

# Metabolic Products and Myocardial Ischemia

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Metabolic products accumulate in ischemic myocardium secondary to reduced coronary flow, which prevents adequate washout of vascular spaces, and to reduced oxidative metabolism. The most notable products that accumulate are NADH, H<sup>+</sup>, lactate, CO<sub>2</sub>, long-chain acyl-CoA, and long-chain acyl carnitine. These products interfere with the production of ATP and the functioning of the myocardium. Glycolytic production of ATP is inhibited by accumulation of NADH, H<sup>+</sup>, and lactate. Mitochondrial and plasma membrane function may be altered by the acyl esters of

CoA and carnitine. Mitochondrial membranes become structurally distorted and fragmented, and lipid-containing amorphous densities appear in the matrix. Structural alterations of mitochondria occur more frequently in hearts receiving high concentrations of fatty acids and correlate with high tissue levels of acyl esters of CoA and carnitine. Addition of acyl carnitine to mitochondria isolated from normal hearts results in nodulose-appearing cristae and fragmentation of mitochondrial membranes. (Am J Pathol 1981, 102:282-291)

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MYOCARDIAL ISCHEMIA has been studied extensively in recent years, and a great deal of descriptive work has been accomplished. From these studies, it has become clear that ischemia cannot be defined in simple terms of coronary flow. Any definition must take into account oxygen delivery and flow rate in relation to the energy demands of the tissue. A heart can survive large reductions in flow if the oxygen content of that flow is adequate 1) to meet the energy requirements of the tissue by completely oxidizing carbon substrates to CO<sub>2</sub> and by neutralizing H<sup>+</sup> by production of H<sub>2</sub>O, and 2) to prevent metabolic products from accumulating in the vascular space either by their complete oxidation to CO<sub>2</sub> and H<sub>2</sub>O or by washout if complete oxidation is not possible. An actual reduction in coronary flow is not required to produce ischemia if the energy demand is increased without a corresponding increase in flow. This is perhaps the most common type of ischemia seen clinically, where partially occluded arteries will not permit coronary flow to increase in response to increased cardiac work and energy demand. Thus, many cardiologists have resorted to the use of the term "energy supply to demand ratio" to distinguish between normal and pathologic conditions. Unfortunately, most studies on cardiac metabolism during ischemia have used animal models where coronary flow is reduced and cardiac work decreases only in

response to low oxygen supply, ie, ischemia induced by decreased flow. Few data are available for experimental conditions where flow is held constant and energy demand is increased, ie, work-induced ischemia. Thus, since the metabolic consequences of reduced coronary flow have been studied more extensively, the present discussion will be restricted to this type of ischemia.

## General Effects of Ischemia on Energy Metabolism

A reduction in coronary flow and O<sub>2</sub> supply below that required to meet the needs of the tissue results in several characteristic changes. An immediate response is a reversible decrease in myocardial contractility. This rapid reduction in function has been demonstrated in several experimental models of ischemia and appears to be a general phenomenon. It may serve to protect the jeopardized tissue, but its mechanism is unknown. Tissue levels of high-energy phos-

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Table 1—Effects of Coronary Flow on Myocardial Energy Metabolism

Coronary flow (ml/min)	O <sub>2</sub> consumption (μmoles/g/min)	Glycolysis	FA oxidation	Total adenine nucleotides (μmoles/g dry tissue)
15	30	5	0.85	24
5	20	10	0.60	19
4	16	8	—	—
3	12	6	0.40	14
2	8	3	0.20	—
1	4	2	0.16	10

Hearts were perfused for 20 minutes at the coronary flow rates indicated. The perfusate was Krebs-Henseleit bicarbonate buffer containing either 11 mM glucose alone when nucleotide levels, glycolysis, and O<sub>2</sub> consumption were measured or a combination of glucose (11 mM) and palmitate (1.2 mM) when fatty acid oxidation was measured. Total adenine nucleotides includes the sum of all ATP, ADP, and AMP present.

phate are near normal at the time contractility first declines, indicating that muscle contraction is not substrate-limited.<sup>1-4</sup> A rapid alteration in Ca<sup>2+</sup> metabolism due to altered cellular pH could decrease muscle activation,<sup>5</sup> but cellular pH does not appear to change until after contractility declines.

