Papers and Originals**THE LUNGS IN MITRAL STENOSIS***

BY

W. MELVILLE ARNOTT, T.D., M.D., F.R.C.P.*William Withering Professor of Medicine in the University of Birmingham*

The most striking feature of mid-twentieth-century medicine is the extent to which the whole complex field of Man in his reaction to disease has been invaded by scientific thought. It is now universally accepted that an important way to the prevention and control of disease is by a study of its effects in terms of quantitative chemistry and physics. Medicine therefore becomes an applied science, immensely complex and baffling, but susceptible to interpretation in the same terms and according to the same laws that govern the mechanical, electrical, and chemical machines we make. There is this difference, however, that instead of devising the machine we are presented with the working model and asked to construct a picture of it by analysis of its structure and its functions and the reactions of these to forces whose quality and intensity we know and can, perhaps, regulate.

The study of what has been called the "phenomenology" of disease, so brilliantly exploited by Harvey, has been nevertheless a major pursuit during only the last 30 years or so—in fact, only intensively since the last war. Up till then the tendency was to define syndromes and pictures of what were regarded as specific diseases in terms of patterns of symptoms and signs in much the same way as Linnaeus taught us the various classes of the botanical world. Phenomenology concerns itself with seeking explanations in physical, chemical, and mathematical terms of these symptoms and signs. There are many examples of how knowledge gained in this way has uncovered fundamental mechanisms of disease, leading to recognition of causes and methods of diagnosis and effective treatment.

The relationship between the heart and lungs is structurally and functionally very close, a circumstance which, although obvious, seems to have had little influence on clinical knowledge and practice until comparatively recently. Cardiologists have not, in general, concerned themselves with the complexities of pulmonary function in health and disease, and chest physicians have not until recently taken an interest in cardiology. The chief reason for this unfortunate dichotomy has been the dominant influence of tuberculosis in chest medicine. This disease being infectious has led to the intellectual as well as physical isolation of disordered lung function. To me it is now inconceivable that one can specialize in a scientific sense in "pure" cardiology as opposed to "pure" chest diseases. Useful investigation and competent clinical practice demand their fusion.

Classification of Heart Disease

A simple classification of heart disease is into intrinsic, in the sense of those conditions, like coronary disease and the various forms of myocarditis, which interfere with the contractile power of the heart either by disordering the rhythm or by diminishing the force of contraction. Other forms of intrinsic heart disease, such as rheumatism and syphilis, damage essentially by narrowing valve orifices or

distorting the cusps so as to destroy the unidirectional quality of the valve. Extrinsic heart disease, on the other hand, occurs when the heart is subjected to demands for excessive work principally as the result of increased peripheral resistance either in the systemic circulation as in hypertension or in the pulmonary circulation as in the many varieties of lung disease which reduce the pulmonary vascular bed.

All forms of organic heart disease, whatever be their origin, eventually cause disability because of loss of pumping efficiency. The result of this reduced cardiac output is that the pattern of regional distribution of blood flow is altered in order that territories of high survival value such as the cerebral circulation are maintained at the expense of reduction of blood flow to other territories such as the splanchnic, renal, and limb. Another outstanding effect is elevation of pressure in the vascular areas upstream from the defective chamber of the heart or the partially obstructed vascular territory. From these two mechanisms of altered territorial blood flow and zones of raised pressure stem the principal clinical disturbances of heart disease.

It is not surprising that the principal functional abnormalities of mitral stenosis are referable not only to the pulmonary circulation but to the whole function and structure of the lungs. If one approached the syndrome of mitral stenosis without reference to the abnormal shape, the disordered rhythm, and the characteristic noises of the heart, one would regard the whole condition as a pulmonary disorder. The patient's chief complaint is shortness of breath, particularly on exertion. There are a whole range of disordered respiratory mechanisms, and the most striking effect of the operation of valvotomy is to reduce the magnitude of these respiratory abnormalities. Furthermore, there are important structural changes in the lung which carry great physiological significance and which influence treatment.

