BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 6 1952

DYNAMICS OF HEART FAILURE*

BY

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Nearly thirty years ago, when I was a second-year student of medicine, I first heard of Dr. George Oliver, of Harrogate, from my first teacher of physiology, Sir Edward Schäfer. They had shared in the discovery of adrenaline, the tale of which has been too well told to bear repetition from me (Dale, 1948). Dr. Oliver had come under the influence of William Sharpey. Born in Arbroath in 1802, Sharpey was a graduate of Edinburgh. While a lecturer in that city he discovered ciliary motion. Later he migrated south, where he became the first British scientist to devote his entire career to physiological teaching and research. As such he was recognized as the father of British physiology, becoming the teacher of such men as Michael Foster and John Burdon-Sanderson. Sharpey must have been a lovable character, inspiring devoted admiration by his pupils, one of whom, Sir Edward Schäfer, later added Sharpey to his own name by deed poll to ensure that his memory should not fade. Dr. Oliver, for the same purpose, endowed these lectures "to promote physiological research by observation and experiment and encourage the application of physiological knowledge to the prevention and cure of disease and prolongation of life." It is a privilege and honour to be called on to sustain this high purpose in succession to a distinguished list of predecessors.

LECTURE I

The present century has witnessed several distinct phases in our consideration of heart disease. In the first decade attention was diverted from murmurs and the mechanical consequences of narrowed or leaking valves by Mackenzie's superb analysis of the irregularities, work which was further amplified by Lewis's critical electrocardiographic studies. The third and fourth decades saw the electrocardiographic developments which made this instrument our most valued aid in topographical diagnosis of myocardial lesions. In the background, and barely impinging on clinical medicine, a distinguished group of physiologists were perfecting methods for the study of the heart as a pump. Starling's success with the heart-lung preparation clarified and established some fundamental laws of cardiac behaviour, while Haldane's respiratory studies and the development of the foreign gas principle by Krogh and Lindhard (1912) showed the way to the determination of the output of the heart in man by the Fick principle, using the most ingenious tricks of respiratory technique. By the early nineteen-thirties these respiratory methods had produced an accumulation of data on the output of the heart in health and in some patients with heart disease who could co-operate in the somewhat exacting procedures. It was perhaps surprising to find that patients could be in heart failure with no apparent depression of cardiac output at rest, and it was very natural for our clinical predecessors to be suspicious that the methods might be wrong.

Harrison, in the United States, however, had the courage to accept the established data at their face value, and in 1935 he produced his book *Failure of the Circulation*, emphasizing the gross and obvious differences between hypokinetic syndromes (shock states), and the dyskinetic syndrome of congestive failure. It appeared that the body's reaction to heart disease was to maintain the minute volume of the circulation at the expense of hypertrophy, and later of congestion of the lungs and engorgement of the veins. Later these secondary consequences may choke the life out of the patient while the minute volume of the circulation seems to be adequate, at least for resting metabolism. A healthy soldier standing at ease may have a lower heart output per minute than many a cardiac patient within an hour or two of death. Harrison certainly realized our fundamental ignorance of the true processes involved in congestive failure, and work which has been done since his day with the more accurate method of cardiac catheterization has amply proved the general validity of the facts on which he built his ideas.

Failure of the central pump brings in its train such a host of complex consequences that it is difficult to take a broad and comprehensive view of the whole at any one moment. In these lectures I shall regard such problems as blood-volume regulation and disturbances of renal function in relation to cardiac oedema as secondary phenomena and concentrate attention on the behaviour of the heart itself.

The Problem of Definition of Heart Failure

In the presence of a heart lesion the clinical picture of breathlessness, engorgement of the lungs, venous congestion, and liver swelling, with or without oedema, leads inevitably to the clinical diagnosis of heart failure. As I shall show, one of the mistakes made by investigators up to the recent past, including ourselves, was the assumption that this represented a final common picture with more or less identical features whatever the initiating type of heart disease. In actual fact the various aetiological varieties of failure differ very considerably from one another in the detail of their

*The first of two Oliver-Sharpey Lectures delivered to the Royal College of Physicians of London on March 11 and 13.