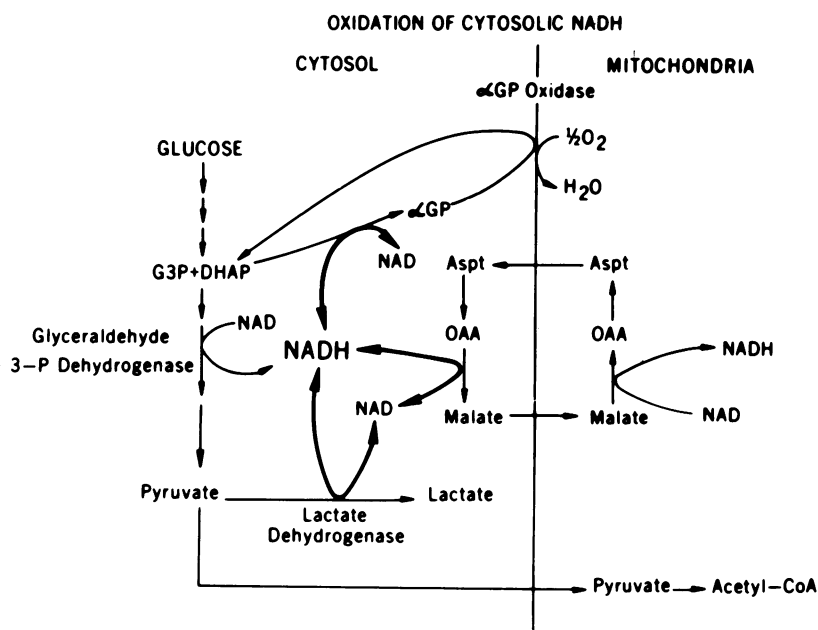
Continuation of the unfavorable energy supply to demand ratio results in loss of cellular high-energy phosphates and depletion of total adenine nucleotides.<sup>3,5-9</sup> Table 1 shows the loss of total nucleotides in an isolated, globally ischemic rat heart after 20 minutes of perfusion. The rate of nucleotide loss is proportional to the reduction in coronary flow; in mild forms of ischemia, the heart may reach a new steady state, where depressed function reduces energy demand to match the lower supply<sup>10</sup> and only partial depletion of nucleotides occurs. However, a more severe restriction in coronary flow results in a

greater depletion of adenine nucleotides, and it is thought that this loss of nucleotides may be either responsible for or closely associated with the onset of irreversible cellular damage.<sup>6-8,9</sup> The ability of isolated rat hearts to recover mechanical function with reperfusion following ischemia correlates very closely with the residual adenine nucleotide pool.<sup>9</sup>

Although the loss of adenine nucleotides may account for lack of recovery of tissue adenosine triphosphate (ATP) levels on reperfusion and thus be directly responsible for loss of such critical cellular functions as cell volume control, ion metabolism, and substrate activation reactions, as well as for development of contracture, there are numerous other changes occurring that may also contribute to the development of an irreversible state.

A major metabolic change that develops in low-flow ischemic states is the inhibition of metabolic

Figure 1—Pathways of oxidation of cytosolic NADH. Cytosolic NADH is normally produced by glyceraldehyde-3-phosphate dehydrogenase and lactate dehydrogenase. It is oxidized by the malate-aspartate shuttle and α-glycerophosphate oxidase. In the absence of oxygen, lactate dehydrogenase produces lactate and oxidizes NADH, and glycolysis can proceed at maximum rates only when lactate can be produced and removed from the tissue.