Work in Birmingham

When, almost exactly 17 years ago, I was elected to the chair of medicine in the University of Birmingham I was asked about my research plans. I was no more specific than to state that I hoped to continue the study of the factors which govern pressure and flow in the vascular system in the various forms of cardio-respiratory disease. In this pursuit my department has met with some success. Why I can say this without risk of appearing to boast is because I myself have played the part of a non-playing manager concerning myself with the provision of facilities for the quantitative study of respiratory and cardiovascular function in the variety of patients who pass through a clinical unit which has some bias towards cardio-respiratory disease. The inspiration and work have come from a succession of able colleagues such as Kenneth Donald, George Whitfield, Owen Wade, John Bishop, Peter Harris, to mention only a few, with the able technical assistance of A. C. Pincock and the stimulating surgical collaboration

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of A. L. d'Abreu, J. L. Collis, and Leon Abrams, along with many other associates, particularly Donald Heath, of the department of pathology.

My colleagues have investigated many aspects of cardio-respiratory function in heart disease, principally mitral stenosis, and also in lung disease, especially chronic bronchitis and emphysema. These investigations have been the subject of many publications, including Professor Donald's (1959b) Bradshaw Lecture in 1958, my own Oliver Sharpey Lectures in 1954 (Arnott, 1955), and monographs by Harris and Heath (1962), and by Wade and Bishop (1962). It has been a rare pleasure to witness the evolution of these studies, and I propose in these two lectures to outline as simply as I can the effect on pulmonary function of mitral valve disease, drawing freely from the observations and deductions of my colleagues in Birmingham.

Damage to the mitral valve is the principal factor causing the disability of chronic rheumatic heart disease. Apart from disturbance of rhythm, such as atrial fibrillation, there is little evidence that the myocardium as a contractile machine is impaired. Indeed, there is ample evidence of its high efficiency in the way it increases and maintains over many years a much augmented load with little tendency to sudden arrest or ventricular fibrillation. The cardiac failure which eventually supervenes is due either to atrial fibrillation or—and this is more important—to the fact that the contractile power of the right ventricle, powerful as it is, cannot force an adequate amount of blood through the pulmonary circulation and on through the narrowed mitral valve. There is ample evidence that involuntary muscle increases its contractile force to match the resistance offered to it, constituting a sort of inversion of Newton's third law of dynamics so that to a "reaction there is an equal and opposite action." For a time this adaptation is rectilinear, but there comes a time when the response ceases to be simply proportional and the force of contraction fails to match the resistance.

During diastole the area of the mitral orifice is from 4 to 6 sq. cm. (Gorlin and Gorlin, 1951). As the normal valve is open for only about half the time, the velocity of flow must be approximately double the mean cardiac output. As flow is related approximately to the square of the area of the valve, pressure being constant, and as pressure is inversely related to the square of the area, there is a rapid build-up of pressure across the valve.

The resistance to the flow of blood is not a simple function of the area of the valve, as the stenosis causes turbulence which still further impedes the passage of blood into the left ventricle. The obvious effect of this obstruction at the mitral valve is to raise the left atrial mean pressure and mean pressures throughout the lung vasculature and in the right ventricle.

Pulmonary Blood Flow and Pressure

When the cardiac catheter was freely used to obtain samples of blood entering the pulmonary circulation and to measure pressures in the pulmonary artery it was soon found that the cardiac output was low and the pulmonary arterial pressure was high in mitral stenosis. Borden, Ebert, Wilson, and Wells (1949) studied 30 patients and found a good inverse correlation between pulmonary blood flow and pulmonary arterial pressure. That the pressure in the pulmonary artery was elevated in mitral stenosis had for long been inferred, as it is a self-evident result of the valvular stenosis, while the right ventricular hypertrophy combined with the tendency to atherosclerotic changes in the pulmonary artery constituted strong supporting

evidence. Cardiac catheterization has, however, revealed much detailed knowledge of the characteristics of pulmonary blood flow and pressure. When the catheter is advanced into the pulmonary circulation to the point where it plugs into a vessel of its own diameter the lumen is in direct communication with a vascular pool extending to the mitral valve, enabling the measurement of left atrial mean pressure (otherwise known as pulmonary capillary or pulmonary wedge pressure) (Hellems, Haynes, and Dexter, 1949).

