Virchows Arch. Abt. A Path. Anat. 347, 44—56 (1969)

Changes in Enzyme Activity and Electrolite Content in the Myocardium in Experimental Myocardial Hypertrophy and Insufficiency

A. M. VIHERT and N. M. POZDYUNINA

Laboratory of Pathological Anatomy, the A. L. Myasnikov Institute of Cardiology, USSR Academy of Medical Sciences, USSR, Moscow

Received June 10, 1968

Veränderungen in der Aktivität des Enzym- und Elektrolytgehalts des Myokardiums bei experimenteller Myokardhypertrophie und Insuffizienz

Zusammenfassung. Unter experimentellen Bedingungen durchläuft die Entwicklung einer Herzmuskelhypertrophie folgende Stadien:

a) Frühstadium, welches weiterhin unterteilt werden kann in eine Phase der akuten Muskelinsuffizienz und in eine zweite Phase der funktionellen Anpassung.

b) Das Stadium der Hypertrophie mit andauernder Myokardüberlastung.

c) Das Stadium der Hypertrophie mit latenter Herzinsuffizienz.

d) Das Stadium der Hypertrophie mit chronischer Herzinsuffizienz.

Die verschiedenen Stadien der Herzmuskelhypertrophie sind mit Stoffwechseländerungen der Herzmuskelfasern verbunden, die sich sowohl in einer Verschiebung der Enzymaktivitäten wie der Elektrolytbilanz des Myokards manifestieren.

Summary. During the development of hypertrophy, the myocardium of experimental animals passes through the following stages:

a) "Emergency" stage, which can be subdivided into two further phases: the phase of acute insufficiency of the heart muscle and the phase of functional accommodation of the heart muscle,

b) the stage of hypertrophy with persistent hyperfunction,

c) the stage of hypertrophy with latent cardiac insufficiency,

d) the stage of hypertrophy with chronic cardiac insufficiency.

All of the stages of myocardial hypertrophy listed above are characterized by significant and specific changes in myocardial metabolism, resulting in changes of enzyme activities and electrolyte balance of the myocardium.

To date, there is no integrated concept of the biochemistry of myocardial processes occurring during cardiac compensation and decompensation. Most of the data on myocardial metabolism in these conditions have been obtained biochemically with histochemistry playing thus far a minor role. The few but rather independent histochemical studies which exist fail to provide enough information to enable one to understand the dynamics of changes in myocardial compensation and decompensation. Accordingly, an attempt was made in this study to characterize changes in the enzyme systems of the myocardium by means of histochemical methods of experimentally produced changes. Flame photometry was used to study variations in electrolytes at different stages of cardiac compensation and decompensation.

Material and Methods

The experiments were carried out with albino male rats weighing 100 to 300 g (43 animals in the experimental groups and 40 in the control group). Myocardial hypertrophy and cardiac failure were induced experimentally in the animals by high coarctation of the aorta followed by additional physical loading (POZDYUNINA and POSTNOV, 1967).

Histochemical and *histological techniques* were used to study the myocardium of rats that 1. died 15 minutes to 20 hours after operation from acute circulatory failure with signs of pulmonary edema, 2. that survived up to 48 hours after the aortic coarctation, 3. that lived 10—15 days and 2—3 months post-operatively; and 4. that succumbed to chronic cardiac failure. Histochemically the following enzymes were assayed: succinate dehydrogenase by the method of NACHLAS *et al.;* malate dehydrogenase (HESS, SCARPELLI and PEARSE), NAD- and NADF-diaphorase (SCARPELLI and others); cytochromeoxidase (MOOG); ATP-ase of myosin at pH = 9.4 (PADYCULA and HERMANN); alkaline and acid phosphatases (GOMORI); 5-nucleotidase (WACHSTEIN and MEISEL); non-specific esterase (NACHLAS and SELIGMAN); and leucylamine-peptidase (BURSTONE and FOLK).

Concentrations of *electrolytes* (sodium, potassium and calcium) were determined by flame photometry in pieces of myocardium dried at 100—120° C to a constant weight and then dissolved in nitric acid.

Experimental Data

Our results show that under experimental conditions the development of hypertrophy and myocardial insufficiency involves considerable changes in enzyme activity and electrolyte content in the myocardium.

The rats under study were divided into 4 groups.

The *first group* included those rats that died within the first 24 hours post-operative of acute circulatory failure as well as those that survived 48 hours after aortic coarctation.

The myocardium of these rats showed focal decrease of all oxidation-reduction enzymes studied. This decrease was bigger in the myocardium of those animals that died (Fig. 1a and b).

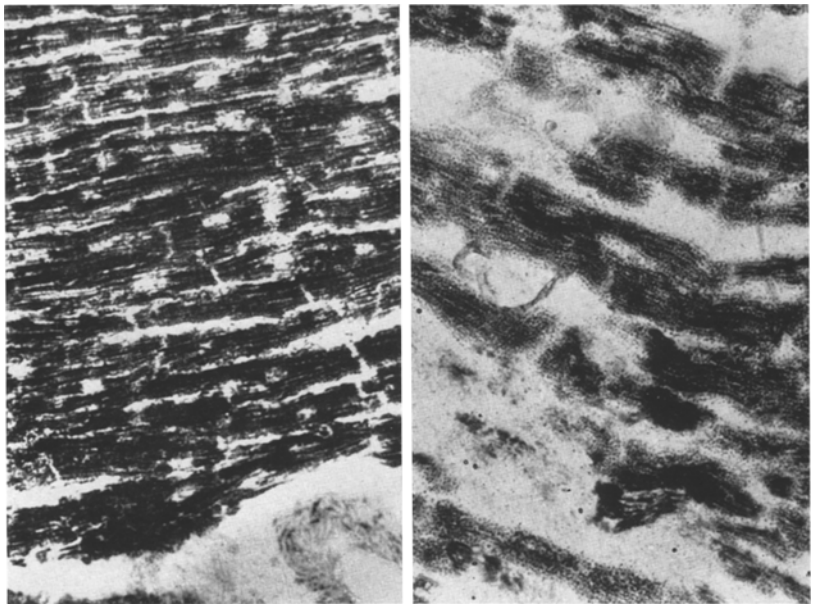
The ATP-ase activity of myosin in the myocardium of rats that died of acute cardiac failure remained unchanged (i.e. normal); whereas in the myocardium of rats that died 48 hours after operation it was slightly increased.

