A ROLE for abnormal lipid metabolism in the pathogenesis of atherosclerosis was suggested over a century ago, when Virchow proposed that transport of plasma lipids into the walls of blood vessels contributed to the development of atheromatous lesions. Lipid abnormalities are now firmly established as one factor leading to ischemic heart disease, although the mechanism by which they lead to coronary artery occlusion remains incompletely understood. More recently, abnormalities of lipid metabolism have been implicated in another quite different aspect of the pathogenesis of ischemic heart disease. A large body of evidence now indicates that altered lipid metabolism can alter cardiac function by changing the properties of cardiac cell membranes, and that these functional changes may contribute to the decline in myocardial contractility, the arrhythmias, and the eventual cell death that follow coronary artery occlusion. This article will review some of these disorders in lipid metabolism and possible mechanisms by which they might modify membrane function in the ischemic heart.

Disorders of Lipid Metabolism in the Ischemic Heart

There are now at least three well-defined mechanisms by which lipid metabolism may be altered in the heart after coronary artery occlusion (Table 1). Each of these mechanisms has been implicated in the pathogenesis of the cardiac abnormalities seen in patients who sustain an acute myocardial infarction. Elevated Serum-Free Fatty Acids

High levels of circulating free fatty acids (FFA) have been observed in patients after myocardial infarction (Kurien and Oliver, 1966; Oliver, 1972; Vetter et al., 1974; Opie, 1972, 1975), and elevated FFA levels have been correlated with the appearance of ventricular arrhythmias (Kurien et al., 1971) and extent of enzyme release from the ischemic myocardium (de Leiris and Opie, 1978).

A number of mechanisms can contribute to the elevation of circulating FFA in patients who sustain an acute myocardial infarction. Most of these are initiated by catecholamines, which commonly are elevated in these patients. Increased hydrolysis of depot triglycerides liberates fatty acids from adipose tissue stores when a hormone-sensitive triglyceride lipase is activated by circulating catecholamines and by sympathetic stimulation (Kruger et al., 1967; Steinberg, 1976; Steinberg and Khoo, 1977; Fain and Shepherd, 1975). These effects are mediated by activation of adenylyl cyclase and resulting stimulation of a cyclic AMP-dependent protein kinase (Steinberg and Khoo, 1977). The activity of the triglyceride lipase of adipose tissue also has been found to increase during starvation (Steinberg, 1976), possibly in response to glucagon. Catecholamines also appear to promote lipolysis in the myocardium itself, but evidence for the existence of a cyclic AMP-activated lipase in heart muscle is incomplete (Lech et al., 1977; Severson, 1979). Elevated catecholamine levels, such as occur in myocardial infarction, also have been suggested to increase FFA by suppressing insulin secretion (Christienson and Videbaek, 1974). Circulating FFA may also be elevated by reduced carbohydrate intake (Opie et al., 1975) in patients who experience anorexia and vomiting, and by reduced carbohydrate delivery to the peripheral tissues in patients with severely impaired left ventricular function and low cardiac output. It appears likely, however, that catecholamines constitute the most important stim-
TABLE 1  Lipid Abnormalities in the Ischemic Heart

<table>
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<tr>
<th>Abnormality</th>
<th>Possible pathogenic mechanism</th>
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<tr>
<td>Elevated serum-free fatty acids</td>
<td>High circulating catecholamines</td>
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<td>Impaired tissue perfusion</td>
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<td>Reduced carbohydrate intake</td>
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<td>Hydrolysis of membrane phospholipids</td>
<td>Activation of phospholipases</td>
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<td>Phospholipid depletion</td>
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<td>Lysophosphatide accumulation</td>
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<td>Intracellular accumulation of fatty acids</td>
<td>Tissue hypoxia</td>
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<td>and their metabolic derivatives</td>
<td>Inhibition of citric acid cycle</td>
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<td>Inhibition of β-oxidation</td>
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Hydrolysis of Membrane Phospholipids

Most membrane phospholipids consist of a 3-carbon glycerol chain in which a fatty acid is esterified to two of the three hydroxyl groups of the glycerol "backbone" (Fig. 1). The third hydroxyl group is bound to a phosphate-containing polar group. A number of phospholipases are able to hydrolyze these membrane phospholipids (Fig. 1). One of these enzymes, phospholipase A₂, catalyzes the hydrolysis of the ester bond holding the fatty acid to the 2 carbon of the glycerol backbone, thereby liberating the free fatty acid and a lysophosphatide.

Phospholipase activity is found in a number of cardiac membranes (Weglicki et al., 1971, 1972), as well as in cardiac lysosomes (Franson et al., 1972), and lysosomal enzyme activity increases in the ischemic heart (Kennett and Weglicki, 1978). Myocardial phospholipid content has been found to decrease during ischemia (Bruce and Myers, 1972; Chien et al., 1980), presumably due to phospholipase activation. Tissue lysophosphatide levels were reported, over a decade ago, to rise after liver ischemia (Boime et al., 1970), and liberated lysophosphatides have been proposed to play a role in the pathogenesis of some of the cardiac abnormalities in ischemic heart disease, although the magnitude of the rise in lysophosphatide concentrations in the ischemic heart is controversial (Bruce and Myers, 1972; Sobel et al., 1978; Vasdev et al., 1979; Shaikh and Downar, 1980).

