

Papers and Originals

THE HEART AND DIGITALIS*

BY

J. McMICHAEL, M.D., F.R.C.P., LL.D., F.R.S.

From the Department of Medicine, Postgraduate Medical School of London, Hammersmith

LECTURE I: THE MOTION OF THE HEART

In the early part of the scientific period of human history, which is now only in its fourth century, progress of ideas in medicine was made by discrete steps, each marked by the significant contribution of a single individual. Thus we have the physiological landmarks created by William Harvey, Malpighi, and Stephen Hales, and the clinical progress of such astute observers as Morgagni, Heberden, and, in the same century, William Withering, whose remarkable account of the effects of the foxglove was published in 1785.

It was Withering's profound collateral studies in botany (he was known as the British Linnaeus) which enabled him in 1775, when aged 34, to identify digitalis leaves as the potent agent in a hotchpotch of herbs used in Midland folk medicine. Withering exemplifies "the beauty and power of a liberal education . . . having reached out into the world of ideas and brought together in himself, self-taught, a large number of fields of interest" (Alan Gregg). He was physician, botanist, chemist, and geologist.

It has been suggested that new drugs should never be used until their pharmacological effects are fully understood. Had this proscription been effective, digitalis would be prohibited even to-day, nearly 180 years after Withering's monograph, for we still fall considerably short of full understanding of the mode of action of this remarkable remedy. To commemorate your greatest historical medical figure in this city I can only express pride in your invitation tempered with humility.

The text of my discourse is based on Withering's own final inference based on his precise clinical studies, that digitalis "has a power over the motion of the heart to a degree yet unobserved in any medicine and . . . this power may be converted to salutary ends."

My first lecture deals with the motion of the heart. I venture to think that we stand to-day on the threshold of new conceptions of cardiac physiology, much of it appreciated only in the last decade, revealing new problems and a wide vista of investigative possibilities. I shall try to review our present knowledge in the light of personal experience.

Starling's Law

Let us take as our starting-point Starling's law. Fifty years ago Knowlton and Starling (1912) perfected what was for its time a magnificent technical physiological feat in isolating the dog heart and lungs for recirculation experiments. The heart, cut off from nervous and hormonal influences, responded to an increased inflow of blood, resulting from elevation of the filling pressure, by elongation of the ventricular myocardium, which responded to the stretch by a substantially increased stroke output. This was really a demonstration on the heart itself of a fundamental property of striated muscle which, within certain limits, is in an improved functional state with

regard to output of work when stretched. For many years this "law of the heart" was regarded as accounting for the behaviour of the heart under most physiological conditions. Almost certainly it plays an important part in the fall of cardiac output on standing, and in the beat-to-beat regulation of output with inspiration and expiration (Lauson *et al.*, 1946). Questions began to be raised, however, when before the war Swedish workers (Liljestrand *et al.*, 1938) showed by their excellent radiological techniques that the human heart in exercise underwent no diastolic dilatation. Methods of measuring the output of the heart in man at that time involved complicated respiratory rebreathing gymnastics which were almost impossible to repeat during short test periods of exercise, so the debate remained somewhat unsettled.

In 1941 Cournand and Ranges applied Forssman's technique of catheterization of the heart, and had the courage to leave a catheter *in situ* for a sufficiently long period of time to make sequential observations. During the war it was realized that this method might be applicable to the study of wound shock, and Sharpey-Schafer and I began to apply the technique in the latter part of 1942. In test subjects we confirmed the postural drop of cardiac output on standing, which is generally ascribed to a diminished filling pressure resulting from pooling in the lower half of the body, and we also showed a broad general direct relation between venous filling pressure and cardiac output when venous pressure was elevated by saline infusions or depressed by venesection or cuffs round the legs blown up to diastolic pressure to dam back blood (McMichael and Sharpey-Schafer, 1944a). There was, however, considerable individual variation in the measurable cardiac output responses, and the increase in volume flow seldom bore a direct linear relationship to the change in venous pressure. Changes in heart rate were variable during infusions, perhaps depending on whether the Bainbridge or carotid sinus reflexes were dominant. Figs. 1 and 2 illustrate the variability of response of the normal human heart in such tests. In our publication we emphasized the positive correlation between venous pressure and cardiac output in a statistical way, but soon afterwards Warren *et al.* (1948) put more emphasis on the individual unpredictability of the results and suggested that Starling's law might not apply in intact man. One obvious difference between the human experiment and Starling's experiment was the presence of hormonal nervous and reflex influences in intact man which could interfere with any isolated myogenic response of the heart.

There the matter stood until Sarnoff and his associates, in a very remarkable series of important contributions (reviewed by Sarnoff and Mitchell, 1961), proceeded to repeat Starling's experiments on dogs, applying much more precise modern instrumental techniques. Realizing, for example, that the filling pressure determining the output of the right ventricle might be modified by the intervening lungs so far as aortic flow was concerned, they concen

*The William Withering Lectures delivered in Birmingham on November 5 and 6, 1962.

trated their attention on left filling pressure and left ventricular output. With this greater precision of measurement of the related variables they showed quite clearly that Starling's law certainly applied in the isolated dog heart. More recently Braunwald and his associates have taken the opportunity of observing these relationships in

lating effect on cardiac contractility without affecting the heart rate. At any given rate of faradic stimulation of the left cardiac sympathetic nerves the response of the ventricle to increments of filling pressure was practically linear. Increasing rates of sympathetic stimulation reset the cardiac stroke work at new higher levels, but on sustaining any particular sympathetic impulse frequency the response to increments of filling pressure is linear. The level of the output of the heart, at any venous filling pressure is thus dependent on the degree of sympathetic tonus (Fig. 3).

