Hormonal and Metabolic Reactions Evoked by Acute Myocardial Infarction

LESZEK CEREMUŻYŃSKI

RECOGNITION of the importance of humoral balance in the body originated in the work of Claude Bernard (1855) and was developed later mainly by Cannon (1915) and Selye (1950). Recent myocardial infarction (MI) has been reported to elicit humoral disturbances which, a little more than a decade ago, were not considered of importance. The recognition that they may influence the clinical course of the disease came in recent years as a consequence of better understanding of the complex character of MI and the nature of its complications.

In this review I intend to show briefly the accumulated data on the pattern of humoral, mainly hormonal, disorders accompanying MI which have been relatively well elucidated. Their interrelations and the mechanism of their possible influence on the clinical course of the disease also will be outlined. The therapeutic implications of this knowledge will be discussed briefly and some areas which require further research will be suggested.

Adrenergic Nervous System

The Adrenergic Response to Myocardial Infarction and Its Effect on Cardiac Function

Following the preliminary reports by Forssman et al. (1952), it has been well established both in animals and in the clinic that MI is accompanied by increased catecholamine content in blood (Forssman et al., 1952; Gazes et al., 1959; Ceremuzynski et al., 1969; McDonald et al., 1969; Ceremuzynski, 1970; Siggers et al., 1971; Lukomsky and Organov, 1972; Christensen and Videbaek, 1974; Vetter et al., 1974) and urine (Valori et al., 1967; Januszewicz et al., 1968; Hayashi et al., 1969; Ceremuzynski, 1970; Jequier and Perret, 1970; Lukomsky and Organov, 1972; Prakash et al., 1972; Januszewicz et al., 1974; Ceremuzynski and Sandler, 1978). Numerous authors found an association between the catecholamine content in blood or urine and the severity of MI (Valori et al., 1967; Januszewicz et al., 1968; Ceremuzynski, 1970; Jequier and Perret, 1970; Prakash et al., 1972). This increased adrenergic activity initially has thought to serve as a compensatory mechanism for the diminished mechanical performance of ischemic and necrotic heart muscle. This was contrary to the opinion best formulated in Raab's work (1963) which considered that a pronounced adrenergic reaction was likely to cause deterioration of ischemic heart disease and lead to further myocardial infarction. Much evidence has now been accumulated in favor of this viewpoint.

In some patients the increase of catecholamines preceded the major complications of MI (Prakash et al., 1972). A similar sequence of events was shown in dogs subjected to coronary occlusion (Ceremuzynski et al., 1969). Arrhythmias did not occur before the rise in catecholamines. However, within a few minutes after catecholamine (mainly epinephrine) release, cardiac rhythm disturbances occurred, often terminating in ventricular fibrillation. In those experiments on dogs in which no increase of circulating catecholamines occurred, sinus rhythm usually was maintained despite the large area of infarction produced by subsequent occlusion of the second and sometimes even the third coronary artery. Major arrhythmias were provoked easily in these dogs by epinephrine administered in small doses which did not disturb sinus rhythm when given before coronary occlusion (Ceremuzynski et al., 1969). This exaggerated response of ischemic heart muscle to catecholamines confirmed the early observation by Maling and Moran (1957).

How Do Catecholamines Harm the Heart?

In recent years, numerous data have helped to clarify the mechanisms whereby catecholamines may exert their deleterious effects on heart muscle.
It has been shown that catecholamines stimulate the activity of adenylyl cyclase in the myocardial cell membrane with subsequent elevation of cyclic adenosine 3',5'-monophosphate (cAMP) content (Robinson et al., 1965; Drummond et al., 1966; Wollenberger et al., 1967). An increase in plasma cAMP, which may reflect intracellular changes, has been found in humans with MI and is correlated significantly and positively with plasma catecholamines. Patients with the worst prognosis have the highest plasma concentrations of cAMP and catecholamines (Strange et al., 1974). An increased cAMP content in ischemic regions has been found to precede severe dysrhythmias in cats (Corr et al., 1978) and ventricular fibrillation in baboons (Podzuweit et al., 1978). Accordingly, it has been established that the rise of cAMP in the heart tissue is associated with a fall in the fibrillation threshold (Lubbe et al., 1978). These findings are compatible with the concept of an arrhythmogenic action of catecholamines in MI. The evidence for a role of enhanced adrenergic activity in triggering serious arrhythmias in MI is reviewed by Wit et al. (1975) and by Corr and Gillis (1978).

