The Sixty-Ninth Mary Scott Newbold Lecture

The Mechanism of Cardiac Failure

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It is a privilege to have been asked to give the sixty-ninth Mary Scott Newbold Lecture. The list of my predecessors is indeed distinguished. The topic, cardiac failure, was chosen because my colleagues and I have been concerned with this problem for almost a quarter of a century. In this lecture I propose to outline my present concepts based on the evolution of thinking which has resulted from our work in this field and the impact of the literature. I shall give scant attention to the work of others, not because their work is unimportant, but because time is limited and the material to be covered extensive.

What Is Cardiac Failure?

At the outset, let us define the task of the heart. It is the task of the heart to supply an adequate quantity of blood to meet the requirements of the various organs in the body at rest and during activity, so that they may perform their several functions without handicap. A heart that does this is competent. One that does not is incompetent. Incompetence of the heart includes another concept. An incompetent heart is not only one that fails to pump an adequate amount of blood to the organs because the compensatory mechanisms are inadequate, but it may be one which does its assigned task, provided the compensatory mechanisms are adequate. Encroachment upon cardiac reserves occurs, therefore, whenever the heart becomes incompetent.

An incompetent heart with an inadequate output exhibits “forward failure” phenomena. An incompetent heart with an adequate output exhibits congestive phenomena behind the incompetent chamber. An incompetent heart with an inadequate output may show such congestive phenomena also, in addition to “forward failure.”

Failure of the circulation in supplying the organ needs at rest or during effort may be cardiac or extracardiac. Extracardiac circulatory failure may be due to peripheral vascular collapse, when the systemic peripheral vessels dilate and blood is pooled within them instead of being returned to the heart. It also occurs in shock, which should be clearly defined as a progressive oligemia with hemococoncentration and compensatory systemic vasoconstriction. Here too the decreased venous return to the heart is the primary mechanism for the inadequate circulation. In both of these circumstances, the inadequate circulation is not initially due to an incompetent heart, but is due to circulatory disorders in the vascular system. Thrombosis in major veins, or other forms of venous obstruction, is another mechanism interfering with the venous return to the heart, and may lead to circulatory failure without the presence of an incompetent heart.

Cardiac circulatory failure, in which the inadequate blood flow is due to an incompetent heart, need not always be myocardial in origin. It may also be due to: (1) a dynamically significant valvular dysfunction, as in severe stenosis or free regurgitation; (2) a pericardial tamponade, a concretia cordis or a constrictive pericarditis; or (3) a tachycardia with its associated reduction in minute-filling time.

The recent trend of semantics in which the terms congestive failure, low output failure and high output failure, have come into vogue, has led to some confusion to the uninitiated, and these terms should be dropped. Low output failure is a loosely used concept, including many things. Low output of the heart may ensue for a number of reasons and need not be pri-
Mararily cardiac. When, however, in the course of shock or peripheral vascular collapse, or any other extracardiac mechanism leading to low output, incompetence of the heart ensues, then the latter can contribute to the low output.

High output failure is a misnomer that can only confuse the issue. High output of the heart is a compensatory mechanism which enables the body to get an adequate supply of oxygen for the tissues, when this is impossible at normal levels of output. This may ensue in arterial hypoxemia (e.g. anemia, inadequate ventilation in the lungs), in hyperthyroidism and in someavitaminoses. In some fashion the output of the heart per minute is augmented in these circumstances. If the strain is too much for the heart then it becomes incompetent and cardiac circulatory failure ensues even though the cardiac output may still be above the average normal. Chronic cor pulmonale is a frequent example of this circumstance.

Congestive failure too is a misnomer. Congestion may accompany incompetency of the heart whether or not there is cardiac circulatory failure. It may also ensue from disorders of the vascular system when the heart is competent. The mechanisms are in part vascular and in part renal; the latter are dealt with below. The former represent damming up behind the obstruction, whether this be a narrowed vein, a stenosed valve or an incompetent chamber of the heart, with the resulting consequences of this congestion. It may be behind the left or behind the right heart. Such congestion in the pulmonary veins impairs the ventilatory indices, increases the residual volume of the lungs, decreases the vital capacity and leads to pulmonary edema, first manifested by rales. It also leads to elevated "wedge" pressure and often to pulmonary arterial hypertension. Such congestion in the systemic veins leads to venous hypertension and engorgement, liver enlargement, anasarca and edema, as well as to interferences with the most effective operation of the various organs including the heart itself. Such states have been called respectively "left" and "right heart failure."

Not only is the heart attuned to put out as much blood as it receives when in dynamic equilibrium, but this applies equally to each individual side of the heart. Thus, in dynamic equilibrium, the right and left ventricles pump out equal amounts of blood, whether this is low, high or average. Only when a patient is going into circulatory failure, coming out of it, or is moribund, is there any extended period of disequilibrium between the two hearts, as far as their minute output is concerned. So called "right" or "left heart failure," or more properly circulatory failure due to right or left heart incompetency, therefore, is not a disparity in output of the two sides of the heart. A moment's reflection will show that if the left heart were to pump 5 cc. more per stroke than the right, and if the right ventricle pumped 60 cc. per stroke and the heart beat 80 times per minute, and if the circulating blood volume is of the order of 5 liters, then in about 10 minutes all of the blood would have been pumped into the systemic circuit and none would remain in the lungs. This reductio ad absurdum is simply mentioned because of the loose thinking sometimes encountered in dealing with this subject.

One of the problems that has become of practical significance latterly, is the identification of how much of the lung congestion is due to mitral stenosis or mitral regurgitation and how much is due to a myocardial incompetent left ventricle. Furthermore, as every clinician appreciates, pulmonary disease itself produces signs, symptoms and changes in the laboratory measures of ventilatory efficacy in many respects imitative of that produced by an incompetent left heart.

