Mechanism of hypertrophy of the heart and experimental prevention of acute cardiac insufficiency

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It is known that hyperfunction of the heart arising from cardiac defects, systemic hypertension, pulmonary hypertension, and over activity of non-affected regions of the heart in cardiac infarction, is regularly followed by myocardial hypertrophy, which after a prolonged period not infrequently results in chronic cardiac insufficiency. Thus hyperfunction, hypertrophy, and cardiac insufficiency represent three links of a unique process having a fundamental importance in modern cardiology. The dynamics of structural, biochemical, and physiological alterations constituting this process has already been the object of extensive investigations and has been described in numerous reviews and monographs (Meerson, 1960; Sonnenblick, 1968; Spann et al., 1965; Meerson, 1969a, b; Gudbjarnason, Telerman, and Bing, 1964; Büchner and Weyland, 1968). This allows us to restrict our paper to analysis of the principal mechanism of development of cardiac hypertrophy and to the consequences of the current concept of this mechanism in the prevention of acute cardiac insufficiency in overload of the heart.

Basis of hypertrophy

More than 10 years ago it was shown that the basis of hypertrophy of the heart was the activation of nucleic acid and protein synthesis arising in myocardial cells in response to hyperfunction of the heart (Meerson and Zajats, 1960). Soon it became obvious that this activation of nucleic acid and protein synthesis in response to augmented physiological function was common to all cells, organs, and physiological systems of a whole organism, and that in particular it was the basis of compensatory hypertrophy of most diverse organs in their protracted continuous hyperfunction.

Essentially, activation of nucleic acid and protein synthesis in response to augmented function is an expression of interrelation between the genetic apparatus and the physiological function of the cell, the interrelation which is the structural basis of various adaptability reactions of the organism. This implies that the question of the mechanism of cardiac hypertrophy is also pertinent in the biological problem concerning the interrelation between the genetic apparatus and the physiological function of the cell. Here a direct and an inverse relation between the genetic apparatus and the cellular function, definitely expressed in the heart muscle, are distinguishable. The direct relation is that the genetic apparatus, on the basis of the known scheme DNA → RNA → protein, ensures the formation of basic structures of the muscle cell, the myofibrils, mitochondria, and membranes of the sarcoplasmic reticulum – that is, of structures of the myocardial cell which perform its function. Since it is known that the intensity of the breakdown of structures of the muscle cells as well as of other differentiated cells increases in proportion to the increase in their function (Meerson et al., 1964b; Hyden, 1962) it is obvious that even the most direct relation cannot ensure an opportune renewal of myocardial structures and the persistence of the contractile function of the heart. This essential effect may be achieved only if the intensity of RNA and protein synthesis is opportune altered after the change in intensity of functioning and breakdown of structures, thus preventing exhaustion of structures and functional disturbance. In other words, to ensure perfect structural contractile function, precisely regulated changes in activity of the genetic apparatus – changes in intensity of RNA synthesis on active genes of DNA – must occur in due time. For this the genetic apparatus should receive exact and opportune information about the level of the contractile function of the myocardial cell. This kind of information about the functional level sent from the cytoplasm to the cellular nucleus plays the part of an inverse relation, regulating the activity of the genetic apparatus and preventing the exhaustion of cellular structures.
In continuous compensatory hyperfunction of the myocardium, where the abrupt breakdown of cellular structures may be well demonstrated by biochemical (Meerson et al., 1964b) and electronmicroscopical data (Hatt and Swnghedaw, 1968), it is the realization of the inverse relation that enables the function 'to lay increased claims to protein synthesis' and ensures activation of synthesis and the development of cardiac hypertrophy. The decisive part played by the inverse relation between function and genetic apparatus of myocardial cells in the development of compensatory hypertrophy of the heart has been the object of many investigations.