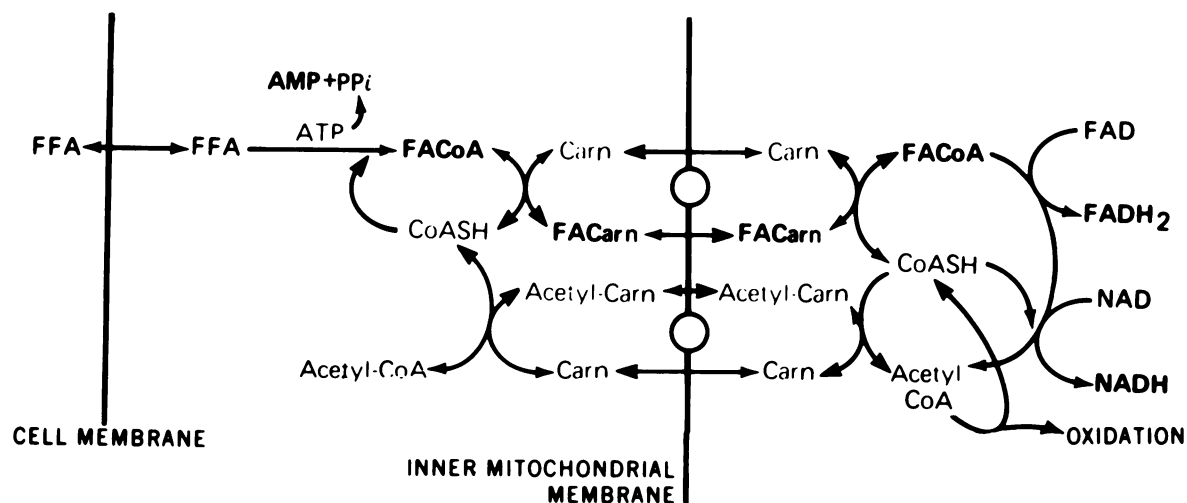
pathways other than the decreased oxidative phosphorylation. Glycolysis is the only significant source of anaerobic ATP production in cardiac muscle. In hypoxic muscle where coronary flow is high, this source of ATP is stimulated.<sup>10,11</sup> However, when hypoxia results from low coronary flow, glycolysis is inhibited.<sup>10,11</sup> With intermediate levels of coronary flow, glycolytic rate increases (Table 1), but not to the same level, of about 17  $\mu$ moles/g/min, as that seen in high flow hypoxic hearts.<sup>10</sup> At the very low flow rates, glycolysis is reduced to below the control level (Table 1). Fatty acid oxidation is also reduced in proportion to the reduction in coronary flow and oxygen supply<sup>12</sup> (Table 1).

The inhibition of these metabolic pathways results from accumulation of metabolic products, which cannot be oxidized completely to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and/or are not washed out of the tissue due to low coronary flow. There are three major metabolites whose accumulation can account for inhibition of glycolysis.<sup>13</sup> These are NADH, lactate, and  $\text{H}^+$ . Figure 1 shows the pathway of cytosolic NADH metabolism. Normally, the NADH produced by glycolysis is oxidized by the mitochondria via the malate-aspartate shuttle, but during ischemia or hypoxia, this oxidative route is nonfunctional. Thus, in the ischemic and hypoxic hearts, conversion of pyruvate to lactate is the only means of oxidizing cytosolic NADH. With high coronary flow hypoxia, the lactate is washed from the tissue and glycolysis can be accelerated by the low energy state of the cell (Pasteur effect). However, with the low flow ischemia, lactate accumulates causing cytosolic NADH to build up to very high

levels and glycolysis is inhibited at the level of glyceraldehyde-3-*p* dehydrogenase.<sup>4,10</sup> In addition to NADH, both high lactate and high  $\text{H}^+$  also reduce the activity of this enzyme. Thus, accumulation of these three metabolic products results in inhibition of the only significant source of anaerobic ATP and contributes to a more rapid decline in cellular energy levels and to cell death.

Inhibition of fatty acid metabolism results from accumulation of mitochondrial NADH but does not in itself result in a loss of ATP production. However, inhibition of the  $\beta$ -oxidation portion of the pathway (Figure 2) secondary to the increase in NADH and  $\text{FADH}_2$  does cause an accumulation of the long chain acyl-CoA (FACoA) and acyl carnitine (FACarn) intermediates of the pathway. The extent to which these metabolites accumulate depends on the amount of exogenous fatty acid present (Table 2). With high levels of palmitate present in the ischemic rat heart, 4694 nmoles/g dry tissue of acyl derivatives (FACoA + FACarn) accumulated (Table 2).