Intracellular Accumulation of Long-Chain Fatty Acids, Fatty Acyl Carnitines, and Fatty Acyl-CoA

The accumulation of neutral fat in infarcted human myocardium, first noted over 40 years ago (Tennant et al., 1936; Mallory et al., 1939), has been confirmed in several recent experiments (Wartman et al., 1956; Bryant et al., 1958; Sommers and Jennings, 1964; Friedman et al., 1975). Buja et al. (1977) and Bilheimer et al. (1978) noted the appearance of lipid droplets in ischemic zones peripheral to infarcted myocardium in experimental animals as early as 5 hours after coronary occlusion, and lipids have been found to accumulate in the hypoxic myocardium after approximately 1 hour (Gordon et al., 1977; Burton et al., 1980).

Evans (1964) and Scheuer and Brachfeld (1966) reported that the uptake of labeled fatty acids is increased in the hypoxic and ischemic heart, but Whitmer et al. (1978) observed that palmitate uptake was reduced when coronary flow was lowered. Lipid accumulation has been reported in hypoxic hearts when the perfusate is lipid free (Burton et al., 1980) and increased incorporation of labeled acetate into phospholipids has been observed in anaerobic hearts (Christ, 1968; Gloster and Harris, 1972; Hull et al., 1973). These latter observations indicate that the lipids that accumulate in the hypoxic and ischemic heart may be derived, at least in part, from endogenous sources. Lipid synthesis under these conditions probably is initiated by an increased ratio of reduced to oxidized coenzymes (e.g., NADH:NAD⁺), which in turn is secondary to the lack of molecular oxygen for electron transfer. The resulting inhibition of the citric acid cycle, and the condensation of the 2-carbon fragments, acetyl CoA and acetyl carnitine, to form long-chain acyl derivatives of fatty acids are probably responsible for lipid synthesis from endogenous sources in the

![Figure 1](http://circres.ahajournals.org/)

**Figure 1**  Structure of a phospholipid. Two fatty acids (R₁ and R₂) are esterified to the 1 and 2 carbons of glycerol and one of a number of polar phosphatides (X) is esterified to the 3 carbon of the glycerol "backbone." The ester bonds linking these functional groups to glycerol can be hydrolyzed by a number of phospholipases as shown on the figure. (Letters in squares Phospholipase B is a mixture of phospholipase A₁ and A₂.)
hypoxic or ischemic heart. Inhibition of tissue triglyceride lipase by palmitoyl CoA recently has been suggested to contribute to lipid deposition in the ischemic heart (McDonough et al., 1979).

**Inhibition of the Citric Acid Cycle**

Multiple control points in the citric acid cycle are modified in the hypoxic or ischemic heart. These important modifications tend to slow the cycle and, indirectly, to inhibit reactions that depend on, or are closely coupled to, individual reactions in the citric acid cycle (LaNoue et al., 1970). These reactions include those controlled by pyruvate dehydrogenase, citrate synthetase, and isocitrate dehydrogenase. All of these changes appear to be initiated primarily by the accumulation of reduced coenzymes that occurs when the heart does not receive a continuing supply of molecular oxygen.

The flux from pyruvate to acetyl CoA, which is regulated by *pyruvate dehydrogenase*, is inhibited when NADH accumulates in the heart. This inhibitory effect may reflect both a direct effect of the increased NADH:NAD ratio and potentiation of inhibitory effects of acetyl CoA on pyruvate dehydrogenase that accompany the conversion of NAD to NADH. *Citrate synthetase* plays a major role in controlling flux through the citric acid cycle by catalyzing the formation of citrate from oxaloacetate and acetyl CoA. This enzyme has a low $K_m$ for oxaloacetate, so that citrate formation is highly sensitive to the fall in oxaloacetate concentration that occurs in the hypoxic or ischemic myocardium. Citrate synthetase is deprived of its substrates in these pathological states as the oxidation of malate to form oxaloacetate is inhibited and acetyl CoA levels fall (see below). The formation of $\alpha$-ketoglutarate through the action of *isocitrate dehydrogenase* is also inhibited in the hypoxic or ischemic myocardium. Although ADP, which accumulates in the hypoxic or ischemic heart, can act as an allosteric activator of isocitrate dehydrogenase, NADH exerts a more powerful, and thus dominant, effect to inhibit this enzyme in cardiac ischemia.

The effects of slowing of the citric acid cycle on the metabolism of the hypoxic or ischemic myocardium are magnified by the tight coupling that exists between flux through the citric acid cycle and the rate of oxidative phosphorylation, which is virtually abolished under these conditions. This inhibition of the citric acid cycle not only contributes to the inhibition of ATP regeneration, but also impairs the ability of the heart to oxidize fatty acids.