Dystrophic or necrotic changes occurred in some of the myocardial fibres 24—48 hours postoperatively, these changes were considerably less significant in the myocardium of animals that survived 48 hours after operation.

The activity of oxidation-reduction enzymes was reduced in dystrophic muscular fibres. Formazan granules in these fibres were enlarged, irregular and distributed abnormally within the sarcoplasm (Fig. 2a and b). Dystrophic fibres had reduced ATP-ase (Fig. 3) and alkaline phosphatase activities but elevated acid phosphatase, 5-nucleotidase and non-specific esterase activities (Fig. 4a); they also showed signs of leucylamine-peptidase activity (Fig. 4b).

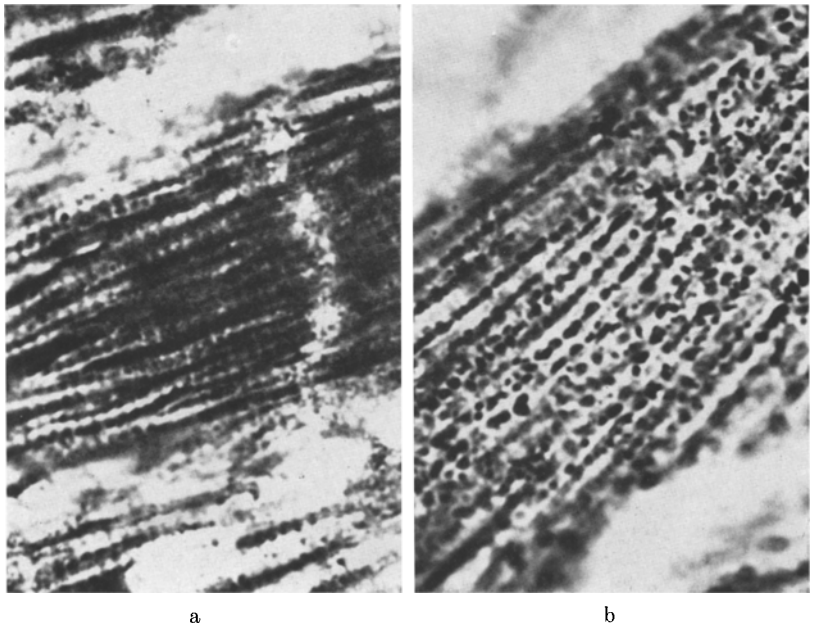
24 to 48 hours following coarctation of the aorta a statistically significant increase in the amount of sodium and calcium was noted in the myocardium of the left ventricle; in contrast, the potassium content tended to decrease (Table).

The *second group* included those rats that survived 10—15 days or 2—3 months postoperatively. In these animals we were able to study enzyme activity and electrolyte content from the onset of myocardial hypertrophy up to the point when it had developed significantly. 10 to 15 days after the operation the weight of the heart had increased by 20%, and 2—3 months later, by 100%. Rats of this



a b

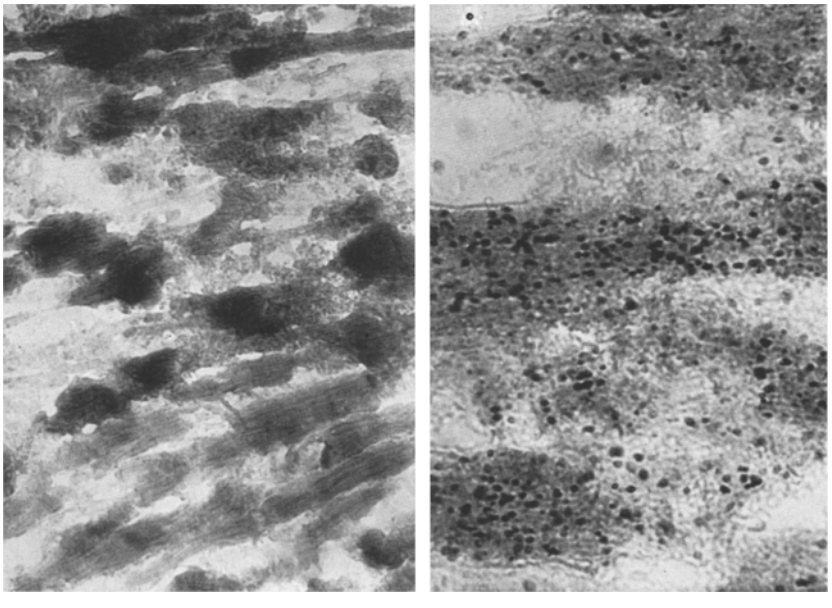
Fig. 1. a Succinate dehydrogenase in the myocardium in health. Reaction with nitro blue tetrazolite. × 225. b Activity decrease in succinate dehydrogenase in muscular fibres of rat myocardium in acute cardiac insufficiency. × 225



a b

Fig. 2. a Malate dehydrogenase in the myocardium of control rats. Localization of enzyme activity in muscular fibres correspond to the sites of mitochondria. Reaction with nitro blue tetrazolite. × 1,500. b Malate dehydrogenase in a dystrophically changed muscular fibre. Changes in shape and distribution of formazin granules in sarcoplasm are seen. × 1,500