It is thus apparent that heart failure arises from incompetency of the heart, sometimes leading to cardiac circulatory failure—an entity distinct from extracardiac circulatory failure—and sometimes leading to congestion. Furthermore, it should now be clear that not all forms of incompetency of the heart are due to myocardial incompetency; they may result from abnormalities of other parts of the heart's structure or from disturbance in its rhythm. Finally, even the normal myocardium may be put to so much strain that its reserves are exhausted, and it too can become incompetent
under these excessive conditions of stress. The distinction between a normal and a diseased myocardium is that the stress required to lead to this breaking point is less for the diseased than for the normal myocardium.

**Regulation of the Normal Cardiac Output**

The heart normally is so attuned that it pumps out, over any extended period of time, as much blood as it receives. In this respect, it is no different than the peripheral circulatory tree, which ordinarily forwards to the heart as much blood as it receives over any extended period of time. A number of servomechanisms are involved in this fine attunement of the circulation. Some of these are mechanical, some are humoral and some are neurogenic.

The most important of the humoral mechanisms are those involving the hormones of the adrenal medulla, l-epinephrine and l-nor-epinephrine, although doubtlessly other hormones, especially those of the adrenal cortex and pituitary, play their role. Closely bound up with the adrenal medullary hormones are the autonomic nerves which richly innervate the heart and peripheral blood vessels. They are linked with end organs, both chemoreceptors and baroreceptors, located in the lungs, in the pulmonary and systemic vascular trees, and in the heart itself. The autonomic nerves are also influenced by messages relayed from end organs located in various somatic structures, and including the special senses. They are also subject to the outpourings of the several stations in the central nervous system which constitute a complex cybernetic arrangement, far more complicated than that used by engineers.

A little more needs to be said about the mechanical factors controlling the flow of blood in the periphery. The capacity of the peripheral vascular bed is subject to change by humoral and neurogenic influences. This can occur by opening or closing of blood reservoirs and so adding to or extracting blood from that in active circulation. In like manner, changes in venomotor tone may strikingly alter the capacity of the peripheral vascular bed, shifting blood to or away from these vessels, which constitute a large variable capacity. Similarly, vasomotion in the smallest vessels may be enhanced, leading to accelerated forward flow. This acceleration of forward flow is brought about by virtue of the presence of valves in the circulatory tree which convert any intermittent forces operating upon the blood into forward flow. Such intermittent forces may also be caused by the movements of the innumerable villi in the intestines, by the partial tetanic contraction of the skeletal muscles which gives them their tone, by the motions of the limbs as in walking, and by the swaying accompanying the maintenance of an upright stance. Just as significant is respiration itself, since the thorax and abdomen can be considered as alternating bellows. Even the heart plays its role in this regard, over and above the *vis a tergo* it imparts, some of which still remains when the capillaries are reached. Thus, during its systole, the auriculoventricular junction moves toward the apex, tending to cause a drop on the pressures within the atria and thereby facilitating the flow of venous blood toward the heart.*

There are thus a number of factors which adjust venous return to the heart and act as a powerful adjuvant to the pumping power of the systole of the ventricles. To them must be attributed a major part in maintenance and regulation of blood flow.

Adjustment of the heart itself also plays an important role in regulating the cardiac output. In part, this is brought about by variations in heart rate, which is dependent upon the action of the nerves supplying the heart, aided and abetted by the adrenal medullary hormones. In part, cardiac output is dependent upon the size of the ventricles when systole begins, that is, upon the right and left ventricular end diastolic volumes. This in turn is dependent upon the systemic resistance (the blood not pumped out in the previous systole), the tone of the ventricles which determines its resistance to

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*This motion of the base of the heart toward the apex during systole has another pumping effect: the aorta and pulmonary artery are elongated while their valves are open, so that when these vessels shorten again in diastole with the valves closed, a small amount of blood is, as it were, "lifted" and added to that already ejected by the heart during its systole.*
MECHANISM OF CARDIAC FAILURE

Fig. 1. Diagram of the volume curve of one ventricular cavity of the human heart at an assumed rate of 80 beats per minute, a stroke volume of 60 cc. and a systolic residue of 15 cc. (Based on the studies of Wiggers and Katz.) The curve starts in diastole. When the impulse in the sinus node spreads to the atria it causes them to contract and then relax (between VIII and IX and the homologous part of the curve ahead of I). The atria contribute little to filling; about 5 cc. net at ordinary heart rates. Actually while they add 10 cc. during their contraction, they "take back" 5 cc. during their active relaxation. The impulse reaches the ventricles at I, and they begin to contract, at first isometrically (between I and II). Then ejection begins. In the short period of time, from II to IV, the blood is ejected from the ventricle (except for the systolic residue). Most of the blood is expelled during the rapid ejection period (II to III) and the remainder in the reduced ejection period (IIII to IV). Diastole begins at IV with a short protodiastole phase (IV to V) and an isometric relaxation period (V to VI). Most of the filling of the heart occurs in the rapid inflow phase (VI to VII). Filling here is just as brusque, and the period of filling is just as short, as that of the rapid ejection phase. In other words, the heart fills with a rush over a short period and not deliberately and uniformly over the whole of diastole. After rapid inflow, there is the period of passive filling, diastasis (VII to VIII), due to the vis-a-tergo of the blood coming back to the heart.

filling, and the duration of diastole, especially the period of its rapid inflow phase (fig. 1). In addition to the action of end diastolic volume and heart rate, both of which are partly determined by extrinsic conditions lying outside the heart, there is another mechanism altering cardiac output which is dependent upon change in the contractile power of the heart. This last is affected by extrinsic influences, resulting chiefly from alterations in the tone of the cardiac nerves and in the hormonal content, especially of adrenal medullary hormones, present in the blood irrigating the heart.