Effect of increased function

The first question to be answered is whether the activating effect of the increased function is really directed to the genetic apparatus. In other words, is it true that the increased tension of myofibrils in cardiac cells activates the RNA synthesis on the genes of chromosomal DNA through a definite mechanism?

Since the increase in function is regularly followed by the rise of RNA concentration in the cell, while the whole RNA, in particular the ribosomal one, is synthesized only on the matrices of DNA—that is, on genes—it appeared some years ago, when the concept of the inverse relation was advanced, that this question might be answered affirmatively (Meerson, 1963). However, the scepticism which met the proposed formulation of 'interrelation of function and the genetic apparatus' served as a stimulus for undertaking special experimental work in this direction.

At the first stage of investigation in our laboratory the antibiotic actinomycin, which inhibits with relative selectivity the RNA and DNA synthesis—that is, the process of transcription—was used. Introduction of this preparation into the animal organism in nontoxic doses does not decrease the concentration of RNA in such organs as heart and kidney, and does not disturb therein the protein synthesis, since protein continues to be synthesized on available matrices of the messenger RNA formed before injection of actinomycin. At the same time, in animals in which hyperfunction of the heart was produced by aortic stenosis, or hyperfunction of the left kidney by removal of the right kidney, actinomycin fully prevented activation of RNA and protein synthesis which usually arises in intensely working myocardium, and inhibited the development of hypertrophy (Meerson et al., 1964a). This evidence has confirmed that the activating influence of the increased function may be effected through some intermediate links and is directed to the genetic cellular apparatus. Some years later these experiments were successfully developed by a group of workers (Schreiber, Oratz, and Rothschild, 1967; Schreiber et al., 1968) who imposed an overload on the isolated rat heart and at the first stage reproduced our results. They obtained activation of RNA and protein synthesis under the influence of the overload, and prevented this activation by adding actinomycin to the perfusing fluid. Later they showed that the ability of ribosomes obtained from isolated hearts to synthesize protein had grown one hour after the overload had been imposed on the organ. The hyperactivity of ribosomes was fully prevented by actinomycin and this action was not followed by an increase in the number of ribosomes.

Since one of the probable causes of increase in synthesizing activity of ribosomes is the programming of the increased number of ribosomes of the messenger RNA, an experiment was performed to discover the extent of programming. Synthetic polyuridin (poly-U) was added to ribosomes. This polynucleotide, like natural messenger RNA, programmes the ribosomes, activating not the protein synthesis but that of the polypeptide, consisting only of phenylalanine-polyphenylalanine.

Poly-U elicited this effect on the ribosomes obtained from the group of control hearts: incorporation of labelled precursor-phenylalanine was increased. On ribosomes obtained from intensely working heart such an effect was not produced. It has been assumed that the poly-U could not enter into activated ribosomes since they had been programmed beforehand by the normal information of RNA, which was synthesized in increased amounts on DNA and within an hour could reach the ribosomes. In other words, in hyperfunction of the heart the messenger RNA is very rapidly transported into ribosomes, ensuring the activation of protein synthesis and by this the structural basis of the heart's hyperfunction.

The work of Nair and his colleagues (Nair et al., 1968) was the next step, identifying more precisely the influence activating the increased function. The authors determined the polymerase activity of nuclei isolated from the myocardium of animals in which an intense hyperfunction and extensive hypertrophy of the heart were produced by aortic stenosis. It was found that 12 hours after the onset of hyperfunction the polymerase activity of such nuclei—that is, their ability to syn-
thesize RNA on matrices of DNA – was essentially increased, especially in relation to ribosomal RNA synthesis.

