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From the Department of Pathology, University of Montreal, Montreal (Canada)

Nutritional Factors in the Pathogenesis of Cardiac Necroses

Part II.*)

By E. Bajusz

With 11 figures in 17 details and 1 table

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I. Cross-Resistance to cardiotoxic agents

Simple- and cross-resistance against the cardiotoxic effect of stress.—It will be recalled that certain Na-salts (e.g., the acetate) fail to produce cardiac necroses in corticoid-pretreated rats, unless the animals are exposed to stressor agents. The question arose whether the cardiotoxic effect of stressors would gradually vanish as a result of adaptation. To explore this problem, rats were pretreated with F-COL plus Na-acetate and then exposed (with or without previous adaptation) to various stressors, such as restraint or forced muscular exercise. Large patches of infarct-like cardiac necroses were elicited in almost all of the electrolyte plus steroid-pretreated animals suddenly exposed to intensive muscular exercise or restraint. On the other hand, gradual adaptation to the stressor agents was very effective in protecting the rats against the development of cardiac necroses. In this regard, it is important to note that at the end of the experiment both the adapted and unadapted rats were exposed to stressors until they died. This procedure was necessary because adapted animals need much more severe and prolonged stress before exhibiting any signs of damage. Thus, the rats all died during the final exposure to stressors, but the adapted animals were all completely protected against the cardiac necrosis eliciting effect of the stress situation (129). This is an example for stress-induced simple resistance of the heart muscle, since the stimuli used for adaptation and eliciting were identical.

Our next task was to establish whether (in suitably pretreated animals) the cardiotoxic action of one stressor could also be prevented by pretreatment with another stressor, that is, by cross-resistance.

It was observed that, in the F-COL plus Na-acetate sensitized rats, true cross-resistance to the cardiotoxic action of various stressors can develop: the cardiac necrosis eliciting effect of muscular exercise could be prevented by

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pretreatment with cold, that of cold by muscular exercise, that of noradrenaline by restraint, that of restraint by noradrenaline, and that of bone fractures by muscular exercise (129).

It is evident from these observations that exposure to one stressor protects against the cardiotoxic effect of other stressors that are fundamentally different in their nature. This kind of resistance cannot result from any specific metabolic adjustment that adapts the body to cold, muscular exercise, forced restraint, noradrenaline or bone fracture, in particular, since the specific effects of all these agents are different. Of course, all stressors increase corticoid secretion, but such an adaptive response could hardly explain this kind of cross-resistance. Under no circumstance would the adrenal be likely to secrete corticoids in amounts that could significantly influence the severe hypercorticoidism that we induced by F-COL overdosage in this experiment. Besides, the extreme compensatory adrenal atrophy that resulted from the F-COL treatment may be assumed to have greatly inhibited the endogenous secretion of corticoids that usually takes place under stress. Yet, some of our observations —as we shall see it later—strongly suggest that the adrenals play some role in the mechanism of stress-induced cross-resistance.

Another experimental series showed that after sensitization with DHT plus NaH_2PO_4, sudden exposure of rats to the stress of restraint or bone fractures produces a rapidly fatal syndrome characterized by a calcifying cardiopathy and nephrocalcinosis. Under these conditions, true cross-resistance can be again demonstrated, in that the cardio- and nephrotoxic effects of restraint are prevented by pretreatment with either restraint or noradrenaline, and those of bone fractures by cold baths (130).

It would be tempting to ascribe, here again, the protection by gradual inurement, which is seen in the cases where the stimulus used for adaptation and eliciting was identical, to the fact that a given period of restraint is less damaging to the adapted than to the unadapted rat. However, in fact, 60% of our adapted animals died during the prolonged exposure and even they did not exhibit any detectable renal or cardiac damage (see Table 1). It seems, therefore, that the cardiac and renal tissues themselves rather selectively acquire a high degree of topical resistance, which remains effective even when