In order for the heart to adjust its cardiac output, alterations in its energy releases take place. These, as ordinarily measured in terms of cardiac oxygen consumption, are determined not only by the end diastolic volume of the ventricles, but also by the character of the actual contraction of the ventricles and by extracardiac neurogenic and humoral mechanisms. When the work of the heart is measured in terms of the product of cardiac output and blood pressure in the aorta and pulmonary artery, and this is compared with the oxygen consumed by the heart to do this work, it is found that the ratio of work to oxygen consumed is quite variable at any end diastolic volume. In fact, oxygen consumption may go down as work increases even though heart size is augmented and heart rate unchanged. This demonstrates that cardiac oxygen consumption like cardiac output is determined by other factors in addition to end diastolic volume.

WHAT DISEASE OF THE HEART DOES

Let us now turn to disease of the heart and see what it does. Disease may increase the stress upon the heart. It may lead, for example, to systemic hypertension. It may lead to pulmonary arterial hypertension which catheterization has demonstrated to occur often; pulmonary arterial hypertension is a frequent complication of a strained left heart, and has as its clinical measure, crude though it be, accentuation of the second pulmonic sound. Disease may lead to increased venous return because often the body metabolism is increased; metabolism is increased either because of the dyspnea produced, the restlessness of the patient, or an associated hyperthyroidism. Added to this, there is an increased venous return whenever anemia or hypoxemia complicates the picture, or when there is a chronic cor pulmonale. Certain vitamin deficiencies are another cause for increases in venous return in heart disease. In addition, disease may lead to valvular stenoses, valvular regurgitations, obstructions, atresias, coarctations, and shunts.
These hidden stresses must be uncovered from their concealment by the examining physician.

The diseased heart will respond to these loads in the same way as the normal heart. It will call for a mobilization of compensatory mechanisms much as in the case of the normal heart. By so doing it will cut down the cardiac reserves.

Disease of the heart may decrease the upper limits of the adjusting compensatory mechanisms from which benefits may be derived and in this way also reduce the cardiac reserve. Thus, for example, the turning point from benefit to detriment as far as heart rate is concerned will occur earlier. This is demonstrated constantly by the relatively greater seriousness of paroxysmal tachycardia of equal degree in hearts that are diseased, than in those that are not. In the case of hypertrophy, the presence of serious coronary disease leading to narrowing of the arteries will summate with the normal factor limiting hypertrophy, so that there will be less chance for maximal hypertrophy than in the normal heart. (Heart weight is a deceptive measure of heart hypertrophy since it also weighs tissues in the heart other than muscle, viz., fibrosis and necrosis. Proper evaluation of true hypertrophy should take this into account.) The upper limit of dilatation is also reached sooner in some forms of heart disease. It would seem that under certain circumstances the heart cannot dilate as much when it is diseased as normally, before reaching the point where the dilatation is detrimental rather than beneficial. While too little is known about the detailed effect of disease upon the heart's contractile power, it is obvious that if the machinery of the heart is impaired, the effectiveness of extraneous mechanisms in increasing contractile power may be lowered. Thus, in several ways, disease of the heart by reducing the maxima of compensation from which benefits may be derived, cuts down the reserve of the heart.

Finally, disease of the heart may impair the contractile power of the heart. When it leads to an obvious anatomic defect like myocardial infarction, which may destroy the machinery of up to one-fourth or more of the left ventricle, the defect in contractility is obvious and apparent. Disease may operate more subtly without such gross change. This may be revealed as cloudy swelling or fatty degeneration histologically, but often it is more subtle than this in lessening cardiac contraction and relaxation. We know so little about the details of the chemistry of this machine, that I will not indulge in any speculations on this topic. When heart disease alters the contractile machinery of the heart, the heart may work inadequately. The heart compensates for an impairment in contractility in the same manner as it does for an increase in stress. At the bedside, therefore, the demonstration of compensatory mechanisms may indicate an increase in stress upon the heart or an impairment in its contractile power.

**Stress on the Heart and the Manner of Meeting It**

In order to understand better the subject of myocardial incompetence and the sequences resulting therefrom, I think we must turn to the normal heart and consider the stresses to which it is subjected and the compensatory mechanisms by which it meets these stresses. Stress upon the heart is threefold in character. It may be due: to an increase in venous return, i.e., in its input load; to an increase in the blood pressure of the systemic or pulmonary arterial system, i.e. in its resistance load; or to certain hidden loads not so easily revealed. Exercise and many emotional disturbances produce an increased input load. They also lead to an increased resistance load on the left heart and often also on the right. Trauma may produce some hidden loads in an otherwise normal heart.

These increases in load have been reproduced in the experimental animal and the mechanisms by which they are met studied. What are these compensatory mechanisms? They are four in number:

1. There is dilatation.
2. If time elapses, there is hypertrophy.
3. There is tachycardia.
4. There is an increase in the contractile power of the myocardium produced by hormonal, humoral or reflexogenic mechanisms.
MECHANISM OF CARDIAC FAILURE

These same mechanisms, as already hinted, operate also upon the diseased heart when its load is increased or when its contractile power is impaired. Dilatation is a simple mechanism resident in the heart and can be seen in the isolated heart, and so may be considered a primary mechanism which is able to attune the output of the heart to its input. At the bedside, dilatation of the heart should be considered compensatory to enable the heart to meet an increased load. In this modern era of catheterization, too many physicians imagine that the pressures in the heart at the end of diastole are a good measure of the size of the heart at that time. Actually the relationship between the end diastolic volume and the end diastolic pressure is not linear, but curvilinear (fig. 2). There is, therefore, under ordinary circumstances, little or no change in the end diastolic pressure with rather large changes in end diastolic volume. It is to the end diastolic volume change that the ventricle's energy release, ability to work and pump blood, is related, and not to its end diastolic pressure. The difficulties of obtaining information regarding end diastolic volume should not permit loose employment of end diastolic pressure, or worse still, the average or mean atrial pressure as an index of the adjustment of the heart by dilatation to an increased load, an error that has unfortunately crept into modern thinking on the part of certain individuals.

