Special Article
Compensatory Hyperfunction of the Heart and Cardiac Insufficiency
By F. Z. Meerson, M.D.

In heart failure and arterial and pulmonary hypertension, the preservation of normal hemodynamics, of clinical compensation, and eventually of the patient's life, depends to a great extent on a stable, compensatory hyperfunction of the heart. When the hyperfunction of most organs takes place in a healthy individual as a reaction to physiological stress, ordinarily it is transient and disappears after the cessation of the stress. On the other hand, compensatory hyperfunction of the heart, caused by destruction of the valves or by persistently high arterial blood pressure, is protracted, for the lesions that have developed in the body are irreversible and the continuity of hyperfunction becomes necessary to life.

Folborth, while studying the relationship between exhaustion and restoration in organs subjected to high functional strain, came to the conclusion that repetition of functional stresses may cause two opposite states to develop. When the organ has had time to attain a state of complete restoration after a preceding exhaustion, it becomes adapted and its working capacity is gradually enhanced. When it is subjected to sustained activity before having attained a condition of stable restoration, it becomes chronically exhausted.

This state of affairs is not at all applicable to compensatory hyperfunction of the heart, since despite unremittingly strenuous activity the phenomenon of exhaustion is not observed until very late. Thousands of people with heart disease and hypertension live for decades and often go on performing considerable physical work.

The mechanism involved in preventing exhaustion of the heart under these conditions remains unclear and cannot be explained by any concept of "reserve forces of the heart" ("Reservekraft des Herzens"), which has been proposed earlier. Despite a number of investigations, the mechanism of cardiac exhaustion, which often develops after many years of compensatory hyperfunction and gives rise to decompensation, is just as obscure.

To study these questions, we have duplicated compensatory hyperfunction of the heart by producing experimental stenosis of the aorta in animals.* Stable controlled stenosis of the aorta in 450 rabbits and 12 dogs was produced in such a manner that the transverse section of the aortic lumen, distally from the semilunar valves, was decreased three to four times (fig. 1).2-3

A detailed study of myocardial function, metabolism, and structure showed that during the period of compensatory hyperfunction the heart passes through three main stages.2-4

The first or transient breakdown stage is characterized by symptoms of left ventricular insufficiency with pulmonary congestion, hydrothorax, ascites, and death of 20 per cent of the animals.

One observes during this stage cardiac dilatation, inversion of the T wave with displacement of the S-T segment, swelling of heart muscle fibers, loosening of the myo-

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*The detailed description of methods and the quantitative characteristics of single experimental series are represented in the following book by the author: Compensatory Hyperfunction and Cardiac Insufficiency, Moscow, Academy of Medical Sciences of the U.S.S.R., 1960.
fibrils, development of protein and fatty dystrophy of the myocardium, a marked drop in the myocardial glycogen content, a decrease in creatine phosphate to one-tenth to one-twentieth of normal with a slight increase above the normal level of lactic acid and adenosinetriphosphate (ATP) in the myocardium. The weight of the heart during the first four to five days increases at the rate of 10 to 12 per cent per 24 hours; the rate of protein synthesis in the myocardium, judged by incorporation of tagged S-35 methionine, is increased about twofold. The concentration of ribonucleic acid is increased by 32 per cent and the concentration of desoxyribonucleic acid is changed; myoglobulin and the n-fraction of myogen content are increased, with simultaneous decrease of the m+1 fraction of myogen. The concentrations of free aspartic acid, glutamic acid, threonine, and alanine are decreased, while those of phenylalanine and tyrosine, the precursors of epinephrine, are increased three to four times.

The essential characteristic of this stage appears to be a contractile insufficiency caused by acute cardiac strain and a deficiency in the activity of certain enzymes. This leads to a temporary mobilization of glycogen and creatine phosphate and the resynthesis of ATP by the inefficient anaerobic pathway. As a long-term measure, myocardial hypertrophy occurs associated with an increase in protein synthesis.

Changes described in this stage can probably be observed clinically in traumatic cardiac failure, in acute failure due to infarction of the papillary muscle, in acute hypertensive states, in severe physical strain imposed on the heart in untrained individuals, and to a lesser extent during the period of formation of rheumatic defects of the heart.

The second or protracted stage of relatively stable hyperfunction is characterized by the absence of cardiac insufficiency and of pulmonary congestion, hydrothorax, and ascites; by arrest of enlargement of the heart; by disappearance of pathological modifications of the T wave and the S-T segments; as well as by absence of signs of protein and fatty dystrophy of the myocardium. Hypertrophy of muscular fibers, compact disposition of myofibrils, and moderate focal atherosclerosis are present. The glycogen, phosphocreatine, and ATP content in the myocardium are within normal limits, while myocardial lactic acid may rise by 200 per cent. The weight of the heart is about twice that of the normal heart and remains stable (fig. 1).
Heart of rabbit (no. 736) 45 days after creation of aortic stenosis. Weight of heart 10.9 Gm. Heart of normal animal weighs 5.1 Gm.