Whether or not these acyl compounds have a detrimental effect on cellular function and contribute to cell death is not known for certain, but there is a good possibility that they do when present in high concentrations. These compounds have been shown to affect several enzymatic reactions, and they are active detergent agents. FACoA inhibits several enzymatic processes,<sup>14</sup> including adenine nucleotide translocase,<sup>1,15</sup> acyl-CoA synthetase, and triglyceride lipase (unpublished data). Long-chain acyl carnitine also inhibits several cellular functions such as  $\text{Na}^+$   $\text{K}^+$  ATPase and  $\text{Ca}^{2+}$ -stimulated ATPase of sarcoplas-



**Figure 2**—Pathway of fatty acid oxidation. Metabolic intermediates that are elevated during ischemia are shown by heavy lettering.  $\text{FADH}_2$  and  $\text{NADH}$  are produced by reactions in  $\beta$ -oxidation of the long-chain acyl-CoA (FACoA) and normally oxidized by electron transport. During ischemia and lack of  $\text{O}_2$ , these reduced nucleotides accumulate.

Table 2—Effects of Ischemia on Tissue Levels of Acyl-CoA and Acyl Carnitine

Substrate	Condition	FACoA (nmoles/g dry tissue)	FACarn
Glucose (11 mM)	Control	95 ± 6	303 ± 14
	Ischemic	251 ± 15	987 ± 25
Glucose plus palmitate (.4 mM)	Control	93 ± 7	638 ± 47
	Ischemic	248 ± 10	2424 ± 177
Glucose plus palmitate (1.2 mM)	Control	179 ± 4	872 ± 56
	Ischemic	333 ± 10	4361 ± 241

Hearts were perfused with glucose (11 mM) and the concentrations of palmitate shown above. Perfusions were conducted with either control (15 ml/min) or ischemic (less than 5 ml/ml) coronary flow rates. Long-chain fatty acyl-CoA (FACoA) and long-chain fatty acyl carnitine (FACarn) were measured at the end of 20 minutes.

mic reticulum.<sup>16</sup> High concentrations of FACarn, when added to isolated mitochondria, inhibit mitochondrial respiration (Table 3).

Irreversible damage to the myocardium can occur in less than 1 hour of ischemia.<sup>3,9,17</sup> Among the many events that occur during the development of irreversibility is a damage to membranes. Mitochondrial membranes are broken and rearranged,<sup>11,17-20</sup> while plasma membranes become leaky very early.<sup>2,17,21</sup> The cause of this membrane damage is not clear. Activation of hydrolytic enzyme systems does occur,<sup>22,23</sup> and membrane phospholipids are degraded.<sup>22,24,25</sup> However, significant loss of membrane phospholipids does not appear to occur for several hours, long after the membranes have become leaky to small molecules and even to enzymes and also perhaps long after the cell has become irreversibly damaged. The mechanism of membrane damage is not clear. It is certainly possible that the detergent action of accumulated fatty acids, FACoA, FACarn, and lysophosphotidyl compounds (breakdown products of membrane phospholipids) can collectively disrupt the membrane structure and interfere with normal function. This may be particularly true for mitochondrial membranes. Approximately 95% of the total CoA present in heart cells is located in the mitochondrial matrix.<sup>26</sup> When mitochondria are isolated from ischemic hearts, a large fraction of the FACarn is associated with the mitochondrial fraction. Also, incubation of isolated mitochondria with acyl carnitine results in its extensive binding to the mitochondria (up to 50 nmoles per mg mitochondrial protein binds readily). If one considers the total amount of FACoA and FACarn present in the ischemic hearts perfused with palmitate (Table 2), there are 4694 nmoles of detergent per gram dry tissue. Since heart muscle contains about 280 mg mitochondrial protein per g dry tissue,<sup>26</sup> approximately 18 nmoles of the acyl derivatives exist for each milligram of mitochondrial protein. Most of this FACoA and FACarn could bind to mitochondrial membranes.