Table 1. Cross-resistance to cardio- and nephrptoxic effects of stressors

Treatment with stressors[1])		Cardiac Necroses		Neprhocalcinosis		Mortality (%)
Repeated for adaptation	Sudden for eliciting	Grade (0–3)	Incidence (%)	Grade (0–3)	Incidence (%)	
None	None	0	0	0.4 ± 0.08	30	10
None	Restraint	2.4 ± 0.18	100	2.5 ± 0.23	100	100
Restraint		0	0	0	0	60
Noradrenaline		0.1 ± 0.10	10	0.4 ± 0.06	30	0
None	Bone fracture	2.0 ± 0.21	90	2.6 ± 0.17	100	40
Cold bath		0.1 ± 0.10	10	0.3 ± 0.06	20	0

[1]) In addition to the treatment listed above, the rats in all groups received DHT + NaH_2PO_4.

systemic resistance to the fatal effects of stress breaks down under the influence of excessive exposure. It seems that we are dealing with a rather generalized defense phenomenon, through which susceptibility to various pathogens can be basically altered.

Cross-resistance against specific cardiotoxic agents.—It may be argued that, even in the case of cross-resistance between stressors, the non-specificity of the induced tolerance is only apparent. Whatever the conditioning procedure (e. g., F-COL plus Na-acetate, or DHT plus NaH_2PO_4), the prophylactic and eliciting agents (e. g., restraint, muscular exercise, cold, trauma) are comparable as regards their stressor effect, which is obviously the decisive factor in their pathogenicity.

Therefore, it was especially important to establish that pretreatment with various stressors (e. g., muscular exercise, restraint, electric shock, reserpine, noradrenaline) can also protect the myocardium against such highly specific types of lesions as are induced by plasmocid, papain, DHT, nephrectomy, and combined treatment with DHT plus NaH_2PO_4, without additional exposure to stressors (131–133).

In evaluating these data it should be kept in mind that, for example, an acute intoxication with papain (a proteolytic enzyme) and plasmocid (an antimalarial) produces different forms of often fatal cardiac necroses. Yet, both types of lesions are prevented by previous exposure to stressor agents. In this respect, forced restraint, cold baths, or electric shocks are at least as effective as the injection of adrenaline, noradrenaline, or reserpine. We note, furthermore, that as judged by the final body weight, adrenal enlargement, and thymus involution, only some of the stressors used in these studies (e. g., restraint, quadriplegia, diplegia, reserpine) produced a severe alarm reaction, while others (e. g., cold bath and electric shock) elicited very slight, if any, detectable signs of it. Thus, the prevention of cardiac necroses does not presuppose a particularly intense stress-reaction.

This powerful prophylactic action of stress suggests the necessity for great caution in evaluating allegedly specific inhibitors of experimental cardiac damage. For example, the cardiac necroses normally produced by sudden exposure to severe stressors in the corticoid-sensitized rat are largely prevented by pretreatment with reserpine; hence, it was thought that there is "a fundamental causal involvement of metabolic catecholamines in the origin of stress-induced myocardial damage" (109, 110). It must be kept in mind, however, that at the doses used, reserpine is highly stressful in itself and, on the other hand, a number of other stressors—as our observations showed—offer at least as good a protection as reserpine. In view of these facts, it remains questionable whether the latter exerts its prophylactic effect through a specific mechanism, as supposed.

It would be premature to attempt any theoretical evaluation of these observations; but evidently, the protective effect of adaptation to stressors is not directed against any pathogen in particular. Perhaps this type of induced resistance depends upon the shielding of some sensitive chemical processes in the myocardium, a biochemical mechanism whose breakdown is the decisive factor in the development of diverse cardiac lesions.

Like many other stressor agents, hemorrhage also protects against the induction of cardiopathies by various agents. Some of our observations, how-

ever, suggest that in this respect hemorrhage does not act merely through its non-specific stressor effect. For example, the cardiac necrosis normally produced by plasmocid is prevented by pretreatment with restraint, muscular exercise, cold baths, noradrenaline, reserpine, but not by hemorrhage. Furthermore, the "spotty myolysis" resulting from noradrenaline-overdosage cannot be prevented with previous exposure to restraint or to other stressors, but is easily prevented by hemorrhage.

Under other experimental conditions, the administration of noradrenaline aggravated the cardiotoxicity of the most diverse agents. The severe lesions produced by the concurrent administration of noradrenaline do not exhibit the histologic characteristics of noradrenaline-overdosage ("spotty myolysis"), but they always retain the specific histologic features characteristic of the agent given in combination with the adrenergic hormone. As a working hypothesis, is was postulated—though not yet proven—that hemorrhage acts by decreasing, and noradrenaline by increasing, cardiac work (134, 135).