In order to define the pressure/flow relationships of the pulmonary circulation in mitral stenosis the results of Donald, Wade, Bishop, and colleagues will be reviewed. These constitute the largest reported body of data on cardiac output and pulmonary vascular pressure. They have been accumulated under reasonably uniform conditions employing a standardized procedure of measuring cardiac output by the Fick method both at rest and during exercise, the intensity of which was indicated by the rate of oxygen uptake. Between 1953 and 1958 the Birmingham group studied 229 patients with rheumatic heart disease, 193 of whom had mitral stenosis without evidence of mitral incompetence or of other valvular lesions. In all these patients the clinical state was sufficiently disturbed to warrant consideration of mitral valvotomy. The clinical grades of 181 of these patients were assessed by the classification prepared by the New York Heart Association (1953), with the addition that grade III was subdivided into class A, in which the patient, despite slight discomfort in the normal activities of life, is able to walk a mile or more on the flat at his own speed and can climb stairs slowly without undue discomfort, and class B, in which the patient is capable only of the lightest of activity without discomfort and can walk only short distances on the flat without resting and has difficulty in going upstairs.

Although the mean resting cardiac index of 2.73 l./min./sq. m. is within the range reported for normal subjects, it is lower than the normal value found in our laboratory (Donald, Bishop, Cumming, and Wade, 1953). While the cardiac outputs of 2.80 and 2.98 l./min./sq. m. for grades I and II collectively and grade IIIA are of the same order as the mean for the whole group, the value of 2.57 for the aggregate of grades IIIB and IV suggests a possible correlation between cardiac output and degree of disability. It was found that these differences between the grades were in the main due to differing proportions of patients with sinus rhythm and atrial fibrillation. The 110 patients with sinus rhythm had a mean cardiac index of 3.02 as compared with a value of 2.31 for the 71 patients with atrial fibrillation. It is clear, therefore, that cardiac output in mitral stenosis is significantly reduced when atrial fibrillation is present and is in the low-normal range with sinus rhythm.

There is no doubt that the mean pulmonary arterial and "pulmonary wedge" pressures are grossly elevated in mitral stenosis and that this is associated with elevation of the pulmonary vascular resistance. The mean pulmonary artery pressure ranged from 32 mm. Hg in grades I and II to 53 in grades IIIB and IV, with an average of 48 for the whole group as compared with a range of 8 to 21 in normal people. The corresponding wedge pressures ranged from 23 to 31, with an average of 28, as compared with the normal range of 5 to 13.

A Significant Correlation

Bishop and Wade (1963) have made a detailed study by analysis of variance of the interrelationships of disability, cardiac output, and pulmonary vascular pressures in 168

of the patients with mitral stenosis in whom the data were quite complete. It was found that the pulmonary arterial mean pressures increased with increasing clinical disability. In each clinical grade there was no significant difference in pulmonary arterial mean pressure between those in sinus rhythm and those with atrial fibrillation.

There was a highly significant correlation between the pulmonary wedge pressure and the degree of disability.

This analysis did not find any significant correlation between the degree of reduction of cardiac output and the severity of the disability. As the fundamental basis of the clinical grading is the degree of dyspnoea it follows that this important essentially pulmonary symptom is not significantly related to cardiac output. Similarly, there was no significant relationship between age and cardiac output or pulmonary hypertension. There was, however, a slight inverse correlation between cardiac output and pulmonary artery pressure.

In summary, therefore, it may be concluded that these extensive observations show that cardiac output at rest is usually reduced in mitral stenosis, but not proportionately to the degree of disability, except that it is more marked where atrial fibrillation is present. On the other hand, the pulmonary pressures, both arterial and wedge, are markedly elevated in proportion to the disability—that is, to the dyspnoea. In those with grade IIIB and grade IV disability the mean pulmonary artery pressure is 53 mm. Hg, a value which is about 30 mm. greater than the normal.

Effect of Exercise

Studies of cardio-pulmonary haemodynamics in patients with mitral stenosis during light exercise have been in many ways much more revealing. This is only one example of the application to clinical medicine of the principle of "testing under load" which has for long been current in engineering practice. The importance of this is particularly obvious to us in Birmingham, as not far from the hospital there is a hill up which a constant stream of new automobiles undergo load-testing, and the rail journey to London by the Midland route passes the large test bed at Rugby, where locomotives are run at varying loads while attached to recording instruments.