### Mitochondrial Damage During Ischemia

Ultrastructural analysis of ischemic myocardium has demonstrated several characteristic changes in mitochondria.<sup>7-19,27</sup> In general, the matrix becomes electron-lucent, the space between cristae that is continuous with the intramembrane space becomes enlarged, and the cristae break. At early times, breakage of the cristae occurs when the outer membrane appears to be intact. Jennings et al<sup>17</sup> described the development of amorphous densities in mitochondria of ischemic dog heart and suggested that these densities represented accumulated lipids, due to their decreased metabolism. However, from chemical analysis of mitochondria, the total content of complex lipids does not appear to change dramatically (unpublished data). Free fatty acid,<sup>18,19</sup> acyl-CoA, and acyl carnitine levels do increase, but the amount of increase would not appear to be sufficient to account for the mass occupied by the amorphous densities. It would seem more likely that these densities represent a rearrangement of the normal mitochondrial lipids. In this respect, it is possible that the breakup of mitochondrial cristae (inner membrane) forms aggregates of lipid membrane particles that appear as the amorphous densities. Schaper et al<sup>20,28</sup> have described the structural changes in mitochondrial cristae during ischemia and reperfusion in dog and human hearts. Characteristically, cristae break early in ischemia (15 minutes), and breakage grows progressively worse with perfusion time. Reperfu-

Table 3—Effects of Palmityl Carnitine on Mitochondrial Respiration

Palmityl carnitine added (nmoles/mg protein)	Mitochondrial state 3 O <sub>2</sub> consumption (natoms/min/mg protein)
0	406
18	392
27	359

State 3 rates (ie, with added ADP) were measured following 1 min of incubation with the level of palmityl carnitine show.



**Figures 3 and 4**—Electronmicrographs of ischemic rat hearts. The hearts were perfusion fixed with glutaraldehyde and stained as previously described.<sup>21</sup> **Figure 3**—The hearts were perfused for 60 minutes with ischemic coronary flow rates of about 1 ml/min by the working heart technique.<sup>13,30</sup> The perfusate was Krebs bicarbonate buffer containing 11 mM glucose as substrate and gassed with 95:5, O<sub>2</sub>:CO<sub>2</sub>. *ID* = intercalated disk. (x 16,000)



**Figure 4**—The heart was perfused as for Figure 1, except the perfusate contained 1.2mM palmitate bound to 3% bovine serum albumin.

sion after short periods of ischemia (up to 30 minutes) results in reassembly of the cristae, suggesting that the lipids are not lost from the mitochondria, perhaps because the outer membrane remains intact. With irreversible ischemic damage (60 minutes or more), reassembly does not occur with reperfusion.

The mechanism of this breakage of mitochondrial cristae is not known. It probably does not result from increased activity of lysosomal hydrolases.<sup>23</sup> At the time breakage occurs, lysosomal enzyme activities appear to be still latent or particulate, suggesting that they do not have access to the mitochondrial cristae. Swelling of the matrix space could cause physical rupture of the inner membrane, but most of the swelling appears to occur in the space between cristae (ie, intramembrane space). It seems more likely that the cristae break because of some chemical modification of the membrane structure. Breakage of the cristae membranes may result from physical pressure induced by swelling, but only because the normal membrane structure is already disrupted by binding of large amounts of detergent active compounds such as free fatty acids, FAcCoA and FAcCarn. In this regard, De Leiris and Feuvray<sup>21</sup> found that the intramitochondrial amorphous densities developed in isolated ischemic rat hearts only when fatty acids were provided in the perfusate. Glucose and insulin alone or in combination with palmitate prevented or greatly slowed the development of these mitochondrial densities as well as reducing the release of creatine phosphokinase. Likewise, globally ischemic rat hearts show the appearance of dense material in local areas along the inner mitochondrial membrane.