2); the rate of protein synthesis in the myocardium, as judged by the incorporation of S-35-methionine, is normal. The concentration of RNA is likewise within normal limits, while the concentration of DNA is decreased to one-third; the contents of myo-albumin and the n-fraction of myogen are increased, while the m+1 fraction is normal, phenylalanine and tyrosine are increased two to three times, and the other amino acids are within normal limits.

The essential feature of this stage is the hypertrophy of the myocardium which gives rise to an adequate oxidation and oxidative phosphorylation, an inhibition of anaerobic resynthesis of ATP and a restoration to normal of the creatine phosphate and glycogen content in the myocardium. At the same time, hypertrophy leads to a decrease in the number of coronary capillaries per unit of mass and to moderate myocardial hypoxia with accumulation of lactic acid.

The sum total of changes described by us in the stage of relatively stable hypertension is apparently typical of the condition of the heart during clinical compensation to cardiac failure and hypertension.

The third or protracted stage of progressing cardiosclerosis and gradual exhaustion is in a number of cases characterized by: (a) the development of cardiac insufficiency; (b) marked and continuously progressing myocardial fibrosis in all cases; (c) the appearance of focal fatty degeneration; (d) a deficit in DNA, the concentration of which in the myocardium falls to 30 to 40 per cent of normal; (e) a decrease of 50 to 60 per cent in the rate of protein synthesis in the myocardium, as judged by the incorporation of S-35-methionine; and (f) a decrease of the ATP level in the myocardium by 10 to 20 per cent. The other factors remain the same as in the second stage of this process.

The third stage is a period of moderate, sustained hypoxia, which in turn leads to depression of the normal process of resynthesis of the myocardial protein structure, to marked fibrotic changes, and to decrease of the contractile capacity of the heart.

Changes such as those described in stage three may apparently be seen in patients with cardiac failure and hypertension of long standing. In such cases, depending on the degree of perfection of the neuro-endocrine control and on the extracardiac factors of compensation, the condition of the patients may be either one of stable clinical compensation or of various forms and stages of decompensation.

Curves in figures 3, 4, 5, and 6 reflect the behavior of biochemical factors during the compensatory readjustment of the heart, while the microphotos in figure 7 (left and
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right) show the morphological changes in the myocardium.

With these gradual functional, morphological, and biochemical changes in the heart, there are parallel modifications in cardiac reflexes. The first, or breakdown stage, is associated with an increase of vagal reflex control, while the sympathetic reflex, causing tachycardia, remains unaltered.

The second stage of relatively stable compensatory hyperfunction is accompanied by a sustained decrease of vagal reflexes and by an increase of the sympathetic reflex.

During the third stage of progressing myocardial degeneration and exhaustion with cardiac insufficiency, the reflex tachycardia decreases, and the range of variations of the cardiac rhythm is markedly decreased.

The three main stages of compensatory hyperfunction develop gradually. The transition from the breakdown stage into the stage of relatively stable compensation is noteworthy in that all the signs of the breakdown stage—the degenerative changes in the muscle fibers, the drop in creatine phosphate and glycogen, the concomitant changes of the T wave and the S-T interval, and the small hemorrhages in the myocardium—totally disappear, while the strain on the heart which had caused them remains unabated.

The transformation of an organ on the brink of exhaustion into a state of relatively stable hyperfunction is the outstanding feature of the compensatory readjustment of the heart. The regression of symptoms of acute cardiac insufficiency, and of the pathological modifications in metabolism and structure which had initially developed in the myocardium, can be explained only by the fact that as the compensatory process evolves gradually new factors join in to ensure more perfect adaptation of the heart to the high level of functional activity.

Our investigations enable us to describe the following of these factors, which play an important role in the prevention of myocardial exhaustion despite continuous hyperfunction.

1. Hypertrophy signifies an increase in the mass of energy-producing and contractile structures of the heart. It decreases the work imposed upon each unit of myocardial tissue.
and, at the same time, increases the total energy-producing capacity in the form of ATP for transformation of this potential energy of phosphate bonds into the kinetic energy of cardiac contractions. There is also an increase of mass of mitochondria in which are located the enzymes of the tricarboxylic acid cycle, the electron transport system, and the enzymes of oxidative phosphorylation. This may lead to a more effective aerobic resynthesis of ATP. Consequently, the less effective anaerobic resynthesis of ATP associated with breakdown of glycogen and creatine phosphate becomes unnecessary, and the level of these substances in the myocardium rises to normal figures. Hyperfunction of the heart acquires a stationary and relatively stable character.