**Intensity of functioning of the structures**

On the whole the data obtained seem to agree with the original concept that the activating influence of the increased physiological function is directed through some intermediate links to the genetic cellular apparatus. The second question, in considering the influence of function on the genetic apparatus, is by which parameter of function the genetic apparatus is determined. This aspect of the problem was first encountered during the study of the dynamics of nucleic acid and protein synthesis in the development of compensatory hyperfunction and hypertrophy of visceral organs. It was found that the important feature of the process of hyperfunction – hypertrophy of the heart in aortic stenosis, of the single kidney after unilateral nephrectomy, of the hepatic lobe after partial hepatectomy, and of the single lung after removal of the other lung – is that the activation of nucleic acid and protein synthesis arising during the subsequent hours and on the day after the onset of hyperfunction gradually ceases in the course of development of hypertrophy of the organ. Such dynamics of the process is determined by the fact that at the beginning of the process the hyperfunction is effected by a still unhypertrophied organ and the amount of function per unit of mass of the organ is sharply increased. Just such an increase in amount of function per unit of mass of cellular structures produces activation of the genetic apparatus of differentiated cells. After full development of hypertrophy of the organ its function is distributed within the increased mass of cellular structures, and as a result the amount of function performed by the mass unit of structures returns to or approaches the normal level. Then activation of the genetic apparatus ceases and the nucleic acid and protein synthesis also returns to the normal level (Meerson, 1960, 1968).

If hyperfunction of the organ still subjected to hypertrophy is eliminated, the amount of function performed by 1 g. of the myocardium will become abnormally low. As a result, the protein synthesis in differentiated cells of the organ is decreased and the mass of the organ begins to decrease.

Owing to this decrease the amount of function per unit of mass is gradually increased, and after it becomes normal the inhibition of protein synthesis in the organ cells ceases: its mass is not decreased further (Meerson, 1969a, 1965).

The data presented suggest that in differentiated cells and mammalian organs formed by the latter, the amount of function performed by the mass unit of the organ – the intensity of functioning of the structures (IFS) – plays an important part in regulating the activity of the genetic cellular apparatus. The increase in IFS corresponds to the state when 'there is restriction of space for function in the structure'. This involves activation of protein synthesis and increase in mass of functioning, energy-producing, and supporting structures. The decrease in the given parameter corresponds to the situation when 'there is too ample space for function in the structure', which results in decrease in intensity of synthesis with a subsequent removal of excessive structure. In both cases the intensity of functioning of the structures returns to the optimal value proper to a normal organism.

Thus the intracellular mechanism effecting bilateral interrelation between physiological function and genetic apparatus of the differentiated cell ensures the state in which 'the intensity of functioning of the structures' (IFS) is simultaneously the determinant of activity of the genetic apparatus and the physiological constant maintained at a permanent level owing to opportune changes in activity of this apparatus (Meerson, 1965).

There are other factors concerning the interrelation of function and the genetic apparatus of myocardial cells. They are considered elsewhere, and represent but a premise to the essential main question about the interrelation of function and genetic apparatus, namely: In what manner and through which intracellular mechanism does the intensity of functioning of the structures exert its influence upon the activity of the genetic apparatus of myocardial cells?

**Two concepts**

In an attempt to answer the main question two further concepts should be considered:

1) In intense compensatory hyperfunction of the heart (Meerson, 1964b), of neurones (Hyden, 1962), and apparently of other differentiated cells, there regularly occurs an increase in the breakdown of cellular structures. This breakdown of structures itself serves as a stimulus to activation of the genetic cellular apparatus, as has been demonstrated in recent experiments which showed that by itself the increased breakdown of myocardial structures caused by moderate ischaemia of the heart regularly produces activation of nucleic acid and protein synthesis and the development of hypertrophy of the heart without hyperfunction of this organ (Gudbjarnason, Braasch, and Bing, 1968). It has also been shown that
compensatory hyperfunction of the kidney, produced after a brief deprivation of the blood supply of this organ, leads to a considerably greater activation of nucleic acid and protein synthesis and to the development of a greater hypertrophy of the organ, than does hyperfunction of the ischaemic kidney (Hübner, 1967). In other words, the breakdown of structures caused by a hypoxic lesion of the tissue, and the breakdown due to hyperfunction of this tissue, together create a stimulus to much greater activation of nucleic acid and protein synthesis than can be induced by these factors separately.