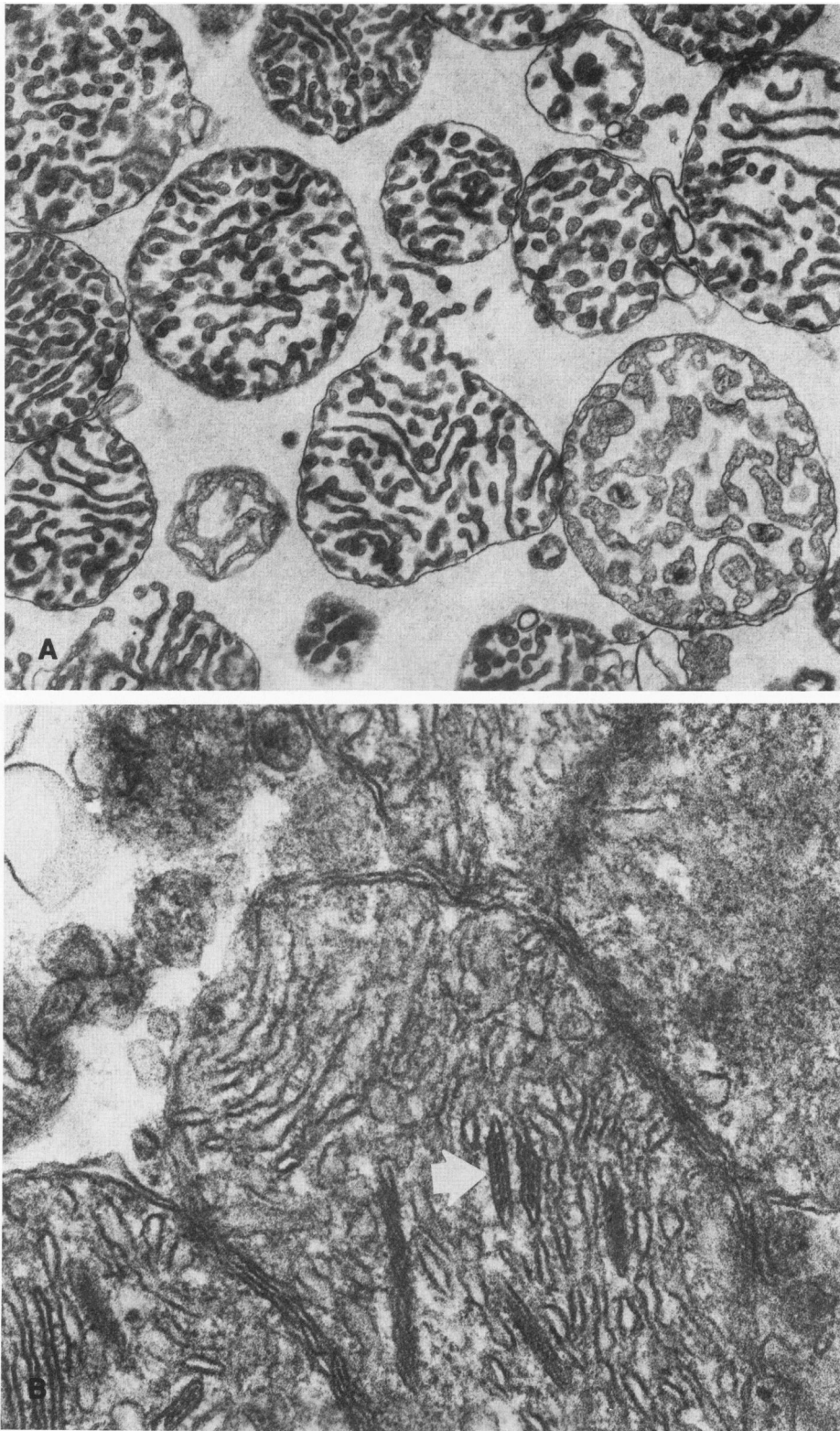
Figures 3 and 4 illustrate sections of rat hearts perfused *in vitro* for 60 minutes. Figure 3 is from an ischemic heart receiving only glucose as substrate, and Figure 4 is from an ischemic heart receiving both glucose and 1.2 mM palmitate. The mitochondria in the hearts receiving glucose are fairly intact, with few inclusions. However, hearts receiving palmitate showed large numbers of areas of tissue like that illustrated in Figure 4. The mitochondria in these regions contain many rodlike electron-dense areas along the cristae. The cristae membranes appear more pronounced and, in general, more electron-dense. Figure 5B shows a higher magnification of the mitochondrial membranes. It appears that the rodlike dense areas may include more than one cristae membrane or fragments of membranes. The composition of this dense material is not known, but its appearance in the mitochondria of ischemic hearts correlates with the presence of high levels of FAcCoA and FAcCarn in the tissue. Therefore, it is interesting to speculate that binding of high amounts of these detergents to the