Fig. 3. Reduction of ATP-ase activity in some of the muscular fibres in the myocardia of rats that died of acute circulatory failure. × 587



a b

Fig. 4a and b. Myocardium of a rat that died 20 hours after coarctation of the aorta from acute circulatory failure. a Marked increase of esterase activity in some fragments of decomposing muscular fibres. × 245. b Appearance of leucylamine peptidase activity in muscular fibres subject to lumpy decay. × 620

Table. *Sodium, potassium and calcium content in the myocardia of rats during the development of its hypertrophy and insufficiency*

		Na	K	Ca
	Control	150.7 ± 5.8	346.0 ± 1.8	16.1 ± 1.6
1st stage	24 hours after operation	175.6 ± 6.8 $p < 0.05$	342.9 ± 6.5 $p > 0.1$	29.5 ± 3.0 $p < 0.01$
	48 hours after operation	187.1 ± 2.5 $p < 0.001$	334.4 ± 4.1 $p > 0.05$	24.9 ± 1.3 $p < 0.001$
2nd stage	10—15 days after operation	153.4 ± 3.5 $p > 0.1$	368.1 ± 4.4 $p < 0.002$	21.4 ± 3.5 $p > 0.01$
	2—3 months after operation	152.6 ± 4.8 $p > 0.1$	366.4 ± 2.1 $p < 0.05$	15.8 ± 0.9 $p > 0.1$
3rd stage	1—3 months after operation	168.3 ± 2.3 $p > 0.05$	326.0 ± 4.4 $p < 0.02$	20.5 ± 1.3 $p < 0.05$
	Decompensation of cardiac activity	170.3 ± 2.4 $p < 0.05$	297.5 ± 8.8 $p < 0.002$	23.4 ± 2.1 $p < 0.02$

group exhibited no signs of disturbed cardiac activity. Their myocardium showed a marked hypertrophy of fibres, but few dystrophic fibres. As the hypertrophy progressed the activity of oxidation-reduction enzymes in the muscular fibres was gradually restored, to increase thereafter (Fig. 5a and b). The ATP-ase activity of myosin (Fig. 6a and b), the alkaline phosphatase, the non-specific esterase and the 5-nucleotidase were likewise increased.

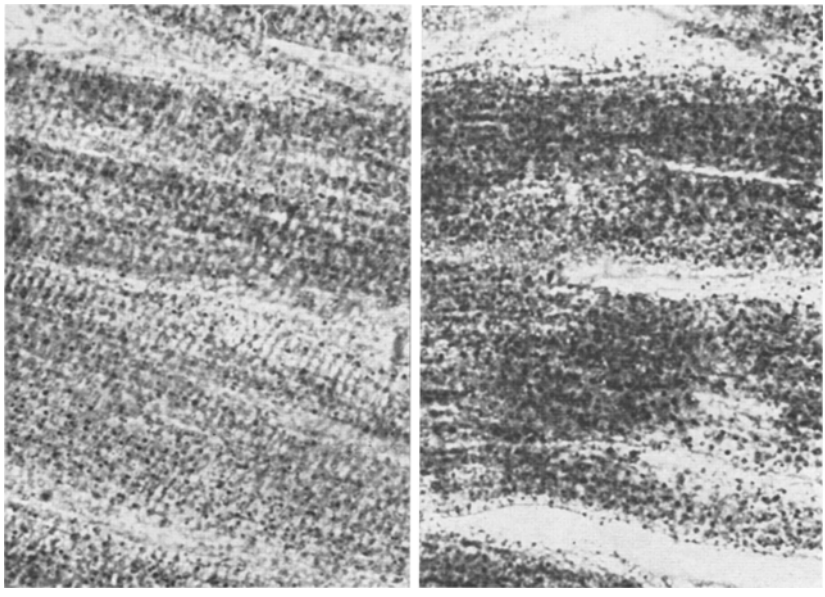
Over the period of 2 weeks to 3 months sodium and calcium content in the myocardium of rats with marked fibre hypertrophy but without signs of impaired activity remained within the normal range. Potassium content on the other hand was 5% more than normal (Table).

The *third group* included those rats which survived 1—3 months after operation and which, although different periods of time had elapsed after the operation, had the following common features: pronounced cardio-sclerosis against the background of muscular fibre hypertrophy; cardiac failure cells in the lungs and congestive phenomena in the liver (nutmeg liver). The myocardium of these animals showed lower activities of oxidation-reduction enzymes, ATP-ase, alkaline and acid phosphatase, and 5-nucleotidase, as compared with the second group and also, in some of the fibres, as compared with normal values (Fig. 7a—c).

Potassium values were reliably 8% less than in the control group, and 12—13% less than in the group with hypertrophy of the myocardium and slight cardio-sclerosis. Sodium and calcium levels on the other hand were found to increase again as during the first day after operation (Table).