Hypertrophy is another mechanism which, by increasing the mass of the heart, permits it to release more energy so that it can overcome the increased load. It requires time, however, and is not available at once but comes into play progressively if the load is sustained over time. We do not know the mechanism of cardiac hypertrophy, although we have reason to believe that it is associated with dilatation, with relative hypoxia and with relative increase in the work of the heart, and is, in some fashion, induced by the release of certain hormones of the pituitary gland. The mechanism of hypertrophy needs intensive exploration. Hypertrophy will occur in a normal heart subjected to increased load as well as in a diseased heart. Obviously, therefore, both

**Fig. 2.** A diagrammatic representation of the distensibility (P/V) curve of the fully relaxed (lower) and fully contracted (upper) left ventricle. It will be seen that at volumes between 0 and 20 cc. the change in pressure at the end of diastole is minimal. Only above 40 cc. does the pressure change become marked. On the other hand, the pressure change at the end of systole is marked at volumes between 0 and 10 cc., reaching a maximum at about 35 cc. and then declining. In isobaric contraction the change in volume during systole and diastole is set on a horizontal line at the level of pressure at which the heart contracts and relaxes, the limits being determined by the two P/V curves. In isovolumetric contraction the change in pressure during systole and diastole is set on a vertical line at the level of the diastolic filling at which the heart contracts and relaxes, the limit being determined by the two P/V curves. Under ordinary conditions of the heart beat, a closed figure is set up (a work-diagram) which begins and ends at the fully relaxed P/V curve, and is determined by the conditions under which the heart begins its systole. The shapes of the systolic and diastolic portions of the curve, and the point where the curve of the work-diagram intercepts the fully contracted P/V curve, are determined by the conditions under which its contraction and relaxation take place. (Copied from Patterson and Starling, J. Physiol. 48: 465-513, 1914.)
dilatation and hypertrophy are not necessarily signs of heart disease unless it is clear that they occur without an increased load upon the heart.

Tachycardia which operates in the intact animal, and is not seen ordinarily in the isolated denervated heart, is a mechanism brought about in some fashion by an increased load. It would take us too far afield in this discussion to enter into the several mechanisms by which this tachycardia could be produced. Suffice it to say that it involves a lessening in tone of the cholinergic nervous mechanism and an enhancement in tone of the adrenergic nervous mechanisms, in all likelihood aided and abetted by the release of L-norepinephrine and L-epinephrine, with the possibility of other humoral agents also operating. Tachycardia, too, is to be considered a compensatory mechanism as easily available as is dilatation to permit the heart to overcome an increased load.

Closely allied with this are changes in the intrinsic machinery of the heart, part of which may operate upon the viscous-elastic properties which we call its tone, but more primarily they operate upon the machinery of its systole, its contractile power. Like tachycardia, these changes in the contractile power of the heart are brought about by reflexogenic and hormonal mechanisms, and it would have been surprising indeed if in the intact animal this had not developed. It is not too difficult to show, upon the exhibition of sympathetic nerve stimulation or the administration of ordinary epinephrine, as I did as far back as 1918, that such changes can be produced in the contractile power of the heart without dilatation and independent of the tachycardia (fig. 3). Exactly how this is brought about and upon which part of the intricate machinery of fat and carbohydrate metabolism—whether upon glycolysis, the Krebs cycle, the actin-myosin mechanism, or the ionic milieu surrounding the muscle—remains to be clearly established. Our department is now engaged in a long-term evaluation of this problem. Suffice it to state that tachycardia and changes in contractile powers of the heart, which are extracardiac in their mechanism, play as important a role as do the intrinsic adjustments of dilatation and hypertrophy.

When all four compensatory factors are simultaneously operative, they are interdependent; the more there is of one, the less need there is for the others to come into play. It would appear that dilatation is one that gives way, the one that is held more in reserve; so is tachycardia. Thus, for example, we are all aware of the fact that a patient with essential hypertension may for years have no tachycardia or no dilatation of his heart, the compensatory mechanism to meet the increased resistance load being accomplished by hypertrophy of the left ventricle.

![Fig. 3. A series of volume curves of the open-chested anesthetized dog drawn so as to superimpose the end of systole of the several beats, in order to show the effect of vagus stimulation (A and B) and epinephrine effect (D and E), as compared with the control (C). Attention is drawn primarily to the shorter duration and accelerated rate of ejection which was produced by epinephrine. These changes are disproportionate to the changes in heart rate and end diastolic volume, indicating a specific action of epinephrine upon the contractility of the heart (from Wiggers and Katz)](image-url)

Cardiac Reserve

One of the concepts that has been loosely employed is the term cardiac reserve. From our work and the impact of this work upon our thinking, I believe, cardiac reserve can be defined more precisely in terms of dilatation, hypertrophy, heart rate and contractile power, since for each of these there is an upper limit beyond which further increase is not possible or, if possible, it becomes detrimental instead of beneficial. Cardiac reserve according to this concept is the difference between the size of the heart existing under the given load and the upper limit from which benefit can be derived; it is the difference between the heart weight existing under the load and that which can be produced; it is the difference between
MECHANISM OF CARDIAC FAILURE

the heart rate existing under the load and the upper limit of heart rate from which benefits can be derived; and it is the difference between the contractile power of the heart existing under the load and the maximum that can be obtained. More properly, however, it is the sum of these four measures of cardiac reserve that gives an index of the total cardiac reserve available to meet increased loads. Now, admittedly it is not always possible in our present state of knowledge to define clearly these measures of cardiac reserve, but this in no sense nullifies the merit of such a concept.

