has been longstanding, right ventricular hypertrophy is present and even though there has been no clinical manifestation of right heart failure, cor pulmonale already exists. However, I think there is one absolute hemodynamic finding this is consistent with hypertrophy. Hypertrophy is difficult to detect from the x-ray film or electrocardiogram. We can’t
measure the thickness of the right ventricle; angiocardiography is of little or no value. If the patient has a high end diastolic pressure in the right ventricle, I think this represents ventricular hypertrophy. We have satisfied ourselves that this is the case in the left side for example, in aortic stenosis. As you know, the diastolic pressure in the right ventricle is 0 to 5 mm. Hg normally. We have seen patients develop a high end diastolic pressure, i.e., up to 10 mm. Hg or above, during exercise. I think that these patients have right ventricular hypertrophy. Now you may say the elevated diastolic pressure represents heart failure. I don't think so. I think it is an expression of hypertrophy and the resistance that the thickened right ventricle is offering to filling. To understand this, one must consider the pressure-volume curve of the ventricle. The pressure varies as the volume of the chamber in a curvilinear fashion. This is the classic Frank-Starling curve. When hypertrophy supervenes, this curve shifts to the left and tends to become more linear. This means that the chamber has become more rigid and offers more resistance to filling during diastole, i.e., the pressure in the ventricle is higher for any given volume contained during diastole. This does not mean the ventricle has failed. As I said, we have an analogous situation in the left heart in patients with aortic stenosis. The latter have been found to have high end diastolic pressures in the left ventricle which they have been able to tolerate for years without any evidence of clinical heart failure. As long as a patient can increase his cardiac output during exercise, he is on the ascending limb of Starling's curve, and not in heart failure.

Dr. Mack: Thank you, Dr. Goldberg. You have shown us that by the time an elevated end-diastolic pressure is found in the right ventricle on catheterization, one would be correct in assuming that right ventricular hypertrophy is present. I am not sure this is an extremely early finding, however. I think actual failure or considerable hypertrophy must be present. It is difficult for me to conceive that an increase in the thickness of the right ventricle of only 2 mm. could produce this. Are we justified in considering the right ventricular wall a passive structure during diastole, behaving according to simple rules of elasticity? There has been a tendency to place the whole emphasis of the pathogenesis of the right ventricular hypertrophy on pulmonary hypertension. This is one of the reasons why I prefer the terms pulmonary heart disease or cor pulmonale to pulmonary hypertensive heart disease. I think in the last large category where pulmonary pathologic changes are predominantly vascular or perivascular, a marked increased resistance to the blood flow through the lung is indeed the major factor in increasing the load on the right ventricle and leading to right ventricular hypertrophy and failure. In chronic diffuse obstructive emphysema or in chronic alveolar hypventilation syndromes, it is not pulmonary hypertension alone which causes all the changes in the right ventricle. It is very hard for me to see that the magnitude of the pressure elevation found in the lesser circulation could alone lead to the degree of hypertrophy we see, and to the manifest congestive heart failure. There are many other causal factors in the hypoxic type of chronic cor pulmonale. There is chronic hypoxia, and frequently polycythemia with accompanying increased blood volume. All these factors act with increased pulmonary vascular resistance to produce the clinical and anatomic picture of pulmonary heart disease.

Dr. Goldberg: What Dr. Mack said is to be well taken. It is true that patients with chronic pulmonary emphysema may not have a severe degree of pulmonary hypertension. If Dr. Mack will go back to a chapter he wrote some years ago, he will recall that it is the acute episodes which occur in the course of a patient's illness that throws him into heart failure. That is to say, pulmonary infection and other illnesses will suddenly place a load upon the right heart. It is during this time that the
patient goes into failure. Studies by the Bellevue group have shown that patients with chronic pulmonary disease in right heart failure who are definitely on the descending limb of Starling's curve and who respond to acute digitalization all have pulmonary hypertension. It is true that in the early and even late stages of the disease these patients may not have severe pulmonary hypertension, but can develop rather severe degrees of pulmonary hypertension during exercise and during period of stress. Right heart failure by the existing clinical and hemodynamic criteria may not be present. There are patients in this group with high right ventricular diastolic pressures who can increase their cardiac output during stress. By definition, these patients are not in failure. I think you are right in questioning the definition of heart failure and pulmonary hypertensive disease. However, when patients with chronic pulmonary disease go into heart failure, they do so because of pulmonary hypertension. This may occur acutely due to infection, atelectasis, pulmonary infarction etc. In acute pulmonary embolism, the pulmonary arterial pressure just prior to the accident may be normal. When the right ventricle is presented suddenly with an acute rise in the pulmonary circuit, the right heart fails. It does so because the right ventricle, unlike the left, is not adapted to this kind of work load.

Dr. Mack: Dr. Mattingly, would you have some comments on the priority of pulmonary hypertension?