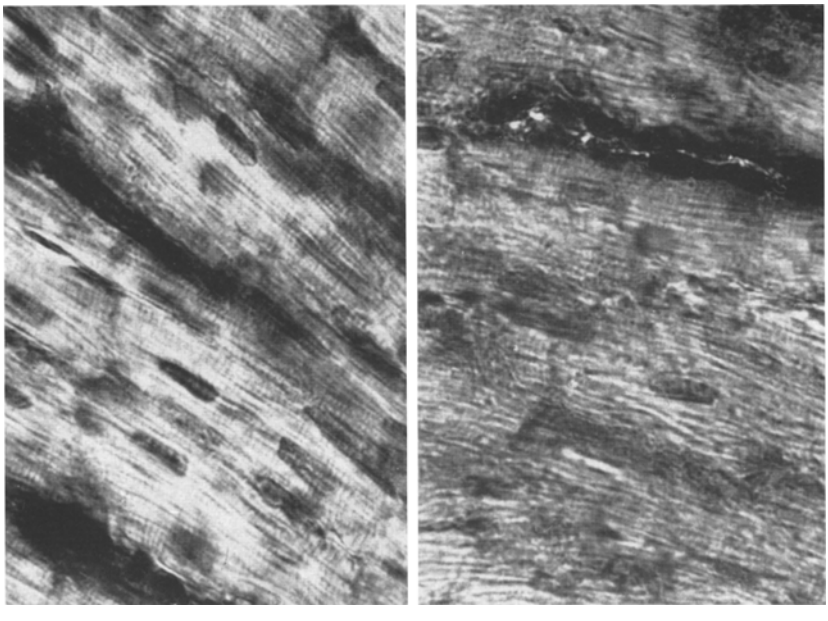
Those rats given additional physical loading 2—3 months postoperatively developed cardiac decompensation, as was evidenced by hydrothorax, ascitis, nutmeg cirrhosis and brown induration of the lungs (group 4).

The study of myocardial enzymes in these rats revealed sharply reduced activity of oxidation-reduction enzymes, primarily of succinate dehydrogenase and cytochrome oxidase as compared with the two preceding groups with compensated cardiac activity (Fig. 8a and b). ATP-ase activity of myosin and the



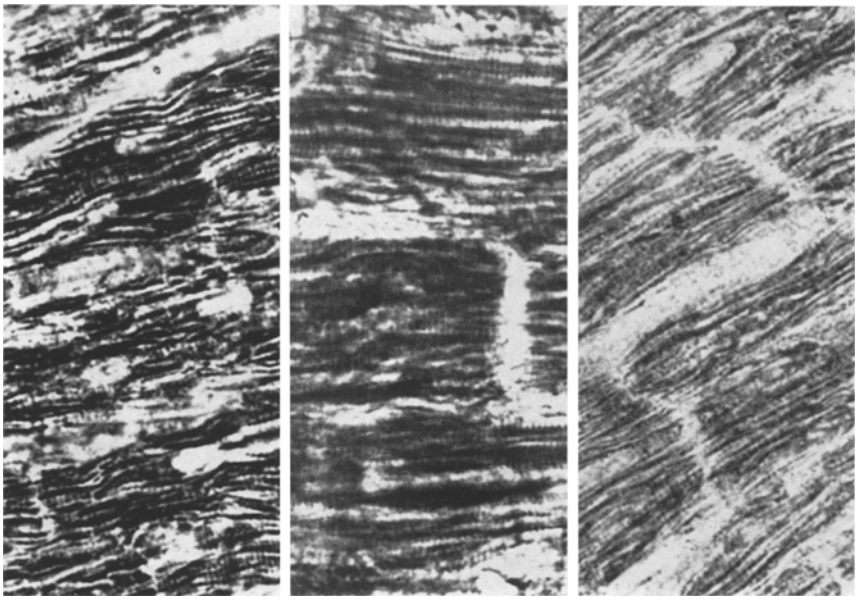
a b

Fig. 5a and b. Cytochrome oxidase in rat myocardium. a Enzyme activity in muscular fibres of control myocardium. × 625. b Enhancement of enzyme activity in hypertrophic muscular fibres. × 625



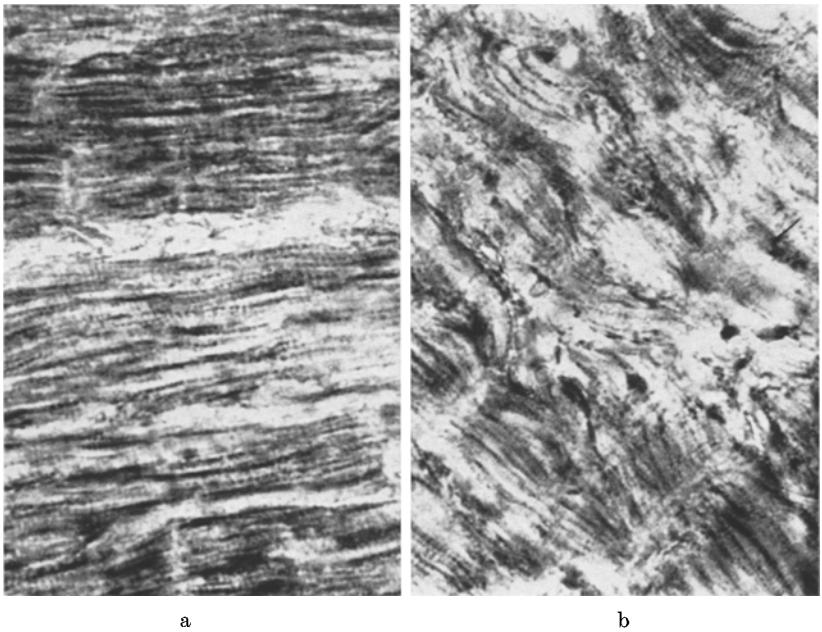
a b

Fig. 6a and b. ATP-ase in rat myocardium. a ATP-ase of muscular fibres in control myocardium. × 620. b Enhacement of ATP-ase activity in muscular fibres at the second stage of myocardial hypertrophy. × 620