**Inhibition of Fatty Acid Oxidation (Whitmer et al., 1978)**

Fatty acid metabolism, which normally represents the major source of high energy phosphates in the aerobic heart, is regulated by both the uptake and oxidation of the fatty acids. Low extracellular fatty acid concentrations limit the rate of uptake of this substrate in the well-oxygenated heart, whereas, at higher extracellular concentrations, fatty acid uptake and oxidation are limited by the rate of flux through the citric acid cycle (see above) and by the cytosolic concentration of reduced coenzyme A (Hochachka et al., 1977). The rate of $\beta$-oxidation itself does not appear to play a major role in regulating fatty acid metabolism in the aerobic heart. In the hypoxic or ischemic myocardium, however, the increased NADH:NAD ratio and the inability of the myocardium to reoxidize FADH$_2$ cause $\beta$-oxidation to become significantly inhibited. As a result, $\beta$-oxidation becomes the rate-limiting reaction of fatty acid oxidation in these pathological states.

**Accumulation of Long-Chain Fatty Acid Derivatives in the Ischemic Myocardium**

Inhibition of $\beta$-oxidation in the hypoxic or ischemic myocardium prevents the stepwise degradation of long-chain fatty acids to acetyl-CoA, thereby causing the accumulation of long-chain fatty acyl derivatives and a fall in acetyl-CoA concentration. The latter probably contributes to slowing of the citric acid cycle and oxidative phosphorylation by inhibiting oxaloacetate formation, as described above.

The accumulation of long-chain fatty acids and their derivatives in the cells of the ischemic myocardium thus can be attributed to several metabolic abnormalities: Fatty acid breakdown is inhibited when $\beta$-oxidation becomes rate-limiting (Neely and Morgan, 1974; Hochachka et al., 1977), net fatty acid synthesis occurs (Christ, 1968; Gloster and Harris, 1972; Hull et al., 1973), and fatty acid uptake may be increased (Evans, 1964; Scheuer and Brachfeld, 1966). The long-chain fatty acid derivatives appear in the heart as free fatty acids, acyl-CoA, and acyl carnitine (Whitmer et al., 1978; Idell-Wenger et al., 1978; Idell-Wenger and Neely, 1978; Liedtke et al., 1978; Shug et al., 1978; Lochner et al., 1978; Weishaar et al., 1979), and inhibition of $\beta$-oxidation leads to the accumulation of $\beta$-hydroxy fatty acids (Hull et al., 1975).

**Effects of Lipids on Membrane Function**

There is growing evidence that cardiac function can be influenced by changes in the lipid composition of the cellular and subcellular membranes of the myocardial cells. Such changes can be induced by variations in the nature of dietary fats, which have recently been reported to influence heart rate, cardiac tolerance to catecholamines (Gudbjarnason and Hallgrimsson, 1979), and myocardial contractility (Peterson et al., 1979), presumably by modifying the fatty acid composition of membrane phospholipids. In addition, the alterations in lipid me-
tabolism that occur in patients with ischemic heart disease appear able to produce significant abnormalities in cardiac function by modifying the structure of cardiac membranes.

Many of the lipid substances that accumulate in and around the ischemic myocardium in patients who sustain a myocardial infarction (Table 1) represent soluble amphiphiles in that they contain both hydrophilic (polar) and hydrophobic (non-polar) groups. These amphiphilic substances can induce major changes in membrane function by the insertion of free amphiphile molecules into the lipid bilayer of the membrane, by a detergent-like effect that depletes the membrane of some of its lipids, and, in the case of some phospholipids, by exchange with membrane phospholipids (Helenius and Simons, 1975). Whereas the latter reaction is quite slow (Roseman and Thompson, 1980), it can be facilitated by a number of phospholipid exchange proteins (DiCorleto et al., 1979).

At low concentrations, amphiphiles exist in solution as monomers that can be inserted into the hydrophobic environment of the lipid membrane. The incorporation of a variety of amphiphiles into biological membranes can change the physical properties of the lipid bilayer, often resulting in major changes in the physiological function of the membrane.

At high concentrations, amphiphile monomers aggregate into micelles (Fig. 2) in which the hydrophobic regions of the molecules remain in contact with the aqueous medium and the lipolytic portions are clustered in a hydrophobic core. These micelles, which are thermodynamically stable colloid aggregates of the amphiphile, have the ability to incorporate membrane lipids into their structure, thereby forming mixed micelles. The incorporation of high concentrations of amphiphiles into membranes can physically disrupt the lipid bilayer, liberating endogenous membrane lipids. This latter effect, which represents a “detergent-like” action, can cause biological membranes to break down into mixed micelles containing both the natural membrane lipids and the lipids of the added amphipile. In this way, high amphiphile concentrations are able to destroy the integrity of biological membranes. The lysophosphatides, which are incorporated into biological membranes as wedge-shaped structures, can also disrupt biological membranes by their effects on overall membrane topography (Lucy, 1970; see below).