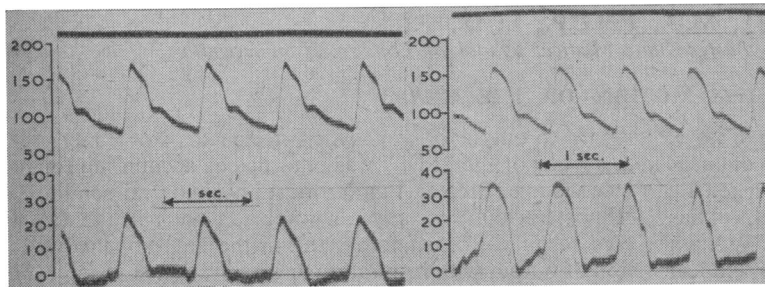


FIG. 1.—Arterial pressure and right ventricular (R.V.) pressure.

	B.P.	R.V.	Rate	Cardiac output
Left: Before saline infusion ..	178/84	24/1	67	5.0 l./min.
Right: After 1 litre/5 mins. ..	162/75	36/6	76	7.9 l./min.

Note increased output, R.V. pulse pressure, end-diastolic pressure, and heart rate.

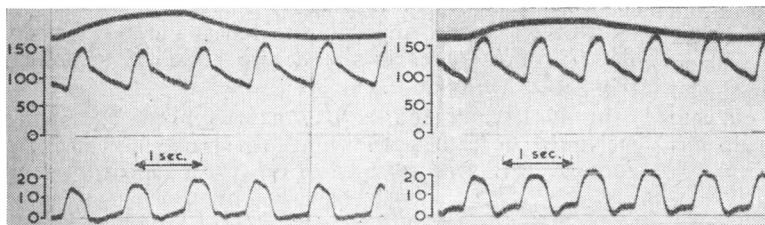


FIG. 2.—Respiration, arterial pressure, and R.V. pressure.

	B.P.	R.V.	Rate	Cardiac output
Left: Before saline infusion ..	156/88	17/3	65	3.4 l./min.
Right: After 500 ml./7 mins. ..	173/98	20/6	69	3.4 l./min.

Note no change in R.V. pulse pressure in spite of elevated end-diastolic pressure, slight rate increase, and no change in output.

the human heart during cardiac surgery: the heart behaves consistently and precisely as Starling predicted when nervous influences are reduced by hexamethonium or other ganglion-blocking agents (Frye and Braunwald, 1960; Braunwald *et al.*, 1960).

Influence of the Sympathetic Nerves

Sarnoff's analysis proceeded further. He found that in the dog the cardiac sympathetic nerves, and particularly those leaving the left stellate ganglion, exercised a stimu-

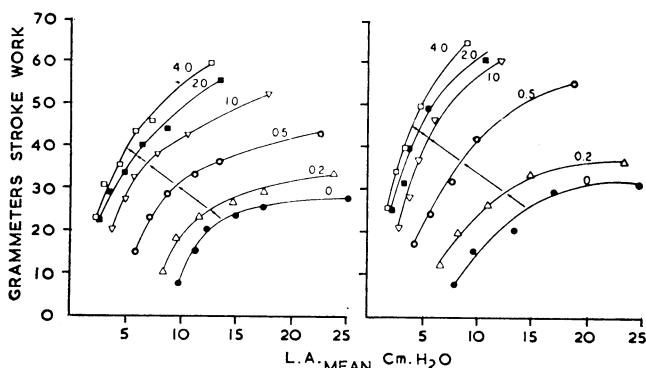


FIG. 3.—In the left panel are curves showing the relation between left atrial pressure and left ventricular stroke work during the control period (0) and during stimulation of isolated left stellate ganglion at 0.2, 0.5, 1.0, 2.0, and 4.0/second, using 7 volts and an impulse duration of 10 m.sec. Rami to right stellate ganglion and both vagi sectioned. Heart-rate held constant at 150/min. by atrial pacing. One hour 15 minutes later the experiment was repeated; the resulting curves are shown in the right panel. (Dog heart experiment reproduced by permission of Sarnoff, Brockman *et al.* (1960) and the Editors of *Circulation Research*.)

small area in the hypothalamus, in producing a remarkable increase in the cardiac output. Furthermore, under these conditions of hypothalamic stimulation the carotid sinus reflexes are completely suppressed. The artificially stimulated "emotional" rise in cardiac output is accompanied by a rise in blood-pressure, cardiac acceleration, splanchnic vasoconstriction, and vasodilatation in muscles. Clearly the rise in arterial pressure fails to elicit the expected baroreceptor reactions of cardiac slowing and splanchnic vasodilatation.