a b c

Fig. 7. a Malate dehydrogenase in muscular fibres of control myocardium. × 620. b High malate dehydrogenase activity in muscular fibres of the myocardium at the stage of hypertrophy with persistent hyperfunction. × 620. c Reduction of malate dehydrogenase activity in the remaining fibres of the myocardium at the stage of hypertrophy with latent cardiac insufficiency. × 620



a b

Fig. 8. a Succinate dehydrogenase activity in rat myocardium at stage 3 of hypertrophy. × 620. b Reduction of succinate dehydrogenase in muscular fibres of the myocardium in chronic cardiac insufficiency. × 620

activities of alkaline phosphatase and non-specific esterase in chronic cardiac failure were likewise reduced. In the myocardia of the animals, potassium continued to fall, whereas the sodium and calcium contents increased (table).

Discussion

Coarctation of the aorta led to a sudden, marked increase in the mechanical load on the myocardium and to augmented contractile activity of heart muscle fibres. For some rats this narrowing of the aorta proved too much and resulted in their death by acute circulatory failure within 24 hours postoperatively. To perform an increased amount of work a bigger amount of energy accumulated in the macroergetic phosphate bonds of course was necessary; i.e. there was a need for more intensive phosphorylative processes which are the main source of energy in the heart.

However, in the myocardium of rats which died within 24 hours after the operation and the myocardium of those animals which survived for the first 48 hours we observed, as already indicated, a reduced activity of oxidation-reduction enzymes. This reduction appears to have been associated with an exhaustion of enzyme systems due to a greater demand for them, to provide for the considerably increased contractile function of the myocardium. With the dramatic decrease in the activity of oxidative-reduction enzymes lactic acid accumulated in the myocardium, thus lowering the pH and decreasing further the activity of specific dehydrogenases.

Oxidative processes in the cycle of tricarboxylic acids and in the final chain of electron transport appeared to be reduced during the first 24 hours after aortic coarctation. This resulted in insufficient re-synthesis of macroergetic phosphorus compounds. This has also been observed by others (Bing, 1959; Szekeres and Shein, 1959; Gertler, 1961; Schwartz and Lee, 1962; Hochrein *et al.*, 1963; Scheuer, 1967).

There are reasons to believe that the deficient aerobic re-synthesis of macroergetic phosphorus compounds is compensated by the activation of the anaerobic routes; i.e. by the transformation of glycogen and creatine phosphate, which decompose to maintain the ATP-concentration at the required level. In addition, during this period the energy of the lipoid compounds is extensively utilized by the heart. If this compensatory mechanism fails acute cardiac failure will develop and the animal will die. This phase in myocardial hypertrophy is termed by us *the phase of acute insufficiency* of the heart muscle. If the activity of oxidation-reduction enzymes in the myocardium is reduced less markedly, other ways of energy formation, as indicated above, may make up for the deficiency. This results in the compensation of cardiac activity and in the onset of myocardial hypertrophy. These circumstances seem to have existed in the myocardium of rats which survived 48 hours after operation. We call this the *phase of functional accommodation* of the heart muscle. On the basis of their common features we have combined both these phases into a single "emergency" stage (group 1). This term has been suggested by Meerson to designate the first stage in the development of myocardial hypertrophy.

At present there is no agreement as to the state of oxidation-reduction processes in the myocardium in the first "emergency" stage. Meerson points

out in his latest papers that this stage involves intensified processes of oxidation which contradicts our findings and those of others (APANASYUK, KLYUCHAREVA *et al.*, 1962; RUBEL *et al.*, 1963; MARKOVSKAYA *et al.*, 1965).

This disagreement seems to be due primarily to the fact that MEERSON extends the duration of the mergency stage to 10—15 days of the experiment; i.e. when a pronounced hypertrophy of the myocardium has already taken place. Our results indicate, however, as soon as 48 hours after operation the compensatory modification of metabolism occurs in the myocardium; processes that increase the muscular mass begin. MEERSON identifies the increase in coronary flow following coarctation of the aorta with an increase of oxidation-reduction processes in the myocardium. However, as RAISKINA (1964) has shown the increased coronary flow merely indicates a greater oxygen diffusion into the tissue, rather than an increased oxygen uptake by the tissue.

Information about the ATP-ase activity of myosin indicates that in the emergency stage the contractile proteins of the myocardium undergo no changes and that by the end of this stage the myosin capacity for enzymatic hydrolysis of ATP increases.

Following the emergency stage and as hypertrophy develops the heart gradually enters the hypertrophy stage with persistent hyperfunction (from 10—15 days to 2—3 months postoperatively, group 2). The gradual increase in the activity of oxidation-reduction enzymes during this stage appears to be associated with the growing number of mitochondria in the myocardial fibres. This is in agreement with the data of SOBEL and COCHEN (1958), TOBIAN *et al.* (1960), MEERSON *et al.* (1964) and SARKISOV *et al.* (1966), who noted increased numbers of mitochondria in the muscular fibres in hypertrophy. These findings also agree with results of ROSSI and DIANZANI MOR (1958), MEERSON and RAIKHLIN (1961) and DALLMAN (1966) on the increased activity of biological enzymes of respiration in hypertrophy of the myocardium. This intensifies oxidation phosphorylation and, hence, the formation of bigger amounts of ATP.