consequences. Although there are superficial similarities, dyspnoea and venous congestion differ greatly in their causation in hypertensive left ventricular failure and in heart failure of pulmonary origin. Some cases of heart failure seem to be the long-term consequence of an overload on the heart, and these in turn probably differ in their mechanism from those in which active rheumatic inflammation impairs the function of the myocardium. Recognition of tonogenic and myogenic forms of heart failure was developed by Kirch (1935). There are yet other instances, like constrictive pericarditis, in which the contractile properties of the myocardium itself probably remain unimpaired but the pump fails to maintain an adequate performance because of the mechanical restriction of its movement in a rigid case. We must also take into account states of functional imbalance between the two ventricles: the conception of *left* heart failure was only slowly accepted in this country, but modern work puts it beyond all doubt that the left ventricle can be in a state of failure while the right ventricle still responds in a physiological manner.

Apart from diseases of the lungs, there are other extracardiac disorders which make excessive demands upon the circulation, such as severe anaemia and arteriovenous aneurysms. Under these circumstances the output of the heart may rise to double or treble the normal value and yet the phenomena of venous congestion with or without oedema can make their appearance. The high venous pressure in such cases cannot be the consequence of any back pressure, and we have been tempted to regard it as a compensatory phenomenon maintaining output at a necessarily high level (Sharpey-Schafer, 1944; McMichael, 1949).

It is clear, then, that the clinical phenomena usually accepted as heart failure may be varied in their course and causation, and we reach a philosopher's dilemma in an attempt to define heart failure. An overload may be met at first by hypertrophy, and sooner or later there is some elevation of the pressure filling the affected ventricle. The law of Starling and also of Frank (1895) relating filling pressure and cardiac output may be superseded in the normal subject by nervous and humoral control of rate and strength of myocardial contraction (*Lancet*, 1951). The normal ventricle probably contains some residual blood at the end of systole (Friedman, 1951). By increased strength of contraction (e.g., adrenaline) the stroke output can be increased, and with accompanying acceleration of rate the normal heart meets moderately increased demands without any increase in venous pressure. In progression toward heart failure, however, these normal mechanisms of regulation of cardiac performance are lost. The heart loses its reserve and can no longer be stimulated to stronger contraction by adrenaline (Reichel, 1950), the rate becomes more or less fixed about 100 a minute, and the last remaining "compensating" mechanism is the venous filling pressure (Richards, 1947; Harrison, 1948; McMichael, 1949; Reichel, 1950).

We have learned that it is erroneous to judge the response of the heart by measuring cardiac output alone. We need not only cardiac output measurements but also measurements of the filling pressure and the arterial pressure against which each stroke volume is ejected.

Cardiac work = output × mean arterial pressure.

Taking the pressure factors into account, we can re-draw the curves established by Starling and his associates in the manner shown in Fig. 1.

When the heart is called on to meet an unusually severe strain (such as that imposed by the sudden obstruction of large pulmonary embolism) it meets this excessive demand by elevation of the venous pressure. The first rises in venous pressure are not necessarily associated with a hypodynamic state of the myocardium, and may be truly compensatory in nature. The continuance of load or strain may be met by hypertrophy with restoration of some reserves of strength: normal reactivity of the heart to rate change develops once more and the venous filling pressure may subside (Fig. 1). On the other hand, the load may be too great or other conditions may be inimical to meeting the demands by physiological reactions, and the overloaded heart fails increasingly in strength, becoming hypodynamic. The heart is now in a metabolic or physical state resembling muscular fatigue. Its fibres contract less strongly than before and it is less capable of responding to the demands of bodily activity. An overworked heart may thus have a high venous filling pressure — always an index of strain—but may still behave physiologically. As it becomes hypodynamic, however, the filling pressure rises to still higher levels with less and less work achieved as a result.

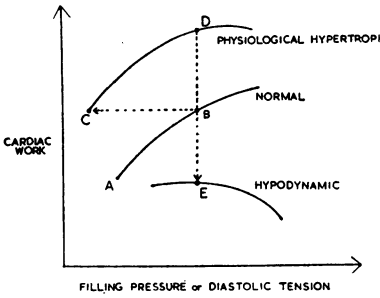

FIG. 1.—A normal ventricle does work A at a low diastolic tension. Acute load B is accomplished at a higher filling pressure. Development of hypertrophy BC may cope with a chronic load, or the myocardium may be overstrained and become hypodynamic, BE. Hypodynamic state may also develop after physiological hypertrophy, DB.