There also is considerable evidence that cAMP influences Ca++ influx channels, thus affecting the contractile state and electrical activity of the heart (Reuter, 1974; Tsien, 1973). The role of cyclic nucleotides in cardiac function recently has been reviewed by Drummond and Severson (1979). Increased entry of Ca++, a consequence of catecholamine stimulation of the heart cell, is thought to be an important factor in the production of ischemic necrosis (Fleckenstein, 1971; Shen and Jennings, 1972). This is relevant to the observations that the majority of patients who die with pheochromocytoma have diffuse patchy myocardial necrosis (Van Vler et al., 1966; Baroldi, 1974). It should be stressed that the patients with complicated MI can excrete amounts of catecholamines in the range noted in proven pheochromocytomas (Valori et al., 1967).

The increase in contractile force and in the heart rate produced by the adrenergic response results in augmented myocardial oxygen consumption (MVO2) which is deleterious in MI. A rise of MVO2 may well be the common denominator of different metabolic influences in MI. A contributing factor in the case of catecholamines may be an oxygen wasting effect which results from mitochondrial uncoupling (Challoner and Steinberg, 1966; Sobel et al., 1966). In a pioneering study, Raab (1963) stressed the importance of augmented MVO2 as a reason for catecholamine-induced myocardial ischemia in the presence of impaired ability of the coronary arteries to dilate. More recently, Iimura et al. (1974) designed an experimental model to imitate natural conditions occurring in the atherosclerotic human heart. They found that a small amount of catecholamine infused into the dog with a moderately constricted (25–50%) coronary artery resulted in slight adverse hemodynamic, metabolic, and electrocardiographic alterations. These changes were greatly pronounced if more than 50% narrowing of the vessel was produced.

Metabolic Abnormalities Associated with Catecholamine Release

Herbszczyńska-Cedro (1970) found that, when coronary occlusion in the dog was accompanied by excessive release of epinephrine, the content of several enzymes (succinic dehydrogenase and ATPase) in the healthy portion of the heart muscle was considerably diminished; this was not the case if the experimental MI did not produce excessive release of catecholamines. This study is relevant to that of Gudbjarnason (1971) who found a decrease in the content of ATP and phosphocreatine in the non-ischemic portion of the infarcted heart. More recently, some experimental evidence has been obtained which suggests that the above metabolic alterations observed in the myocardium may be linked causally with the phenomenon of adrenergic response evoked by MI. Infusion of epinephrine into healthy dogs in a dose similar to that released spontaneously after coronary occlusion resulted in a marked decrease in myocardial ATPase and succinic dehydrogenase (SDH) activity (Ceremuzynski et al., 1978). Ultrastructural changes in heart muscle (predominantly in mitochondrial shape and structure) also have been found. Thus, catecholamines by themselves may produce damage of the heart muscle in both experiments on dogs and in patients with pheochromocytoma. The dose of epinephrine used in the canine experiments increased the level of circulating epinephrine by a factor of 10–20. An adrenergic reaction in this range is likely to occur in humans with MI but also in various everyday stresses such as automobile driving, public speaking, etc. (Taggart et al., 1972).

The clinical relevance of these experimental findings has been substantiated recently by Mueller and Ayres (1978). They showed a link between the magnitude of the sympathetic response in humans with MI, the heart muscle metabolism, and accompanying hemodynamic and clinical disorders. The lowest content of blood catecholamines was found in subjects with normal cardiac metabolism in which the myocardium mainly utilizes carbohydrates. These patients displayed an uncomplicated clinical course and undisturbed hemodynamic measurements. In patients who reacted to MI with about a 6-fold increase in the catecholamine level, a change in heart metabolism was observed with a lowered extraction ratio of free fatty acids (FFA) and pyruvates from the coronary circulation with concurrent lactate production. Hemodynamic measurements were much altered; systemic vascular resistance and pulmonary wedge pressure were increased, and stroke index and coronary blood flow were found to be lowered. An intermediate catecholamine blood level was associated with a pre-
dominant metabolism of FFA along with a considerable increase in MVO₂ and deterioration of the hemodynamic state.