2. The increase in the activity of the oxidation-reduction enzyme systems of the myocardium can play the role of a compensatory factor even during the early stage of hyperfunction, but it acquires its greatest significance when the hypertrophy of the heart becomes marked, for hypertrophy, like all the adaptational reactions of the body, is only useful in a relative sense. It causes a decrease of the number of the coronary capillaries in proportion to the myocardial mass and increases the pathway of oxygen diffusion from the capillary wall to the center of the muscle fiber. One of the factors which may more or less compensate for this is the increase of an oxidative enzyme such as succinic dehydrogenase, demonstrated in our histochemical studies in which we used the method of Seligman and Rutenberg. Increased myoglobin content in the hypertrophied myocardium, which ensures the transportation of oxygen from the capillaries to the mitochondria, may also play a role. These changes are significant in that, with capillaries deficient, they may to some extent

*The histochemical determination of succinic dehydrogenase activity was carried on by us conjointly with N. T. Reikhlin.
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overcome the development of hypoxia in the hypertrophied myocardium and thus promote a sustained stable hyperfunction of the heart.

3. In our experiments, an increase of the sympathetic cardiac reflexes preceded the transition of the heart from the breakdown stage into the stage of relatively stable hyperfunction. Such a preponderance of the sympathetic innervation of the heart may exert an important influence on the compensatory readjustment of the heart as it causes increased rate and strength of contraction, increase of coronary flow, increase of oxygen consumption, and increase in ATP metabolism. These effects of sympathotonia represent an integral part of the altered state of myocardium at the stage of stable compensatory hyperfunction in cardiac disease. Such changes in myocardial metabolism ensure the adjustment of the heart to a higher functional level and ipso facto the transition from the breakdown stage into the stage of a relatively stable compensatory hyperfunction.

It goes without saying that the factors described above do not exhaust all the armamentarium of adaptational resources used by the body to ensure stable compensatory hyperfunction of the heart. An important role in this process must be played also by other changes in the heart muscle of an adaptative nature. The effectiveness of such a complicated adaptive reaction as the compensatory readjustment of the heart is directly dependent on the perfection of the neuro-endocrine control of the circulation as a whole and on the mobilization of the extracardiac factors of compensation. This aspect requires further study.

Data on the compensatory hyperfunction provide indispensable prerequisites for the study of the mechanism of cardiac insufficiency.

Acute cardiac insufficiency, developing immediately after cardiac strain, and chronic cardiac insufficiency, coming on gradually after a prolonged period of relatively stable compensatory hyperfunction, differ from each other both in their clinical manifestation and in the essential changes that take place in the myocardium. While an acutely supervening cardiac insufficiency following severe strain is only a result of direct overstrain of the energy-producing and contractile myocardial structures, the slowly developing cardiac insufficiency which appears after a lengthy period of compensatory hyperfunction may be attributed not only to strain, but also to those metabolic disturbances which appear in the hypertrophied myocardium as a result of deficiency of the coronary capillaries.

Acute cardiac insufficiency, which is encountered clinically in traumatic cardiac failures, in acute hypertensive states, and in failures caused by infarction of the papillary muscle, is apparently accompanied by a host of changes in the myocardium typical of the breakdown stage of the compensatory hyperfunction of the heart, as seen in our experiments in which symptoms of acute cardiac insufficiency manifested by mitralization of the aortic defect, hydrothorax, and ascites, were also observed.

That the same state of the myocardium is denoted by "breakdown stage of compensatory hyperfunction of the heart" and by "acute cardiac insufficiency" undoubtedly means that under acute cardiac strain, cardiac insufficiency in an intact body is correlated with the mobilization of adaptational resources which are typical of the breakdown stage and which in time will ensure the disappearance of the insufficiency itself. It is for this reason that in our experiments, despite the maintenance of high strain which in the beginning brought the heart to the verge of exhaustion, only 20 per cent of our animals succumbed, and in the remainder, the cardiac function as the time wore on proved itself adequate for the maintenance of a relatively stable compensation. In a considerable proportion of patients, the very same early mobilization of adaptational resources, in the form of increased coronary blood flow, developing hypertrophy, and modifications of the neuro-endocrine control of the heart, is
the cause of replacement of acute cardiac insufficiency by a more or less stable compensation.

