Normally, myocardial metabolism is almost exclusively aerobic. The substantial quantities of adenosine triphosphate (ATP) required for muscle contraction and the much smaller amounts necessary for the maintenance of functions such as ion transport, rhythmicity, and conduction and the synthesis of membrane and protein constituents of the myocardium are supplied almost exclusively by mitochondrial oxidation of fatty acid and carbohydrate substrates. Even under conditions of stress such as those that exist during severe exercise, when the cardiac ATP requirement may be increased considerably, the capacity of the mitochondria for oxidative phosphorylation appears to be adequate to meet the requirements. The high level of and the capacity for oxidative metabolism in the heart are reflected morphologically in the remarkable observation that mitochondria constitute more than 35% of the cardiac cell volume as measured by quantitative electron microscopic stereological procedures (1).

Acute changes in energy requirements such as those that occur during strenuous exercise appear to be effectively met by increased mitochondrial synthesis of ATP, and the synthesis is finely adjusted to ATP requirements by the respiratory control mechanism. Increased utilization of ATP results in transient accumulation of adenosine diphosphate (ADP), which acts as a phosphate acceptor and stimulates the mitochondrial oxidative rate by decreasing the level of mitochondrial high-energy intermediates (2) or the proton-motive force across the inner mitochondrial membrane (3), according to the chemical or chemiosmotic theories of oxidative phosphorylation, respectively.

Sustained levels of increased preload or afterload, however, activate another more slowly responding mechanism that results in the stimulation of myocardial synthetic processes, thus producing an increase in the functional mass of mitochondria and other cardiac cell constituents. In this way, the capacity of the cell to synthesize ATP is increased, the reserve capacity of the myocardium is maintained, and the heart's ability to respond acutely to changes in volume or pressure work is preserved.

It is now quite clear that many types of physiological stimuli which increase the cardiac work load result in enlargement of the cardiac muscle cell and the heart (4). A factor common to all of these stimuli is an increase in ATP utilization, usually secondary to an increase in wall tension or inotropic state (5). This fact has led to the hypothesis that ATP depletion or more likely an accompanying secondary metabolic event is the common signal that initiates the synthesis of new mitochondria and other cellular constituents (4, 6, 7).

In this review, we will summarize some of the information available concerning the response of the systems involved in the synthesis and degradation of mitochondrial components to stimuli that lead to cardiac hypertrophy. Our aim is to relate these findings to mechanisms possibly involved in the activation of the synthesis of mitochondria and other cardiac muscle cell components during the development of hypertrophy. For better understanding, we will also briefly review some aspects of what is now known about the assembly of mitochondria, a complex process that involves two separate genetic systems.

RESPONSE OF CARDIAC MITOCHONDRIA TO STIMULI THAT LEAD TO CARDIAC HYPERTROPHY

If cardiac enlargement in response to an increased work load were a completely effective adaptive response, it might be expected that the various constituents of the cardiac muscle cell would accumulate proportionately so as to maintain optimal cell organization and function, presumably represented by the state existing in the
normal heart. Thus, mitochondrial functional mass relative to other cell constituents might be expected to remain constant during hypertrophy. This situation is clearly not the case, however, in cardiac muscle responding to pressure-induced hypertrophy or thyroid hormone administration; under these conditions, there is a dissociation between mitochondrial and myofibrillar mass. It therefore seems likely that either the stimuli that control the accumulation of different cardiac muscle components are multiple, preferentially affecting one or another of the myocellular constituents, or that, under pathological conditions, the normal organization of the cell is disrupted.

Electron microscopic (8) and biochemical (9) evidence indicates that there is a preferential accumulation of mitochondrial components during the earliest stage of pressure-induced hypertrophy. Our biochemical studies on rats (9) indicate a significant increase in mitochondrial cytochrome content and respiratory enzyme activity per gram of cardiac muscle protein 24 hours after constriction of the ascending aorta. The response is analogous to much larger changes in mitochondrial activity per gram of skeletal muscle noted after exercise conditioning (10). The metabolism of normal skeletal muscle, however, differs fundamentally from that of cardiac muscle in that oxidative metabolism is less well developed in skeletal muscle and glycolysis supplies a substantial amount of the ATP used during severe exercise. After exercise conditioning, mitochondrial oxidative capacity increases, and a greater proportion of the ATP requirement is supplied by oxidative metabolism. Heart, however, normally functions at optimal levels of oxidative capacity, so that glycolysis with lactate formation does not ordinarily occur. Exercise leads to no detectable change in the relative mitochondrial function mass in heart muscle (11), whereas pressure-induced hypertrophy does cause such a change. In any event, it is clear that both skeletal and heart muscle mitochondria may accumulate in excess of the proportion existing in normal muscle.