**Catecholamines and Coronary Artery Spasm**

Adrenergic overstimulation is likely to be involved in the chain of events resulting in coronary artery spasm, a phenomenon which has received much attention recently (Oliva et al., 1973; Maseri et al., 1975). It has been suggested that the underlying mechanism here is α-adrenergic receptor stimulation (Yasue et al., 1974; Ricci et al., 1979) due to either local (Cobb et al., 1976) or systemic (Yasue et al., 1974) release of catecholamines. Phentolamine reversed spasm during coronary angiography, and administration of the long-acting α-blocking agent, phenoxybenzamine, prevented the occurrence of the symptoms of variant angina during a follow-up period of several months (Ricci et al., 1975). It has been suggested that the underlying mechanism here is a-adrenergic receptor stimulation (Hamberg et al., 1975) thus may create a vicious cycle. Catecholamines which are known to be potent vasoconstrictor and proaggregatory substance (Hamberg et al., 1975) may further aggravate or possibly even initiate this chain of events. Thromboxane A₂ (TXA₂) is released immediately after coronary occlusion in the cat. In the later stages of infarction, other non-reflex factors may become important, such as circulatory disturbances due to cardiac insufficiency, the release of humoral and chemical agents from the necrotic myocardium or poorly perfused peripheral organs (Staszewska-Barczak, 1971). Release of catecholamines from the adrenal medulla also may be directly stimulated by increases in [H⁺] (Euler, 1967).

The mechanism of catecholamine release in humans is much more complex than in anesthetized experimental animals. Psychological stimuli evoked by pain and distress certainly play an important, if not decisive, role in triggering sympathetic arousal.

Catecholamines are eliminated mainly in urine as inactive metabolites (methoxy catecholamines and vanillylmandelic acid) after enzymatic breakdown. It is interesting to note that in MI complicated by serious dysrhythmias, heart failure, or hypotension, there was an increase of the catecholamine:metabolite ratio, as compared to that in uncomplicated MI, suggesting that impaired catecholamine inactivation may be present when the disease has a serious clinical course (Ceremużyński, 1970; Jequier and Perret, 1970; Januszewicz et al., 1974; Ceremużyński and Sandler, 1978). It is not clear at present whether there is a causal relationship between catecholamine metabolism and the clinical picture of MI, although it seems very probable. The underlying mechanism of the decreased activity of the catecholamine-inactivating enzymes also remains to be elucidated.

**Thyroid Hormones**

An interest in possible thyroid involvement in MI originated in the study of Hamolsky et al. (1957), who found that in a considerable fraction of patients the uptake of triiodothyronine (¹³¹I-T³) by erythrocytes was enhanced markedly. Later it was found that, in severe MI, red cell T₃ uptake and PBI both are increased (Ceremużyński, 1970). Increased levels of circulating free thyroxine (T₄) also were noted in single cases of MI (Bernstein and Oppenheimer, 1966). Others obtained opposite results: serial measurement of PBI (Volpe et al., 1969) and T₄-secretion rate (Harland et al., 1972) were found to be normal.

In recent years it has become apparent that T₃ plays a more important role than T₄ in the maintenance of metabolic rate by the thyroid gland. Our early study revealed that, unexpectedly, the serum level of this hormone was below the normal range in complicated cases of MI. This was in contrast to mild infarcts, in which T₃ was normal (Nauman et al., 1975). Low T₃ values in MI also were reported by other authors (Larty et al., 1975; Westgren et al., 1977). This phenomenon also has been found in other non-thyroidal illnesses such as cerebrovascular accident (Larty et al., 1975), infective diseases...
(Chopra et al., 1975), and after major surgery (Burr et al., 1975).