A functional significance for these two different types of effect of added amphiphiles on biological membranes, one occurring when low monomer concentrations are incorporated in the membrane, the other resulting from membrane disruption due to mixed micelle formation at high amphiphile concentrations, was suggested over a decade ago by Kwant and Seeman (1969). These investigators observed that low concentrations of several local anesthetic agents exerted a stabilizing effect on the erythrocyte membrane that was manifest as an increased resistance to osmotic and mechanical lysis, whereas higher concentrations of these same agents caused membrane lysis. The “membrane-stabilizing” effect of low amphiphile concentrations has been implicated in the mechanism by which a variety of lipid-soluble compounds act as anesthetic agents (Seeman, 1972), whereas the lytic effects of high amphiphile concentrations represent “detergent-like” actions. A similar biphasic effect is also seen when erythrocyte membranes are exposed to fatty acids (Fig. 3, Raz and Livne, 1973), and appears to represent a general property of the interaction of amphiphiles with biological membranes (Sheetz and Singer, 1974; Becker et al., 1975; Helenius and Simons, 1975; Brotherus et al., 1979). Similar phenomena are seen with muscle membranes. The calcium permeability of sarcoplasmic reticulum vesicles is reduced when these membranes are exposed to low concentrations of the local anesthetic agents.
agent, dibucaine, whereas higher dibucaine concentrations markedly increase calcium permeability (Nash-Adler et al., 1980). A similar biphasic response has been noted when these membranes are preincubated with palmityl carnitine (Adams et al., 1979) or oleic acid (Katz et al., 1979).

The ability of low amphiphile concentrations to protect erythrocyte (Kwant and Seeman, 1969; Raz and Livne, 1973) and other membranes (Schramm et al., 1967) from lysis ("membrane-stabilizing effect") may be explained in part by an increase in the volume of the membrane (Seeman, 1972). However, several lines of evidence suggest that incorporation of amphiphiles may have more specific effects on membrane structure, and thus on membrane function (Seeman, 1972; Helenius and Simons, 1975; Sanderman, 1978). These effects involve changes in the physical state of the long fatty acid chains that form the hydrophobic core of the phospholipid bilayer. In some regions of the bilayer, these fatty acid chains fit tightly together, allowing little vibrational motion. This arrangement represents a tightly ordered and relatively rigid "gel phase" within the membrane. In other regions of the membrane bilayer, however, these hydrophobic chains may be free to move, resulting in a structure where they could be bent, kinked or otherwise loosely packed. Each phospholipid molecule in this more disordered "lipid phase" of the bilayer would occupy a greater volume than in the more ordered regions of the membrane. These ordered and disordered membrane phases are not static; instead, phase transitions can occur both within and between regions of different physical structure (Fig. 4). The physical state of the membrane, and the phase transitions within the phospholipid bilayer, can be influenced by many factors. These include temperature, the ionic environment around the membrane, the composition of the phospholipid polar head groups, and the length and degree of saturation of the hydrophobic fatty acid chains (Chapman, 1970; Chapman et al., 1974).

The mobility and conformation of intrinsic membrane proteins, and thus their functions as receptors, enzymes, channels, etc., can be influenced by the physical state of the surrounding membrane lipids (Bauman and Muller, 1974; Trudell, 1977; Sanderman, 1978). Incorporation of low concentrations of amphiphiles, like fatty acids, tranquilizers, and anesthetic agents, into a membrane can profoundly affect the function of these important membrane proteins. These effects have been proposed to arise from at least three different types of action.

A variety of amphiphiles, when incorporated into erythrocyte membranes, can expand these membranes by volumes 10 times those of the incorporated amphiphile. This disproportionate change in membrane surface suggests that the effects of these amphiphiles may be related to a lipid phase transition from the gel to liquid state (Chapman et al., 1974). Temperature-dependent phase transitions in phospholipid bilayers can be altered by barbiturates.
(Lee, 1976), and it has been shown that high pressure, which reverses clinical anesthesia (Seeman, 1972), can reverse the disordered phospholipid arrangement and accompanying change in membrane function induced by anesthetic concentrations of halothane (Trudell et al., 1973). The membrane expansion caused by the incorporation of amphiphiles may cause conformational changes in ion channel proteins within the membrane that inhibit the ion movements normally responsible for excitation (Fig. 4). It has been suggested that these effects may be due partly to an increase in membrane thickness (Haydon et al., 1977; Ashcroft et al., 1977), although this view has been challenged by Turner and Oldfield (1979).

A second possible effect of the incorporation of certain amphiphiles into biological membranes is the displacement of Ca\(^{2+}\) ions from negatively charged binding sites on the membrane phospholipids (Fig. 4). Because Ca\(^{2+}\) is an important modulator of membrane function, this effect may be of physiological importance. Local anesthetic agents have been shown to displace Ca\(^{2+}\) from phospholipid monolayers, possibly by altering the arrangement of phospholipid head groups so as to separate anionic sites to distances that impair their ability to bind Ca\(^{2+}\) (Hauser and Dawson, 1968). Support for this hypothesis has been obtained in an erythrocyte membrane model, in which a variety of anesthetic agents were shown to displace Ca\(^{2+}\) from high affinity inner membrane binding sites (Low et al., 1979).