The heart is thus, in the intact animal and presumably also in man, subject to sympathetic control which at any increased level of stimulation sets the rate and contractile responses of the heart at a new and higher level (Fig. 3). It is hardly surprising, therefore, from what we know

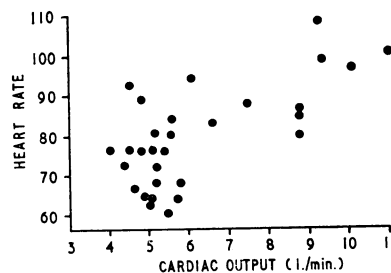


FIG. 4.—Effect of heart rate on resting cardiac output in man. With excitement or anxiety cardio-acceleration is accompanied by a substantial elevation of cardiac output. (Redrawn from McMichael and Sharpey-Schafer (1944a), *British Heart Journal*, 1944.)

of neurohumoral mechanisms, that the heart should also respond to minute dosage of adrenaline with a 20 to 50% increase in stroke output (Fig. 5). Neither adrenaline nor atropine given alone, however, can reproduce the greatly increased cardiac output which occurs with

fear or excitement. To my mind many observations on the cardiac output in man have been spoiled by inattention to the emotional state of the subject. No amount of technological, documentary, or statistical expertise can compensate for the effects of anxiety, which may easily dominate the whole physiological situation.

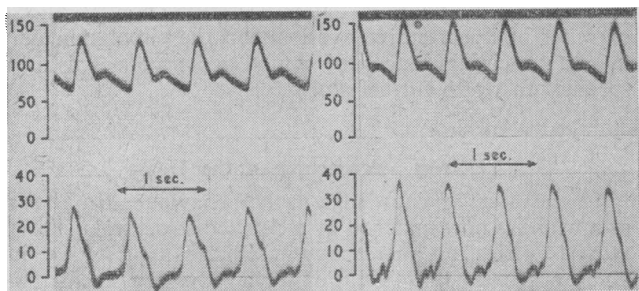


FIG. 5.—Arterial pressure and R.V. pressure.

	B.P.	R.V.	Rate	Cardiac output
Left: Before adrenaline	140/75	27/3	87	8.2 l./min.
Right: After 0.25 mg./2½ mins. I.V.	156/84	37/5	95	9.7 l./min.

Note increase in output and R.V. pulse pressure.

Intrinsic Mechanisms

In addition to such "extrinsic" regulating factors as filling pressure and sympatho-adrenal influences, heart muscle itself possesses some remarkable intrinsic mechanisms of self-adjustment or "homoeometric" regulation (Sarnoff, Mitchell, *et al.*, 1960). These reactions take place in response to changes of work and rate.

Slow Potentiation (Staircase Phenomenon)

Starling's observations on the isolated dog heart showed that increased filling pressure produced an increased diastolic volume and increased output. Using a leak-proof method of recording heart volume, Rosenblueth (1962) has shown that during the subsequent five minutes the diastolic volume returns gradually towards its initial value while the stroke output is maintained at its increased level. Thus intrinsic factors enable the heart to accomplish the increased work load while restoring the diastolic volume towards normal. Every student who has tied a Stannius ligature round a frog heart has induced the (Treppe) "staircase phenomenon" of stepwise improvement in cardiac contractility, steadily improving contractions with successive electrically induced beats, first observed by Bowditch in 1871. Its interest and significance in integrated physiological responses of the heart to changing work load have generally been neglected until recently.

Sudden changes of heart rate can also be accompanied by corresponding adjustments. Dr. Alison Dale (now Lady Todd) (1930) observed in an artificially paced frog heart stronger contractions at increasing rates and, conversely, weaker contractions with slowing. The adjustments are not immediate but increase beat by beat up the "staircase." Similar adjustments to rate change take place in the mammalian (Figs. 6 and 7) and probably also in the human heart. Acceleration by atropine may transiently increase the cardiac output, but more constantly the venous pressure falls and an unchanged output is maintained at a substantially lower filling pressure (McMichael and Sharpey-Schafer, 1944b). The converse importance of these phenomena in man lies in the recent realization that patients with complete heart-block may be in a state of circulatory failure at their slow idioventricular rhythm, but when accelerated to 70 per minute or so by an artificial pacemaker may be "paced" out of failure.

Rapid Potentiation

The best example of this phenomenon is the large beat following an extrasystole. An old idea suggested that this was due to the compensating pause with increased filling during this period. This is now discounted, as the beat may be large without a compensating pause. Vaughan Williams (1959) suggests that some substance subserving energy of contraction is released by the electrical action potential, and if the extrasystole is weak some of this unused substance remains to add to the strength of the subsequent contraction.

DIFFERENT MECHANISMS

That these two processes of slow and rapid potentiation are based on different mechanisms is suggested by Rosenblueth *et al.* (1959) and independently by Kruta and Braveny (1962). Rosenblueth has shown that rapid (post-extrasystolic) potentiation can be superimposed on the slow staircase adaptation. Kruta has shown that metabolic

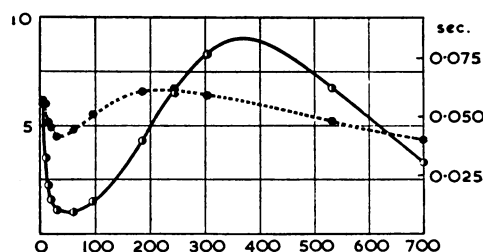


FIG. 6.—Variations of amplitude (continuous line) and of duration (broken line) of contraction of left atrial myocardium of guinea-pig at 35° C. From about 60 to 250 per minute there is a steady increase in amplitude with increasing rate and also an increased speed of contraction. Beyond 350 the response falls off. (Reproduced by permission from Kruta and Braveny (1962).)