Mitochondria may accumulate preferentially during the earliest stages of pressure-induced hypertrophy, but at somewhat later times, i.e., 3-10 days after severe constriction of the ascending aorta in rats, mitochondrial cytochrome content per gram of tissue (9) and the relative volume occupied by mitochondria in the cardiac muscle cell decrease (12). Relative myofibrillar volume increases above normal, so that the myofibrillar-mitochondrial volume ratio increases substantially (12). It is evident, therefore, that mitochondrial and myofibrillar masses can respond to a work overload differentially and that they may be controlled by different mechanisms (13).

To reconsider the various patterns of mitochondrial response observed in hypertrophy produced by different procedures, the variations in the experimental designs must be examined. The most important variables that affect the pattern of mitochondrial development in cardiac hypertrophy appear to be (1) the character of the stimulus that produces the overload, i.e., pressure or volume overload, (2) the rapidity with which the enlargement is produced, (3) the stage of cardiac hypertrophy, i.e., early, sustained compensated, or decompen-sated, at which the measurements are made, and (4) the magnitude of the hypertrophy obtained. When enlargement develops in response to a gradually imposed pressure overload such as that in renal hypertension (14) or congenital pulmonic valvular stenosis in the dog (15), no decrease in the relative mitochondrial volume is noted during sustained hypertrophy. Similarly, in volume overload secondary to an arteriovenous fistula (16) or prolonged forced exercise in rats (11), the relative mitochondrial mass is unchanged. A transient increase in mitochondrial volume has been observed in rats subjected to an enforced swimming program (17). This overshoot in mitochondrial concentration resembles our own observations 1 day after aortic constriction (9).

The importance of the abruptness with which the work overload is applied is emphasized in the work of Wollenberger and his colleagues (18, 19). Aortic stenosis produced acutely in adult dogs leads to a decrease in the ratio of mitochondrial volume to myofibrillar volume (18). However, when aortas of young dogs are constricted so that the pressure overload increases gradually during growth, no change in relative mitochondrial volume occurs. These results could arise from different responses in young and adult dogs, but they are probably related to the rapidity of the development of hypertrophy.

Studies of long-term compensated pressure-induced hypertrophy in animals (8, 12, 18-23) and patients (24) consistently show a decrease in the ratio of mitochondrial volume to myofibrillar volume.

A dissociation of mitochondrial and myofibrillar growth responses has also been noted following administration of thyroid hormone to thyroidectomized and normal rats (25). Thyroid hormone causes not only an increase in the relative cell
volume occupied by mitochondria but also an increase in the density of the inner mitochondrial membrane (26 and Jakovcic, Swift, and Robinowitz, unpublished observations), the site of oxidative phosphorylation. Thus, in heart and liver, inner membrane development is stimulated, resulting in an increase in the capacity of individual mitochondria for oxidative metabolism and ATP synthesis. Thyroid hormone therefore appears to play an important role in the control of the structure and the functional capacity of an individual mitochondrion as well as in the control of the total functional mass of mitochondria. Tata et al. have shown that thyroxine increases mitochondrial (27) and cytoplasmic ribosomal protein synthesis (26) and stimulates nucleolar ribonucleic acid (RNA) polymerase activity (28) as well as the incorporation of precursors into nuclear and cytoplasmic RNA (29). These effects are inhibited by actinomycin, suggesting that thyroid hormone acts at the level of transcription control (30). Page et al. (31) have shown that, in contrast to the different responses of mitochondrial and myofibrillar components to different types of cardiac hypertrophy, there is a remarkable constancy in the ratio of the cell surface membrane (i.e., sarcolemma plus the T-tubules) to the volume of the cell and in the ratio of the sarcoplasmic reticulum surface area to the myofibrillar volume. These results indicate that there are stringent controls that maintain a constant relationship of these membranes to cell size and structure.

