Summary

A method of locating and demarcating brain tumours, using P^{32} and a Geiger-Müller probe counter, is described. It is a valuable additional aid to the surgeon at operation in selected cases, particularly in the taking of a small biopsy specimen through a burr-hole.

We are indebted to Dr. C. S. Gilbert, of the Christie Hospital, Manchester, for his assistance in starting this work and to Dr. Ralston Paterson for providing the isotope.

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DYNAMICS OF HEART FAILURE*

BY

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LECTURE II

Mitral Stenosis

The evolution of mitral stenosis shows a variety of reactions of considerable diversity and interest. The relation of the varied haemodynamic responses to different degrees of valvular obstruction and of associated mitral incompetence is not yet fully understood. A great many facts, however, have been collected, and these can be seen to fall into various patterns (Bayliss *et al.*, 1950a). In discussing pressures in the pulmonary artery in mitral stenosis it should be kept in mind that in normal subjects the lung vessels dilate to accommodate the increased blood flow of moderate exercise without any significant increase in pressure (Hickam and Cargill, 1948).

Some mitral stenoses are so mild as to cause little in the way of radiological signs, and many of these show an absence of any rise in pulmonary vascular pressures, at least at rest. More than half the patients, however, show elevation of pulmonary vascular pressures at rest and in a few pulmonary hypertension is extreme.

There is a well-recognized group of mitral stenotics with some associated mitral incompetence who have massive dilatation of the left auricle. There is little or no detectable enlargement of the pulmonary artery. Daley and Franks (1949) have shown that these patients may be astonishingly comfortable for many years and even for decades. On the radiological evidence of absent pulmonary artery enlargement they surmised that there was little pulmonary hypertension. This surmise

seems to be correct. In one example the pulmonary systolic pressure was 36 mm. Hg at rest, and the patient was capable of increasing her cardiac output from 3.8 to 6.2 litres a minute on effort. Although the pulmonary pressure rose *pari passu* (36 to 63 mm. Hg) with the cardiac output, it subsided very rapidly to nearly normal in a minute or two after the exercise was over. This contrasts with the reaction to effort in other mitral stenotics (cf. Fig. 8). The relative mildness of symptoms in this group is presumably related to the absence or transient nature of pulmonary vascular engorgement.

The auricle must hold the blood which flows into it while the ventricle is contracting. Opdyke *et al.* (1948) have shown that the left auricle is normally less distensible than the right. If the auricle is small the normal volume inflow will cause a considerable rise of pressure during the later part of ventricular systole, but if the chamber is greatly enlarged the pressure will not rise nearly so much (Dock, 1949). The same volume of blood can be accommodated in a large chamber with less linear stretching of its walls. It seems possible, therefore, that a very large auricle may permit the maintenance of a reasonable blood flow through the lungs at a lower pressure than would otherwise be required.

In another group of mitral stenotics the pulmonary artery is enlarged radiologically: the pressure in the pulmonary artery is moderately elevated at rest but rises to very high levels during exercise. It is an interesting point that the rise in pulmonary artery pressure which takes place during exercise in mitral stenosis in such patients is not associated with any significant increase in the cardiac output (Fig. 8). During exercise,

FIG. 8.—A woman aged 37 with mitral stenosis. Exercise increased the pulmonary arterial systolic pressure from 33 to 85 mm. Hg without significant cardiac output change.

therefore, resistance to blood flow through the lungs is considerably increased. The resistance might conceivably develop as a result of shorter diastolic time from the resulting tachycardia. Where diastole is short there is less time for the left auricle to empty into the left ventricle, and blood could collect in the left auricle until pressure was high enough to restore flow through the narrow valve in the limited diastolic time. The second alternative is that a vasoconstrictive reaction develops in the pulmonary arterioles. In favour of the latter hypothesis are the following facts:

(a) Acceleration of the heart by atropine in a few instances of mitral stenosis has not in our experience been accompanied by any significant rise in pulmonary arterial pressure (unpublished).

(b) Studies with the dye method on pulmonary blood volume show that this is not greater than normal during exercise (Ball *et al.*, 1952). If elevation of pulmonary vascular pressures had resulted from a rise of pressure in the left auricle an increased blood content of the lungs might be expected.

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(c) During exercise there is an increased pulmonary arteriolar resistance (Draper *et al.*, 1951), and Eliasch *et al.* (1952) have also shown that the pulmonary arterial pressure rises out of proportion to the pulmonary capillary pressure.