Low T3 Syndrome

Obviously, the low-T3 syndrome, as it is now called, is a nonspecific phenomenon which may be considered as a part of a general stress reaction. Is this phenomenon involved in mechanisms leading to complications or, on the contrary, does it depict a favorable compensatory reaction? This important question remains unsolved. Westgren et al. (1977) suggest that the low T3 syndrome is a favorable response; they found that it is accompanied by an elevation of reverse-T3 which is the metabolically inactive product of thyroxine. Hence the authors concluded that in MI, thyroxine is converted preferably to reverse-T3 with a subsequent decrease in T3 resulting in an attenuation of the metabolic rate. This is a beneficial effect. The weak point of this assumption is that the clinical symptoms of increased, instead of lowered, metabolism are commonly found in MI. In MI with a serious clinical course which is most frequently accompanied by the low T3 syndrome, nitrogen balance remained negative for several days (Ceremuzyński, 1970). This phenomenon was much less pronounced and transient when MI followed a mild clinical course.

Another doubt stems from the fact that if increased reverse T3 and low T3 levels reflected a beneficial, compensatory mechanism, this pattern should be found predominantly in uncomplicated MI. This was not the case, at least with the low T3 syndromes observed in our study. On the contrary, the lowest values of T3 in our study were found in patients dying from stroke or MI was reported by Larty et al. (1975).

Alterations in T3 Receptors

On the basis of preliminary experimental results, it may be suggested that the low T3 syndrome can also be produced by another mechanism. Under physiological conditions, approximately 40–50% of all the available nuclear receptor binding sites for T3 are occupied by the hormone (Oppenheimer and Dillmann, 1978). In dogs with acute coronary occlusion, occupancy of nuclear receptor binding sites was found to be increased to 63%, indicating more T3 bound to the receptors (Nauman et al. 1976). This was accompanied by a considerable diminution of T3 levels in the blood. The same effect was observed in intact dogs infused with adrenaline in a dose comparable to that released spontaneously after coronary occlusion. In this study, the number of receptor-binding sites and the affinity of the hormone to the receptor both were unchanged. It may be expected that increased saturation of the receptors with T3 results in augmentation of the metabolic rate, since the metabolic action of the hormone is initiated by its accumulation at the nuclear receptor sites. Indeed, Oppenheimer et al. (1976) have shown that the biological effect of T3, as measured by the rate synthesis of malic enzyme, was almost doubled when receptor saturation increased by 10%. If such an augmentation in metabolic rate, resulting from increased tissue uptake of T3 and reflected by low serum T3, occurs in patients with acute MI, it should be considered as detrimental. Some hints favoring such an interpretation of the low T3 syndrome were earlier expressed by Chopra et al. (1975). Summing up, it may be stated that the involvement of thyroid hormones in the reaction elicited by MI is likely, although more data are needed to substantiate both operating mechanisms and clinical significance of this phenomenon.

Insulin

Disturbed carbohydrate metabolism in MI has been recognized for a long time. In the majority of patients, an increase in the blood glucose level or impaired glucose tolerance has been found; occasionally the occurrence of ketone bodies was reported, even in individuals who were apparently healthy before the onset of MI. Some clarification of the underlying mechanism has been possible since the introduction of a reliable radioimmunoassay for insulin. In the first hours after MI there is a decrease in immunoreactive insulin (Ceremuzyński, 1970; Vetter et al., 1974) or an impaired response of the hormone to a glucose or tolbutamide stimulus (Allison et al., 1965; Taylor et al., 1969). These reactions occur more frequently in severely ill patients. The majority of patients who displayed a suppressed insulin response in the first days of MI had a normal insulin-glucose balance a few weeks later (Boden, 1971).