Dietary factors influencing myocardial resistance.—When rats were kept on a synthetic basic diet containing all the necessary electrolytes, various types of cardiac lesions (the DHT plus NaH_2PO_4 myocarditis, the infarct-like cardiopathy produced by stress after sensitization with F-COL plas Na-acetate, the cardiac necroses caused by papain or plasmocid) could be prevented by pretreatment with stressors, just as in rats maintained on the normal laboratory food, "Purina Fox Chow". We learned, however, that adaptation to stressors no longer increased resistence of cardiac and renal tissues when the dietary chloride intake was lowered from a basic 0.935% to 0.035% (136).

Nothing is known as yet about the mechanism through which a short period of Cl-deficiency can thus block cross-resistance phenomena. It will be recalled in this connection that our earlier investigations suggested that variations in dietary intake, not only of certain cations (such as K and Mg) but also of the anions (such as Cl and PO_4), play an important role in the pathogenesis of some necrotizing cardiopathies. In particular, Cl-deficiency was found to enhance the susceptibility of the myocardium to the production of various lesions (necrosis, inflammation or calcification) by a number of cardiotoxic agents. It is difficult to decide, therefore, whether Cl-deficiency specifically blocks the normal development of cross-resistance or whether it merely so raises the sensitivity of the heart that the defensive stress reactions are no longer effective. The first hypothesis appears to receive some support from the observations that a Mg-deficient ration – well known to enhance disease susceptibility in the heart muscle – did not affect the normal development of cross-resistance (136). Perhaps the Cl-ion plays in indispensable part in the biochemical changes responsible for cross-resistance. It remains to be shown whether the role of Cl is specific here, since – apart from the experiments on Mg-deficient diet – no comparable investigations have been performed as yet in animals deficient in other food-constituents; but simple starvation, far from preventing cross-resistance of the heart, actually produces it.

Food deprivation protects the heart against the production of necrosis, inflammation, and/or calcification by plasmocid, papain, DHT plus NaH_2PO_4, DHT plus Ca-acetate, nephrectomy plus Na_3-citrate as well as against the infarctoid lesions normally elicited by restraint in the F-COL plus Na-acetate sensitized rats. This is considered as an additional example of stress-induced