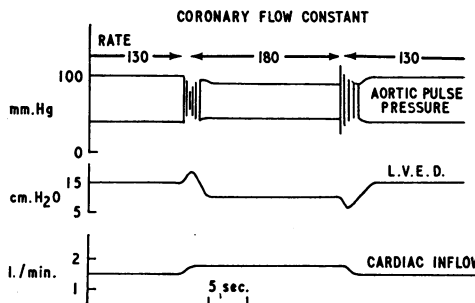


FIG. 7.—Bowditch rate effect. Isolated dog heart: on sudden acceleration the first beats are weaker (falling pulse pressure) while sustained inflow elevates ventricular volume and diastolic ventricular pressure (L.V.E.D.). Then contractility improves as L.V.E.D. falls to and then below its previous level. A new equilibrium is reached with output (inflow) maintained at a slightly higher level but at a lower filling pressure (L.V.E.D.). On sudden slowing improved contractility is clearly shown by the wider pulse of the first beats and the lower L.V.E.D. at which these occur. A downward "staircase" then occurs until the control values are re-established. (Redrawn from Sarnoff and Mitchell, 1961.)

inhibitors (dinitrophenol and fluoroacetate) suppress the slow cumulative staircase potentiation but leave the immediate post-extrasystolic potentiation effect unchanged. Reserpine, which drives out noradrenaline and reduces adrenaline, does not interfere with either form of potentiation.

Sarnoff and his associates support the idea of Hajdu and Leonard (1959) that this staircase adaptation to change of work load may be due to greater potassium efflux from increased myocardial activity, as a slight potassium loss enhances contractile power. This view, however, is not everywhere accepted (Braveny and Kruta, 1958).

The Vagus and Contractility

Does the vagus depress cardiac contractility? In 1888 that distinguished Aberdeen physiologist, John MacWilliam, published tracings showing slowing of the mammalian heart on mild stimulation of the vagus and depression of ventricular force with stronger stimulation. Reeves and Hefner (1961) reported from Tinsley Harrison's department in Birmingham, Alabama, diminished amplitude of ventricular contractions on vagus stimulation. Maintaining vagus stimulation, however, and driving the heart more rapidly by a series of induction shocks, the amplitude of the contractions was restored. Similar experiments were also conducted by MacWilliam (1930) with the same results. It would thus appear that unopposed vagus action with slowing induces a reversed staircase phenomenon as a consequence of the reduction of cardiac work load. These staircase phenomena with varying rates may be explicable on the hypothesis put forward by Vaughan Williams (1959), as follows:

"The magnitude of contraction in (atrial) muscle is determined by the amount of a substance . . . released after the beginning of action potential, and this substance is made available for release at a slow rate in the absence of action potentials and at a faster rate in the presence of action potentials in proportion to their frequency. . . . When the interval between contractions is long the size of the contractions would be larger the longer the interval. . . . The initial effect of a change to faster frequency would be to reduce contractions (see Figs. 7 and 8) though the contractions ultimately become larger (staircase)."

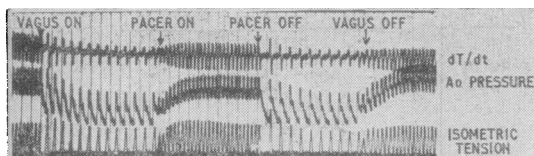


FIG. 8.—Dog heart experiment. With vagus stimulation the first heart beat is larger than the control value, but subsequently the beats decrease in strength. While maintaining vagus stimulation and restoring the original heart rate by an electrical pacemaker the beats again increase gradually in amplitude. (Reproduced by permission from Reeves and Hefner, 1961.)

We have thus come a long way from the acceptance of the dominance of the Starling principle in the regulation of the cardiac output. The principle holds, as Starling himself said, "other things being equal." In the intact mammalian and human organism, however, other things are very often not equal and we have to take into account autonomic regulation of rate and contractility, hypothalamic control through its neurohumoral mechanisms, and intrinsic autoregulation or homeometric regulation. As clinicians we are compelled to keep the complex interaction of these variables constantly in our minds.

The powerful drugs we use in the treatment of hypertension may have a beneficial effect against the threat of hypertensive heart failure, and indeed in the days of ganglion-blockers reversal of hypertensive heart failure could often be demonstrated as a result of blockade or

partial blockade of both sympathetic and parasympathetic. Since the introduction of selective sympathetic blockade by bretylium, guanethidine, and methyl dopa we have seen with each and all of the latter drugs aggravation of heart failure in spite of good blood-pressure reduction. All these drugs may diminish the catechol amine content of the heart and also reduce its rate. By unopposed vagus action, slowing, and the reversed staircase phenomenon the effects of relief of hypertensive overload on the circulation may in certain circumstances be counterbalanced. This is a speculation worth further study.

Electron Microscopy of the Heart

The advance of knowledge in the behaviour of the heart as a whole is now matched by a detailed structural study of muscle by electron microscopy in which Hugh Huxley and Andrew Huxley (unrelated) have played a prominent part. The long-chain protein filaments of actin are evenly interdigitated between the myosin strands, and these rods or threads seem to slide between one another with contraction and relaxation. Small saw-edge bridges seem to link the two proteins. Although most of the work has been done on striated muscle, to which heart muscle bears a close similarity, one outstanding difference is that the heart-muscle cells contain very large mitochondria, up to 500 times the volume of those in the psoas muscle. The large mitochondria bear some relation to the endless beating of the heart in life. In the muscle of the wings of a locust mitochondria are so enormous that they are actually visible to the naked eye. Between the fibres and under the sarcolemma there is a fine canal called the sarcoplasmic reticulum, polarization of the surface of which may play a part in activating contractions (review by Kuschner and Lobdell, 1959).