MITOCHONDRIAL SYNTHESIS AND TURNOVER IN NORMAL HEART

Before proceeding to the consideration of the mechanisms involved in mitochondrial accumulation during cardiac hypertrophy, we must briefly review the current knowledge of the processes involved in normal mitochondrial assembly and destruction. During the past decade, it has been firmly established that mitochondria possess a genetic system independent of that in the nucleus and the cytoplasm (32–35). Mitochondria contain their own unique species of deoxyribonucleic acid (DNA) (36, 37) from which mitochondrial messenger RNA (38, 39), ribosomal RNA (40, 41), and transfer RNAs (42–44) are transcribed. A functionally and structurally independent system of ribosomal protein synthesis is present in the mitochondria, as are the enzymes necessary for replication of mitochondrial DNA and transcription of mitochondrial RNA. However, most of the proteins in mitochondria (more than 85%) including the mitochondrial ribosomal proteins (45), the initiation and elongation factors involved in protein synthesis, and the enzymes involved in the synthesis of mitochondrial DNA and RNA are synthesized outside the mitochondria on cytoplasmic ribosomes with information derived from the nuclear genome (35). Mitochondrial DNA in higher organisms is known to transcribe the following: mitochondrial ribosomal RNA (46), 12 transfer RNA’s (44), and poly A-containing RNAs (38, 39) that probably are messenger RNAs coding for some of the peptides of cytochrome oxidase (47, 48), cytochromes b (49) and c1 (50), and a component of the oligomycin-sensitive adenosinetriphosphatase (51, 52). On the other hand, RNA and DNA polymerases, mitochondrial ribosomal proteins, Krebs cycle enzymes, and all outer membrane and matrix enzymes are probably coded for by nuclear DNA and are synthesized on cytoplasmic ribosomes and then integrated into the mitochondria (32, 34) (Fig. 1). It is of special interest that apparently not all mitochondrial transfer RNAs are transcribed from the mitochondrial DNA in higher organisms (44) and that some are probably imported from the cytoplasm. The intimate interaction and cooperation between the nuclear and mitochondrial genetic systems is also strikingly illustrated by the fact that a single enzyme complex, such as cytochrome oxidase, is composed of seven different subunits, four of them synthesized in the cytoplasm and three in the mitochondria (48, 53, 54).

It is also of interest that many of the characteristics of mitochondrial protein synthesis resemble those in bacteria and differ from those in eukaryotic cytoplasmic systems. Protein synthesis in both mitochondria and bacteria is initiated by formylmethionyl transfer RNA (55, 56) and inhibited by chloramphenicol but not by cycloheximide (57); thus, it differs from protein synthesis in cytoplasmic ribosomes. The similarity of mitochondrial and bacterial ribosomes is also shown by the ability of bacterial initiation and elongation factors to sustain mitochondrial ribosomal protein synthesis (58). Another similarity between mitochondria and bacteria is that mitochondrial membrane-bound DNA-replicating complexes resemble those in bacteria (36). These similarities have led to the hypothesis that mitochondria have evolved from symbiotic bacteria that entered cells early in evolution (59).

Mitochondria thus are composed of components synthesized by the organelle itself and components synthesized externally and subsequently assembled. Stimulation of mitochondrial synthesis must represent a coordinated and controlled effort by
Nucleic Acids

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Outer Membrane</th>
<th>Inner Membrane (Cristae)</th>
<th>Matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesized</td>
<td>All synthesized outside mitochondria</td>
<td>Some synthesized in part by mitochondria</td>
<td>Site of synthesis</td>
</tr>
<tr>
<td>Mitochondrial DNA†</td>
<td>Cytochrome b₆</td>
<td>Cytochrome a₄a₃</td>
<td>M+C</td>
</tr>
<tr>
<td>Ribosomal RNA</td>
<td>Cytochrome c reductase (rotenone insensitive)</td>
<td>Cytochrome b</td>
<td>M+C</td>
</tr>
<tr>
<td>Messenger RNAs</td>
<td>Monoamine oxidase</td>
<td>Cytochrome c</td>
<td>M+C</td>
</tr>
<tr>
<td>tRNAs (only 12 synthesized in mt — others probably of nuclear origin)</td>
<td>Fatty acid thikinase</td>
<td>Oligomycin-sensitive ATPase</td>
<td>M+C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glutamic dehydrogenase</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Succinic dehydrogenase</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-Keto acid dehydrogenase</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ferrrochelatase</td>
<td>C</td>
</tr>
</tbody>
</table>