A few words are not amiss concerning the reasons why there is an upper limit to each of these compensatory mechanisms. Thus, it has been established that the heart cannot dilate indefinitely and produce an increase in work. Actually, after a certain point, further dilatation leads to a decline in work (fig. 2). An optimum thus exists in the size of a heart below which further dilatation is beneficial, above which it is detrimental. This fact has been established beyond question. It has been found to be true also when skeletal muscle is lengthened. I like to think in terms, therefore, of a dilated, compensated heart, and an over-dilated, failing heart.

The upper limit of hypertrophy is due to the fact that the number of capillaries do not increase as the heart hypertrophies. This inability of the capillaries to increase in number as the heart mass increases, puts an upper limit to the continued increase in heart weight. This is so since the oxygen and nutritive materials in the blood, and the carbon dioxide and waste products in the tissues move from one site to another by simple diffusion, dependent on their relative concentration at the two sites. As a consequence, the tissues further removed from the capillaries are less well serviced than those close to the capillaries, and as the distance from the capillaries increases, a point will be reached in which the material is not supplied or the waste not removed in adequate amounts commensurate with proper functioning. It is on this basis that the maximum mass of the heart is limited.

When it comes to the extracardiac mechanisms leading to increase in cardiac contractile power, the limits have not been thoroughly explored, but it is just a matter of logic to conceive that these stimuli cannot continue indefinitely to increase the power of the heart. An upper limit must of necessity be reached. What it is, and how much greater than the ordinary contractile power of the heart it will be, remain to be clearly defined.

In the case of heart rate, a number of considerations come into play to point out that one cannot continuously increase the heart rate and get benefit therefrom. This depends in part upon the shape of the filling curve of the ventricles (fig. 1) from which, if we ignore compensatory mechanisms as a first approach to our understanding, it will be seen that as the heart speeds up, it affects at first only an abbreviation of diastasis. Consequently the minute output will go up. This is so since stroke output depends on diastolic filling. When, however, the rate becomes so rapid that it cuts more and more into the rapid inflow phase, then the product of stroke volume and heart rate will decline. In fact, if the rate is so rapid that diastole consists only of isometric relaxation, then no filling will ensue and the heart will therefore have to draw upon its systolic residue for emptying, and this can soon be exhausted within a few beats. Thus, in this department, we have recorded pressure curves from the aorta in man during premature systoles which occurred so early that no evidence of a pressure rise was seen. Compensatory mechanisms tend to overcome this mechanical obstacle of tachycardia, but even they cannot ultimately prevent this decrease in minute volume output with acceleration of the heart. That this is so is shown by the fact, as all of you know, that paroxysmal tachycardia can lead to circulatory failure, and/or to congestion—which can be remedied immediately upon the conversion of the tachycardia to the slower sinus rate.

Tachycardia also becomes detrimental because it cuts down the recovery time. The heart has very little ability to go into oxygen debt. It must make up in the next diastole or two for the oxygen for which it goes into debt during its systole; and since it is constantly beating, this cannot be out of balance for
long without setting up a progressive deteriorating mechanism. Now, as the heart accelerates, the acceleration is primarily at the expense of diastole when recovery occurs, since systole varies only with the square root of the cycle length. Thus, progressive tachycardia puts an increasing strain upon the recovery mechanisms of the heart, and a rate will ultimately be reached that will make the strain so great that the heart cannot by this mechanism meet the increased load.

Furthermore, with tachycardia it is clearly established that the mechanical efficiency, estimated in terms of oxygen consumed for work done, declines progressively as the heart accelerates. Further, it is established without controversy that as the heart progressively speeds up, insufficiency of its coronary blood flow eventually ensues. Hence, not only is there strain upon the recovery time with acceleration because of less time to recover, but there is greater need for oxygen to do the work and there is less adequate coronary flow to permit this recovery to take place.

Consequence of Inadequate Compensating Mechanisms

Thus, it will be seen that the adjustments of the heart which compensate for an increasing load are limited in extent and when these limits are exceeded and when the reserves of the heart are exhausted, the heart cannot meet any further increase in load (fig. 4). The classification of the American Heart Association could be viewed in these terms. With increasing load the upper limits for compensation are reached earlier in the class IV patient than in the class III or class II patient (fig. 5).

With progressive encroachment upon the cardiac reserve, a point will be reached when the compensatory mechanisms become inadequate. With inadequacy of the compen-

![Fig. 4. Factors determining cardiac reserve (R) in the normal and diseased heart (from Katz19). The reduction in R between bed rest and ordinary activity is shown both for the normal and for the diseased heart. Note, however, that the maximum capacity is reduced by disease. Cardiac reserve applies to all the compensatory mechanisms whether it be dilatation, hypertrophy, tachycardia, or change in contractile power. Discussed in text.](http://circ.ahajournals.org/)

![Fig. 5. Relation of work done to heart size in normal subjects (N) and patients with heart disease falling into classes, I, II, III, and IV of the American Heart Association Classification (Katz19). In class I, the individual has the normal limitation in his ability to carry on activities. In the other classes—II with slight, III with moderate restriction of activity and IV requiring complete bed rest—the work done by the heart progressively declines at a given heart size. Therefore, to do the same amount of work as the patient in the class with less impairment of the heart, the patient requires a larger heart size. This encroaches on cardiac reserve. Discussed in text.](http://circ.ahajournals.org/)
sating mechanisms, whether brought on by an increase in load, a decline in the maxima of compensatory mechanisms, or a decline in contractile power of the heart, a new chain of events will ensue. There will develop cardiac circulatory failure, at first only during periods of stress, but later also during ordinary activity and ultimately even at bed rest. Death will then not be far away.