Another group of mitral stenotics have gross pulmonary hypertension. The pulmonary artery enlarges and great hypertrophy of the right ventricle becomes obvious on clinical and electrocardiographic examination. Pulmonary artery pressures are found to be elevated to systolic figures between 90 and 150 mm. Hg at rest. With the tachycardia of effort the mean pressure rises to still higher levels, although the systolic pressure may not rise any further. These extreme elevations of pressure, which may on occasion exceed the systemic arterial pressure in the same individual, can reasonably be ascribed only to an increased pulmonary arteriolar resistance. The studies of Dexter and his associates (1950) have shown that when pulmonary capillary pressure rises above 25 mm. Hg in mitral stenosis the pressure in the pulmonary arteries rises to very high levels, and it is clear that a considerable pressure gradient has developed between the main pulmonary artery and the capillaries (Table I*). Therefore the pulmonary arterioles are constricted. It is noteworthy that the pulmonary arterial pressure rises higher in these mitral stenotics than in any of the other common varieties of acquired heart disease (Table I).

These curious vascular reactions in the lung contrast sharply with those usually seen in left ventricular failure. In the latter, failure tends to be episodic, punctuated by dramatic attacks of orthopnoea, recovering with rest and digitalis. In mitral stenosis, by contrast, a chronic obstruction to flow is present at the mitral valve, and perhaps by its very persistence a variety of adaptations result. Enlargement of the left auricle to some extent buffers the effects of congestion and, alternatively, the development of gross pulmonary hypertension throws the load on to the right ventricle, with some resulting protection of the lung capillaries and pulmonary veins, especially during exercise. In the severe pulmonary hypertensive group, where the right ventricle takes the load, effort tolerance may remain remarkably good for some years. One such patient rejected for military service occupied himself as a lumberjack during the war; a second served in the strenuous African campaigns; while a third took part in athletic pursuits, and a few months before the finding of our record pulmonary arterial systolic pressure of 150 mm. Hg was playing club cricket. It is tempting to think that an intermediate stage in the development of persistent severe pulmonary hypertension in mitral stenosis is a phase of pulmonary arteriolar constriction in exercise. Gorlin *et al.* (1951), however, still find this matter debatable.

These unexpected varieties of vascular reaction in the lungs of mitral stenotics are now being supported by other evidence. The dye method of estimation of intrathoracic blood volume has shown no very significant increase in the pulmonary blood volume in mitral stenotics, as contrasted with patients in left ventricular failure, who do show the expected increased pulmonary blood volume (Kopelman and Lee, 1951). Angiography of the lung blood vessels in mitral stenosis has been shown by Goodwin *et al.* (1952) to demonstrate a well-defined narrowing of the pulmonary arteries in the neighbourhood of their tertiary divisions. Other factors involved in the reduction of the lung vascular bed may, of course, be pulmonary emboli, which are so frequent in the later stages of mitral stenosis. The lung arterioles show quite remarkable thickening and may even

show necrotizing arteriolitis in mitral stenosis with severe pulmonary hypertension (Larrabee *et al.*, 1949).

In the complex and variable haemodynamic circumstances of mitral stenosis it is not to be wondered at that responses to digitalization are more unreliable than those seen in left ventricular failure. Digitalis only occasionally produces a significant increase in the usually low cardiac output. Similarly, Howarth *et al.* (1947) showed that theophylline ethylenediamine, usually producing striking responses in left ventricular failure, had little effect on mitral stenotics. Digitalis can decrease ventricular tachycardia in auricular fibrillation, but it cannot strengthen a fibrillating auricle or change a sclerotic mitral buttonhole. With a fixed obstruction ahead, increasing the strength of a failing right ventricle may merely increase pulmonary vascular pressure with little clinical benefit. Fig. 9 shows the action of digoxin on a

FIG. 9.—Increase in right ventricular pulse pressure in mitral stenosis following digoxin: the cardiac output increase was slight and possibly pulmonary vascular resistance was increased.

hypodynamic right ventricle in mitral stenosis with a pronounced increase in pulse pressure. The rise in pulmonary pressure is out of proportion to the scarcely significant change in cardiac output, and examples like this cause us to wonder if a full dose of digoxin sometimes increases pulmonary vascular resistance in the same manner as it may increase systemic arterial pressure.

The effect of reduction of ventricular rate in auricular fibrillation in mitral stenosis could conceivably give more time for an engorged left auricle to empty through the narrow valve into the ventricle, and one or two instances in which digitalis was accompanied by significant cardiac output improvement had, in fact, been fibrillating with a rapid ventricular response. Kelly and Bayliss (1949), in a general study of the effects of rate reduction by digitalis, showed that reduction of rate played little part in cardiac output improvement, but their study included other varieties of heart failure as well as mitral stenosis, and in some of the latter the ventricular rate was not unduly rapid before digitalization.