Hypertrophy of myocardial fibres leads to increased amounts of contractile proteins, particularly of myosin (CARNEY *et al.*, 1967). The increased ATP-ase activity of myosin is evidently linked up with its increased content in the muscular fibres. It can also be regarded as indicating an increased capacity of myosin to utilize the ATP-energy for contractions. In this respect our histochemical findings agree with the data of MEERSON *et al.* (1961) obtained by biochemical methods which also suggest an increased ATP-ase activity of myosin in the hypertrophic myocardium.

The stabilization of metabolism at a higher energy level brings about increased activity of other enzymes. The higher activity of alkaline phosphatase is indicative of intensified nucleic acid metabolism, enhanced formation of fibrillary proteins and more active transport of metabolites through the membranes, particularly of glucose. The higher activity of non-specific esterase and 5-nucleotidase and the appearance of leucylamine-peptidase in hypertrophic muscular fibres indicate that metabolism of esters is activated, specifically that of fats, proteins and their derivatives.

The hypertrophic myocardium that works long under an additional physical load, gradually develops changes which eventually result in its exhaustion and

in cardiac decompensation. This late stage of hypertrophy of the myocardium of rats with no signs of cardiac failure we have termed the stage of myocardial hypertrophy with *latent cardiac insufficiency* (group 3). The reduced activity of oxidation-reduction enzymes in the myocardium of rats at the 3rd stage of hypertrophy seems to be associated with, among other things, the disturbed structure of mitochondria and their reduced number in muscular fibres. This assumption is confirmed by the data of BAAR (1957), KOLLIN (1961), WOLLENBERGER (1963), WOLLENBERGER and SCHULTZ (1963) and MEERSON *et al.* (1963, 1964).

During later stages of hypertrophy, the synthesis of specific myocardial proteins is impaired, thus the myocardium becomes altered in its properties. For instance, our data show that myosin has a smaller capacity for enzymatic hydrolysis of ATP, as has been also noted in biochemical studies of MEERSON *et al.* (1961) and STEIN, CHANG, ALLEY and ALBANY (1962).

The reduced activity of enzymes such as alkaline and acid phosphatases and 5-nucleotidase appears to be associated with the disturbance in lower levels of tissue metabolism, in particular, with the reduced rate of synthesis of specific proteins in the myocardium.

The stage of myocardial hypertrophy with latent cardiac insufficiency can, it seems, last indefinitely. Additional loading, however, quickly leads to cardiac decompensation (group 4). The reduced activity of oxidation-reduction enzymes in the myocardium of these rats demonstrates that cardiac decompensation is associated with progressive decrease of respiratory efficiency in myocardial tissue and indicates the exhaustion of energy stores of the myocardium. The same conclusion follows from the works of BING *et al.* (1964) and PLECHATY *et al.* (1966).

The lower ATP-ase activity of myosin in the myocardium of rats with chronic cardiac insufficiency is indicative of changes in contractile proteins, which does not contradict the findings of a number of investigators who have noted inadequacy of myocardial proteins in cardiac decompensation (JOHNSON, 1956; KAKO and BING, 1958; OLSON, 1959; ARAS and HASS, 1962; SCHRYVER and CUDBJARNASON, 1965; and others).

Further evidence on metabolic deterioration of the myocardium in chronic cardiac insufficiency is proved by the reduced activities of alkaline phosphatase, non-specific esterase and other enzymes in most of the remaining hypertrophic muscular fibres.

At this period, dystrophic and dead muscle fibres are replaced by connective tissue. This replacement starts at the emergency stage and is progressive, leading to a situation where the remaining fibres are incapable of performing the contractile function of the myocardium.

The stages in the development of myocardial hypertrophy are also characterized by some unique changes in electrolyte balance in the myocardium. The accumulation of sodium ions we observed in the myocardium in the first 24 hours of aortic stenosis has also been noted by other authors (MEERSON, EVNINA and POGOSOVA, 1963; HOCHREIN, NAGANO and WOLLHEIM, 1963; WOLLHEIM, 1963). It probably is connected with insufficient tissue metabolism, primarily with the insufficiency in biological oxidation processes during the emergency stages. As the result, some potassium ions cannot be retained by the cell; they leave it and

are carried away with the blood. This involves a change in permeability of the cellular membrane. Sodium ions are given a chance to penetrate into the cell and there they accumulate. The increased amount of calcium may similarly be explained.

The increased potassium content throughout the second stage suggests that myocardial hypertrophy and all the associated changes of metabolic processes and contractile activity of the myocardium are correlated with potassium metabolism. Potassium takes part not only in stimulation and contraction processes in muscular fibres, but it is also intimately bound up with oxidative phosphorylation in mitochondria, being an activating agent for a number of enzymes in the tricarboxylic acids' cycle. An increase in potassium content with the sodium concentration remaining unchanged in muscular fibres of the myocardium during the second stage may also be associated with activation of the "potassium-sodium pump", when the contractile activity of the myocardium is enhanced.

The stage of myocardial hypertrophy with latent cardiac insufficiency is marked by increased sodium and calcium contents and by a reduction in potassium content. Presumably, this is due to death of some muscle fibres and their replacement by a connective tissue known to be rich in sodium (Davies *et al.*, 1952; Sal'manovich., 1962), and also to a decreased level of certain metabolic processes in the myocardium (decreased oxidative phosphorylation in mitochondria and reduced rate of "potassium-sodium pump").