An essential preliminary to this aspect of the study was to determine what constituted a steady state of exercise. To enable this to be done, Donald, Bishop, and Wade (1954) elaborated the Fick method to make it possible to follow rapid changes of blood-oxygen saturation and to measure expired air frequently and thus to estimate the cardiac output minute by minute during a five-minute period of supine exercise on a bicycle ergometer and for the first five minutes after exercise had finished. An initial step in this study was the application of a photometric method (M. Gatman, personal communication, 1952) of measuring rapidly the oxygen saturation of large numbers of blood samples (Wade, Bishop, Cumming, and Donald, 1953). Donald, Bishop, Cumming, and Wade (1955) reported the application of this technique to 16 normal people. The oxygen saturation of mixed venous blood fell when exercise began, and even when the exercise was heavy enough to consume oxygen at the rate of 1,047 ml./min./sq. m. a steady state was achieved in one and a half minutes and remained constant over the next three minutes if the steady exercise was continued. Indeed, in some subjects the constancy of the cardiac output was greater during exercise than at rest. The instability at rest is probably due to the influence of emotion on the cardiac output.

The exercising state overrides this instability. Wade and Bishop (1962) point out that this instability is analogous to the "hunting" of an engine in the absence of a load.

Cardiac Output

In healthy people the cardiac output rose with increases of activity of up to eight times the resting oxygen consumption. The relationship was linear in respect of the steady-state values. The mean pulmonary arterial pressure rose in all subjects. The average value at rest was 18 mm. Hg, while the average rise on exercise was 7 mm. Hg. The pulmonary arteriolar resistance did not change greatly on exercise, and the work of the right ventricle against pressure was found to rise roughly in proportion to the severity of the exercise performed. It was found that ventilation and the respiratory exchange ratio continued to change long after the cardiac output had reached a steady state. This suggests that control of the ventilation and of the circulation is not closely associated, a circumstance which has very interesting implications in respect of the fact that disordered ventilation is the principal physiological disturbance of mitral stenosis.

Hickam and Cargill (1948) were the first to report measurements of cardiac output by the Fick method during exercise in patients with mitral stenosis. They found that the cardiac output did not rise as much as in normal subjects and that the pressure in the pulmonary artery was high at rest and rose still further on exercise.

Applying the technique already outlined an analysis has been made of the Birmingham data in 156 patients with mitral stenosis. They exercised in the supine position on a bicycle ergometer for five minutes at the greatest intensity which could be attained without distress. Measurements were made of the cardiac output during the last minute of exercise, and pressure recordings were made immediately before and after this minute of observation. Nineteen patients had a normal response of cardiac output to exercise (0.6 to 0.65 l./100 ml./min. increase of oxygen uptake), 33 had a response which lay between 0.6 and 0.4 l./100 ml./min. uptake (category 1), 42 had outputs which were between 0.4 and 0.29 l./100 ml./min. uptake, and in 62 the output was less than 0.29 l./100 ml./min. oxygen consumption. An interesting comparison was made between the categories of depression of cardiac output and the clinical grades of severity. Rather surprisingly there was found to be a lack of correlation. Some patients with severe impairment of output response had little disability, while some with severe disability had a relatively normal cardiac output response. It is appropriate to emphasize again that, important as are the alterations in cardiac output, and inversely of arteriovenous oxygen difference, in mitral stenosis, these do not appear to play an important part in the causation of pulmonary disability, although they result in considerable reductions of blood flow to many regions, notably the splanchnic and renal.

As in the studies of resting patients it was found that atrial fibrillation was associated with severe impairment of cardiac output response. No fibrillating patient had a normal response, and in all but three of the 54 patients with this arrhythmia the response was less than 0.42/100 ml. uptake (categories 2 and 3).

Pulmonary Artery Pressures

Pulmonary artery mean pressures were greatly elevated during exercise, occasionally reaching or even exceeding systemic arterial pressures. Not only does the pulmonary

arterial pressure rise during exercise but the wedge pressure is also raised often to values above 40 mm. Hg, thus exceeding the plasma oncotic pressure of 25 mm. Hg.