Apart from a reduction of tachycardia, then, drug treatment of the chronic failure of mitral stenosis does not offer very much. It is for this reason that surgical help has been welcomed in recent years. Even though gross anatomical changes in the pulmonary arterioles may occur in the severe pulmonary hypertensive group, these are in no sense a bar to operation. Brock (1951) has been able to report that very high pulmonary arterial pressure can fall considerably after successful valvotomy. He gives an example in which pulmonary systolic pressure fell from 130 mm. Hg before operation to 40 mm. Hg after operation.

Tricuspid Insufficiency

When the right ventricle becomes grossly dilated, particularly in mitral stenosis, the tricuspid valve may become incompetent. In some instances it is also shrunk by the direct effect of rheumatic inflammation to the point of virtual disappearance as a functioning valve. Under these circumstances very gross pulsations take place during right ventricular systole in the central caval-auriculo-ventricular

*Table I appeared in the first lecture, which was published in last week's issue.

pool (Fig. 10). The veins beyond the nearest functioning venous valves collectively replace the auricle. Blood is held up in those veins during ventricular systole and then flows on into the central pool in diastole. We thus have the phenomenon of a higher mean pressure in the great veins near the heart than that recorded in the peripheral veins. In cases such as this the liver shares in the pulsation of the central venous pool. On occasion the downhill course of heart failure with pulmonary engorgement seems to be changed for the better by the development of tricuspid incompetence, for it is impossible for the right ventricle to maintain pulmonary engorgement with a large backward leak into the great veins. Adams recognized this safety-valve action of the tricuspid valve in 1828 (Rolleston, 1928).

The subject of Fig. 10, who had developed heart failure in pregnancy in 1939, created considerable alarm by the severity of her pulmonary oedema: following the pregnancy her activity was much restricted. By 1943, however, she had developed gross tricuspid incompetence with a pulsating liver; but there was no peripheral oedema, and the lung fields had cleared radiologically with disappearance of her dyspnoea. She remains remarkably well to-day, is able to do her housework, and has been capable of milder social activities over the last 10 years. The overworking right ventricle is clearly functioning very physiologically and a new equilibrium has been established.

Cossio and Perianes (1949) have actually recommended the creation of tricuspid valvular incompetence as a treatment for severe mitral stenosis. Unfortunately, such good results from the spontaneous development of tricuspid incompetence are unusual, and when tricuspid insufficiency appears it is more often a manifestation of extreme failure and marks a phase in the downhill progression of the disease.

Pericardial Disease

Disease of the pericardium, whether it consists of an effusion or an adherent rigid case restricting movement, interferes with filling of the heart. Dr. Charles Fletcher (1945) published a study on a single case showing that the rise in venous pressure in pericardial effusion was simply enough to maintain a more or less normal effective filling pressure of the heart in excess of the external pressure upon

FIG. 10.—Woman aged 37 (R.H.D., M.S., T.I.). Pressures in the right ventricle, right atrium, innominate and axillary veins (lower right) in gross tricuspid incompetence. Note the sudden drop in pressure as soon as the catheter is withdrawn through a nearly competent venous valve. The last record (lower right) shows a slight rise in pressure during ventricular systole, possibly due to a slight leak through the valve.

it. When fluid was removed from the pericardium, filling pressure and external pressure upon the heart fell in parallel and the output remained unchanged. We have since repeated this observation in a pericardial effusion resulting from Hodgkin's disease with essentially similar results.

In constrictive pericarditis the tracings of right ventricular pressure are very characteristic (Fig. 11). During early diastole there is a steep dip in pressure followed by a quick rise to a diastolic plateau at a high pressure level (Eliasch *et al.*, 1950). As blood rushes in from the auricle, limited expansibility of the ventricle causes the pressure to rise rather steeply to a plateau, at which it is maintained until the ventricle contracts. In contrast with most other types of heart failure the right ventricular pulse pressure remains normal. Pressure in the veins near the heart is high, corresponding to the high diastolic filling pressure of the ventricle. Digitalis is without influence on the pressure curves, cardiac output, or venous filling pressure in such cases.

The protodiastolic sound of constrictive pericarditis coincides with the steep dip in ventricular pressure (McKusick, 1952). The careful studies of Hansen *et al.*

R.V. PRESSURE 43/19

FIG. 11

FIG. 12

FIG. 11.—Right ventricular pressure curve in a male with constrictive pericarditis. Note the steep dip of pressure in early diastole and the sharp rise to a plateau. The pulse pressure (43—19) is normal. FIG. 12.—Rheumatic aortic incompetence in severe failure. The right ventricular pressure in diastole rises steeply, somewhat like constrictive pericarditis. The pulse pressure is high and rises still higher under digitalis.