Cardiac Metabolism

In skeletal muscle, Szent Györgyi has shown that the anaerobic source of energy is the liberation of high-energy phosphate bonds from adenosine triphosphate, and with the resynthesis of adenosine triphosphate the muscle relaxes. Potassium, calcium, and magnesium are all involved in the process of energy release. Heart muscle, however, cannot continue contracting anaerobically, and though the phosphate energy mechanism is the same it is dependent on continuous oxidative metabolism. Among other differences which have been noted is that cardiac muscle myosin is about half the molecular weight of myosin in skeletal muscle.

The heart can metabolize fat and carbohydrate, the former mainly during conditions of rest, and increasing use is made of readily available carbohydrate during exercise. The work of Bing (1961) has shown that in heart failure cardiac metabolism is scarcely altered from the normal and the sources of energy are the same in the failing as in the normal heart. The heart, however, in failure has become less efficient in the utilization of available energy. In experimental heart failure in dogs Olson (1961) suggests that the myosin has undergone some alteration, having changed its molecular weight, while Kako and Bing (1958) established that actomyosin from the failing heart contracts less strongly.

There is little doubt that the detail now being revealed by electron microscopy and the biochemical approaches to the fundamental problem of contraction of muscle are going to add substantially to our knowledge and understanding of the wonderful muscular pump which keeps us alive throughout our allotted span.

LECTURE II: A POWER OVER THE MOTION OF THE HEART

William Withering's clinical observations were much dependent on noting the diuretic effect of digitalis in oedema affecting limbs and lungs (probably cardiac). He realized, however, that the drug was ineffective in many other types of dropsy such as ascites alone (probably cirrhotic). In his clinical analysis, too, he observed that, if the pulse was feeble or intermittent, diuretic effects were frequently observed. He also noted that, while true spasmodic asthma was not relieved by digitalis, if the so-called asthma was accompanied by oedema of the legs and anasarca of the lungs the attacks might be curable: to-day we can interpret this as Withering's recognition that the drug was effective in left ventricular failure with cardiac asthma. He also describes the cases of two patients who had been treated for angina pectoris but who had developed hydrothorax; one did not survive, but the other was greatly relieved within eight days of taking powdered digitalis leaf and she remained well after six months. No doubt these were instances of ischaemic heart disease, one of which recovered from failure.

In spite of Withering's observations (of great precision in the medicine of his day), digitalis therapy continued to be poorly managed until the present century, and even to-day there are some respected elders of the profession who still believe that its only effect is achieved by the control of ventricular rate in atrial fibrillation. Cushny, Mackenzie, and Lewis were all deeply interested in this irregularity and emphasized the part played by digitalis in the control of the rapid and irregular action of the ventricles. The effect of digitalis in reducing the rate when this was rapid was often very remarkable and was accompanied by clinical improvement; when I worked at University College some thirty years ago Sir Thomas Lewis was forbidding his house-physicians to use digitalis except in the presence of fibrillation. Both Mackenzie and Cushny, however, had been more cautious in their opinions. Mackenzie emphasized that the actions were observed most strikingly in the presence of atrial fibrillation, but this did not exclude an effect when the heart was in sinus rhythm; while Cushny, who was my teacher of pharmacology in Edinburgh, was insistent that it had an action in strengthening the beat of a weakened or fatigued heart. Although Lewis was the accepted doyen of British cardiology, many of his British colleagues, such as my former chief Professor W. T. Ritchie, did not accept his views and digitalis was regularly used in most patients with cardiac failure whether they had atrial fibrillation or not.

Understandable Confusion

The confusion about digitalis was readily understandable for the following reasons. (1) There are many types of cardiac failure in which digitalis seems often to be ineffective. These include severe aortic valve disease, certain types of cor pulmonale, and anaemic heart failure. (2) Digitalis seems to confer benefit at a particular stage of the development of cardiac failure. It is ineffective merely in cardiac hypertrophy and it also becomes ineffective in the later and terminal stages of cardiac failure. (3) Its beneficial action is particularly well marked in hypertensive and ischaemic heart disease involving the left ventricle—that is, when the failure is mainly muscular and when improved contractility is unimpeded by obstructed or incompetent valves. This responding group was emphasized by Marvin (1926) and indeed by Withering himself in his notes on cardiac asthma.

(4) The drug has singularly little demonstrable action on the dynamics of the normal human or normally functioning animal heart. This led many pharmacologists, such as Cohn (1915) and at one stage Katz *et al.* (1938), to declare that they could find no evidence of any stimulating effect of digitalis on contractility of the heart.

When Sharpey-Schafer and I began to use right atrial catheterization in human heart failure we were able to add cardiac output measurements to clinical observations hitherto limited to venous filling pressure and heart-rate changes, hoping that this would help to clarify the somewhat confused situation. The results we obtained were roughly as follows: (1) digitalis had no effect on the output of a normal heart though venous pressure and cardiac output often fell in the period of observation; (2) with failing hearts the venous pressure nearly always fell, sometimes slightly but often considerably; (3) the fall in venous pressure could occur with an improvement in cardiac output, but it could also occur with no change whatsoever in the cardiac output; and (4) in many patients with cardiac failure reduction of the venous pressure by venesection could lead to an improvement in the cardiac output.

We naturally questioned whether a primary reduction of venomotor tone (then a somewhat novel concept) might be of some primary importance in contributing to digitalis action (McMichael and Sharpey-Schafer, 1944b). Although the cardiac output effects of digoxin and venesection were intriguingly similar, we also noted that left ventricular work (output \times B.P.) was significantly greater after digitalis (Howarth *et al.*, 1946).