2) In acute pronounced hyperfunction of the heart the use of energy in the form of ATP in myofibrils exceeds the capacity of mitochondria to effect ATP resynthesis by oxidative phosphorylation. As a result there is a lack of energy, shown by the fall in concentration of creatine phosphate and glycogen together with activation of glycolysis and accumulation of lactic acid in the myocardium (Vyalykh and Meerson, 1960; Fox, Wikler, and Reed, 1965; Feinstein, 1962) – that is, there arise shifts similar to those occurring under the direct action of hypoxia upon the myocardium, which limits the intensity of processes of oxidation and oxidative phosphorylation (Gudbjarnason et al., 1968; Chang, 1938). Recently evidence has been obtained showing that such lack of energy and associated decreased in pH regularly produce a lysosome effect in the myocardium which is increased in hyperfunction of the heart (Meerson et al., 1970) and under the action of hypoxia (Ravens and Gudbjarnason, 1969; Leighty et al., 1967).

In sum, these two ideas suggest that the lack of energy arising in intense and protracted hyperfunction of the organs becomes the cause of labilization of lysosomes, and the breakdown of structures produced by lysosome ferments is the stimulus leading to activation of nucleic acid and protein synthesis in the cells. This activation and the ensuing hypertrophy finally result in decrease in intensity of functioning of structures of the organ and to increase in capacity of the mechanisms ensuring energy transformation. Thus the lack of energy and the increased breakdown of structures are eliminated and the hyperfunction of the hypertrophied organ becomes relatively stable.

This concept implies that the breakdown of structures caused by the lack of energy is an important link in the mechanism connecting function and genetic cellular apparatus. This raises the question, how may the breakdown of structures activate the genetic cellular apparatus? The study of this still unresolved question is in fact being made on the basis of two different hypotheses.

The first hypothesis is that the increased breakdown of structures leads to accumulation in the cell of products of breakdown of organospecific proteins and RNA – ‘metabolites of wear’. Metabolites of this kind can play the part of inductors activating the processes of transcription – RNA synthesis on structural genes of DNA. This activation may be effected by decrease or abolition of the inhibitory influence exerted by special regulatory genes upon structural genes – that is, on the basis of principles formulated for the microbial cell by Jacob and Monod (1961).

Mechanism of activation

The ability of breakdown products to stimulate organospecifically nucleic acid and protein synthesis has been demonstrated in many investigations on mammalian organs (Lahtiharju and Teir, 1964; Mahler et al., 1958; Polezhaev et al., 1962). The phenomenon of synthesis induction under the influence of hormones and other metabolites is also well known in these organs (Lev-Montalcini, 1964; Korner, 1969; Naets and Wittek, 1969). Therefore in the past, while formulating the concept of connexion of function of the genetic apparatus, the author could assume that ‘metabolites of wear’ formed in the myocardium in hyperfunction of the heart activate the nucleic acid and protein synthesis, acting like inductors in the Jacob and Monod scheme.

The second hypothesis is that in usual conditions the normal concentration of proteins in the differentiated cell is the factor restraining the synthesis of these proteins. In hyperfunction of the organ the increase in IFS involves the breakdown or increased ‘export of proteins’. As a result there is a decrease in their concentration at different points of the cell, and the lack of proteins becomes a factor producing activation of their synthesis. In this circumstance the decrease in concentration of myofibrillary proteins, actually observed at the damage stage of hyperfunction of the heart, may accelerate the rate at which the molecules of these proteins leave the matrices of the messenger RNA in polyribosomes. As a result, the intensity of use of the RNA matrices and of their breakdown may increase. As a result, the rate at which available RNA matrices leave the structural genes of chromosomal DNA is accelerated and the whole process DNA→RNA→protein becomes activated. If this hypothesis, advanced some years ago, is true, and activation of protein synthesis in polysomes really constitutes the initial link of the process necessary for realization of its subsequent links, then
apparently elimination of the given link by the inhibitor of protein synthesis under conditions of hyperfunction should prevent not only the activation of protein synthesis but also that of the synthesis of RNA. Investigation of the effect of puromycin on the compensatory hyperfunction of the heart, produced by stenosis of the aorta by Posner and Fanburg (1968), has shown just this result.