(1951) show that this early diastolic dip is not an artifact as might be suspected (Katz, 1930). Fibroplastic endocarditis and myocardial fibrosis may produce similar curves (McKusick, 1952; Hansen *et al.*, 1951). It is to be noted that a similar dip and rapid climb to a higher level may be seen in some cases of severe heart failure. The shape of the curve in the latter cases may alter with digitalization, the pressure dip becoming less obvious as the diastolic filling pressure of the ventricle comes down to a lower level (Fig. 12).

Acute Nephritis

In acute nephritis a state of affairs may be seen which is barely distinguishable from hypertensive heart failure (Davies, 1951). The blood pressure is raised moderately, the venous pressure is nearly always high in the acute phase (La Due, 1944), and, of course, there is a well-recognized liability to the development of more gross cardiac failure, the incidence of which has been put at figures ranging from 20% (Ellis, 1936) to 71% (Whitehill *et al.*, 1939), depending on the severity of congestive phenomena demanded by the authors as their criteria. In the cases we have studied, which have shown only raised venous pressure, the cardiac output has been normal and there has been no response of either cardiac output or venous pressure to digitalization. It would therefore seem that these cases were not in a hypodynamic state.

It is at present difficult or impossible to put one's finger on the initiating mechanism of this type of heart failure. It may be hypertensive, or it may be that retention of salt and water creates haemodilution and a circulatory overload. A somewhat similar state of affairs can be induced in normal subjects by the administration of D.C.A. and salt.

The Present Position

In our earlier studies we were limited to right auricular filling pressure and cardiac output changes in the consideration of types of heart failure. Our approach to-day tends to put much less stress on cardiac output change, for heart failure may be present at any level of resting cardiac output, and considerable clinical improvement can take place without any change in cardiac output so long as elevated pressure, particularly in the lungs, is relieved. The function of a single ventricle may be assessed not only on the amount of blood which it ejects but also on the magnitude of the pulse pressure it can achieve at any given diastolic tension.

In the whole complex pattern of heart failure we should recognize *hypodynamic congestion* likely to be relieved by digitalis so long as the terminal unresponsive stage has not been reached, and *compensatory states of congestion* in which the drug seems to have little effect (Table II).

TABLE II.—*Causes of Heart Failure*

Cause of Load	Myocardial Function
1. Valvular: obstructive and backflow lesions	Compensatory, or "physiological" OR Hypodynamic, or "pathological"
2. Myogenic: damage or destruction of muscle by inflammation, oxygen lack, or ischaemia	
3. Mechanical: pericardial disease	
4. Extrinsic:	
Physical: systemic hypertension; pulmonary hypertension; anaemia; Paget's disease; salt and water retention; nephritis; D.C.A.; etc.	High venous pressure
Metabolic: beriberi; hyperthyroidism; uraemia; cholaemia	

In the production of venous congestion there are many factors. The mechanical effect of valvular obstruction and of tricuspid incompetence may create a true backward pressure. In still other instances, where there is no valvular obstacle and where the resting output is actually high, there is clearly no obstruction to flow within the heart, and the high pressure in the veins must result from an increased volume of blood within them or an increased tone of the venous wall.

Some recent observations by Braun and Fryd (1951) and Halmágyi *et al.* (1952) have shown that the administration of sympathicolytic and ganglionic blocking agents lowers the venous pressure in most forms of heart failure, and that such venous pressure reduction is absent in normal subjects. These effects indicate the possible importance of autonomic control of venomotor tone, a possibility I have previously stressed (McMichael, 1949). There are, however, several other consequences of the administration of such drugs, and the subject clearly requires more detailed analysis.

There are various peripheral vascular reactions in heart failure which must also be taken into account. In the high-output types with a normal arterial pressure (anaemia) there must be peripheral vasodilatation. Conversely, the low-output types are associated with vasoconstriction and cold extremities. Brigden and Sharpey-Schafer (1950) have shown that patients with left ventricular failure develop reflex peripheral vasoconstriction in recumbency as contrasted with vasodilatation which takes place in normal subjects. Recumbency may precipitate attacks of orthopnoea, and in acute attacks of left ventricular failure the systemic arterial pressure is practically always found to be elevated above the previous level. The place and nature of these reactions in the complex picture of acute left ventricular failure still remain to be clarified. We can all observe from time to time in the dying patient with left ventricular failure an intense peripheral constriction which may lead to actual gangrene of the tip of the nose and fingers (Swan and Henderson, 1951). In one such patient Dr. Graham Bull (unpublished) demonstrated that there was also a very gross reduction of renal blood flow to less than one-tenth the normal value.