In our earliest studies we considered it unjustifiable to put a catheter beyond the right atrium, and it was a few years later, when we repeated some of the work with right ventricular pressure measurements, that the answers became clearer. Only then did we grasp that an improved performance by the left ventricle could be accompanied by a reduction of pressure ("congestion") in the pulmonary blood-vessels with a consequential fall of right ventricular work and a drop in the systemic venous filling pressure. Improved performance of the left ventricle was not necessarily accompanied by an increase in the cardiac output, but decrease of congestion in the lungs could extend through the vascular system, relieving the right heart with a fall of pressure in the systemic veins (McMichael, 1952).

Later studies suggest strongly that the beneficial effects of venesection may depend on decreasing the dilatation of the right ventricle, with reduction of tricuspid incompetence (McMichael and Shillingford, 1957). Following this manoeuvre less blood will go back and more will go forward. Incompetence of the atrio-ventricular valves seems often to underlie the development of a falling cardiac output response in the "Starling curve" (Sarnoff and Berglund, 1954). Similar results on output and venous pressure following digitalis and venesection may thus result from entirely different mechanisms.

Another cause of confusion is the occasional discrepancy between demonstrable pharmacological effects and clinical results. For example, in the presence of pulmonary hypertension in mitral stenosis a digitalis increase in pulse pressure of a failing right ventricle may be followed by little clinical improvement. Indeed, increasing the strength of a failing right ventricle could add to pulmonary congestion, making the patient worse. Rapidly acting intravenous strophanthin, which was so commonly used by French

and German physicians, was regarded by them as contra-indicated in mitral stenosis as it might induce pulmonary oedema (Frankel and Thauer, 1934).

The myocardium has to be in some type of hypodynamic state before the positive inotropic action of digitalis improving myocardial contraction can be demonstrated. So long as the myocardium is acting normally no change in cardiac output or in intracardiac pressure pulses can be demonstrated. There is a very extensive body of opinion to the effect that the normal heart is uninfluenced by digitalis. Braunwald *et al.* (1961), however, have produced some evidence from observations with a ventricular surface-strain gauge at cardiac operations (when the heart was by-passed and coronary perfusion was maintained) that isometric contraction of slightly stretched isolated segments of non-failing left ventricular muscle may be increased by the injection of strophanthin. They agree, however, that the output remains unchanged by digitalis when the heart is normal.

The anaemic heart and the asphyxiated heart of bronchitic cor pulmonale may also fail to respond to digitalization. In general we are in agreement with Marvin that non-valvular left ventricular failure is the type in which the most favourable responses can be demonstrated. Contrary to an opinion often held, thyrotoxic heart failure is frequently of the low output type and digitalis alone can produce remarkable functional improvement, although the cure is not completed until thyrotoxicosis is brought under control by other means.

Slowing of the Heart

Full digitalization is accompanied by bradycardia, which results from stimulation of the vagal centres. It is doubtful, however, if slowing of a heart in sinus rhythm initiates benefit. The slowing in patients with sinus rhythm is progressive over a few days and at least is partly due to general improvement of the circulatory state. The major action of digitalis in slowing ventricular rate is seen in atrial fibrillation. The early phase of this action is mainly dependent on vagal inhibition of conduction through the bundle of His, as in these early stages slowing can be abolished by atropine; later digitalis has a direct blocking action on the conducting tissues. Even here it can be questioned whether slowing of rate is really responsible for much of the clinical improvement. Kelly and Bayliss (1949) showed that when the slowing of ventricular rate was accompanied by improvement in cardiac output abolition of the slowing by atropine did not lead to any depression of the improved minute-output of the heart. It is thus possible that in these circumstances the real improvement results from improved contractility of the ventricular muscle and that digitalis control of rate is merely an accompaniment which is particularly useful in the control of therapeutic dosage of the drug.

Other Actions of Digitalis

Reduction in Venous Pressure.—While it is now widely agreed that the fall in venous pressure is the result of improved cardiac contractility, Ross *et al.* (1960) have studied venous pressure responses in dogs being perfused by an extracorporeal pump. Under these circumstances when the pump output is under strict mechanical control the injection of digitalis leads to a fall in venous pressure uninfluenced by volume flow. In dogs, however, this is apparently due to constriction of hepatic veins, as suggested by Dock and Tainter (1930), and it is doubtful if this action is very important in man, in whom the hepatic veins have

less muscle than in the dog. It has also been shown that full intravenous doses of the glycoside elevate the arterial pressure by a generalized vasoconstriction. This action is occasionally responsible for temporary unexpected exacerbations of left ventricular failure when full doses of the rapidly acting preparations are given intravenously with therapeutic intent.

Ectopic Rhythms.—Large doses of digitalis produce a variety of rhythm disturbances in the experimental laboratory. Heart-block and premature beats are the most common. In the early stages of heart failure full therapeutic digitalization seldom produces any abnormality of rhythm, but in the more advanced stages ectopic beats, and particularly coupled beats, may be produced by quite small doses of digitalis. Loss of potassium from cardiac muscle cells may play a part in promoting these rhythm disturbances, and the simultaneous administration of potent diuretics causing further potassium depletion may precipitate serious trouble or even fatal arrhythmia unless potassium balance can be maintained.