Present Methods of Study

The output of the heart can be measured during catheterization with a standard error of 6% (Pugh and Wyndham, 1949). In our early work we limited ourselves to catheterization of the right atrium, which gave a measure also of the venous filling pressure of the heart. The information then obtained permitted the broad recognition of high-output types of failure occurring in anaemia, emphysema, and arteriovenous aneurysms, and low-output types resulting from intrinsic heart disease—valvular and ischaemic or from hypertension. Recognizing that digitalis did not always increase the cardiac output, although the venous pressure usually fell, we worked for a time on a hypothesis that digitalis might reduce venous pressure as a primary action (McMichael and Sharpey-Schafer, 1944). Although our facts were substantially correct, we had not allowed for the complexity of variables interposed between the filling pressure of the right auricle and the output of the left ventricle, nor had we yet grasped the variety of syndromes associated with venous congestion. In the last three years the adoption of optical pressure recording from the right ventricle and pulmonary artery has permitted a more detailed appraisal of the problem along new lines and brought our present views (Bayliss *et al.*, 1950b) more or less into line with similar work by Harvey *et al.* (1949) in America and Lagerlöf and Werkö (1949b) in Sweden.

In an optical record from the right ventricle pressure climbs during ventricular diastole as the ventricle fills. The end-diastolic pressure just before ventricular contraction (synchronous with the S wave of the electrocardiogram) represents the true pressure or tension on the ventricular wall just before systole. Taking a frontal plane 5 cm. posterior to the sternal angle level, this pressure is usually zero ±2–3 mm. Hg. This ventricular filling pressure usually is close to, or parallels changes in, the mean venous filling pressure of the right auricle. As the ventricle contracts the pressure rises, the pulmonary valves open, and the top of the ventricular pressure curve is identical with the systolic pressure in the pulmonary artery. A right ventricular pressure curve therefore permits measurement of the filling pressure immediately before systole—that is, initial tension of the ventricle—and of pulmonary artery systolic pressure. This latter pressure normally ranges from 15 to 30 mm. Hg.

A catheter passed down the pulmonary artery to the point of blocking allows the withdrawal of arterialized blood

drawn back from the alveolar capillaries. The pressure in this situation is often referred to as the "pulmonary capillary-venous pressure." A great deal of interesting work on this pressure has been done by Lagerlöf and Werkö (1949b) in Stockholm and by Dexter and his associates (1950) in Boston. The pressure rises in the pulmonary capillaries as might be expected in mitral stenosis and in left ventricular failure (see Table I). Using this pressure as an index of pressure in the left auricle and knowing volume flow and diastolic time, Gorlin and Gorlin (1951) have developed a formula for estimating the degree of narrowing of stenosed mitral valves.

TABLE I.—*Pulmonary Vascular Pressure (From Dexter et al., 1950)*

	Pulmonary Arterial Pressures			Pulmonary Capillary (Mean)	Arterio-capillary Gradient (mm Hg) (Mean)
	Systolic	Diastolic	Mean		
Normal	19–26	6–12	15	9 (6–12)	6
Left ventricular failure	35–65*†		46	31	15
Mitral stenosis:					
Capillary pressures below 25 mm Hg	24–50*		29	20	9
Capillary pressures above 25 mm Hg	50–150*		62	31	31
Emphysema heart failure	40–80*			? normal	? increased

* Figures modified from our own experience.
† May rise higher in severe orthopnoea.

Another technique of great value is Hamilton's dye method of estimation of cardiac output. Dye is injected into an arm vein and timed blood samples are collected from the opposite brachial artery, the concentration of colour in the samples being plotted against time (Fig. 2).

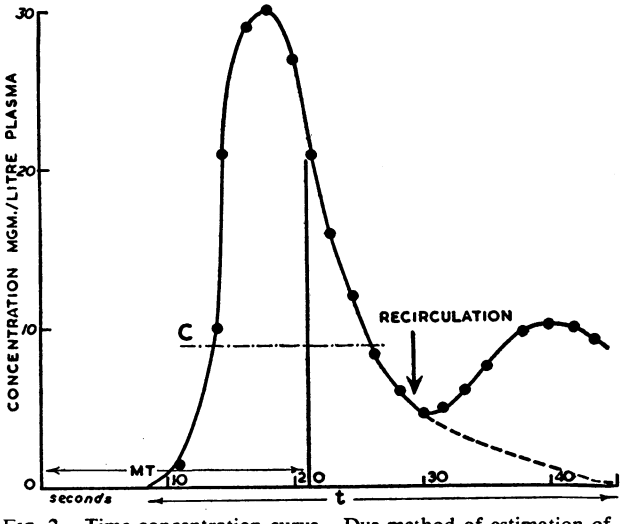

FIG. 2.—Time concentration curve. Dye method of estimation of cardiac output. Dose of dye divided by its mean concentration (c) gives the volume of plasma flowing in the arterial system from the time of appearance to disappearance of the dye (t).