Past Errors and Future Prospects

It is now some 16 years since I became involved in the study of haemodynamics in heart failure. I have been intrigued and fascinated by the digitalis problem and have constantly sought some explanation of its striking success in some cases and equally miserable failure in others. The possible clue of primary venous pressure reduction influencing the healthy and failing heart in different ways was thoroughly explored some eight years ago. Though superficially attractive the idea was abandoned as soon as inconsistencies came to light. There are other explanations for failure of digitalization, partial successes, and complete success, as I hope I have shown. We have had to learn in a painful and difficult transition that the unitary conception of heart failure as a single entity was incorrect. A large number of variables are involved in the complex interaction of the two sides of the heart, each of which may be in a different dynamic state when failure is developing. Congestive phenomena can certainly make their appearance in the absence of a hypodynamic myocardium. The responses of the lung vessels, as seen in mitral stenosis, may produce a further series of complex reactions altering the picture. Pure pulmonary heart failure in emphysema seems to result from episodes of pulmonary hypertension occurring in the bronchitic attacks (Mounsey *et al.*, 1952).

Knowing my own fallibility only too well, I wish to emphasize that I have merely presented a current view of heart failure. Researches with modern tools began only some five years ago. The sequence of events between the beginning of heart disease and the development of congestive phenomena is still a matter of speculation. Starr (1949) produced experimental infarction of practically the whole of the right ventricle of a dog with no resulting measurable rise in venous pressure. Conversely, I hope it has become clear that some patients with venous engorgement have normally functioning, though loaded, right hearts. So what do we mean by right heart failure? The term is too loosely used. When patients with myocardial infarction develop congestive phenomena a few days have usually elapsed from the acute episode, and in a few more days the congestion may vanish. What is happening during this sequence

of events? Why does the cardiac patient pass into a dying state with a resting minute volume of circulation the same as that of an upright soldier?

The realization of ignorance brings its gleam of hope that continued research will add to our therapeutic power: cardiac surgery and new technical developments in investigation are adding daily to our knowledge and extending our experience in depth. In time some of the pictures crudely sketched in these lectures will be more clearly perceived, and be submitted once again to a much more rational and complete interpretation than we can give to-day.

(Figs. 5, 6, and 7 are reproduced from *Acta Medica Scandinavica*, 1952, Supplement 266, p. 701, by kind permission of the Editor.)

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Whales are popular among doctors nowadays. Not only are their pituitary glands a useful source of A.C.T.H., the whales are also the quarry of the cardiologist. Dr. Paul D. White has recently returned to Boston from Alaska with a one-ton beluga whale's E.C.G. The electrodes were brass-headed harpoons (*Time*, August 25).

RHEUMATIC FEVER

SOME OBSERVATIONS ON A.C.T.H., CORTISONE, AND SALICYLATE THERAPY

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Hench and his colleagues (1950) have demonstrated the rapid benefit afforded by A.C.T.H. and cortisone to sufferers from rheumatic fever. They could not, however, determine whether such treatment lessened the incidence or degree of valvular damage. They also showed that these hormones have a profound effect on the metabolism of protein, fat, carbohydrate, and electrolytes, and that the continued administration of them led to some of the clinical and biochemical changes observed in Cushing's syndrome. Treatment with salicylate has hitherto been the basic method and evidence is accumulating that this well-tried remedy actually engenders adrenocortical excess. In this paper we give an account of the use of A.C.T.H. and cortisone in four selected cases of rheumatic fever and describe the response of four other cases to treatment with salicylates. We add to the evidence that salicylate has an A.C.T.H.-like effect, and we give our present impressions of the value of A.C.T.H., cortisone, and salicylate in the treatment of rheumatic fever.

Cortisone Treatment

We gave the cortisone to severely ill patients who had not responded to salicylates. The dosage in each case is set out in Fig. 1. Cortisone acetate was given by intramuscular injection daily for six days each week. We thought at first that the hormone could be discontinued once we had abolished the tachycardia, corrected the anaemia, and reduced the raised E.S.R. to normal. As will be seen, recrudescence of the disease often followed the cessation of treatment at such a stage. Because of this and the similar experience of others (Dorfman *et al.*, 1951) we increased the period of therapy by at least four to six weeks, with the aim of suppressing these signs. The duration of treatment varied from 44 to 110 days.

FIG. 1.—Effects of cortisone on patients who did not respond to salicylates.