A third mechanism by which amphiphiles can modify membrane function is suggested by evidence that the biological activities of intrinsic membrane proteins can be influenced by the phospholipid environment around the hydrophobic region of the protein that is inserted into the lipid bilayer (Helenius and Simons, 1975; Sanderman, 1978). The calcium pump ATPase protein of the sarcoplasmic reticulum has served as a useful model for the study of these functionally significant phospholipid-protein interactions (Bennett et al., 1980). In these membranes, an “annulus” of approximately 30 molecules (Warren et al., 1975; Bennett et al., 1980) or less (Dean and Tanford, 1977) of phospholipid per mole of protein has been found to be essential for the biological function of the calcium pump ATPase. The phospholipids in this annulus (also referred to as boundary-layer lipids) have been reported to have different physical properties from those in the remainder of the lipid bilayer (Nakamura and Oishi, 1975; Warren et al., 1975; Hesketh et al., 1976), and the chemical structure of these boundary-layer lipids has been shown to influence the enzymatic activity of the calcium pump ATPase (Warren et al., 1974; 1975; Hesketh et al., 1976; Hidalgo et al., 1978). It thus is clear that a potentially important interaction exists between the hydrophobic regions of membrane proteins within the membrane and the surrounding boundary-layer lipids, although the concept that this annulus is composed of phospholipids that exchange only slowly with the surrounding membrane phospholipids remains controversial (Chapman et al., 1979). The existence of an annulus region of the membrane proteins raises the possibility that selective penetration of the boundary-layer lipids by a given amphiphile could alter the functional properties of these membrane proteins (Fig. 4). Such a mechanism has been proposed by Gordon et al. (1980) to explain the observation that incorporation of benzyl alcohol into liver plasma membranes modifies differently a number of enzymes, both in terms of the amount of incorporated amphiphile needed to produce an effect and the nature of the response (inhibition or stimulation).

That specific interactions of a given amphiphile with the lipid annulus can modify the function of an intrinsic membrane protein in a selective manner is suggested also by our recent observation that incorporation of oleic acid, an unsaturated C\(_8\) fatty acid, has different effects on the calcium pump of the sarcoplasmic reticulum than does incorporation of the same amount of stearic acid, the corresponding saturated C\(_8\) fatty acid (A.M. Katz, P.A. Nash-Adler, J. Miceli, and F.C. Messineo, unpublished observations).

Fatty acids have long been known to exert hemolytic and bacteriostatic effects, and to inhibit a variety of metabolic reactions. Fatty acids are potent uncouplers of oxidative phosphorylation (Pressman and Lardy, 1956; Lehninger and Rambert, 1959; Borst et al., 1962; Bos and Emmelot, 1962; Pande and Mead, 1968) and can exert a biphasic effect on membrane permeability and stability (see above). Unsaturated fatty acids have been reported to inhibit adenyl cyclase activity and to modify hormonal activation of this enzyme in non-cardiac tissues, although these effects may be different among animal species. Low fatty acid concentrations inhibit brain Na-K ATPase (Ahmed and Thomas, 1971). Long-chain acyl-CoA, which accumulates almost entirely in the mitochondria of the ischemic heart (Idell-Wenger et al., 1978) can inhibit mitochondrial oxidative phosphorylation (Pande and Blanchaer, 1971) and adenine nucleotide translocase (Shug et al., 1975; Vignais, 1976). The latter enzyme, which catalyzes ATP-ADP exchange across the mitochondrial inner membrane, provides a critical link between the energy metabolism of the mitochondrial compartment and that of the cytosol. It recently has been reported, however, that long-chain acyl-CoA within the matrix of isolated mitochondria does not significantly inhibit this enzyme (J.A. Watts, C.D. Koch, and K.F. LaNoue, unpublished observations). Micromolar concentrations of palmitoyl-CoA also have been found to inhibit mitochondrial respiration (Wood et al., 1977a), Na-K ATPase (Wood et al., 1977b), and triglyceride lipase (McDonough et al., 1979). Long-chain acyl carnitines, which accumulate mostly in the cytosol of the ischemic heart (Idell-Wenger et al., 1978) have been reported to inhibit Na-K ATP-
Lysophosphatidylcholine was lost from the myocardium, whereas addition of exogenous lysophosphatidylcholine could cause either a positive inotropic effect or contracture. These investigators postulated that different stereoisomers of this phospholipid caused these different effects. More recent studies have shown that lysophosphatidylcholines can influence adenylyl and guanylyl cyclase activities in non-cardiac tissues. These substances have been reported to inhibit cardiac sarcoplasmic Na-K ATPase (Karli et al., 1979) and to induce a number of electrophysiological abnormalities resembling those seen in the ischemic heart (Sobel et al., 1978; Corr et al., 1978; Adams et al., 1979), and palmityl carnitine inhibits the calcium pump ATPase, an effect that is partially reversed by readdition of fatty acids to the membranes (Fiehn and Hasselbach, 1970). Added lysolecithin also reverses the effects of fatty acid removal on ATPase activity, but not the inhibition of phosphoryltransfer (Fiehn and Hasselbach, 1970). These findings indicate that the mechanism by which phospholipase A₂ alters the function of biological membranes is complex. The detrimental effects produced by hydrolysis of the fatty acid-glycerol bond, which both liberates free fatty acids within the membrane and causes formation of lysophosphatidylcholines, appear from these studies to be potentiated markedly by removal of the liberated fatty acids.