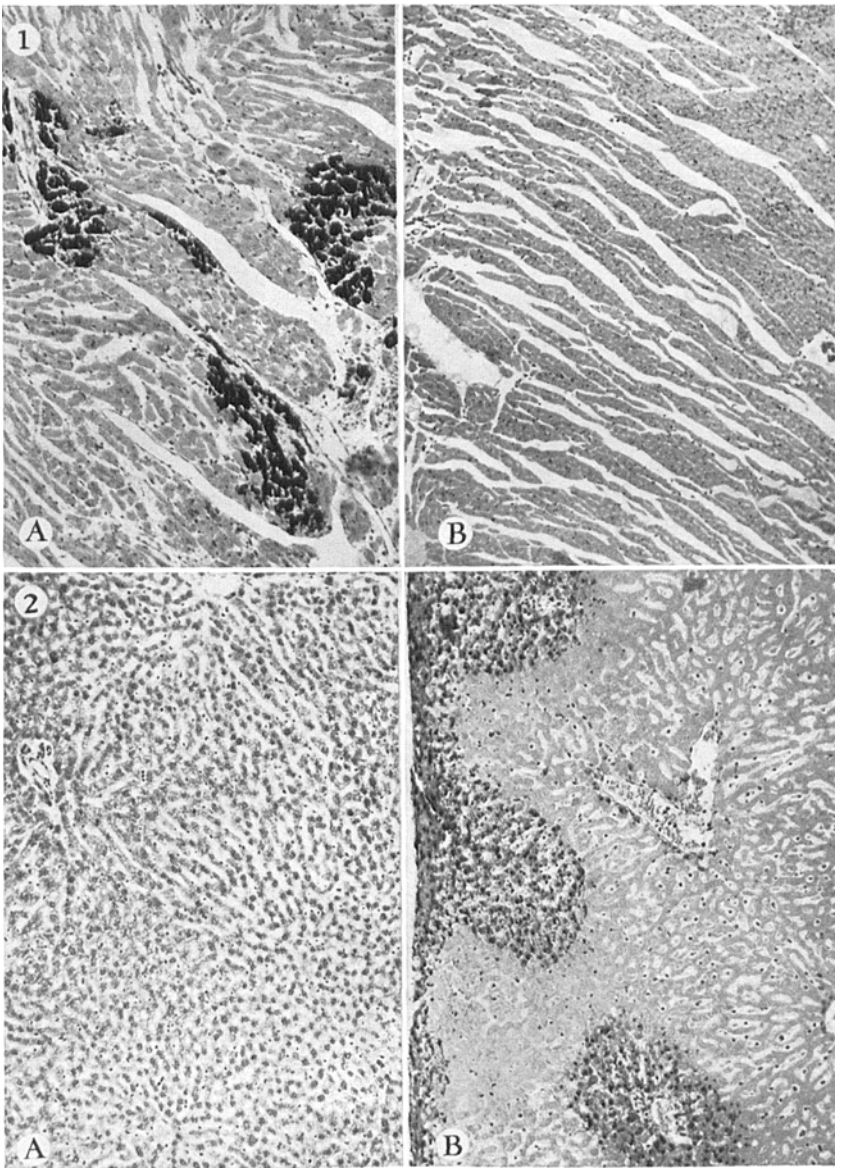

Fig. 1. *Prevention of papain necrosis by stress-induced cross-resistance.* – *A:* Calcified necrotic foci in the heart of a rat kept on a basic diet and given a single intravenous injection of papain. *B:* This rat received the same amount of papain as did the animal shown in the previous photograph A. Here, however, cross-resistance was induced by the stressor action of cold baths (celestine blue). (Ref. 136).

Fig. 2. *Prevention of cross-resistance to a potentially hepatotoxic agent by low-Cl intake.* – *A:* Normal appearance of hepatic tissue in a rat maintained on a low-Cl diet, showing that combined fluorocortisol plus Na-acetate administration does not usually produce any detectable morphologic abnormality in the liver. *B:* Diffuse hepatic necrosis in a rat on the same low-Cl diet and treated similarly to the animal shown in the previous figure A. In addition, this rat was repeatedly restrained (hematoxylin-phloxine). (Ref. 136).

cross-resistance of the heart muscle, since it is highly probable that in this regard starvation acts through its nonspecific stressor effect. Thus, various gradations of food deprivation can serve as protective agent which raises the resistance of the myocardium to the cardiotoxicity of many unrelated factors. The question, however, why the cardiovascular actions of DHT overdosage are even aggravated, while the effects of noradrenaline, isoproterenol and gastric fistula are not influenced by food deprivation, remains to be further clarified (138).