Proteins

- Cytochrome bB
- Cytochrome c reductase (rotenone insensitive)
- Monoamine oxidase
- Fatty acid thikinase
- Cytochrome a+a₃
- Cytochrome b
- Cytochrome c
- Oligomycin-sensitive ATPase
- Glutamic dehydrogenase
- Succinic dehydrogenase
- α-Keto acid dehydrogenase
- Ferrrochelatase
- Ribosomal proteins
- Initiation and elongation factors
- Krebs cycle enzymes
- Fatty acid oxidation enzymes
- DNA polymerase
- RNA polymerase
- Malate dehydrogenase
- Glutamate dehydrogenase
- Ornithine transcarbamylase
- 6 aminolevulinic acid synthetase

**FIGURE 1**

Site of biosynthesis of various mitochondrial enzymes and nucleic acids. M = mitochondrial, C = cytoplasmic, and Mt = mitochondria.† Most of the data on the site of synthesis of components are derived from experiments carried out in yeast or Neurospora crassa. The mitochondrial DNA in these organisms is four to five times larger than mammalian mitochondrial DNA (32) and therefore may code for a larger number of mitochondrial components. † Forms replication complex with inner mitochondrial membrane (85). The electron micrograph of a rat heart mitochondrion was kindly provided by Dr. E. Page; the area occupied by the matrix was darkened by the artist to improve the visualization of membrane structures.

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both the nuclear-cytoplasmic and the mitochondrial genetic and synthetic systems. Almost nothing is currently known about the coordination of these systems. Barath and Künzel (60) have observed an increased concentration of several mitochondrial enzymes synthesized outside the mitochondria on cytoplasmic ribosomes following inhibition of the synthesis of mitochondrial RNA or protein in Neurospora. They have therefore postulated that a product of mitochondrial protein synthesis inhibits and controls the transcription of messenger RNAs derived from the nucleus that code for mitochondrial proteins. The control of nuclear and mitochondrial systems, however, is...
still almost completely obscure and is currently the subject of intense investigation in several laboratories.

In heart muscle as well as in other tissues, mitochondria are constantly being synthesized and destroyed, thereby maintaining a steady-state level. Our studies on rat heart and liver have shown that several components of the inner mitochondrial membrane turn over with similar half-lives of 5–6 days; these components include cytochromes aa, (61), b, and c, (61, 62), cardiolipin (G. S. Getz, unpublished observation), an acid phospholipid that is localized in the inner mitochondrial membrane (at least in liver) (63, 64), and mitochondrial DNA (65). Outer mitochondrial membrane components and matrix enzymes may turn over much more rapidly; for example, δ-aminolevulinate synthetase, a matrix enzyme (66), turns over with a half-life of 90 minutes (67). We have postulated that at least a major component of the inner mitochondrial membrane turns over as a unit (32), perhaps secondary to being engulfed and digested by lysosomes (68). Matrix and outer mitochondrial membrane proteins, however, appear to be inserted and removed independently.