**Effects of Lipids on the Heart**

Fatty acids have two general types of effect on the myocardial cell. The first, in which low substrate levels of fatty acids influence the flux through metabolic pathways within the cell, is exemplified by the ability of fatty acids to inhibit the rate of aerobic glycolysis in the myocardium (Shipp et al., 1961; Newsholme et al., 1962; Garland et al., 1963). This effect can be seen in response to changing concentrations of a number of substrates, e.g., citrate, which plays a major role in the physiological integration of glycolytic rate with that of oxidative phosphorylation (Neely and Morgan, 1974). The second general type of effect of fatty acids is the result of their interactions with cellular membranes, described above. In the range of concentrations at which fatty acids exert their effect by these membrane actions, lower fatty acid concentrations can reduce membrane permeability by the membrane-
stabilizing effect discussed above (Seeman, 1972), whereas higher fatty-acid concentrations, by their detergent-like actions, can abolish the ability of the membrane to serve as a permeability barrier (Helenius and Simons, 1975).

Fatty acids are known to have an "oxygen-wasting" effect, which results in an increased cardiac oxygen consumption for any given level of cardiac work (Challoner and Steinberg, 1966; Mjøs, 1971). This effect may be related to the ability of fatty acids to increase mitochondrial oxygen consumption without a corresponding increase in phosphorylation (see above). This "uncoupling" of oxidative phosphorylation could be due to interactions with the mitochondrial membrane that interfere with the ion fluxes that effect oxidative phosphorylation, inhibition of adenine nucleotide translocation across this membrane (Shug et al., 1975; Schrago et al., 1976), or an increased oxygen demand that accompanies the oxidation of the fatty acids themselves (Pearce et al., 1979).

Fatty acids recently have been reported to accelerate glycogenolysis in the ischemic heart (Cowan and Vaughan Williams, 1980), an effect that may influence cardiac function by reducing a "pool" of glycolytic ATP that has been proposed to be used selectively by some membrane systems (MacCleod and Prasad, 1969; McDonald et al., 1971; Entman et al., 1977; Bricknell and Opie, 1978). Selective depletion of glycogen by fatty acids might be of significance to the pathogenesis of ischemic cardiac damage in view of a reported protective effect of glycogen or sustained glycolysis in the anoxic or ischemic heart (Dawes et al., 1959; Scheuer and Stezoski, 1970; McDonald and MacCleod, 1973; Hewitt et al., 1973; Smithen et al., 1975; Iyengar et al., 1976). The ability of glucose to inhibit, partially the fatty acid-induced release of intracellular enzymes from the ischemic myocardium (Opie and Bricknell, 1979) also is consistent with this hypothesis.

A variety of lipids has been found to influence both the mechanical and electrical properties of the heart. A negative inotropic effect of fatty acids is well documented (Sevareid et al., 1969; Henderson et al., 1970a; 1970b; Opie, 1970; Kjekshus and Mjøs, 1972), and has been reported by some groups to be more marked in ischemia (Kjekshus and Mjøs, 1972; Russo and Margolis, 1972; Ravens and Ravens, 1976; Caffier and Pfeiffer, 1977; Cowan and Vaughan Williams, 1977; Liedtke et al., 1978). Antilipolytic agents have been reported to reduce the extent and severity of ischemic changes in the epicardial electrocardiogram following acute coronary occlusion (Kjekshus and Mjøs, 1973; Smith and Duce, 1974; Rowe et al., 1974; Russell and Oliver, 1978). Persistent abnormalities in the electrophysiological properties of surviving subendocardial Purkinje fibers after experimental myocardial infarction have been correlated with the appearance of lipid deposits in these cells (Friedman et al., 1975), and lipid accumulation has been implicated in the production of arrhythmias after administration of catecholamines (Maling and Highman, 1958).