The amount of dye injected (i) divided by its mean concentration (c) in the arterial system gives the volume of dyed plasma flowing along the arterial system from the time of its appearance to its disappearance (t seconds). The plasma flow per minute $\left(\frac{i}{ct}\times 60\right)$ corrected for the haematocrit gives the cardiac output. The figures obtained check well with those obtained by the direct Fick method (Werkö *et al.*, 1949; Kopelman and Lee, 1951). The dye method also permits the estimation of mean circulation time from arm to arm (MT seconds). If 6 litres of blood a minute is passing through the lungs and spending an average of one-third of a minute on the way, then clearly the lungs contain one-third of 6, or 2 litres of blood. $\frac{MT}{60}\times$ cardiac output gives an approximate estimation of the volume of blood between one arm vein and the opposite brachial artery, or so-called "intrathoracic blood volume" (Kopelman and Lee, 1951). The work which I shall describe is largely based on the use of these methods.

Right Ventricular Stress

Most forms of heart failure affect first and foremost the left heart. The secondary consequences of left heart disease on the right side are extremely complicated and variable in type at various stages. For this reason it would be well to begin by studying certain types of right heart failure.

Congenital pulmonary stenosis affords an example of a primary overload on the right ventricle created by obstruction to its outlet. In this condition the veins of the neck may be seen to be pulsating, and the liver also may share in this pulsation. The hypertrophied ventricle must raise an enormous systolic pressure, to 150 or 160 mm. Hg, in order to expel its blood. This strong contraction is usually effected at the expense of a high diastolic filling pressure, which is achieved by a high venous pressure and strong contraction of a hypertrophied right auricle (Fig. 3). Auricular systole is responsible for the gross pulsation in the neck veins and in the liver. In some instances, however, hypertrophy of the right ventricle may maintain a very high pulse pressure, such as 100 mm. Hg or more, in the presence of a *nearly normal* filling pressure.

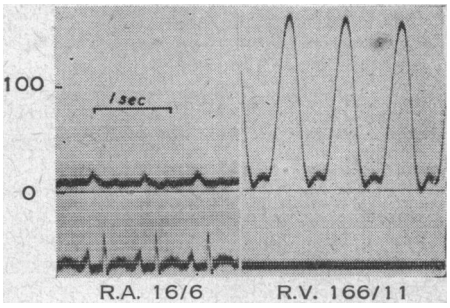

FIG. 3.—Pulmonary stenosis with grossly hypertrophied auricle and ventricle sustaining high pressures. Right auricular pressure curve on left, ventricular on right. Patient, a girl aged 7, able to run short distances, etc.

Such observations bring home important principles: (1) hypertrophy is a physiological response to increased load; (2) the function of a hypertrophied ventricle may be so good that it sustains the extra load without any special increase in diastolic pressure within it; and (3) the increased diastolic tension in the early stages may still be associated with excellent myocardial function.

The increased diastolic filling pressure of the right ventricle, which parallels the venous pressure, exemplified in Fig. 3 is not the result of any true myocardial fatigue. I think we might adopt a term, "compensatory or physiological congestion," to indicate this state. Harvey *et al.* (1951) have shown that hearts which are merely hypertrophied behave like normal hearts on digitalization and show no measurable change in output or strength of contraction. This is an observation with which we can concur.

The next stage reached in right ventricular failure is one in which the right ventricle has become hypodynamic as a result of the strain imposed upon it. The examples we have studied at this stage are mainly drawn from emphysema and allied conditions. In emphysema, as has been shown by Mounsey *et al.* (1952), an intermittent load of pulmonary hypertension is created during the acute exacerbations of chronic bronchitis with intensification of an asphyxial state. The heart is compelled to sustain a higher pressure in the pulmonary vascular system as well as a higher cardiac output than normal during the illness, and it must do so while supplied with blood containing less oxygen. While enumerating these factors we should remember that cyanotic

congenital hearts tolerate greater loads and more asphyxia without congestive failure, the obvious differences being chronicity and powers of adaptation in early childhood.