Diuresis.—Eichna *et al.* (1951) support the general conclusion that digitalis diuresis results from improvement of the general circulation, though this may be indirect, for a diuresis can take place with only a very slight improvement in renal plasma flow and glomerular filtration rate, and indeed in one patient during a diuresis no change in cardiac output occurred although the venous pressure fell. A new and interesting observation (Hyman *et al.*, 1956) is that the injection of 0.06 mg. of digoxin or more into one renal artery in the dog can produce a diuresis from that kidney alone: Cahill (1962) has reviewed the subject and thinks that digitalis directly inhibits the ion transport system in the proximal renal tubule. This interference with the reabsorption of filtered sodium has been analysed by Strickler and Kessler (1961), who found that this action, out of nine glycosides examined, was possessed *only* by those digitalis steroids which act on the heart. Those exhibiting cardiac activity have an unsaturated lactone ring attached to the phenanthrene nucleus. Saturation of the lactone ring makes them inactive. Those known to affect the heart increased sodium excretion on local injection into the renal artery: those which failed to show this renal effect had no cardiac action.

Mode of Action

The mode of action of digitalis on the heart still remains the central problem. The difference between its usual lack of demonstrable action on the normally functioning heart and its striking effect on the failing heart (or the poisoned heart of the pharmacologist) is puzzling. That it has an extracardiac action on veins, arteries (which it constricts), and probably the kidneys there can be little doubt, but it is equally certain that these are of much less significance in relation to its clinical benefits. An old suggestion made by Stewart and Cohn (1932) that digitalis reduces cardiac size can certainly be demonstrated in patients responding to treatment. Such reduction in size could simultaneously account for diminution of output after digitalis in normal hearts and improvement of heart failure. Certainly these effects have been demonstrated, but it is more likely that diminution in cardiac size is a consequence rather than a cause of improved function.

Does digitalis act by restoring the intrinsic regulation exemplified by the staircase effect? This seems unlikely as the rat heart, in which the staircase effect may be slight or absent, responds well at all rates to ouabain (Benforado, 1958).

As already noted, Bing (1961) has demonstrated that in heart failure cardiac metabolism is scarcely altered apart from a slight increase in the proportion of carbohydrate utilized. Carbohydrate utilization by the heart also increases in exercise, and it may be that the failing heart is merely behaving as though it were slightly overworked. The sources of energy thus do not differ from the normal heart, and digitalis does not alter cardiac metabolism as measured in this fashion.

It has also been shown that the release of high-energy phosphate bonds from adenosine triphosphate (A.T.P.) and the synthesis of A.T.P. is not influenced either by heart failure or by digitalis (Wollenberger, 1949). No digitalis effects have been demonstrated on the respiration of mitochondria or of sarcosomes extracted from heart muscle.

It may be noted here that Repke (1958), using ^{14}C -labelled digitoxin made by growing foxgloves in an atmosphere of $^{14}\text{CO}_2$, has shown that there is no special concentration of the glycoside in heart muscle, the effective concentration required to produce an action being of the order of one in a million to one in ten million (10^{-7} to 10^{-6}).

Actomysin threads can be isolated and made to contract *in vitro*, and under appropriate circumstances stronger contraction can be elicited by ouabain (Robb and Mallov, 1953). Kako and Bing (1958), however, found that actomysin bands taken from insufficient hearts were unaffected by digoxin alone, but contraction was restored towards normal by digoxin and calcium. Digitalis may possibly lead to the binding of more calcium ion by myosin, which in turn could improve the normal sliding movement of the actin filaments. By micro-incineration Ca and Mg have been demonstrated in the bridges between the filaments of actin and myosin (Draper and Hodge, 1949). It has already been noted that Olson (1961) has claimed that the myosin of cardiac muscle is altered in cardiac failure, becoming more viscous, and digitalis may have some effect in changing this towards normal.

The part played in all these reactions by intracellular electrolyte changes is still poorly understood. Calcium has a very important part to play, but its intracellular concentration cannot yet be accurately estimated. Potassium loss precipitates the development of ectopic rhythms from digitalis and its administration may counteract them. Daly and Clark (1921) demonstrated that lowering of sodium concentration outside cardiac cells had an effect very similar to that of strophanthin. The demonstration that exchange of ions in the kidney parallels the cardiac activity of various glycosides seems to lend important support to the suggestion that the effects of digitalis on the heart take place by subtle rearrangement of intracellular ions in which calcium may play the most important part.

Conclusion

William Withering indeed pinpointed a problem which all our technical advances have as yet failed to solve. We have learned a great deal more about digitalis, and when we finally understand its action we shall have advanced to a deeper understanding than we have at present of heart failure and of the mechanisms of contraction of cardiac and other striated muscle. Capacity for movement is fundamental to all life, and perhaps the next stage in our analysis will lie mainly with protein and enzyme chemists and electron-microscopists. William Withering's great contribution was to give us a key and leave us with the problem of the mechanism of the lock in which it so frequently works so miraculously.