Even before this, redistribution of the circulating blood volume will take place. Blood will be brought out of the reservoirs and the venules by neurogenic and humoral mechanisms in an attempt to bring about compensatory dilatation of the incompetent chamber of the heart. This blood together with the blood damming up behind the incompetent side of the heart leads to congestion and its sequelae (see above) and in some fashion also disturbs the excretory function of the kidney (see below). Thus, when the heart becomes incompetent, there is set up a complex chain of events involving many parts of the circulation and requiring the interplay of many humoral and neurogenic regulating mechanisms. Much remains to be learned concerning this phase of cardiac failure.

**The Mechanical Efficiency of the Incompetent Heart**

I would like to turn now to the subject of the changes in the mechanical efficiency of the incompetent heart, a subject that has been rather forcefully debated in recent years. There are those who believe that heart incompetency is primarily the result of an impairment in the ability to employ for useful work the energy released. There are others, like myself, who believe that the primary defect is in the release of energy and that the ability to employ this energy for work is not *primarily* impaired in all instances of heart incompetency. This is a fundamental problem which may have to be reinterpreted as our knowledge of the intermediate metabolism of the heart grows and clarifies. I will not belabor you with many of the fascinating details of this controversy, but I would like to leave you with a few facts for orientation.

Mechanical efficiency, as an engineering term, is defined as the ratio of work done to the energy required to do this work, the quotient being calculated in similar units, e.g., Joules, foot-pounds or large calories. The energy cost is ordinarily measured in terms of oxygen consumed, and it is assumed that the respiratory quotient is constant in the incompetent as compared with the competent heart, and this quotient may be assumed to be 1 or, as in the case of the average heart, 0.82. The term *work* has had many definitions, but it is more or less generally agreed that it should be defined as the useful work of the heart; that is, the amount of blood pumped by the heart multiplied by the mean blood pressure. The omission of kinetic energy in this calculation ordinarily introduces no serious quantitative error. In our calculations we have included the work of the right as well as the left heart, and have included the coronary flow in calculating the latter. Obviously by using this method of mean values in calculating the work, instead of integration formulas, certain other errors creep in, but these are not ordinarily of sufficient moment to disturb the concept.

Using the simple method outlined above to calculate mechanical efficiency, it can be shown that mechanical efficiency can decline if tachycardia accompanies heart failure, as is often the case (fig. 6). But this is not primarily due to the heart failure, since tachycardia in a competent heart will have a like effect. Likewise it can be shown that if the cardiac output per minute declines as the heart fails, the mechanical efficiency will decline (fig. 6), but this too is not primary with failure, since it will occur with low output even in the competent heart, as in cases of early shock. Furthermore, if an increase in the pulmonary or systemic arterial pressure, an increase in resistance load, occurs, this too may have a tendency to alter the mechanical efficiency in a downward direction (fig. 6), but this again is not primarily heart failure, since a similar effect will occur under like circumstances in the competent heart. In our own experience, with isolated hearts whose work has been kept constant despite their progressive incompetence, we have found no
change in the oxygen consumption of the heart even though the heart dilated in order to maintain this work.

How can we be sure that incompetence is of the same character in all circumstances? Actually, I believe it is not. It may develop in one fashion under certain conditions and in another fashion in other circumstances. It is erroneous to assume that incompetence of the heart is identical under all conditions.

When we view the mechanical efficiency of the heart even under the best circumstances, we find that it really is at most of the order of 30 per cent. Apparently the rest of the oxygen, or a large part of it, is used to maintain the machinery in repair, i.e., to make up for the wear and tear of the machinery, and not directly for its work. Hence, as the work of the heart declines, there may be a pari passu decline of the oxygen needed for the work, but the reparative processes may go on at the same level as before and so the total oxygen may not go down as much as the work does; hence the efficiency will decline. The contrary will be the case when the work of the heart is increased. Here the proportion of energy needed for work will be increased and that necessary for the reparative processes will be less, per centagewise. Furthermore, to pursue these theoretic concepts, there is no guarantee that the rate and sequence of the many intermediate chemical reactions involved during the systole and diastole of the heart will be the same in the incompetent as in the competent heart, or that even the same reactions are employed; and these circumstances obviously can lead to changes in the mechanical efficiency which may vary from one type of incompetent heart to the next, depending upon how the machinery is deranged. Therefore, the mechanical efficiency of the incompetent heart changes in a very complex fashion, especially when cardiac circulatory failure supervenes, all the details of which are not yet clearly understood.

It therefore behooves the clinician in his every day activities to avoid the term cardiac efficiency and speak more of the efficacy of the heart, a term which need not be confused with the more precise definition to which engineers have assigned the concept of mechanical efficiency. I would predict that in the coming years we will have considerable clarification of this aspect of the mechanics of the incompetent heart as never knowledge of the intermediate metabolism of the heart advances.