SYNTHESIS AND DEGRADATION OF MITOCHONDRIA IN CARDIAC HYPERTROPHY

Synthesis of Proteins and Nucleic Acids.—As discussed earlier in this review, mitochondrial components appear to be synthesized earlier than other cardiac cell constituents in some types of rapidly induced experimental cardiac hypertrophy. Soon after aortic constriction, the rate of incorporation of labeled amino acids into cardiac mitochondrial protein is increased to a greater extent than that into most other cell fractions (69); also, respiratory enzyme-specific activity (9) and mitochondrial cytochrome concentration increase (9). All of these findings indicate an early accumulation of mitochondrial components. Amino acid incorporation into proteins by isolated mitochondria is also greater at this time (70). Meerson, and Pomonitsky (7) have noted a striking increase in the incorporation of labeled precursors into mitochondrial RNA and DNA during developing cardiac hypertrophy. In fact, six- to tenfold elevation in mitochondrial DNA content per milligram of mitochondrial protein has been reported; this surprisingly large increase may be due to methodological difficulties, however. Meerson has suggested that more mitochondrial DNA is necessary as a template for the more rapid RNA transcription that has also been observed (7). Besides, there is a considerable increase in the incorporation of labeled precursors into nuclear RNA; this increase could represent nuclear transcripts that are precursors of messenger RNA coding for the synthesis of new mitochondrial components (7). Of course, enhanced synthesis of nuclear RNA may be involved in the accumulation of many other nonmitochondrial cardiac cell components as well. Although changes in pool-specific activity were not measured in this study and methods for the isolation of mitochondrial DNA and RNA were not completely rigorous, it is likely that there is substantial stimulation of mitochondrial DNA and RNA synthesis in developing hypertrophy. Increased synthesis of mitochondrial and nuclear RNA is most probably involved in the increased rate of synthesis of mitochondrial proteins that has been indicated by incorporation studies (9, 69, 70) and cytochrome and respiratory enzyme analyses (9).

Since it has been established that the normal turnover of cardiac mitochondria is quite rapid, it is apparent that changes in the rate of destruction as well as changes in the rate of synthesis could regulate the level of mitochondria in the cell. Schimke's extensive studies in liver (71) have shown that the level of soluble and endoplasmic reticulum–bound enzymes may be regulated by alterations in the rate of synthesis, the rate of degradation, or, in some cases, the rate of both synthesis and degradation. Changes in rates of degradation as well as rates of synthesis appear to regulate the level of mitochondrial proteins in cardiac hypertrophy. Our laboratory has obtained direct evidence that a decrease in the rate of degradation of cytochrome c accompanies an increase in synthesis early after aortic constriction in the rat (Fig. 2). In this case, synthetic and degradative processes appear to be coordinately controlled in a reciprocal manner: degradation is decreased, whereas synthesis is increased. The result is a highly efficient accumulation of the organelle. Presumably during regression of cardiac hypertrophy, as occurs after corrective aortic surgery or removal of a constricting aortic band (72), there are opposite reciprocal changes in degradation and synthesis rates, but these changes have not yet been adequately measured. Because measurements of the rates of synthesis and degradation of myofibrillar proteins are exceedingly difficult due to the lack of suitable precursors that are not reutilized, it is not clear whether changes in the degradation rate also affect their accumulation during cardiac enlargement.

Control of Synthesis and Degradation of Mitochondrial Components.—Although some descrip-
Changes in the rates of synthesis and degradation of cytochrome c in pressure-induced cardiac hypertrophy. $R_s$ = rate of synthesis, and $R_d$ = rate of degradation. The values were estimated from changes in cardiac cytochrome c content and total radioactivity in cytochrome c (9, 12) and from the half-life of cytochrome c which, in normal rat heart, is 5-6 days (61). The results are presented as percent change from control value.

The signal that turns on mitochondrial or nuclear RNA synthesis and consequent protein synthesis during developing hypertrophy is still unknown, but several mechanisms have been proposed. One theory postulates that the relative concentrations of adenine nucleotides in the cell, which reflect the steady-state rates of ATP utilization and resynthesis, directly control, or more likely reflect, other biochemical changes that control RNA transcription (4, 6, 7). The state of the adenine nucleotides is perhaps best expressed as the phosphate potential, $[ATP] / ([ADP] + [P_i])$ (80). Meerson and associates (7, 81) have shown that several stimuli that decrease the phosphate potential by different mechanisms, i.e., stenosis of the abdominal aorta and hypoxia, result in increased rates of incorporation into cellular and mitochondrial RNA and in cardiac hypertrophy. Furthermore, conditioning with one stimulus for hypertrophy, such as with intermittent hypoxia, which presumably leads to an increased mitochondrial mass and capacity for ATP synthesis, results in diminished augmentation of the RNA and protein synthesis caused by the second stimulus.