A state of affairs somewhat similar to that seen in emphysema and bronchitis develops in a more persistent form in the late stages of kyphoscoliosis, presumably as a result of inadequate pulmonary ventilation in the deformed thorax. The administration of digitalis in such instances may be accompanied by the development of a higher pulse pressure in the right ventricle, and this is maintained at the same or even a lower diastolic filling pressure (Fig. 4). This measurably stronger contraction, however, may be accompanied by such increased resistance to blood flow through the lungs that the minute output of the heart is seldom much improved. In the patient in whom Fig. 4

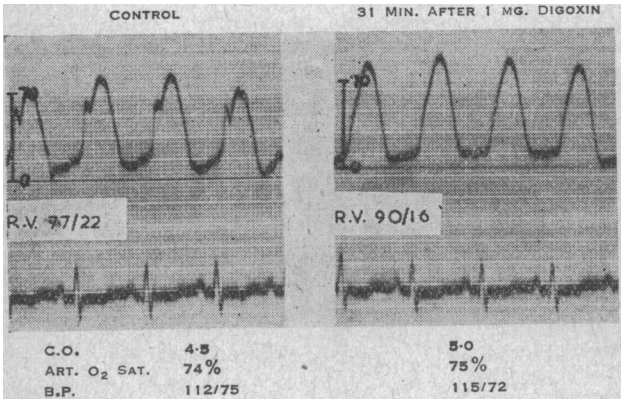

FIG. 4.—Kyphoscoliosis with heart failure. The right ventricle sustained a higher pulse pressure at a lower diastolic tension after digitalization.

was obtained, digitalization alone led to no clinical change and oedema was persistent. The improvement in pulse pressure suggests that the overworking right heart was previously failing to achieve its optimum strength and that digitalis can, in fact, exert a beneficial influence in this state of myocardial fatigue or hypodynamic action. We might use the term "hypodynamic failure" to indicate that state which is capable of improvement (increased pulse pressure and/or cardiac output) under digitalis and where the venous pressure usually falls as a result of giving this drug.

Left Ventricular Failure

Hypertension imposes a load on the left heart which is first met by hypertrophy. Friedman (1951) has shown by careful studies relating heart volume in life and heart weight that the increase in size of the heart is at first due more to hypertrophy than to dilatation. By analogy with what we have seen in the right heart there is presumably no very great rise in pulmonary venous pressure until failure is imminent. The fact that pulmonary arterial pressure is not raised in the ordinary case of high blood pressure without heart failure supports this view. When the myocardium of the left ventricle becomes fatigued it can sustain the output of blood offered by the right ventricle only at the expense of a high filling pressure which affects the pulmonary veins. Pulmonary arteriolar resistance is normally so low that a rise in pressure on the venous side of the pulmonary circulation is almost quantitatively transmitted through the whole pulmonary vascular bed, and a rise in pulmonary arterial pressure results. When left heart failure develops a rise in pulmonary arterial pressure is an invariable accompaniment (Table I).

In studying the action of digitalis on left heart failure it is well at this stage to remind ourselves of some of the significant actions of this drug: (1) it has no measurable effect on the contractile force of a normally functioning myocardium; (2) it strengthens the contraction of a hypodynamic failing myocardium, an action which, however, may be lost in the terminal stages of failure; (3) full intravenous doses cause a rise in peripheral vascular resistance (Bücherl and Schwab, 1952); and (4) it slows the heart, especially in auricular fibrillation with a rapid ventricular response.

The action of the drug in increasing peripheral vascular resistance is an immediate and rather transient effect of full doses, which passes off in about half an hour. It may, however, precede the beneficial effects of the drug on the myocardium. During our observations on the effects of digitalis in left ventricular failure we have had occasion to watch attacks of left heart failure follow administration of the drug. A moderate degree of pulmonary hypertension climbs up to a very high level as the patient's arterial pressure rises, cardiac output falls, and dyspnoea becomes temporarily intensified, with the appearance of audible moist rales at the bases of the lungs (Bayliss *et al.*, 1950b).