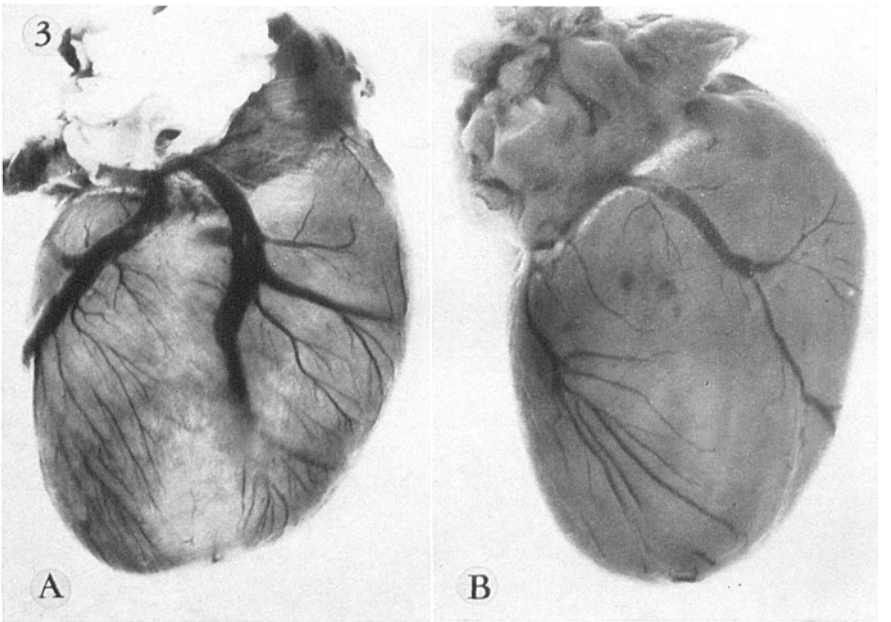

Fig. 3. *Prevention by fasting of cardiac necroses normally produced by plasmocid.* – *A:* Macroscopic appearance of myocardial necroses (here white area) in a rat treated with plasmocid while on normal food intake. *B:* Absence of cardiac lesions in a rat which received the same amount of plasmocid as did the animal shown in the photograph A. Here, however, cross-resistance was induced by the stressor action of food-deprivation

It is notable, that even a kind of "metabolic stress", usually associated with intense catabolism, can activate the defense mechanisms of the organism to resist – at least for a period of time – otherwise lethal cardiotoxic influences. The assumption that starvation does not act through some specific metabolic pathway is supported with findings which showed that all of the cardiopathies prevented by food deprivation are similarly influenced through exposure to other stressor agents (e. g., restraint, muscular exercise, cold, noradrenaline). As we have seen, there are many such examples of cross-resistance in cardiac physiopathology and it may be postulated that the enhancing effect of food deprivation upon the rate of learning ability of animals – described so often in psychiatric studies – is but yet another example of this phenomenon in the sense that previous exposure to the stress of food deprivation increases the adaptability of nervous tissues to efficiently cope with stimuli involved in the learning situation. And although, in these kinds of psychiatric studies, star-

vation is generally considered to be a simple detrimental condition, the results of our studies clearly indicate that various gradations of food deprivation can in fact serve as protective stressors which raise the resistance of the heart and probably also that of other tissues.

We have seen in other experiments that, in the F-COL plus Na-acetate-sensitized rat, oral administration of corn oil is highly active as an elicitor of cardiac necroses; yet pretreatment with this fat protects only against the cardiotoxic action of subsequent treatment with the same substance ("specific or simple-resistance") and not against that produced by other cardiotoxic agents ("non-specific or cross-resistance"). This fact suggests a difference in the mechanism responsible for the cardiac necrosis eliciting actions of stressors and fats. On the other hand, pretreatment not only with oil itself, but also with various stressors (e. g., restraint, muscular exercise, cold, noradrenaline), proved to be highly effective in preventing the subsequent induction of cardiac necroses by oil-feeding (137). Evidently, stressors can induce cross-resistance against the cardiotoxic action of oil. It is highly unlikely that oil acted as a stressor in these experiments, because pretreatment with oil failed to produce any adrenal enlargement. On the other hand, effective pretreatment with any of the stressors used resulted in an increase in the adrenal weight, which suggests the possibility of some adrenal participation in the mechanism of this type of cross-resistance. Even though pretreatment with oil failed to cause such enlargement, it still offered effective protection against the eliciting action of oil. Yet, there seems to be some relationship between the actions of stressors and oil, since pretreatment with various stressors did protect the heart against the eliciting of necroses by oil.

Many of the experimental cardiopathies that can be prevented by the induction of cross-resistance are normally accompanied by high mortality, as well as by lesions in the peripheral vessels, kidney, or liver. In such cases, the induction of cross-resistance against the cardiopathy itself is usually accompanied by a decrease or abolition of mortality and of the associated extracardiac organ lesions. From this, we may conclude that, while the heart serves as a particularly sensitive indicator of cross-resistance, the phenomenon is by no means limited to the heart.