Many investigators have noted that most, if not all, stimuli that lead to hypertrophy involve increased oxygen consumption and ATP utilization. Therefore, a finite drop in the phosphate potential must accompany these stimuli, although the magnitude of the decrease depends on the efficiency and the rate of mitochondrial resynthesis of the ADP produced during the physiological change. Direct measurements of adenine nucleotides and of creatine phosphate content during developing hypertrophy have been contradictory (Table 1). Some workers have found no detectable changes in ATP or creatine phosphate levels; some have noted a decrease in creatine phosphate only, whereas others have detected quite marked decreases in phosphate potential resulting from a decrease in...

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Myocardial Content of High-Energy Phosphate Compounds in Various Stages of Cardiac Hypertrophy

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>Animal</th>
<th>Heart Sample</th>
<th>Condition</th>
<th>Creatine phosphate*</th>
<th>Creatine*</th>
<th>ATP*</th>
<th>ADP*</th>
<th>P_i*</th>
<th>[ATP]†</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Cardiac Overload</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfused heart; 2 minutes of external work</td>
<td>Rat</td>
<td>L &amp; RV</td>
<td>C</td>
<td>8.3</td>
<td>4.8</td>
<td>1.0</td>
<td>5.6</td>
<td>0.7</td>
<td>86†</td>
<td></td>
</tr>
<tr>
<td>Living animal; aortic constriction for 90 seconds</td>
<td>Rat</td>
<td>LV</td>
<td>C</td>
<td>5.9</td>
<td>4.0</td>
<td>1.2</td>
<td>11.3</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living animal; aortic constriction for 5 hours</td>
<td>Rat</td>
<td>LV</td>
<td>C</td>
<td>4.9</td>
<td>4.4</td>
<td>1.0</td>
<td>3.2</td>
<td>1.1</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Aortic insufficiency for 2 days</td>
<td>Rabbit</td>
<td>LV</td>
<td>C</td>
<td>7.7</td>
<td>4.8</td>
<td>0.9</td>
<td>4.1</td>
<td>0.9</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol injections, 2.5 mg/kg, for 3 days</td>
<td>Rat</td>
<td>LV</td>
<td>C</td>
<td>7.9</td>
<td>4.4</td>
<td>4.0</td>
<td>2.5</td>
<td>5.8</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Aortic constriction for 2 days</td>
<td>Rabbit</td>
<td>LV</td>
<td>C</td>
<td>6.0</td>
<td>5.4</td>
<td>1.3</td>
<td>3.7</td>
<td>1.6</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Coronary arterial occlusion; noninfarcted area analyzed</td>
<td>Dog</td>
<td>LV</td>
<td>C</td>
<td>7.5</td>
<td>5.5</td>
<td>0.7</td>
<td>4.8</td>
<td>0.6</td>
<td>91</td>
<td></td>
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<tr>
<td>Compensated Cardiac Hypertrophy</td>
<td></td>
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<tr>
<td>Chronic hypoxia (6% O_2) for 28-35 days</td>
<td>Rat</td>
<td>RV</td>
<td>C</td>
<td>5.8</td>
<td>4.0</td>
<td>1.0</td>
<td>3.3</td>
<td>0.9</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery stenosis for 21-90 days</td>
<td>Cat</td>
<td>RV</td>
<td>C</td>
<td>5.3</td>
<td>4.2</td>
<td>1.0</td>
<td>3.0</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic insufficiency for 5-6 months</td>
<td>Rabbit</td>
<td>LV</td>
<td>C</td>
<td>7.2</td>
<td>4.8</td>
<td>0.9</td>
<td>4.1</td>
<td>0.9</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Thyroxin administration, 1.9 mg/kg, for 7 weeks</td>
<td>Rat</td>
<td>TH</td>
<td>C</td>
<td>7.5</td>
<td>5.4</td>
<td>1.3</td>
<td>3.3</td>
<td>1.7</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Swimming for 7 weeks</td>
<td>Rat</td>
<td>TH</td>
<td>C</td>
<td>7.5</td>
<td>5.4</td>
<td>1.3</td>
<td>3.3</td>
<td>1.6</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