Insulin Deficiency

The mechanism underlying this transient, although sometimes very profound, impairment of insulin release is related predominantly to the sympathetic nervous system which plays an important role in the regulation of insulin secretion in humans. Evidence for this has accumulated from studies on animals both in vitro (Coore and Randle, 1964) and in vivo (Kris et al., 1966) and on man (Porte et al., 1966). Stimulation of α-receptors by catecholamines or β-blockade suppressed insulin release whereas the β-receptor agonist, isoproterenol, or α-receptor blockade with phentolamine potentiated the secretion of this hormone (Porte, 1969; Majid et al., 1970). Impairment of insulin release in MI is obviously a nonspecific phenomenon because similar disorders have been reported in congestive heart failure (Majid et al., 1970) and with low cardiac output states after open-heart surgery (Majid et al.,
Free Fatty Acids

Since the early papers by Kurien and Oliver (1966) and Oliver et al. (1968) which generated attention for the possible detrimental effects of elevated FFA in MI, numerous investigators have worked on the subject. However, results obtained so far have been conflicting. Clinical observations showed that patients with the highest concentration of FFA in the blood displayed serious arrhythmias and other major complications more frequently (Oliver et al., 1968; Gupta et al., 1969; Prakas et al., 1972), but other authors did not confirm these findings (Rutenberg et al., 1968; Nelson, 1970).

The results of experimental studies also were inconsistent. Elevation of circulating FFA in the dog with occluded coronary arteries resulted in a burst of ventricular ectopic activity (Kurien et al., 1971) that was not observed in experiments performed by another group which used a slightly different protocol (Opie et al., 1971). A suggestion has been advanced that the concentration of FFA in blood is in itself less important than the FFA: albumin ratio. If the latter is higher, it is more probable that “an excess” of FFA, not bound to albumin binding sites, will be transferred to the heart muscle (Evans, 1964). Nevertheless, Kostis et al. (1973) produced a high FFA: albumin ratio in dogs with and without coronary occlusion and failed to observe a decrease in the ventricular fibrillation threshold. Thus, no conclusive data have been provided on the postulated detrimental role of FFA in humans with MI or in experimental models. However, there still is evidence suggesting adverse effects of FFA in ischemic myocardium.

It has been shown that FFA stimulate nonphosphorylating types of metabolism (Challoner and Steiberg, 1966) and also increase myocardial oxygen consumption (MVO2) (Mjøs, 1971). In the situation of limited oxygen supply this depresses contractility and also widens the ischemic area (Kjekshus and Mjøs, 1972). When lipolysis is inhibited, the extent and severity of myocardial ischemic injury both are lessened (Kjekshus and Mjøs, 1973).

There also is evidence pointing to the deleterious effects of intermediates of FFA metabolism which accumulate in the heart subsequent to impaired oxidation. These are long chain acyl-CoA esters which have profound effects on energy metabolism of the heart by inhibiting the transport of ADP and ATP across the inner mitochondrial membrane (Shung et al., 1975). In fact, an excess of FFA caused a significant decline in aortic pressure and left ventricular work, together with an increase in myocardial oxygen consumption in perfused working swine heart (Liedtke et al., 1978). An excess of FFA during ischemia resulted in even greater deterioration of hemodynamic function. In these cases tissue contents of acyl-CoA and acyl carnitine derivatives were increased greatly, compared to those found in nonischemic hearts. The data on the role of FFA in metabolic disorders evoked by MI were reviewed by Opie several years ago (Opie, 1975).

More recent investigations cast some doubt as to whether certain of the experimental findings are in fact relevant to human pathology. Rogers et al. (1977) reported that acute elevation of FFA to pathophysiological levels after heparin-induced lipolysis had no effect on MVO2 in patients. The authors concluded that the excess of FFA is stored as triglyrides instead of being oxidized. Simmonsen and Kjekshus (1978) found that the actual FFA concentration was not of primary importance in determining MVO2, unless there has a concomitant catecholamine stimulation. This is consistent with the suggestion of Opie et al. (1971) that catecholamine activity may “sensitize” the heart to the effects of FFA and is relevant to the results of Mueller and Ayres (1978) vide supra.