It is therefore clear that during exercise there must be many occasions in the life of the patient with mitral stenosis when the pulmonary intracapillary pressures are higher than the level customarily regarded as producing an outward flow of fluid or oedema. That the tendency for this to occur is not greater than it is depends on a curious anomaly in the relationship between pulmonary arterial and capillary mean pressures. Whereas in resting patients the levels of these pressures have an approximately rectilinear relationship up to wedge pressures of around 25 mm. Hg, thereafter the wedge pressure rises much more slowly than the pulmonary arterial pressure. This means that at these high levels there must be a substantial pressure gradient between the pulmonary artery and the pulmonary veins. This phenomenon has given rise to the concept of a protective constriction of the small (1,000–100 μ) pulmonary arteries which prevents the pressure in the pulmonary capillaries from exceeding the osmotic pressure of the plasma and thus causing pulmonary oedema. A plot of the wedge pressures against pulmonary artery mean pressures does not suggest that at the 25-mm. level there is any sudden alteration in the shape of the relationship between the two pressures.

Some light on the development of the precapillary impedance is shed by a study of the structural changes which occur in the smaller pulmonary arteries as the result of the prolonged pulmonary venous hypertension caused by stenosis of the mitral valve. In this respect I must pay a tribute to the extensive and detailed work on the pulmonary blood-vessels of my senior colleague in Birmingham, Dr. Oscar Brenner. His publications in 1935 are the foundation of the modern work in this field.

Structural Changes in Small Lung Vessels

In view of the fact that the initial elevation of pressure in mitral stenosis occurs in the left atrium it is not surprising that the early morbid-histological changes are found in the pulmonary capillaries and in the alveolar walls. These consist of undue prominence of capillary and alveolar walls due to a slight diffuse connective-tissue overgrowth. There is also an abnormal amount of coagulated proteinoid material which has exuded through the capillary walls as the result of raised intracapillary pressure. Owing to the distension of the capillaries, red cells as well as fluid are extruded. These erythrocytes are ingested by macrophages which aggregate to form clumps in the lung parenchyma and at various points along the lines of lymphatic drainage, notably in the subpleural layers. The products of disintegration of haemoglobin constitute an irritant exciting an inflammatory reaction with connective-tissue formation and the deposition of haemosiderin, forming siderotic nodules. As this condition progresses there gradually develops what has been termed by Lendrum (1956) "siderofibrosis," which he compares with the similar nodules that are found in the spleen in cases of haemolytic anaemia.

The parenchyma of the lung shows the elastin and reticulin to be impregnated with siderotic material. Here and there crystalline forms of haemosiderin are to be seen and histiocytic reaction results in foreign-body giant cells. These changes may be particularly severe in the walls of the small pulmonary arteries which are actually encrusted with ferric deposits. This process of pulmonary haemosiderosis seems to be associated particularly with pulmonary

venous hypertension, which is, of course, an early and important stage in the generalized pulmonary hypertension of mitral stenosis. Various hypotheses have been advanced to explain this escape of red cells. The view that seems to fit the observed facts best is that of Paul Wood (1954), who believed the source to be pulmonary venules. It is common in the early stages of mitral stenosis at a time when the indurative changes around the small pulmonary venules have not yet advanced so far as to constitute a reinforcement against the bursting effects of surges of pulmonary venous hypertension. It certainly has no close correlation with the degree of pulmonary arterial hypertension.

During the phases of cardiac failure clumps of fibrin may form in the alveolar ducts; these presumably originate in collections of oedema fluid. Changes such as this must inevitably have a profound influence on respiratory function.

These various changes may well impair the ability of the pulmonary lymph channels to accommodate the greatly increased lymph flow of mitral stenosis, thus contributing to the generally oedematous state with excess of fluid in the connective-tissue planes and even filling alveoli and small air passages.

Eventually the lungs reach the stage of "brown induration" in which the parenchyma is extensively infiltrated with macrophages surrounding and spreading from haemorrhages. The alveolar spaces are filled with coagulated oedema fluid which has organized to form new connective tissue. In many areas the alveolar endothelium has undergone metaplasia, with the formation of cuboidal epithelium.

The pleura shows some diffuse with superimposed patchy thickening, particularly marked in the fissures. From time to time during the attacks of congestive cardiac failure there are pleural effusions, which because of the addition of blood from infarcts may be associated with a definite inflammatory reaction which aggravates pleural thickening. All these changes that have been detailed are essentially diffuse. In the later stages of mitral stenosis there frequently occur infarcts, some of which may be due to emboli from the fibrillating right atrium, while others may be due to thrombosis of small pulmonary arteries or of pulmonary veins. The effect of these infarcts is to indurate and distort the lung tissue still further.