The usual demonstrable action of digitalis, however, is strengthening of contraction of the failing ventricle, and as the left ventricle is appreciably more affected than the right the output of the heart may go up and pressures throughout the pulmonary vascular system fall. All the expected clinical improvements accompany this haemodynamic recovery. Kopelman and Lee (1951) have shown by their dye studies that in left ventricular failure the intrathoracic blood volume is increased by about a litre above the normal, and that recovery is accompanied by a considerable diminution in the volume of blood in the thorax. Lagerlöf *et al.* (1949) do not think the volume of blood in the lungs diminishes immediately after digitalization, but their cases were of mixed aetiology and the true left ventricular failures were too few in number to permit firm conclusions.

On occasion haemodynamic improvement in left ventricular failure may occur without any change in the minute output of the heart detectable by our methods. This is illustrated by the following example:

A known hypertensive subject had passed into failure with a falling arterial pressure. It was clear that his left ventricle had become hypodynamic, and that his pulmonary venous pressure was high, as reflected by the raised pressure in the pulmonary artery. Digoxin was followed by a remarkable fall in his pulmonary arterial pressure, indicating relief of his pulmonary vascular congestion, while the systemic arterial pressure rose very considerably (Fig. 5).

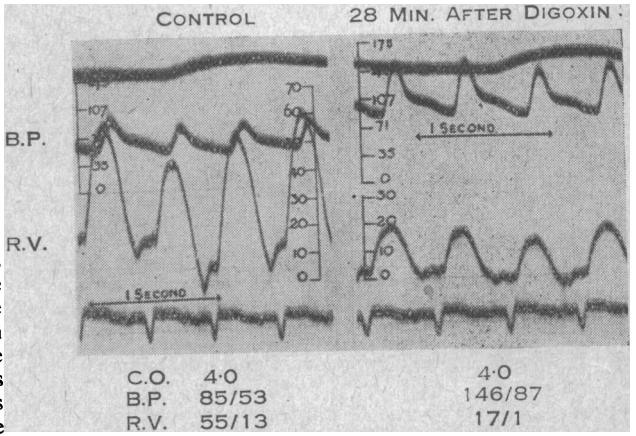

FIG. 5.—From above down: respiration, arterial pressure, right ventricular pressure, electrocardiogram. Left: hypodynamic left ventricle with falling systemic pressure and high pulmonary systolic pressure. Right: after digoxin arterial pressure rose and pulmonary pressure fell; cardiac output was unchanged at 4 litres a minute.

There is no doubt here that the left ventricular pulse pressure was greatly increased, the same volume of blood was ejected against a higher arterial pressure, indicating that the left ventricle was doing more work at a lower filling pressure. The right ventricle, however, was presum-

ably behaving in a more or less normal fashion. Better performance of the left ventricle relieved the right ventricle of an overload, and its filling pressure underwent a considerable drop. We can therefore analyse this case as follows: The left ventricle was stimulated by digitalis. The secondary effects on the right ventricle could simply be called unloading as a result of diminution of pulmonary vascular pressures resulting from improved action of the left ventricle (Fig. 6). The absence of any increased work or output from the right ventricle under digitalis is evidence of nearly normal behaviour of this chamber. It is possible, therefore, to have a hypodynamic left ventricle leading to a secondary load on the right ventricle, the ordinary *physiological* response to which is a raised diastolic tension. This increased filling pressure of the right ventricle is reflected in a rise of venous pressure. This raised systemic venous pressure is a physiological response and does not necessarily indicate any hypodynamic or failing state of the *right* ventricle.

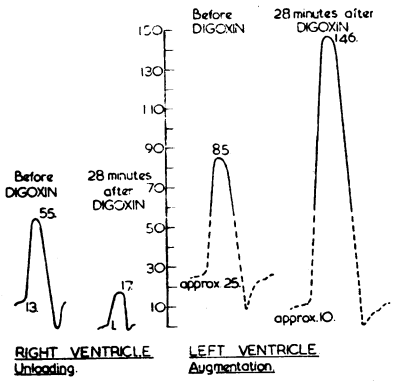

FIG. 6.—Contrasting effects of digoxin on pulse pressures of left ventricle (augmentation) and right ventricle (unloading): from data in Fig. 5. The filling pressure of the left ventricle (calculated as approximately half the pulmonary artery systolic pressure) must have fallen to a normal value.