REFERENCES

- Benforado, J. M. (1958). *J. Pharmacol. exp. Ther.*, **122**, 86.
 Bing, R. J. (1961). *Amer. J. Med.*, **30**, 679.
 Braunwald, E., Bloodwell, R. D., Goldberg, L. I., and Morrow, A. G. (1961). *J. clin. Invest.*, **40**, 52.
 — Frye, R. L., Aygaen, M. M., and Gilbert, J. W., jun. (1960). *Ibid.*, **39**, 1874.
 Braveny, P., and Kruta, V. (1958). *Arch. int. Physiol.*, **66**, 633.
 Cahill, K. M. (1962). *Lancet*, **2**, 445.
 Cohn, A. E. (1915). *J. Amer. med. Ass.*, **65**, 1527.
 Cournand, A., and Ranges, H. A. (1941). *Proc. Soc. exp. Biol. (N.Y.)*, **46**, 462.
 Dale, A. S. (1930). *J. Physiol. (Lond.)*, **70**, 455.
 Daly, I. de B., and Clark, A. J. (1921). *Ibid.*, **54**, 367.
 Dock, W., and Tainter, M. L. (1930). *J. clin. Invest.*, **8**, 467.
 Draper, M. H., and Hodge, A. J. (1949). *Nature (Lond.)*, **163**, 576.
 Eichna, L. W., Farber, S. J., Berger, A. R., Earle, D. P., Rader, B., Pellegrino, E., Albert, R. E., Alexander, J. D., Taube, H., and Youngwirth, S. (1951). *J. clin. Invest.*, **30**, 1250.
 Frankel, A., and Thauer, K. (1934). *Ergebn. inn. Med. Kinderheilk.*, **46**, 208.
 Frye, R. L., and Braunwald, E. (1960). *J. clin. Invest.*, **39**, 1043.
 Hajdu, S., and Leonard, E. (1959). *Pharmacol. Rev.*, **11**, 173.
 Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1946). *Clin. Sci.*, **6**, 41.
 Hyman, A. L., Jaques, W. E., and Hyman, E. S. (1956). *Amer. Heart J.*, **52**, 592.
 Kako, K., and Bing, R. J. (1958). *J. clin. Invest.*, **37**, 465.
 Katz, L. N., Mendlowitz, M., and Kaplan, H. A. (1938). *Amer. Heart J.*, **16**, 149.
 Kelly, H. G., and Bayliss, R. I. S. (1949). *Lancet*, **2**, 1071.
 Knowlton, F. P., and Starling, E. H. (1912). *J. Physiol. (Lond.)*, **44**, 206.
 Kruta, V., and Braveny, P. (1962). *Proceedings of 22nd International Congress of Physiological Science*, **1**, 137.
 Kuschner, M., and Lobdell, D. H. (1959). *J. chron. Dis.*, **9**, 424.
 Lauson, H. D., Cournand, A., and Bloomfield, R. A. (1946). *J. clin. Invest.*, **25**, 913.
 Liljestrand, G., Lysholm, E., and Nylin, G. (1938). *Skand. Arch. Physiol.*, **80**, 265.
 McMichael, J. (1952). *Brit. med. J.*, **2**, 525.
 — and Sharpey-Schafer, E. P. (1944a). *Brit. Heart J.*, **6**, 33.
 — (1944b). *Quart. J. Med.*, **13**, 123.
 — and Shillingford, J. P. (1957). *Brit. med. J.*, **1**, 537.
 MacWilliam, J. A. (1888). *J. Physiol. (Lond.)*, **9**, 345.
 — (1930). *Quart. J. exp. Physiol.*, **20**, 149.
 Marvin, H. M. (1926). *J. clin. Invest.*, **3**, 521.
 Olson, R. E. (1961). *Amer. J. Med.*, **30**, 692.
 Reeves, T. J., and Hefner, L. L. (1961). *Trans. Ass. Amer. Phycns.*, **74**, 260.
 Repke, K. (1958). *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmacol.*, **233**, 271.
 Robb, J. S., and Mallov, S. (1953). *J. Pharmacol. exp. Ther.*, **108**, 251.
 Rosenblueth, A. (1962). *Proceedings of 22nd International Congress of Physiological Science*, p. 144.
 — Alanis, J., Rubio, R., and Lopez, E. (1959). *Arch. int. Physiol.*, **67**, 374.
 Ross, J., jun., Braunwald, E., and Waldhausen, J. A. (1960). *J. clin. Invest.*, **39**, 937.
 Rushmer, R. F., Smith, O., and Franklin, D. (1959). *Circulat. Res.*, **7**, 602.
 Sarnoff, S. J., and Berglund, E. (1954). *Circulation*, **9**, 706.
 — Brockman, S. K., Gilmore, J. P., Linden, R. J., and Mitchell, J. H. (1960). *Circulat. Res.*, **8**, 1108.
 — and Mitchell, J. H. (1961). *Amer. J. Med.*, **30**, 747.
 — Gilmore, J. P., and Remensnyder, J. P. (1960). *Circulat. Res.*, **8**, 1077.
 Stewart, H. J., and Cohn, A. E. (1932). *J. clin. Invest.*, **11**, 917.
 Strickler, J. C., and Kessler, R. H. (1961). *Ibid.*, **40**, 311.
 Szent Györgyi, A. (1953). *Chemical Physiology of Contraction in Body and Heart Muscle*. Academic Press, New York.
 Vaughan Williams, E. M. (1959). *J. Physiol. (Lond.)*, **149**, 78.
 Warren, J. V., Brannon, E. S., Weens, H. S., and Stead, E. A., jun. (1948). *Amer. J. Med.*, **4**, 193.
 Wollenberger, A. (1949). *J. Pharmacol. exp. Ther.*, **97**, 311.

Regulations have been made which increase from £60,000 to £120,000 the limit of the estimated cost of certain capital works that regional hospital boards and boards of governors of teaching hospitals may undertake without the consent of the Minister of Health, and from £1,000 to £3,000 the limit of the estimated cost of certain maintenance works that hospital management committees may undertake without the consent of the regional hospital board.