Cardiac decompensation involves further alterations in the electrolyte balance of the myocardium. Thus, sodium content in the left ventricular myocardium continues to increase as compared with the stage of hypertrophy with latent cardiac insufficiency, whereas potassium content decreases. Our results agree with those of other authors who report an increased sodium concentration and decreased potassium content in the myocardium in chronic cardiac insufficiency (Alexander *et al.*, 1950; Isery *et al.*, 1952, 1955; Elster and Otto, 1956; Bliss and Adolph, 1963; Szczepanaski, 1967).

Bibliographie

Alexander, L. C., A. I. Boyle, L. T. Isery, R. S. McCaughey, and G. B. Myers: Electrolyte and water content of cardiac and sceletal muscle in normals, ventricular hypertrophy and infarction. J. Lab. clin. Med. **36**, 796 (1950).

Apanasyuk, M. P., N. M. Klyuchreva and V. M. Rubel': Zur Frage der Veränderungen biochemischer Vorgänge im Myokardgewebe bei kompensatorischer Überfunktion des Herzens. In the book „Physiologie und Pathologie des Blutkreislaufs", S. 71—73. Moscow 1962 [Russ.]

Aras, A., and H. Hass: ATPase and myokinase activity of myofibrils from normal, hypertrophied and failure human hearts. Fed. Proc. **21**, 132 (1962).

Baar, H.: Succinic dehydrogenase activity of normal and pathological tissue. Schweiz. Z. allg. Path. **20**, 164—191 (1957).

Benson, E. S., E. F. Freier, B. E. Hollaway, and M. I. Johnson: Distribution of fluid and electrolytes and concentration of actomyosin and other proteins in the myocardium of dogs with chronic congestive heart failure. Amer. J. Physiol. **187**, 483—492 (1956).

Bing, R. I.: The heart in congestive failure. Tex. St. J. Med. **55**, 931—936 (1959).

— Wu Clyde, and S. Gudbjarnason: Mechanism of heart failure. Circulat. Res. **15**, 64—69 (1964).

Bliss, M. A., and R. I. Adolph: Effect of experimental congestive heart failure and acethyl-strophanthidin on myocardial electrolyte and water content. Circulat. Res. **13**, 207—217 (1963).

Carney, J. A., and A. Brown: The morphology of myosin in cardiac hypertrophy. Lab. Invest. **16**, 36—43 (1967).

Dallman, P. R.: Cytochrome c in normal and hypertrophied heart. Nature (Lond.) **212**, 608—609 (1966).

Davies, F., R. E. Davies, E. Francis, and R. Whittam: The sodium and potassium content of cardiac and other tissues of the ox. J. Physiol. (Lond.) **118**, 276—281 (1952).

Elster, K., u. H. Otto: Der Kaliumgehalt menschlicher Leichenherzen bei energetisch-dynamischer Herzinsuffizienz. Klin. Wschr. **34**, 1139—1147 (1956).

Gertler, M.: Differences in efficiency of energy transfer in mitochondrial systems derived from normal and failing heart. Proc. Soc. exp. Biol. (N. Y.) **106**, 109—112 (1961).

Hochrein, H., M. Nagano, and E. Wollheim: Intracellular myocardial energy enzyme and electrolyte metabolism in experimental heart failure. In: Mem. 4. congr. mund cardiol. Mexico, Mexico **5**, 230—233 (1963).

Isery, L. T., L. C. Alexander, R. S. McCaughley, A. I. Boyle, and G. B. Myers: Water and electrolyte content of cardiac and sceletal muscle in heart failure and myocardial infarction. Amer. Heart J. **43**, 215—227 (1952).

— A. I. Bouyle, D. E. Chandler, and G. B. Myers: Electrolyte studies in heart failure. I. Cellular factors in the pathogenesis of the edema of congestive heart failure. Circulation **9**, 615—619 (1955).

Kako, K., and R. I. Bing: Contractility of actomyosine bands prepared from normal and failing human hearts. J. clin. Invest. **37**, 465—470 (1958).

Kollin, A.: Contribution to the problem of morphological evidence of hypoxic changes in the myocardium. Cardiologia (Basel) **39**, 114—122 (1961).

Markovskaya, G. I., V. V. Solovjev, S. M. Shenderov, A. A. Gorbachenkov, U. S. Mdinaradze, F. I. Zagarli, A. L. Mikoelyan u. E. B. Shul'zhenko: Hyperfunktion und Insuffizienz des Herzens bei experimentellen Herzfehlern [Russ.] Cardiologia (Basel) **5**, 8—13 (1965).

Meerson, F. Z.: Myokard bei Hyperfunktion, Hypertrophie und Insuffizienz des Herzens. [Russ.] Moscow 1965.

— T. D. Beloshapkina, E. F. Lushnikov, E. M. Leikina, G. I. Markovskaya u. G. V. Chernysheva: Funktion, Struktur und Eiweißstoffwechsel des hypertophaten Myokards [Russ.] Vestn. Akad. med. Nauk **7**, 27—37 (1963).

— G. V. Chernysheva u. L. S. Rozanova: Dynamik der fraktionisierten Eiweißzusammensetzung (der Einzelanteile an Eiweiß) des Myokards und der ATP-Aktivität bei momplasatorischer Überfunktion des Herzens. [Russ.] Vestn. Akad. med. Nauk **5**, 32—37 (1961).