Grades of Vascular Change

Important changes take place also in the small pulmonary arteries, especially those with a considerable amount of muscular tissue in their walls. These vary in size from 100 to 1,000 μ external diameter while pulmonary arterioles are less than 100 μ in size. In describing the changes in the vessels I will follow closely the descriptions of Harris and Heath (1962), who recognize three grades of vascular change as occurring commonly in mitral stenosis.

In grade 1 the media of the muscular pulmonary arteries is abnormally thick and may reach a size of 25% of the external diameter of the vessel. In the arterioles there is a definite muscular media interspersed between the well-defined internal and external elastic laminae. Arteriolar vessels as small as 30 μ in diameter may look like muscular arteries, contrasting with the normal pulmonary arteriole, which has no distinct medial coat except at its point of origin from the parent muscular artery. An exception to this generalization has to be made in respect of the region of the lingula where, even in the normal lung, pulmonary arterioles may be found with a muscular coat. Tissue from

the upper and lower lobes gives a more representative picture, but unfortunately these are not so readily accessible for purposes of biopsy.

Grade 2 is marked by prominent medial hypertrophy with the addition of well-defined cellular intimal proliferation, limited more or less to the smaller muscular pulmonary arteries in the 100–300 μ class and to the arterioles. There is no intimal reaction elsewhere in the pulmonary arterial vasculature. In some arterioles the vascular endothelial cells become rounded and form a prominent epithelium-like lining.

Grade 3 is, in general, the most severe grade of vascular change that is usually found in mitral stenosis, and is defined as the "stage of progressive fibrous vascular occlusion." The inception of this stage is marked by the development of cellular fibrous tissue between the media and the endothelial lining. Later there appear concentric or eccentric masses of fibrous tissue of less cellularity. Splitting of the internal elastic lamina occurs, and for a time elastic fibres can be recognized in the thickened subintimal layers; finally, however, the intimal fibrous tissue becomes quite hyaline. In this grade the media of the muscular arteries and arterioles displays the maximum degree of hypertrophy, reaching a thickness of as much as 30% of the diameter of the vessel. The hypertrophy of muscle in the media of the small pulmonary arteries is not limited to the circular fibres but is prominent in the longitudinal fasciculi. This was pointed out originally by Hubert Turnbull (1915), and has recently been described in detail by Heath (1963), who found well-developed hypertrophy of longitudinal muscle in the walls of pulmonary arteries not only in mitral stenosis but in other forms of pulmonary hypertension. Most of the intimal lesions develop first in the arterioles and small arteries (less than 300 μ). The changes found in the larger muscular pulmonary arteries are more atherosclerotic in nature than intinally fibrotic.

Relationship between Pressure and Structure

The relationship between the elevation of left atrial pressure in mitral stenosis and the development of these abnormalities of the pulmonary vasculature requires some analysis. The increased capillary blood volume is certainly due to raised intracapillary pressure. Although the capillary wall is not in itself a distensible structure, it is known that pulmonary capillary blood flow has a very wide range of adaptability, implying a large range of capacity, as the variations in flow are of much greater magnitude than the pressure changes. It is probable that these changes are mediated in the main by regulation of flow at the small muscular artery level, while the capacity of the capillary bed itself varies by alteration of the shape of the tubes, the cross-sectional profile of which can vary from that of an ellipse of virtually zero area to the maximum area when it is circular. This range can be exploited possibly by back pressure from the venous side.

Harris and Heath (1962) provide a lucid survey of the relationship between pressure and structure in the muscular pulmonary arteries. They start from the generalization that there is a relation between the structure of a blood-vessel and the pressure which exists within it over a prolonged period. This refers particularly to the muscular coat. The higher the intraluminal pressure, the greater the bulk of the muscle. This is seen well in the pulmonary artery itself, which at birth has a structure very similar to that of the aorta, both vessels having had the same pressure during intrauterine life. After birth the thickness of the

pulmonary arterial wall diminishes relative to that of the aorta in conformity with a mean pressure of only about one-quarter of that in the aorta. If, as in large left-to-right shunts, the pulmonary artery pressure remains similar to that in the aorta, then the pulmonary artery retains a muscular media of aortic size. The size of a muscle is related to the amount of work it does. If it is stimulated to contract more often or against greater resistance, or both together, then it hypertrophies and becomes a more powerful contractile machine.