cristae membranes may cause rearrangement of the normal phospholipid structures such that adjacent membranes fuse or aggregates of membrane fragments collect and result in the mitochondrial dense bodies.

Since the mitochondrial structure appeared to be altered either to a different extent or in a different way when fatty acids were present, it was of interest to us to determine what structural changes would occur in isolated mitochondria treated with palmitoyl carnitine. Figure 6 illustrates respectively in panels A, B, C and D, changes that occurred in isolated heart mitochondria when incubated with either 0, 10, 20, or 50 nmoles of palmitoyl carnitine per milligram of mitochondrial protein. Most of the mitochondria incubated in the absence of palmitoyl carnitine have intact membranes with uniformly staining cristae. Some appear to be swollen, and some other membranes are broken. When 10 nmoles of palmitoyl carnitine were added, more mitochondria were swollen and broken, and many of the cristae appeared to form nodular structures. The number of these nodulose-appearing cristae, as well as the number of broken mitochondria, increased with increasing amounts of palmitoyl carnitine. With 50 nmoles/mg, all of the mitochondria contained nodulose cristae. Figure 5A shows a higher magnification of these mitochondria. It is obvious that gross structural rearrangements have occurred in the cristae.

Binding of acyl carnitine, free fatty acids, or other lipid-active compounds may disrupt the membrane sufficiently to cause melting of adjacent cristae membranes, to cause rearrangement of membrane components sufficient to disrupt function, and to cause breakage in severe cases. Conformational changes in the arrangement of enzymes or loss of membrane components such as enzymes, cofactors, and components of electron transport may also occur because of the detergent action of these compounds. These effects on critical components of the membrane may account for the observed decrease in oxidative rates in mitochondria isolated from ischemic tissue.