At this stage, then, it is safe to state that an elevated FFA in MI predominantly reflects profound disturbances of both the autonomic nervous system and the hormonal balance. Augmented adrenergic stimulation “sensitizes” the heart to FFA; i.e., these substances become a major fuel for energy production which is not economical in terms of oxygen consumption and presumably may increase the imbalance between O2 supply and demand. Intermediate toxic products also may provide a significant contribution here. The role of FFA in MI seemed at one time to be crucial. This inclined many groups to focus their attention on metabolic aspects of ischemic heart disease. Although the suspected key role of FFA has not been ultimately confirmed, our knowledge about the complexity of homeostatic disturbances in MI has been advanced considerably.
Adrenal Cortical Function

Glucocorticoids

An early study by Forssman et al. (1952) showed that in many patients with MI, the hormone output from the adrenal cortex is increased. This was assumed on the basis of measurement of 11-oxosteroid and 17-ketosteroid in urine. Other authors confirmed these results. In addition, it was found that urinary excretion of hydrocortisone (Bailey et al., 1967) and of its metabolites (Ceremuzyński, 1967) might be augmented in the first days of MI. Serum levels of cortisol also were reported to be increased (Oka, 1956; Klein and Palmer, 1963; Logan and Murdoch, 1966; Bailey et al., 1967; Prakash et al., 1972) in some cases to the range found in Cushing's disease (Logan and Murdoch, 1966).

It also was revealed that adrenal cortical activity occurring in the first days of MI is much more pronounced in complicated cases than in subjects with a mild clinical course (Klein and Palmer, 1963; Ceremuzyński, 1967; Prakash et al., 1972). The causal relationship of these findings remains uncertain. Klein suggested that a blood concentration of circulating cortisol may be harmful if it exceeded 20 μg% (Klein and Palmer, 1963). At this level of the hormone, transcortin, the hormone-carrying protein, becomes saturated and an excess of cortisol blocks cellular oxidative processes. Serial determinations of the indices of adrenal cortical activity revealed that in complicated cases the cortisol level remained elevated until death (Prakash et al., 1972). Other authors reported that in some patients the excretion of glucocorticoid metabolites fails to increase (Forssman et al., 1952) or may even be below the normal range at about the second week of complicated MI (Ceremuzyński, 1967). Thus the suggestion has been advanced that this may represent poor adrenal reserve or adrenal exhaustion, which may correspond to an exhaustion phase of the general adaptation syndrome described by Selye (1950). Therefore it is tempting to speculate that inadequate secretion might actually contribute to the occurrence of adverse clinical symptoms. In fact, a considerable deterioration of heart muscle function has been found after adrenalectomy (Lefer et al., 1968). The deterioration was reversed after supplementation with cortisol.

Aldosterone

There are also limited data concerning aldosterone in MI. Wolff et al. (1956) reported an increase in the urinary excretion of the hormone, predominantly in severe MI. Other authors interested in this field obtained similar results (Arora, 1965; Ceremuzyński, 1970). Recently, these early findings have been confirmed by radioimmunoassay in studies of large groups of patients with MI (Wedler et al., 1979). Aldosterone in serum was much raised in the presence of major complications (multiple ventricular extrasystoles, conduction disturbance, pulmonary edema). A causal relationship between clinical symptoms and the hormone level is postulated in view of the early findings of Arora and Somani (1962) who established that administration of aldosterone to the dog with coronary occlusion provoked ventricular arrhythmias. This probably was due to an aldosterone-induced increase in Na+/K+ ratio in the ischemic area and, in particular, to the rise of intracellular content of Na+ (Levitin and San Roman, 1977). This results in alterations of the action potential. It also should be noted that cardiac rhythm disturbances provoked by aldosterone in dogs with coronary occlusion were prevented by the aldosterone antagonist, spironolactone (Arora and Somani, 1962). This agent was shown earlier by Selye (1966) to protect against cardiac necrosis induced by mineralocorticoids.

Summing up, it may be suggested that, in the early period after MI, an inadequate secretion of cortisol and an excess of aldosterone are likely to occur in patients with severe disease. This pattern of reaction should be considered deleterious and if this postulate ultimately is confirmed, it may indicate some therapeutic approaches.