In the case of the media of the smaller muscular pulmonary arteries the elevated left atrial pressure is present throughout the capillaries as an expanding force transmitted from the right ventricle through the arterial side of the pulmonary circulation. The media, therefore, in these small arteries is repeatedly subjected to abnormally high stretching forces which during exercise are of considerable magnitude. There is abundant evidence that quick stretching excites contraction in non-striated muscle. How this is mediated is not known, except that it is not dependent on any neural mechanism, being perfectly active in a fully cocaineized muscle strip. The development of medial hypertrophy therefore seems a logical consequence. The increased mass of the media implies a more powerful response to vasoconstrictive stimuli, so that these muscular arteries acquire an increasing share of the resistance offered to the pumping of blood from the right ventricle to the left ventricle. Furthermore, the medial constriction during surges of pulmonary arterial hypertension interposes a considerable pressure gradient between muscular pulmonary artery and capillary. The full force of the pulmonary artery pressure does not, therefore, bear on the capillaries. The development of this precapillary gradient has been called a "protective" mechanism; and indeed it may be so in that it breaks down part of the pressure surges of exercise and emotion. Presumably, however, any rise of precapillary pressure gradient serves only to increase the load on the right ventricle without increasing the gradient across the mitral orifice.

Intimal and Subintimal Changes

As we have seen, there are intimal and subintimal changes in muscular pulmonary arteries, arterioles, and capillaries. It is likely that these have their origin in the escape from the lumen of these vessels of proteinous oedema fluid or serum. One of the fundamental reactions of general pathology is that plasma protein, and of course haemoglobin itself, once outside its normal confines within blood-vessels, excites some degree of inflammatory response characterized by the laying down of new connective tissue of varying cellularity. Eppinger (1949) elaborated this theme and referred to "albuminuria into the tissue." An important effect of all this in these small pulmonary vessels is to narrow their lumen. This is particularly marked in the smaller muscular arteries and arterioles. Therefore when these contract under any stimulus the result is a quite excessive reduction in cross-sectional area with a profound influence on pressure, which at constant flow varies inversely as the square of the cross-sectional area. This is another factor tending to localize at the precapillary level a substantial part of the pressure gradient, which in mitral stenosis extends from the main pulmonary artery to the cavity of the left ventricle during diastole. It is likely that these vascular changes which result in the precapillary pressure gradient are due to the development of hypertrophy and narrowing of vascular channels.

It is only in the more pronounced stages of pulmonary hypertension in mitral stenosis that there is evidence of

this impedance between pulmonary arteries and capillaries. It is probably relevant to note that when pulmonary pressure rises to high levels within a period too short to allow of the development of these vascular changes there are frequently attacks of pulmonary oedema due, no doubt, to the fact that the capillary pressure is very high in the absence of a precapillary gradient. Such is illustrated by the pulmonary oedema of left ventricular failure, as in hypertensive heart failure or coronary disease, and by the liability to pulmonary oedema shown by young women with mitral stenosis who during pregnancy develop severe pulmonary hypertension as the result of the raised blood volume and cardiac output.

A consequence of the increase in amount of muscle in the walls of the pulmonary arteries is a greatly enhanced reactivity to a variety of stimuli. For instance, nearly every patient whose pulmonary arterial pressure was in the 50–59 mm. Hg level showed a substantial fall in pressure when acetylcholine was injected direct into the pulmonary artery, whereas the number who reacted in this way diminished sharply at lower levels of pulmonary hypertension and also at higher levels, owing presumably to the fact that at high levels the degree of damage to the vessel wall so stiffens it that it is incapable of widening even although the tone of the muscle is reduced (Harris, 1957). Similarly, the inhalation of pure oxygen causes a proportionately larger fall in pressure in patients with pulmonary hypertension than in normotensive people.