Edema Formation

In the final portion of this lecture I would like to turn to a different aspect of heart failure, edema formation, in order to emphasize that the syndrome of heart failure is a derangement of function occurring in a complex and interlocking fashion, and extending beyond the heart and the vascular tree. While the heart is the initiating mechanism, a chain of alterations is set up which makes the syndrome of heart failure much more than primary incompetence of the heart. This is not to say

![Fig. 6. The three sets of columns compare respectively, the cardiac output (CO), the heart rate (HR) and the systemic arterial blood pressure (BP) in cardiac circulatory failure (F) and normal circulation (N). The change in each is such as to decrease (>), mechanical efficiency (EFF) of the heart during failure. But like changes in these factors in the competent heart will have a similar effect on efficiency. A number of external factors which can change when the heart fails and thereby alter mechanical efficiency are represented in the square. Since their influence is not known, mechanical efficiency is marked as being changed (≠). There is no reason to believe that similar effects would not be produced by such factors in the competent heart. In the last pair of columns is shown a situation actually obtained in the isolated heart (from Katz29 in which the variables—external factors, cardiac output, heart rate and blood pressure—were kept constant and the mechanical efficiency, consequently, remained unchanged (=). Discussed in text.](image-url)
that one must concentrate on the secondary mechanisms and forget the primacy of the heart, but it shows that heart failure like other syndromes is complicated and not simple. This can best be illustrated, I think, by discussing the mechanisms of cardiac edema. This is a subject which this department has been concerned for a considerable period of time.

The heart initiates the mechanism which causes retention of water and sodium chloride, but this retention is in reality due to a disturbance in the kidney regulation, whose task it is to see that water and sodium chloride neither accumulate nor are depleted from the body. How does this come about? Recently it has been attributed to cardiac circulatory failure ("forward failure"), at least that occurring during periods of stress. It has been emphasized that under these circumstances the sodium chloride and water excretion is dependent upon the glomerular filtration rate. Some years ago we put this to the test by producing pericarditis in the unanesthetized dog (fig. 7). By the use of irritating celophane, an extensive pericarditis ensued and this led chronically to edema; this edema developed long before any change in resting cardiac output, blood pressure, renal blood flow, or glomerular filtration rate, but went, pari passu, with the elevation in venous pressure. It is difficult to believe that this could be produced by a "forward failure" mechanism which reduces the glomerular filtration rate and the renal plasma flow, and so presents the tubules with less water and less sodium chloride to excrete.

What does a reduction in renal plasma flow and in glomerular filtration rate do? This was studied recently by using renal artery constriction (fig. 8), recovery from temporary renal artery occlusion (fig. 9) and recovery from inferior vena cava occlusion above the liver which led to a reversible shock-like syndrome (fig. 10). In all instances the renal plasma flow and the glomerular filtration rate declined, yet the kidney recovered its ability to excrete sodium chloride and water before it overcame the constrictive or post-occlusive decline in blood flow and filtration.

**Fig. 7.** Sequence of physiologic changes in chronic experimental pericarditis with effusion; semi-diagrammatic summary of data obtained on nine dogs (from Fishman and co-workers). V. P., peripheral venous pressure; SCX, thiocyanate space; PL. VOL., plasma volume; A-V, arteriovenous oxygen difference in volumes per cent of oxygen; C.O., cardiac output; B. P., blood pressure (S, systolic and D, diastolic); R.P.F., renal plasma flow; G.F.R., glomerular filtration rate; Na excretion, sodium excretory rate in milliequivalents of sodium per minute, in response to an intravenous hypertonic saline load; (↑ Operation) day of operative placement of irritative celophane bag about the heart, between visceral and parietal pericardial layers. Abscissa represents days postoperative to death (↑ Exitus). Discussed in text.

**Fig. 8.** Acute effect of bilateral renal artery constriction (from Stamler). RPF, renal plasma flow cc. per minute; GFR, glomerular filtration rate, cc. per minute; UF, urine flow, cc. per minute; Na excretion, mEq. per minute. The numbers above the bars represent the numerical values in appropriate units.
rate. It is interesting and well known that the kidney has a protracted period of vasoconstriction following occlusion. The associated changes in renal salt and water exchanges are not due to irreversible damage to the tubules since histologic examinations fail to reveal any such changes, and furthermore, in animals allowed to survive, renal hemodynamics quickly returned to normal. All of these procedures were carried out on the unanesthetized trained dog and it has been the experience of this department that it is best to obtain these results in the unanesthetized animal.

It would follow from these observations that "forward failure," insofar as it reduces the flow through the kidney and its glomerular filtration rate, has no consistent influence on the excretion of sodium chloride or water. The body reacts to a sodium chloride load with a sodium chloride excretory response despite marked changes in the glomerular filtration rate and renal plasma flow. Yet in heart failure the body reacts as if the animal were sodium depleted (fig. 11), despite the fact that actually the animal is overloaded with sodium chloride and with water. Why?

In order to answer this question we have carried out a series of experiments on acute and chronic vein occlusions. For example, when the inferior vena cava is partially occluded above the liver, the animal quickly develops ascites and this edema is sustained chronically. Associated with this there is sodium chloride and water retention (fig. 12). In contrast, when the inferior vena cava is constricted above the kidney, either acutely or chronically, no edema develops. In the acute experiments there is only a transient effect in the sense of water and sodium chloride retention (fig. 13). In the chronic experiments,

Fig. 9. Recovery following bilateral renal artery occlusion (from Stamler and associates\(^3\)). Symbols as in figure 8.

Fig. 10. Recovery following inferior vena cava occlusion above hepatic veins (from Stamler and associates\(^3\)). Symbols as in figure 8.

Fig. 11. Effects of chronic salt depletion (from Frieden and co-workers\(^3\)). Symbols as in figure 8.
no effect is observed (fig. 14). This leads to the conclusion that while transitory elevations of renal venous pressure can produce temporary declines in renal plasma flow and glomerular filtration rate, and associated retention of sodium chloride and water, this quickly disappears and is not seen in animals with chronic renal venous pressure rise, provided no edema ensues. Consequently, one can say that decreased renal sodium chloride and water excretion (with normal renal blood flow and glomerular filtration rate) occurring in association with the chronic ascites produced by narrowing of the inferior vena cava above the liver is not due to the elevated renal venous pressure which persists. On the other hand, inferior vena cava occlusion below the kidney does not lead to edema or to any change in water and sodium chloride excretion acutely or chronically, unless the femoral vein and epigastric vein are also occluded. Under these latter circumstances, edema will develop and sodium chloride and water retention will ensue (fig. 15). It is obvious from such experiments that it is not necessary to interfere with the circulation of the kidney, of the adrenals, or of the liver to produce edema, and, more particularly, to disturb the excretion of sodium chloride and water by the kidney.