Hormonal Interrelations

The humoral disturbances outlined above are interrelated. Catecholamines have been shown to stimulate the uptake and incorporation in organic compounds of iodine and hormonal biosynthesis in isolated cells of calf thyroid. Moreover, the induction of secretion by the thyroid gland and an enhancement of peripheral turnover of thyroid hormones were observed. This area of research has been reviewed recently by Mellander (1977).

It also is recognized that increased adrenergic as well as thyroid activity suppresses insulin secretion, as mentioned above. This pattern of hormonal disturbances stimulates lipoprotein lipase activity which results in an increase of FFA concentration in blood.

Adrenaline acts as a stimulus for cortisol production in humans, but glucocorticoids have been found to depress the activity of the epinephrine-forming enzyme, phenyl-ethanolamine-N-methyl transferase (Wurtman et al., 1967), thus attenuating adrenergic strain. This may constitute a major adaptive mechanism.

Thyroid hormones also stimulate cortisol secretion and greatly enhance cortisol turnover (Galagher et al., 1972). As in the adrenergic system, a negative feedback operates; the administration of hydrocortisone is accompanied by an acute suppression of both the thyroidal iodine release and serum TSH values (Nicoloff et al., 1970).

The effects of catecholamines on the heart, such as an increase in cardiac rate and the force of contraction, are greatly attenuated by insulin. This hormone also possesses its own inotropic action...
which is not dependent on the external glucose concentration (Lee and Downing, 1976). The patterns of major humoral disturbances in MI have recently received much attention and their proven and/or probable interrelations are shown in Figure 1.

Promising Areas of Future Research

The evidence accumulated so far indicates that MI evokes a generalized metabolic reaction which presumably constitutes a nonspecific response to injury or stress. In a fraction of patients, this response is pronounced and accompanied by serious complications and a high mortality rate. There is a considerable body of evidence that a causal relationship does exist here; at least it is justified to say that metabolic alterations per se aggravate the clinical course of MI. This is why the elucidation of the mechanisms involved is a matter of importance.

A key problem seems to be whether and how much the heart muscle and total body oxygen demands are increased in MI by metabolic inefficiency. This review suggests such a possibility, pointing also to some probable underlying mechanisms. An adrenergic "storm" should be considered the most important mechanism in this respect because it influences body and heart metabolism by itself and presumably also acts as a trigger for a variety of metabolic changes. Of these, the suggested catecholamine-induced enhancement of T₃ uptake by specific nuclear receptors seems to be of considerable importance. This phenomenon deserves further research as it may constitute the crucial mechanism accounting for the increase in metabolic rate observed in MI as well as in other acute diseases. Kinetic studies of T₃ combined with measurements of MVO₂ and heart muscle function might cast some light on the nature and clinical significance of the puzzling low T₃ syndrome. If the above assumption is true and the condition proves to be detrimental, some measures aimed at preventing the enhanced T₃ uptake in MI should be devised.

The nature of the adrenergic response remains mysterious. In particular, it is not known why this response is large in one individual and only moderate in another. There are suggestions that the inactivation rate of catecholamines in MI may be variable. Kinetic studies would help to trace the fate of catecholamines in MI, their turnover and uptake. Attention should be focused also on the important link between the adrenergic reaction and the thromboxane A₂-prostacyclin system and related consequences.

The place of aldosterone in promoting adverse symptoms in MI is unclear, although the role of the hormone could be considerable. Spironolactone might be effective here and might be added to the list of so-called metabolic interventions in MI. The actual needs for cortisol in MI are undefined, and it is not clear whether they are adequately supplied in older patients or in those with chronic diseases. We have no data on the turnover rate of the hormone in the various clinical responses to MI. Nevertheless cortisol presumably is increased greatly in the individuals displaying a marked stress reaction.

Finally, the metabolic reaction in MI which has been discussed is nonspecific. Thus, every research achievement in this field will enrich the knowledge of the mechanism of clinical symptoms in several acute illnesses, enabling the introduction of more rational therapeutic approaches.

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L Ceremuzynski

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