The cardiac lesion eliciting effect of stress can be blocked by some neuroleptic phenothiazine derivatives, but this type of inhibition is, of course, not due to cross-resistance. For example, in the F-COL plus Na-acetate-sensitized rat the development of fatal cardiac damage normally resulting from subsequent treatment with stressors (e. g., noradrenaline, restraint, bone fracture) can be abolished if chlorpromazine or cyamepromazine is injected just before exposure to the eliciting stressor. Under similar circumstances, continuous anesthesia with pentobarbital sodium protects against the cardiac necrosis eliciting effect of restraint, but not against that of noradrenaline or bone fractures. Presumably, the phenothiazine compounds block some common, neural, pathways through which certain stressors elicit cardiac necroses. This is all the more remarkable, since large doses of chlorpromazine and cyamepromazine can actually produce cardiac necroses in electrolyte plus steroid-pretreated animals. Perhaps, at high dose levels, the stressor effect of these compounds overcomes their blocking properties, It was also observed that, chlorpromazine and cyamepromazine given during pretreatment with a normally protective stressor

(muscular exercise, restraint, noradrenaline), block its ability to prevent the cardiopathy induced by F-COL plus Na-acetate and an eliciting stressor (139).

The observations just summarized suggest that dietary chlorides, adrenal factors, and some (presumably neural) phenothiazine-sensitive pathways of stress, all participate in the acquisition of cross-resistance of the heart muscle. The precise mechanisms involved are, however, not yet understood. Hormonal and nervous mechanisms help to adjust the activity of different organ systems to changing conditions in the organism or its surroundings. In the hormonal mechanism, the pituitary-adrenocortical system plays a particularly important role. However, the adaptive reactions of the organism are governed by complex neuroendocrine interactions. Developments of the last decade have made it clear that the nervous system itself is, in a sense, a complex endocrine system producing humoral substances for the control of endocrine functions and, probably also, of a number of other bodily activities (140, 141). Thus, chains of alternating neural, neurohumoral, and endocrine processes are enormous.

Stressful circumstances can influence the cardiovascular system through trans- and extra-adrenal neural and humoral pathways. For instance, the vascular reactions subserved by the neural mechanism may range from the altogether peripheral axon reflex through a variety of automatic effector functions mediated via the spinal cord, and reflexes at the level of the brain stem brought about through afferents from specialized receptors in the blood vessels and in the brain. These are sensitive to minor changes in the composition of the blood, especially to reductions in oxygen tension or alterations in blood pH, etc. It is known that the efferent impulses activated thereby may result in widespread and often disabling bodily changes. Information as to precisely what circulatory patterns and cardiac activities are subject to influence from neural centers – which also participate in adaptation reactions in general – is still only fragmentary, but already impressive enough to indicate that the cerebral cortex and the hypothalamus must be considered along with the pituitary and adrenal glands as potentially controlling cardiovascular responses in men and animals (9). All these facts clearly show that the relationship of adaptive reactions to cardiovascular pathology is extremely complex. Thus, the possible elucidation of the fine mechanisms of cross-resistance of the heart muscle is handicapped by the fact that the neuroendocrine relationships and interactions in adaptive reactions are as yet poorly understood. On the other hand, however, there is little question that the corticoids basically influence the regulation of electrolyte balance and affect carbohydrate utilization in tissues. Currently some of the major problems of adaptation and maladaptation are related to questions of how integration and control of metabolism, particularly neural, neurohumoral and hormonal controls, are achieved at the molecular level.

II. General Conclusions

Are all cardiotoxic agents potential pathogens? – One of the most interesting conclusions which can be drawn from our experiments is that most of the agents that are capable of inducing cardiac lesions through some biochemical mechanism are potentially acting pathogens, whose cardiotoxic action largely depends upon other factors. Among these latter, some (corticoids, Na-salts,

dietary deficiency in K, Mg and Cl, acute stress, coronary sclerosis, age) sensitize, while others (Na-deficiency, chlorides, pretreatment with stressors, hemodynamic changes, pregnancy) desensitize the heart to the production of cardiac lesions (necrosis, inflammation, calcification) by most diverse potentially pathogenic agents.