Shortening of action potential duration is one of the more commonly reported effects of fatty acids on the myocardium (Borbola et al., 1974; Wasi-leswska-Dziubinska, 1975; Wasi-leswska-Dziubinska et al., 1975; Mentz et al., 1976; Lüdenitz et al., 1976; Cowan and Vaughan Williams, 1977, 1980; Athias et al., 1979), although some investigators have described an increase in this measurement (Friedman et al., 1975; Coraboeuf et al., 1978). Action potential shortening is also seen in the initial period after the heart becomes hypoxic or ischemic (Trautwein et al., 1954; Webb and Hollandier, 1956; Trautwein and Duder, 1956; Coraboeuf et al., 1958; Kardesch et al., 1958; McDonald and MacCleod, 1973), or when aerobic metabolism is inhibited (McDonald et al., 1971; Cheneval et al., 1972; Hyde et al., 1972). This effect appears to reflect, at least in part, an attenuation of the slow inward (calcium) current (Schneider and Sperelakis, 1974; Sperelakis and Schneider, 1975; Kohlhart and Kubler, 1975). It is possible that the action potential shortening that occurs after brief periods of ischemia and hypoxia may be causally related to a membrane-stabilizing...
effect of low fatty acid concentrations. These lipids could, for example, reduce the calcium permeability of the sarcolemma by reducing calcium influx via the slow channel, and thus cause both the shortening of action potential duration observed by some investigators (see above) and the rapid loss of contractility in the ischemic and hypoxic myocardium (Nayler et al., 1979). The ability of low oleic acid concentrations to inhibit calcium influx from the sarcoplasmic reticulum (Katz et al., 1979), and of palmitic acid (Messineo et al., 1980; Katz et al., 1980) and palmityl carnitine (Adams et al., 1979) to increase calcium sequestration within isolated sarcoplasmic reticulum vesicles could, if these phenomena occurred in the intact heart, contribute to a decreased calcium release from this membrane system in cardiac ischemia and hypoxia. The finding that 24 minutes of ischemia in the rat heart causes dilation and loss of membrane area of the sarcoplasmic reticulum (McCallister et al., 1979) is consistent with the view that fatty acids may be incorporated into this phospholipid membrane in the ischemic heart, but additional studies of these relationships clearly are needed.

The “early pump failure” of the ischemic heart discussed in the preceding paragraph is followed after 20–60 minutes by increased resting tension (Hearse et al., 1977) and cell death. A role for abnormal lipid accumulation in the pathogenesis of this later phase of ischemic damage is suggested by studies of rat liver, in which ischemia of 1–3 hours duration causes a marked increase in membrane permeability to calcium. Over this period, approximately 50% of the cellular phospholipids are lost as the result of degradation, a change that is not accompanied by the appearance of significant concentrations of lysophosphatides (Chien et al., 1978). Prolonged ischemia in the liver is also accompanied by a reduction in the number and a change in the distribution of intramembranous (protein) particles in the microsomal fraction (Chien et al., 1978), progressive loss of respiratory control and adenine nucleotide translocase activity (Mittnacht et al., 1979), and loss of at least one mitochondrial protein (Mittnacht et al., 1979), although the mitochondrial changes are potentially reversible and do not appear to be involved directly in the genesis of irreversible cell injury.

Reperfusion of the myocardium after prolonged (>20–30 minutes) ischemia has long been recognized to lead to extensive myocardial necrosis and hemorrhagic infarction (Tennent et al., 1936; Lowry et al., 1942; Jennings et al., 1960; Bresnahan et al., 1974) that are accompanied by electrocardiographic changes and arrhythmias (Tennent and Wiggers, 1935; Harris and Rojas, 1943; Lang et al., 1974, Kane et al., 1975; Murdock et al., 1980). Morphological studies have demonstrated that this “reperfusion necrosis” is accompanied by marked changes in cellular architecture, including the appearance of contracture bands within the myofilaments and evidence of sarcolemmal disruption (Sommers and Jennings, 1964; Kloner et al., 1974; Jennings and Ganote, 1974; Jennings and Ganote, 1976). Cell disruption also has been observed after reoxygenation following prolonged myocardial anoxia (Hearse et al., 1973; Ganote et al., 1976), and may reflect, at least in part, a massive influx of calcium (Sommers and Jennings, 1964; Shen and Jennings, 1972a, 1972b; Kloner et al., 1974; Jennings and Ganote, 1974, 1976; Hearse, 1977) resulting from sarcosomal damage. The detrimental effects of this calcium influx would be exacerbated by impaired calcium transport into the sarcoplasmic reticulum, also reported to occur after prolonged ischemia (Lee et al., 1967; Nayler et al., 1971; Schwartz et al., 1973; Hess et al., 1979; Feher et al., 1980). At the time that the myocardium becomes susceptible to reperfusion necrosis, deposits of both lipid and calcium are seen within in the mitochondrial matrix (Jennings and Ganote, 1974, 1976), and the sarcoplasmic reticulum becomes vesiculated (McCallister et al., 1978).

A role for phospholipid depletion in increasing membrane permeability to calcium is suggested by studies of the ischemic liver. In this tissue, like the heart, reperfusion after prolonged ischemia is accompanied by a large calcium influx (Chien et al., 1977) that occurs when membrane phospholipids are degraded. This calcium influx has been suggested to contribute to the death of ischemic cells in this tissue (Chien et al., 1977, 1978; Mittnacht et al., 1979). Chien et al. (1980) recently observed that phospholipid depletion also correlates with the extent of irreversible damage in the reperfused myocardium and may account for abnormal technetium-99m pyrophosphate uptake.

Albumin, which binds tightly to fatty acids, is able to remove these compounds from partially digested membranes and exacerbate the effects of lipase action on membrane function (Fiehn and Hasselbach, 1970; Swoboda et al., 1979). Thus, when ischemic tissue is reperfused with serum or whole blood, exposure of the plasma membrane to albumin may potentiate the effects of lipase action by increasing lipid depletion from these membranes, thereby increasing calcium permeability and contributing to reperfusion necrosis.