— I. I. Evnina u. A. V. Pogosova: Einfluß einer Hyperfunktion des Herzens auf den Na- und K-Gehalt des Myokards. [Russ.] In the book „Problema nevnoy trofiki v teorii i praktike meditsiny", S. 194—199 Moscow 1963.

—, u. N. T. Raikhlin: Einige histochemische Veränderungen im Myokard bei kompensatorischer Überfunktion des Herzens. [Russ.] Arkh. Pat. **7**, 36—41 (1961).

— V. M. Rubel' u. G. V. Chernysheva: Proteine und ATPase-Aktivität des Myokards bei kompensatorischer Überfunktion des Herzens. [Russ.] 5th Internat. Congr. of Biochemistry. Summaries of section reports, Moscow **2**, 190 (1961).

— T. A. Zaletaeva, S. S. Laguchev u. M. G. Pshennikova: Dynamik der Änderungen von Struktur und Masse der Mitochondrien des Herzens im Verlauf von dessen Hyperfunktion und Hypertrophie. [Russ.] Tsitologiya **6**, 559—566 (1964).

Olson, R. E.: Myocardial metabolism in congestive heart failure. J. chron. Dis. **9**, 5, 442—464 (1959).

Plechaty, M., M. M. Gertler u. R. G. Guthrie: Intramitochondrial uptake of 32P in adenine nucleotides in congestive heart failure. Biochim. biophys. Acta (Amst.) **127**, 524—526 (1966).

Pozdyunina, N. M., u. U. V. Postnov: Methode der Erzielung von Myokard-Hypertrophie bei Ratten und Insuffizienz der Herztätigkeit. [Russ.] Arkh. Pat. **9**, 78—80 (1967).

RAISKINA, M. E.: Über die Wirkung von Catechinaminen auf die Stoffumsätze im Myokard. [Russ.] In the book „Adrenalin i noradrenalin", S. 192—196. „Nauka" Publ. House 1964.

ROSSI, G. F., u. MOR DIANZANI: In the book by F. Z. MEERSON, Fiziologiya i patologiya serdtsa, S. 150. Moscow 1963.

RUBEL', V. M., M. P. APANASYUK u. F. Z. MEERSON: Stoffwechsel im Myokard bei kompensatorischer Hyperfunktion des Herzens. Aktivität der Carboanhydrase des Myokards bei kompensatorischer Hyperfunktion des Herzens. [Russ.] Vop. med. Khim. **9**, 1, 57—60 (1963).

SALMA NOVITCH, V. S.: Verteilung von K und Na in den Teilen und Geweben des Herzens von Tieren. [Russ.] Bull. eksp. biol. med. **11**, 58—62 (1962).

SARKISOV, D. S., V. D. ARUTYUNOV, L. D. KRYMSKY u. L. S. RUBETSKII: Myokardhypertrophie und dessen Reversion. [Russ.] Moscow 1966.

SCHEUER, J.: Myocardial metabolism in cardiac hypoxia. Amer. J. Cardiol. **19**, 385—392 (1967).

SCHRYVER, S., and S. GUDBJARNASON: Myosin synthesis in chronic heart failure. Proc. Soc. exp. Biol. (N. Y.) **119**, 961—963 (1965).

SCHWARTZ, A., and K. LEE: Study of heart mitochondrias and glycolitic metabolism in experimentally induced cardiac failure. Circulat. Res. **10**, 321 (1962).

SOBEL, H., and F. COCHEN: Proteins of heart in experimental cardiac hypertrophy in the rat. Proc. Soc. exp. Biol. (N. Y.) **99**, 656—658 (1958).

STEIN, A. A., K. S. CHANG, R. ALLEY, and N. I. ALBANY: Histochemical observation on enzyme distribution in surgically resected human myocardium. J. Amer. med. Ass. **182**, 534—537 (1962).

SZCZEPANSKI, L.: Electrolytes within cells of skeletal muscles and myocardium in congestive heart failure. Pol. Med. f. **6**, 13—18 (1967).

SZEKERES, L., and M. SHEIN: Cell metabolism of the overloaded mammalian heart in situ. Cardiologia (Basel) **34**, 1, 19—27 (1959).

TOBIAN, L., O. SEVERSEIKE, and I. CICH: Do mitochondria participate in general cardiae hypertrophy? Proc. Soc. exp. Biol. (N. Y.) **103**, 774—777 (1960).

WOLLENBERGER, A.: Die Mitochondrien im hypertrophischen Myokard während der Entwicklung einer Herzinsuffizienz. Materialien des 2. Allsowjetischen naturwiss. kardiolog. Kongresses unter Beteiligung von Wissenschaftlern der sozialistischen Länder über Probleme der Kontraktionsfunktion des Myokards bei erworbenen Herzfehlern, S. 5—6. [Russ.] Moscow 1963.

— u. W. SCHULZE: Masse und Struktur der Mitochondrien im chronisch überbelasteten hypertrophierten Herz. Physiologie und Pathologie des Herzens. [Russ.] In the book „Fiziologiya i patologiya serdtsa", S. 126—142. Moscow 1963.

WOLLHEIM, E.: Myocardial metabolism in congestive heart failure. In: Mem. 4. Congr. mund. cardiol. Mexico, 1962, **5**, 339—344 (1963).

Dr. Dr. A. M. VIHERT
Laboratory of Pathological Anatomy
The A. L. Myasnikov Institute of Cardiology
USSR Academy of Medical Sciences
Moscow, USSR