On the other hand, the cardiac infarct that can be produced by surgical occlusion of large coronary arteries in the rat, differs basically from all metabolic cardiopathies studied. Ligature of a coronary artery at a given level always produces an infarct of the same extent, irrespective of concurrent treatment or pretreatment with any agent so far examined (143). Even the differences between the ECG alterations of surgically induced cardiopathies and those produced by biochemical means (e. g., by combined administration of corticoids and Na-salts) are quite marked. The cardiac necrosis produced by ligature of the right or left coronary artery, in the rat, did result in ECG records corresponding to those of human cardiac infarcts (fig. 4). However, in the case of the ESCN, no necrosis but arrhythmia as well as consistent prolongation of the *QT* segments were the characteristic electrocardiographic findings (143). Nevertheless, in histologic studies, the chemically induced experimental necroses resemble the usual myocardial infarcts of man more closely than do the induced infarcts that result from ligature of coronary arteries, at least in healthy young animals. Infarcts that follow ligation of the main coronary arteries always leave the subendocardial and subepicardial muscle layers intact and, usually also, the myocardial fibers that surround the cardiac veins within the necrotic area. Furthermore, these purely occlusive infarcts in the otherwise healthy myocardial tissue of young rats show little tendency to become infiltrated and removed by inflammatory cells (142). Conversely, the chemically induced cardiac necroses (e. g., those produced by certain electrolytes plus corticoids, stress plus corticoids, vitamin-D derivatives plus phosphates, administration of plasmocid, noradrenaline or vasopressin. intravenous injection of proteolytic enzymes) show no tendency to avoid the superficial and perivenous muscle layers; indeed, they exhibit a definite predisposition for the subendocardial strata and are rapidly infiltrated and removed by inflammatory cells (9). Any attempt at a complete interpretation of these differences would be premature, but they suggest that interruption of the arterial blood supply may not be the only factor in the pathogenesis of the typical cardiac infarcts of man. Of course, the latter rarely occur in perfectly healthy young heart muscle and their development may be conditioned by biochemical changes resulting from chronic arteriosclerosis and myocardial fibrosis, which usually precede the development of cardiac infarction in man. Yet, from the results of our animal experiments we have to conclude that the occlusion of a coronary vessel is a prototype of primary (or unconditionally) acting pathogens that induce cardiac necroses under any circumstances.

As regards their cardiotoxic actions, noradrenaline and vasopressin occupy a mid-position between the two extremes: potential, and absolutely unconditional, pathogens. The development of the spotty myolytic changes normally produced by noradrenaline or vasopressin are singularly resistant to chlorides, Na-deficiency as well as to stress-induced cross-resistance. Consequently, it would be tempting to assume that this type of cardiac lesions differs basically

from all other metabolic cardiopathies studied. Yet, it will be recalled that pregnancy offered significant protection against both noradrenaline and vasopressin overdosage (144) and that the cardiotoxic action of noradrenaline can

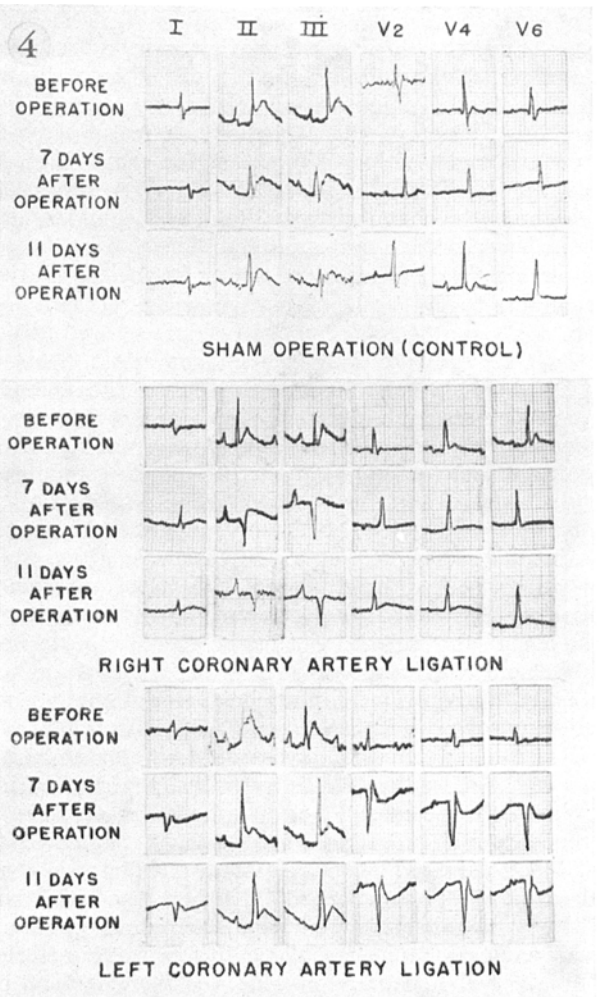

Fig. 4. *ECG alterations in surgically induced cardiac infarcts of the rat.* (Ref. 143).

be inhibited by hemorrhage. Furthermore, as with the many other cardiopathies investigated, the induction of "spotty myolysis" was greatly enhanced by corticoids, DHT, and by sensitization with a K-deficient diet. These observations suggest that there may be something common in the mechanism through which various humoral agents produce cardiac necroses.