Dr. Mattingly: First, I would like to answer Dr. Goldberg's question on hypertensive vascular disease as being a correct terminology for all people who have hypertension without right ventricular hypertrophy. Obviously, we can have physiologic hypertrophy as a transitory mechanism and not produce hypertrophy and I think we can have pulmonary hypertension transiently and physiologically without disease much as we have transient elevated systemic blood pressure. If a patient has pulmonary hypertension for a considerable period of time, even though he may be totally asymptomatic and these patients die in an accident or from non-cardiac causes, one often finds their heart has increased in size and by weight, and yet was not shown to be enlarged on x-ray examination or electrocardiogram. Again, it is a concentric type of hypertrophy one doesn't easily recognize. Now, as to the statement that pulmonary hypertension is not important because pulmonary hypertension is not high in chronic pulmonary disease, I think the exact analogy exists in types of systemic hypertension. For example, the patient who we see terminally with hypertensive cardiovascular disease ending with left ventricular hypertrophy and failure and in whom we recognize old chronic parenchymatous renal disease as the etiology often does not present a clinical picture of severe systemic hypertension during life. On the other hand, where we have a patient with a necrotizing arteritis involving the kidney (malignant hypertension) or renovascular hypertension associated with unilateral renal vascular lesions, the systemic pressure is very high and is an important clinical feature during life. This is similar to the picture of pulmonary hypertension associated with vascular lesions of the lung. There are many of these patients with chronic renal diseases who die with tremendous hypertrophy of the left heart and left ventricular failure who were observed to have only a mild degree of systemic hypertension, often only diastolic hypertension. I think a similar situation occurs in chronic pulmonary disease of long-standing where a mild degree of pulmonary hypertension over years has resulted in right ventricular hypertrophy and failure, but you no longer have persistent or severe pulmonary hypertension. Likewise, as Dr. Goldberg has mentioned, acute stresses bring this out very clearly. Such a chronic patient with an essentially normal resting pulmonary pressure may develop acute elevation of pulmonary pressure with dilated right heart and tricuspid incompetency with the com-
plication of pulmonary infection or some other form of stress.

Dr. Mack: I would like to say that the example you just quoted of patients with rather mild hypertension and chronic renal disease who develop hypertensive heart disease and left ventricular failure is very good analogy because it parallels in some ways the changes in chronic diffuse obstructive emphysema. However, such patients exhibit more than systemic hypertension: they often have a low serum albumin and considerable sodium and water retention. There is no question about the importance of the pulmonary hypertension, but the associated combined abnormalities are equally significant.

I would like to close with several statements about treatment. In all instances, treatment of chronic cor pulmonale will be determined by the cause. Treatment of the manifestations of cardiac insufficiency will be ineffective unless one can reverse at least some of the aberrations of pulmonary structure or function. In chronic diffuse obstructive emphysema, intense treatment of the bronchopulmonary disease to improve ventilation, reduce hypoxia, and increase the size of the pulmonary vascular bed is necessary if specific cardiac therapy is to be effective. In the chronic alveolar hypoventilation syndromes, improvement of alveolar ventilation is the goal of treatment, often necessitating ventilatory aids. In the cardiopulmonary syndrome of obesity, weight reduction may be sufficient. Where the chronic cor pulmonale is due to predominant vascular involvement of the lungs, improvement of the right heart failure will result only if the specific perivascular infiltrations can be reduced by treatment.

---

BRONCHOESOPHAGOSCOPY WITH ANESTHESIA AND MUSCLE RELAXANTS

Bronchoesophagoscopy under anesthesia with the use of short-action muscle relaxants is suggested by the author. The study was carried out under light barbiturate and gas anesthesia with a short-action muscle relaxant and persistent controlled oxygen ventilation in apnea. Lungs have been ventilated through a narrow intubation tube inserted into the trachea up to the bifurcation. To prevent hypercapnia each ten minutes during the investigation, the injection of the relaxant was discontinued and the patient was allowed to breathe with large amounts of oxygen during eight to ten minutes; then the relaxant was injected again and the investigation continued, and so on. This method provides: (1) surface anesthesia, (2) areflexia on the part of the tracheobronchial tree and esophagus, (3) maximal relaxation of the body muscles in maintenance of the gaseous metabolism close to normality. (4) easier technique of endoscopy.


---

THE HUMORAL TRANSPORT OF BERYLLIUM

The immunologic study evaluated by the allergic and anaphylactoid reaction, as well as by the precipitin reaction, failed to show the development of antigenic property by the beryllium-incubated sera. The results were consistent with the assumption that no significant extracellular beryllium-protein interaction takes place in vivo. The dialysis experiment, likewise, demonstrated that presence or absence of protein in the medium has no effect on the diffusion rate of added beryllium at a concentration level of 10^4 Mo./liter. The ultracentrifugal experiment, in addition to corroborating these results by means of demonstrating identical sedimentation patterns of protein at widely different beryllium concentrations (10^2 - 10^6 Mo./liter), as well as in the total absence of beryllium, also showed that the added beryllium is separable into at least two distinct fractions. Both possessed well-defined migration rates in the ultracentrifugal field, indicating that ionic beryllium in excess of 0.01 micromM/ml was no longer present. A form having a density greater than 1.06 appeared to be the orthophosphate. Another form, having a density of about 1.04, seemed to be the hydroxide. The amount of this latter precipitate was minute as long as total BE++ concentration did not exceed 10^3 Mol. An association of beryllium with the serum proteins was not demonstrated.

These results suggest that precipitation of orthophosphate and hydroxide is the form of existence and mode of transport of beryllium in body fluids, including blood and, presumably, lymph, and the interstitial juices of pulmonary tissue.