Another argument in favour of the given hypothesis is that synthesis of one of the muscle proteins, myoglobin, occurring in vitro in the ribosome system, may be activated by the decrease in concentration of myoglobin and inhibited by the rise of concentration of the given protein. Here the change in concentration of myoglobin does not act on the degree of synthesis of other proteins, in particular of that of albumin (Kagen and Linder, 1969). Actually this hypothesis suggests the existence of an economic mechanism of quantitative regulation of transcription of a limited number of genes which are active in the differentiated cell.

Experimental correlation of these two hypotheses is expected in the future. At the same time the concept that the breakdown of structures activates in some way the genetic apparatus of muscle cells already represents a starting point for the prophylaxis of acute heart insufficiency and the active prevention of the process of hypertrophy.

Indeed, if at the onset of compensatory hyperfunction of the heart, at the so-called damage stage of this process, there arises a lack of energy and as a consequence a breakdown of structures with a subsequent activation of synthesis, this situation may be prevented by preliminary increase in capacity of the mechanisms of oxidation and oxidative phosphorylation in myocardial cells.

**Altitude hypoxia and physical load**

Two factors are known which by themselves produce an insignificant hypertrophy of the left ventricle but at the same time lead to a considerable increase in capacity of the mechanism of energy transformation in the myocardium. Such factors are adaptation to disrupted action of altitude hypoxia, and training to physical load.

The adaptation to disrupted action of altitude hypoxia always involves an increase in capacity of the mechanisms responsible for the transport of oxygen to myocardial cells, namely the increase in number of coronary capillaries (Valdivia, 1962) and concentration of myoglobin (Tappen and Reynafarje, 1957; Poupa et al., 1966), with simultaneous increase in concentration of mitochondrial protein (Sobel and Cohen, 1958) and in activity of enzymes of the respiratory chain (Tappen and Reynafarje, 1957). The maximal force of myocardial contraction of trained animals calculated per unit of weight, as well as the rate of isotonic contraction, increased considerably (Meerson and Kapelko, 1970). In this connexion one could assume *a priori* that at the onset of compensatory hyperfunction of the heart, produced for instance by experimental defect in animals previously trained to altitude hypoxia, the lack of energy, breakdown of structures, and disturbance of the contractile function would be less than in the untrained animals, and correspondingly that the activation of nucleic acid and protein synthesis would be less pronounced.

The data represented in Fig. 1–5 illustrate the results of experiments performed on male rats of Wistar line in which, 14 months after preliminary training in the barocamera (at an 'altitude' of 6000 metres for 6 hours daily), an experimental coarctation of the abdominal aorta (narrowing to one quarter the crosssection of the abdominal aorta immediately below the diaphragm) was produced. Fig. 1 (left) shows that one day after coarctation of the aorta the concentration of creatine phosphate in the myocardium of the left ventricle in untrained rats has decreased by almost half; on the right it is shown that in rats previously trained to hypoxia no decrease in

**FIG. 1** Effect of training to altitude hypoxia on the decrease in concentration of creatine phosphate in the myocardium produced by aortic coarctation.
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Fig. 2 Effect of training to altitude hypoxia on the decrease in concentration of glycogen in the myocardium after aortic coarctation.

Creatine phosphate is occurring; there is even some increase, still unexplained.

Fig. 2 (left) shows that in untrained animals the concentration of another reserve of energy, glycogen, is decreased some days after aortic coarctation, not sharply, but quite appreciably by 17 per cent. On the right it is seen that in trained animals there is minimal decrease in glycogen after aortic coarctation.