Effects on Lung Tissue

The picture then, so far as I have drawn it, is that of lungs subjected over years to raised pulmonary venous pressure with, in consequence, a progressive elevation of pressures back to the right ventricle and the development of changes in the walls of the vessels. As the condition advances the lungs are subjected to an increasing number of attacks of oedema with the escape of fluid and sometimes red cells not only into the alveolar spaces but into the walls of vessels, alveolar septa, pleural layers—indeed, throughout the entire structure of the lung. The result of this is the gradual coarsening of the lung tissue so that it becomes stiffer and heavier.

It is of some interest to consider the part played by an increased volume of blood in the pulmonary vessels as opposed to an increase of extravascular fluid and connective tissue. Kopelman and Lee (1951) measured the cardiac output, mean circulation time, intrathoracic or “central” blood volume, total blood volume, and vital capacity in groups of patients with congestive cardiac failure due to mitral stenosis and to left ventricular failure. These data were compared with measurements made on normal people and similar groups after recovery from cardiac failure. Whereas the intrathoracic blood volume was considerably increased in left ventricular failure and diminished somewhat after clinical improvement, in patients with mitral stenosis under similar conditions only a very slight increase in intrathoracic blood volume was found. Bates and his associates (1960) have, however, provided evidence that the pulmonary capillary blood volume is increased in mitral stenosis from a normal value of about 150 ml. to values of the order of 250 ml. Such a change, important as its implications are, is too small to be detectable by the methods of measuring intrathoracic blood volume. If the increased bulk of the lungs in mitral stenosis is not due to intravascular overfilling then it must be due to extravascular fluid and connective tissue.

Functional Respiratory Consequences of Mitral Stenosis

The changes described play havoc with pulmonary function, with the result that most patients with mitral stenosis reach a stage in which the most disabling clinical disturbances—for example, dyspnoea—are due to altered pulmonary function. It is now necessary to consider in detail the effect of these changes on the various mechanisms of pulmonary function.

Historically the magnitude of the divisions of lung volume is one of the oldest measurements to be made. Forty-five years ago Peabody and Wentworth (1917) found the vital capacity to be decreased below 90% of normal in 131 of their 156 unspecified cardiac patients. The reduction was greatest in those with uncompensated cardiac failure, and their working capacity and expectation of life decreased in proportion to the fall in their vital capacity. Twelve years ago we (Richards, Whitfield, Arnott, and Waterhouse, 1951) studied all divisions of lung volume in a group of “low output” cardiac-failure patients the majority of whom had mitral stenosis. The patients were divided into three groups based on the usual four grades of disability defined by the New York Heart Association.

In the first group, which comprised those with grade I and II disability, the most striking change was an increase in the functional residual capacity and residual volume and a decrease in the inspiratory capacity. What seemed to have happened was an elevation of the resting respiratory level. In the second group (grade III) the functional residual capacity and residual volume returned to normal, but there was an even greater reduction in the inspiratory capacity, with a marked reduction in the vital and total lung capacities. In those patients who had congestive failure (grade IV) there was a reduction in all divisions of lung volume except the residual volume, which retained its normal predicted size; there was thus an increase of the R.V./T.L.C. ratio. No satisfactory explanation of this curious sequence of changes has been advanced although it is clearly bound up with the physical changes which take place in the lung parenchyma as the result of pulmonary hypertension and all its consequences.

[The second lecture, with a list of references, will be published in our next issue.]

It is nearly 20 years since the first Ministry of Labour Industrial Rehabilitation Unit opened at Egham, and there are now 17 units at key points in all parts of Great Britain. These cater for men and women who, by the time their medical treatment for sickness or injury is completed, may have lost confidence in their ability to do a job or may need quite different work; some may have never worked at all. Two out of every three persons who come to the units do so on the recommendation of a hospital or their family doctor, and medical practitioners in all areas can recommend their patients for courses. Suitable cases can usually be admitted without undue delay. In order to ensure that the full extent of the facilities available is widely known, the Ministry has prepared a new leaflet designed particularly for the medical profession which explains how the units work. This leaflet, and a supplement describing the results obtained with people disabled by injury, or by medical causes such as bronchitis, psychiatric disorders, congenital disabilities, and heart and rheumatic diseases, is now being distributed. Practitioners may obtain further information from the Manager or Disablement Resettlement Officer at their local Employment Exchange, who can always arrange for a visit to the nearest unit. The work of the I.R.U. at Perivale has already been described in the *B.M.J.* (1961, 2, 1772).