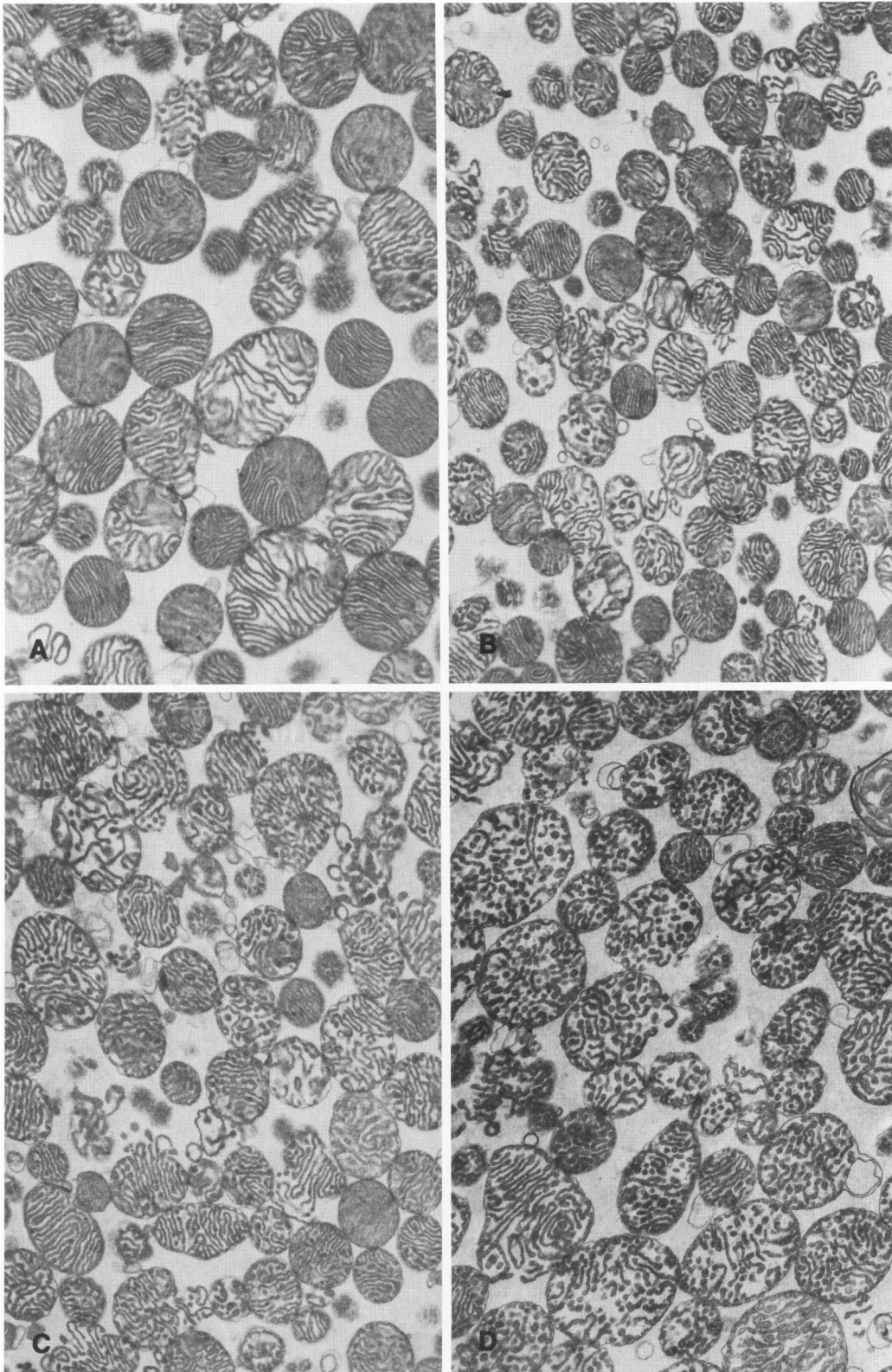
Another example of cellular metabolic products interfering with normal cellular function has been provided by the studies of Dr. Sobel's group. Activation of phospholipases in normothermic ischemic hearts results in cellular accumulation and release of lysophosphotidyl compounds.<sup>24-25</sup> These compounds cause alterations in action potential duration and magnitude when added to isolated Purkinje fibers and cause development of arrhythmias when added to perfused hearts. Long-chain acyl carnitine had similar effects, suggesting again that nonspecific detergent actions of these compounds may contribute



**Figure 5A**—Electron micrograph of mitochondria from Figure 3D showing higher magnification. Notice the multimembranous, dense structures along the cristae (*arrow*).

**B**—Higher magnification of mitochondria from Figure 2.





**Figures 3A-D**—Electron micrographs of isolated heart mitochondria. Mitochondria were isolated as previously described.<sup>28</sup> ( $\times 9000$ ) **A**—Mitochondria incubated 30 minutes in buffer containing no palmityl carnitine. **B**—Same as Figure 1, except that 10 nmoles palmityl carnitine/mg mitochondrial protein were added to the buffer. **C**—Buffer contained 20 nmoles palmityl carnitine/mg protein. **D**—Buffer contained 50 nmoles palmityl carnitine/mg protein, and the incubation time was 10 minutes.

to loss of cellular function during ischemia. It has generally been observed that high concentrations of fatty acids cause more rapid or severe deterioration of ischemic myocardium.<sup>14-15,29</sup> Thus, accumulation of metabolic products and intermediates of fatty acid metabolism may well contribute to cellular damage in ischemic myocardium.

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