The data reviewed above indicate that loss of the ability of myocardial membranes to act as a permeability barrier to calcium plays a significant role in the pathogenesis of cell death in the ischemic or hypoxic heart. In addition to the detrimental effects of phospholipase action, and depletion of membrane phospholipids, this loss of membrane integrity could be caused partly by fatty acid accumulation. High oleic acid concentrations have been shown to increase the calcium permeability of the sarcoplasmic reticulum (Hasselbach and Makinose, 1962; Sarzala and Drabikowski, 1969; Fiehn and Migala, 1971) and cause marked structural abnormalities in isolated sarcoplasmic reticulum vesicles (Fig. 6) (Agostini and Drabikowski, 1969). The view that a detri-
Figure 6 Negatively stained electron micrograph of sarcoplasmic reticulum vesicles isolated from rabbit skeletal muscle. Vesicles were incubated in the absence (A) and presence (B) of 16 μM oleic acid at 25°C for 15 minutes in 5 mM MgATP, 11 μM CaCl₂, 120 mM KCl, and histidine buffer at pH 6.8. The scale bar represents 0.1 μm.
mental effect of fatty acids is partly responsible for reperfusion necrosis is supported by the observations of Bricknell and Opie (1978) who reported that inclusion of palmitate in the medium reperfusing the heart after prolonged ischemia increased both the severity of the accompanying arrhythmias and the release of intracellular enzymes. However, this effect may not be related to the detergent-like actions of palmitate, as it was also produced when acetate was included in the perfusate.

Some of the effects of free fatty acids on the heart have been reported to be reversed by perfusion with carnitine (Bremer and Norum, 1967; Oram et al., 1975; Shug et al., 1975; Shrago et al., 1976; Christiansen et al., 1976; Folts et al., 1978; Liedtke and Nellis, 1979), and the enhancement of calcium sequestration in purified sarcoplasmic reticulum vesicles by palmitic acid (Messineo et al., 1980) can be partly overcome by low concentrations of palmitoyl carnitine (Katz et al., 1980). Addition of carnitine to mitochondrial preparations can lessen the inhibitory effect of long-chain acyl-CoA on adenosine nucleotide translocase (Shrago et al., 1976; Shug et al., 1978), and carnitine has been reported to slow the fall in ATP content in the ischemic heart (Yamazaki and Suzuki, 1979). Carnitine has also been reported to alleviate the arrhythmias and ST-segment elevation in the ischemic heart (Riemersma and Oliver, 1976; Vick et al., 1976; Folts et al., 1978) and the mechanical dysfunction produced by free fatty acids in ischemic hearts (Liedtke and Nellis, 1979). The latter results were attributed to the entry of carnitine into ischemic canine and porcine myocardial cells, and to the lowering of long-chain acyl-CoA levels through the generation of acyl carnitine (Liedtke and Nellis, 1979). However, Neely et al. (1979) found that exogenous carnitine was not taken up by rat hearts, nor did this substance lower the levels of long-chain acyl-CoA. These latter investigators also found that, under conditions of zero coronary flow, there was little rise in long-chain acyl-CoA and acyl-carnitine levels, and that the cellular contents of these lipids could fall later during the period of total ischemia (Neely et al., 1979). It is of interest that the effects of diphertheria toxin, which inhibits fatty acid oxidation and increases myocardial levels of triglycerides (Wittels and Bressler, 1964), also can be partially alleviated by carnitine (Wittels and Bressler, 1964; Bressler and Wittels, 1965; Challoner et al., 1971). Thus, a role for carnitine in protecting the heart against ischemic damage remains controversial.

In conclusion, a large body of evidence indicates that alterations in lipid metabolism may play an important role in the pathogenesis of the cardiac abnormalities seen in patients with ischemic heart disease. Fatty acids, which accumulate both within the myocardial cell and in the blood stream of patients who sustain a myocardial infarction, have complex effects on cardiac membranes. These effects include membrane stabilization, which could impair the transsarcolemmal ion fluxes that are responsible for impulse formation and propagation at the cell surface. Such a membrane-stabilizing effect could also inhibit the calcium movements across the sarcoplasmic reticulum that control the contractile process itself. Higher concentrations of fatty acids and their derivatives can disrupt membranes. This latter effect may contribute to the pathogenesis of cardiac cell death in these patients. Hydrolysis of membrane lipids also may play an important role in producing the abnormalities in cardiac function that accompany ischemic heart disease, both by depleting the membranes of their natural lipid content and by releasing potentially detrimental products of these hydrolytic reactions, notably the lysophosphatides. At the present time, the majority of these studies have been carried out using in vitro models, there being relatively few studies of membrane lipid composition after myocardial ischemia in vivo. Whereas the importance of these lipid abnormalities in producing most of the clinical manifestations of ischemic heart disease remains to be established, the evidence presently available indicates that this represents an important area for future research.

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