Fig. 3 represents data on maximal force of myocardial contraction of the left ventricle calculated per unit of myocardial mass. On the left it is seen that in untrained rats the maximal contraction force developed by the myocardium in brief aortic coarctation is decreased by more than half one day after coarctation. On the right it is shown that in trained animals this decrease of the contractile function is 20 per cent and this difference is not statistically significant.

Fig. 4 shows that two days after the onset of hyperfunction in animals not adapted to altitude hypoxia, the RNA content in the left ventricle has increased by 51 per cent and in trained ones by only 9 per cent.

Fig. 5 shows that two days after aortic coarctation and the onset of hyperfunction of the heart, protein synthesis in the myocardium of untrained animals has increased by 66 per cent, while in those first adapted to the action of altitude hypoxia it has increased by 10 per cent.

Thus the preliminary adaptation to the disrupted action of altitude hypoxia has definitely prevented the disturbance of metabolism, function, and activation of nucleic acid and protein synthesis in the damage stage of the compensatory hyperfunction of the heart.

It is known that training to physical loading, like adaptation to altitude hypoxia, is a factor increasing the capacity of mechanisms transporting oxygen to myocardial cells – namely,
the capacity of the coronary vessels (Leon and Bloor, 1968) and myoglobin concentration (Pattengale and Holloszy, 1967). At the same time, as a result of training there is an increase in mass and number of mitochondria at the expense of activation of the nucleic acid and protein synthesis in these organelles (Laguens and Gómez-Dumm, 1967, 1968; Gollnick and King, 1969) and the increase in capacity of mitochondrial enzyme systems of oxidation and oxidative phosphorylation (Gollnick and King, 1969; Hearn and Wainio, 1956; Gould and Rawlinson, 1959; Holloszy, 1967).

The results of experimental work on the effect of acute heart overloading, produced by experimental aortic coarctation, upon the metabolism and function of the heart in rats first trained to physical load (running in a treadmill at the rate of 14 m. per minute for 3 hours daily with 5-minute intervals each half-hour during 2 months) have been found in principle similar to those in experiments with rats trained to altitude hypoxia. Fig. 6 shows that two days after aortic coarctation and the onset of hyperfunction the RNA content in the left ventricular myocardium taken from untrained animals has increased by 48 per cent, while that in the left ventricle of trained animals has not essentially changed. Fig. 7 shows that the intensity of protein synthesis two days after onset of hyperfunction has increased in the untrained animals by 46 per cent and in trained animals no noticeable activation of protein synthesis is seen.

On the whole, the results of experiments indicate that preliminary training to altitude hypoxia and physical exercise not only increases the myocardial resistance to overloading and decreases the extent of energy lack, characterized by concentration of glycogen and creatine phosphate, but also significantly lowers the
degree of activation of nucleic acid and protein synthesis in the damage stage of heart hypertrophy. The course of training to altitude hypoxia used in these experiments led to an insignificant hypertrophy of the left ventricle – its relative weight was increased only by 18 per cent. Training to physical exercises did not generally produce any significant increase in the left ventricular weight. This means that the result cannot be explained by supposing that in trained animals after coartation IFS was lower than in those untrained. The most probable explanation is that the developed capacity of the mechanisms of energy transformation in trained animals prevented the lack of energy and as a consequence decreased the breakdown of structures and the degree of activation of nucleic acid and protein synthesis.

Although the explanation put forward requires confirmation, it is important clinically to emphasize two points. The first is that preliminary training to altitude hypoxia or physical exercises is the factor capable of preventing the disturbance of metabolism and function characteristic of acute heart failure from overloading. The second implies that, other conditions being equal, the heart possessing a more active system of energy transformation may manifest an intense hypertension function at a lesser degree of activation of protein synthesis and consequently at a lesser degree of hypertrophy.

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