Fig. 12. Chronic effect of constriction of inferior vena cava above hepatic veins (from Stamler and colleagues). VP, venous pressure, mm. water. Other symbols as in figure 8.

Fig. 13. Acute effects of obstruction of inferior vena cava above kidney (from Stamler and colleagues). VP, venous pressure, mm. water. Other symbols as in figure 8.

Fig. 14. Chronic effect of constriction of inferior vena cava above kidney (from Hwang and associates). VP, venous pressure, mm. water. Other symbols as in figure 8.

Fig. 15. Effect of elevated venous pressure in lower extremities on per cent Na excretion and glomerular filtration rate (from Frieden and co-workers). First operation was ligation of inferior vena cava below the renal veins; second operation was ligation of femoral and inferior epigastric veins.
The possibility exists, of course, as has been claimed by others, that occlusion of the superior vena cava may have different effects. This we have tested. In acute experiments following such a procedure, neither edema nor any change in sodium chloride or water excretion occurred. In chronic experiments we have seen some animals develop edema (fig. 16) and others not. Those animals which developed edema behind the region of occlusion showed sodium chloride and water retention in the kidney. Those that did not showed no such effect. These experiments on the superior vena cava failed to reveal any evidence of any special volume receptors in the head—i.e., of receptors that would signal increased renal salt and water excretion as a result of cranial congestion. They failed to reveal that interference with the flow of blood to the hypothalamic and pituitary region has any extra•ordinary influence on sodium chloride and water excretion.

Finally, in some recent experiments in which mercurials were exhibited and found to inhibit sodium chloride absorption by the tubules, and in which sodium nitrate was substituted in part for the sodium chloride, the results suggested strongly that the mercurials operate primarily by interfering with the excretion of the chloride by the tubules, and that the changes in sodium, and presumably in water excretion, are secondary.

In reviewing our work on edema formation in congestion, we have come to the following conclusions: It is not stasis in any special area like the head, the kidney, the liver or the endocrines, per se, which causes sodium chloride and water dysfunction of the kidney, but it is stasis, per se, since stasis even in a region not involving such organs can lead to a similar disturbance. It is not clear from our work, or that reported in the literature, whether it is the local venous hypervolemia, or the elevated venous pressure, or the transudation, or the local changes in the tissues, or the tendency toward hypovolemia in the rest of the circulation when part of the blood is, so to speak, impounded, which is the trigger mechanism. However, the disturbance associated with rise of venous pressure in some fashion and independent of any special area sets up a receptor-effector mechanism that adjusts the kidney excretion of sodium chloride and water so that they are retained. This can readily be brought out when the body is loaded with a sodium chloride solution. We used 1.5 per cent sodium chloride or Ringer's solution at the perfusion rate of 6 to 10 cc. per minute. We do not know the location of the receptor, nor its character. We do not know whether hormonal factors are involved, nor do we understand the role of the central nervous system in this mechanism. Work is now being pursued in this department to try to get the answers to these questions. It is apparent from our work, however, that the mechanisms of sodium chloride and water disturbance operate in the tubules. It would appear that it is the reabsorption of sodium chloride and water that is affected, but it is possible that it may be in part an interference with actual secretion of sodium chloride and/or water from the blood into the tubules.

Edema in heart failure is caused by the heart, but the mechanism as outlined above involves a derangement of kidney function in which the kidney operates as if the body were depleted of sodium chloride and water despite the excess presence of both. In acute incompetence of the heart, the edema may be due in part to local transudation of fluid on a mechanical or reflexogenic basis, aided and

**Fig. 16.** Chronic effect of constriction of superior vena cava (from Frieden and co-workers) VP, venous pressure, mm. water. Other symbols as in figure 8.
abated by "forward failure" which alters renal blood flow and glomerular filtration rate, and by "backward failure" which, by elevation of renal venous pressure, has the same effect. This reduction in glomerular filtration rate may operate to interfere with the ability of the kidneys to excrete sodium chloride and water (glomerulotubular imbalance). However, the renal mechanism so set up is adjusted too quickly and in chronic failure is of little importance. Similarly, during periods of stress there is in the cardiac patient a greater decline in renal flow and in glomerular filtration rate, due to the development or exaggeration of "forward failure" or of renal venous congestion (leading to further glomerulotubular imbalances). This effect upon the kidney during periods of stress is only part of the picture because such stress leads to widespread venous congestion in other areas. If general venous congestion is in some fashion responsible for the derangement of tubular salt and water excretion during the resting state, then this effect would be exaggerated during periods of bodily stress.

In summary, we believe that heart failure sets up a receptor-effector system that results in a disturbance in the ability of the renal tubules to excrete sodium chloride and water so that edema ensues. This in some fashion is associated with the venous congestion.

Analyses of similar complex interlocking disturbances in body function other than those of water and sodium chloride exchanges would be of benefit in completing our understanding of the entire syndrome of heart failure. They would help to improve the knowledge by which rational management and therapy can be planned.

**Conclusion**

In conclusion, you can see that the problem of cardiac failure is not a simple one as at first sight it might appear to be, and that its complexity is only now beginning to be appreciated. I predict that in the future our understanding will bring light upon the obscure relationships. At any rate you will admit that the functional viewpoints expressed concerning cardiac failure point to the direction from which illumination will come.

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