| Heart Failure |       |              |           |                     |          |      |      |      |        |      |
| Pulmonary artery stenosis | Dog | RV | C | 13.0 | 19.8 | 6.1 | 1.1 | 5.3 | 1.0 | 94    |      |
| Pulmonary artery stenosis | Cat | RV | C | 8.3 | 13.3 | 5.8 | 1.0 | 5.0 | 1.0 |      |      |
| Aortic insufficiency | Rabbit | RV | C | 7.7 | 4.8 | 0.9 | 4.1 | 0.9 | 88    |      |
|                      | E     |    | 7.0 | 4.5 | 0.8 | 4.9 | 0.8 |      |      |

C = control, E = experimental, LV = left ventricle, RV = right ventricle, and TH = whole heart.
* Numbers were rounded off to the first decimal place.
† All decimal places as given by authors were used to calculate the phosphate potential.
‡ No decline in ATP concentration was found in guinea pig heart perfused under similar conditions for 5 hours (78).

ATP and an increase in ADP and inorganic phosphate concentrations.

The differences are possibly due to the fact that analyses were carried out at different times during the development of hypertrophy and in hearts with hypertrophy of different severity. It appears probable that, during the rapidly developing stages of cardiac hypertrophy, the phosphate potential decreases, but that, when mitochondria have accumulated, there is a partial normalization of the adenine nucleotide level.

But even if changes in adenine nucleotide and creatine phosphate levels correlate with the stimulation of cardiac hypertrophy, we still know little or nothing about the way in which this stimulation is effected. Ingwall et al. (82) have proposed that increasing concentrations of creatine may act directly to stimulate myosin synthesis. Because the equilibrium constant of the creatine kinase favors phosphorylation of ADP by creatine phosphate, substantial increases in cardiac muscle creatine content must occur before there is any sizable fall in ATP levels. Thus, the creatine-creatine phosphate ratio is a more sensitive indicator of changes in the phosphate potential than is ATP or ADP content. Moreover, external administration of

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creatinine and some creatine analogues has been shown to stimulate myosin synthesis in embryonic cultured myoblasts (82). The mechanism for this stimulation is still unclear, and whether it operates in the development of physiological hypertrophy has not been established. Possibly other enzymatic reactions, which also depend on the phosphate potential or the redox potential of the cell, are the mediators that stimulate RNA and protein synthesis.

The mechanisms by which eukaryote nuclear RNA synthesis is controlled are still obscure but are under intense study in many laboratories and in many experimental systems. Currently, it is thought that nonhistone nuclear proteins may be involved in the control of transcription of specific cistrons (83). Elucidation of these processes is likely to derive from investigations in noncardiac systems, in which factors controlling the synthesis of a single purified messenger RNA can be investigated systematically.

Very little is known about the control of mitochondrial RNA synthesis. Aloni and Attardi (46) have presented evidence in HeLa cells for complete transcription of both strands of HeLa mitochondrial DNA, with subsequent processing and modification of the RNA (addition of poly A to some species) (84) and variable rates of destruction of different RNAs. Thus, the more stable RNA species, such as ribosomal RNA and transfer RNAs, accumulate in larger amounts than the more unstable RNAs. If it is true that mitochondrial DNA is transcribed completely as a unit, the mechanisms of control of mitochondrial RNA transcription must involve either an increase in the amount of mitochondrial DNA available or an increase in the rate of initiation of RNA synthesis. Control of the rate of RNA destruction may also be involved. The control of transcription of individual cistrons on mitochondrial DNA would not be expected; rather, transcription would be an all-or-nothing process.

The mechanisms by which mitochondrial transcription and translation are coordinated with the corresponding processes in the nucleus and cytoplasm still remain to be elucidated. It is likely that very sensitive control processes are acting, which result in coordinate synthesis of nuclear-cytoplasmic and mitochondrial components. Conceivably, such finely coordinated processes are deranged in prolonged pressure-induced hypertrophy and in other pathological conditions, resulting in an abnormal structural arrangement of the myocardium with accompanying physiological abnormalities.
MITOCHONDRIA AND CARDIAC HYPERTROPHY


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