Sometimes failure occurs with a more or less even balance of effects on the two sides of the heart. Fig. 7 is from a patient who had ischaemic heart disease probably affecting

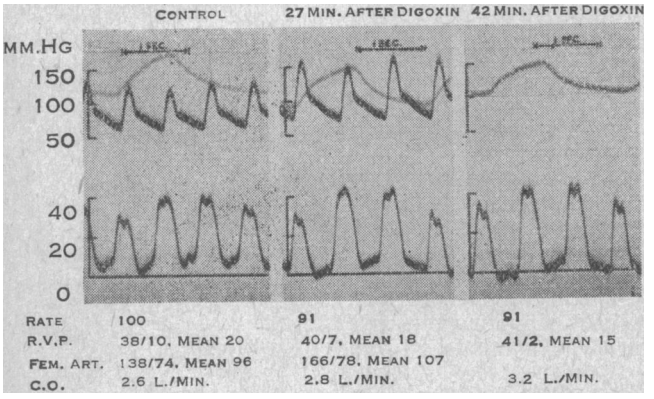

FIG. 7.—A woman aged 76 with ischaemic heart disease. A rise in arterial pressure followed digoxin, while the right ventricular pressure changed from 38/10 to 41/2 mm. Hg in 42 minutes. The cardiac output increased from 2.6 to 3.2 litres a minute. The effect of digoxin is augmentation on hypodynamic left and right ventricles.

both right and left ventricles. The right ventricle was maintaining a raised systolic pressure at the expense of some venous congestion. On digitalization the right ventricular pulse pressure rose and the diastolic filling pressure fell to a lower value; the left ventricular pressure also increased (see arterial pressure record) and the output of the heart rose significantly.

Conclusion

In this lecture I have dealt with some of the most readily analysable forms of heart failure where overload and overwork are more or less directly measurable. We have built up evidence that high venous pressure behind an overloaded chamber may be "physiological" for a time. One index of a "hypodynamic" state of the heart is probably responsiveness to digitalis. When we take into account two cardiac pumps, right and left, each in a different functional state we can begin to understand why responses to digitalis are so variable. This unpredictability of digitalis reactions seemed previously to be a bewildering maze defying rational analysis.

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

THE PATHOGENESIS OF SIMPLE GOITRE*

A REVIEW

BY

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Simple goitre is classified as a type of thyroid insufficiency. That the condition is one of importance is evidenced not only by the disfiguring nature of the disease but by the serious disorders to which it may give rise or predispose—namely, cretinism, myxoedema, and carcinoma of the thyroid gland. Cancer of the thyroid gland is comparatively rare in Britain, but in Switzerland, where simple goitre is common, the deaths from carcinoma of the thyroid gland formed 1.6% of the total deaths from cancer in the years 1901 to 1910 and 0.98% in the period 1911 to 1920 (Renaud, 1923). According to Bérard and Dunet (1924), in 75 to 85% of cases thyroid malignancy develops in an old-standing simple goitre.

Pathology

Before the pathogenesis of simple goitre is discussed reference should be made to its pathology, for it should be appreciated that simple hyperplastic goitre, colloid goitre, and nodular goitre are all stages of the same disease process and are not separate entities with their own particular aetiology. Nodular goitre was once believed to be a different disease from diffuse goitre, and colloid goitre was thought to be due to overactivity of the colloid storage mechanism whereby the normal gland was converted straightaway into a colloid goitre without any intervening stage of hyperplasia. We now know through the work of Marine, although Virchow (1863a) originally pointed it out, that the primary phase of all true goitres is active hyperplasia, and that the development of a colloid goitre from a normal gland by the passive distension of the follicles with colloid is impossible.

Marine and Lenhart (1909a) showed that thyroid hyperplasia is associated with a decrease of the iodine store of the gland. The morphologically normal thyroid gland contains on an average about 0.2% of iodine (measured in terms of dried gland). When the requirements of the organism for thyroid hormone increase the iodine store of the thyroid diminishes, and when it falls below 0.1% the gland is found to be hyperplastic. These changes are brought about by stimulation by the anterior pituitary thyrotrophic hormone, the secretion of which is increased as a result of a fall in the blood level of thyroid hormone.

*Presidential address (abridged) delivered to the Section of Endocrinology, Royal Society of Medicine, on January 23, 1952.