The principal consequence of acute cardiac insufficiency caused by strain lies not in the decrease of the contractile capacity of the heart as compared to the normal, but in the fact that the heart is unable to increase its contractile activity and bring it to the abnormally high level which is required to satisfy the suddenly increased demands of the body. Our data indicate that in acute cardiac insufficiency oxidative phosphorylation becomes insufficient to compensate for the increased loss of ATP brought about by strain. This leads to the less effective anaerobic resynthesis of ATP at the expense of glycogen and creatine phosphate. However, resynthesis of ATP is associated with an increased hydrolysis of this high-energy substance as it reacts with actomyosin, and the ATP content in the myocardium remains normal. It follows that the intensity of processes ensuring liberation of energy and its accumulation in the phosphate bonds of ATP is not a factor which has immediate bearing on further increase of the work of the heart under strain and in acute cardiac insufficiency. This factor is probably represented by the limited capacity of actomyosin, which forms myofibrils, to transform the energy of phosphate bonds into contractile kinetic energy—the activity and mass of the available actomyosin are apparently insufficient to ensure further increase of ATP hydrolysis and of the contractile function.

Chronic cardiac insufficiency, developing after a lengthy period of a relatively stable compensatory hyperfunction, cannot be correlated at the present time with definite morphological changes in the myocardium, as one finds in the hearts of humans and animals dead from congestive heart failure the same changes which are often seen in pathological conditions where stable compensation exists. In chronic insufficiency, the heart takes from the blood a normal quantity of nutritive substances and oxygen, but its output is below normal. This drop in the efficiency coefficient of the heart, according to Olson, is not due to a decreased liberation of energy and its accumulation in the form of ATP, since the level of ATP in the myocardium of the dogs suffering from congestive cardiac failure remains normal while the physicochemical, enzymatic, and contractile properties of actomyosin are definitely abnormal. Hence, according to modern concepts, chronic cardiac insufficiency is a result of a decrease in the capacity of actomyosin to transform the energy of the phosphate bonds of ATP into the kinetic energy of cardiac contractions. The precise causes of these disorders in the enzymatic and contractile properties of actomyosin represent today one of the cardinal problems of pathogenesis of cardiac insufficiency.

Our investigations have shown that, at the beginning of the process of the compensatory hypertrophy of the myocardium, a relative deficiency of coronary capillaries and hypoxia develops. Then occurs a fall of concentration of DNA and later a depression of the protein synthesis in the myocardium. Existing data have made it possible, for discussion’s sake, to outline the concept that the mechanism of cardiac insufficiency includes the following chain of events: increased load on the heart and its compensatory hyperfunction, myocardial hypertrophy, deficiency of the coronary capillaries, moderate myocardial hypoxia, fall of concentration of DNA and affection of the nuclei of muscle fibers, disturbance of nuclear cytoplasmic interrelations, depression of the normal process of restoration of the protein structure of the myocardium, wear and tear of actomyosin, decrease of its enzymic and contractile properties, progressive myocardial fibrosis, possibly disturbances of the permeability of cellular membranes, and modification of concentrations in the extracellular and intracellular electrolytes, which tend to affect the contractile and the enzymatic properties of actomyosin.

From the point of view of this working
hypothesis, which undoubtedly underesti-
mates the true complexity of the process, it is
important to identify the changes that take
place in the actomyosin and lead to cardiac
insufficiency and to decrease of its con-
tractive properties.

In the light of Peri's findings that the
active centers of the myosin molecule, respon-
sible for its interaction with ATP and actin,
are represented by the SH-groups, it is jus-
tifiable to think that one of the changes de-
veloping as a result of depression of the
restoration of the contractile proteins of the
myocardium consists in the decrease of the
free SH-groups. This hypothesis is now being
experimentally tested.

On the whole the present facts and hypoth-
eses do not reveal to us the integral mech-
nism of cardiac insufficiency, but put into
the foreground a concept essential for the
study of the problem, namely, that due to the
increase of the energy metabolism of the
heart sustained compensatory hyperfunction
leads to changes of protein metabolism in the
heart which may be of prime significance for
the development of cardiac insufficiency. This
raises the question of the need for an experi-
mental study of the therapeutic significancen of
a number of factors which could influence
the development of hypertrophy, activate
oxidation-reduction processes in the myo-
cardium, and aid in the restoration to normal
of myocardial proteins. To such factors be-
long cytochrome, methylene blue, vitamin B₁₂,
folic acid, substances such as cysteine which
contain SH-groups and may play an impor-
tant role in muscular contraction, and also
ATP and other nucleotides which, according
to some data, are capable of preventing the
development of cardiac hypertrophy in ani-
imals subjected to repeated physical strain.

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F. Z. MEERSON

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