Are the experimental cardiac necroses in all instances hypokalemic? – As is was pointed out in the introductory paragraph, an overdosage with Na-salts,

administration of corticoids, exposure to stressors, and feeding with a low-K diet are all known to result in a positive Na- and negative K-balance. Consequently, it would be tempting to assume that the metabolic cardiopathies are in all instances, hypokalemic. In this event, the Na-salts could act simply because of the well known antagonism between Na and K, and exposure to stressors merely by increasing mineralocorticoid activity.

Although it seems to be well established that hypokalemia is an important factor that sensitizes the heart to the potentially cardiotoxic actions of various agents, it is not possible to explain all our observations by the oversimplified theory that the various agents or conditions examined predispose to the hypokalemia, and that the cardiac lesions precipitated by different means are merely the consequences of an aggravation of K-deficiency.

It is known, for example, that the pronounced hypokalemia which is induced in rats by heavy overdosage with various mineralocorticoids produces neither cardiac necroses nor skeletal muscle lesions; indeed, in the monkey, the dog and man (but not the rat), such corticoid-induced hypokalemia is accompanied by flaccid muscular paralysis (9, 145, 146). Our experiments revealed, furthermore. that a diet low in Cl-content is just as active in sensitizing the myocardium as is dietary K-deficiency, although lowering the dietary Cl intake does not alter the Na/K ratio in rat's tissues (106). It was also observed that, when rats are kept on a K- or Mg-deficient diet for a brief period, the sensitizing effect of both these diets can be abolished by the administration of KCl or $MgCl_2$ as well as even by a mixture of chlorides of other cations. Notably, in this respect $MgCl_2$ was just as active in rats maintained on K-deficient diet, as KCl in animals kept on Mg-deficient ration. These observations highlight the importance of Mg- and Cl-ions in the development of the syndrome usually ascribed to K-deficiency. It is also clear that, at least under certain experimental conditions, K and Mg can largely substitute for each other's prophylactic effect although some workers believe that there exists an actual antagonism between Mg and K (147, 148). Mg-deficiency can result in secondary K-depletion; however, this is only true if rats are fed a deficient diet over one month (149), and not during only 5–7 days as in our experiments.

Our observations lead us to believe that K-, Mg-, Na-, and Cl-ions, all play an equally important role in the pathogenesis of metabolic cardiopathies; further investigations will be necessary to elucidate the mechanism of these complex ionic interactions.

Theoretical implications. – The observation that exposure to stressor agents can either elicit or prevent cardiac necroses in suitably conditioned rats clearly shows the existence of adaptation mechanisms that basically alter the disease-susceptibility of the haert muscle. We may state that an entirely new approach to the study of the necrotizing cardiopathies was opened up by discovery of *dual actions of stress* in cardiovascular physiology and pathology. Thus, adaptive reactions occupy a key position in the pathogenesis of certain necrotizing cardiopathies, however, we are ignorant at the present time of the precise mechanisms involved. Our observations already suggest that dietary factors (e. g., chlorides), adrenocortical principles, and some (presumably neural) phenothiazinesensitive pathways, all participate in the acquisition of adaptive reactions of the myocardium. Progress along these lines is greatly handicapped by the fact that the neuroendocrine relationships in adaptive reactions are not

only extremely complex, but as yet poorly understood. Furthermore, our knowledge of the metabolic actions of stress and corticoids is not extensive enough to allow any definite conclusion.

It is well known that stressful physical and emotional stimuli may alter cardiovascular function. Briefly, the expected changes include temporary tachycardia and increase in the cardiac output with each beat (stroke volume), followed by return to resting levels at a rate depending upon the intensity of the stimulus (e. g., amount of exercice). In healthy subjects, changes in the pattern of the ECG do not ordinarily occur from the influence of moderately acting stressors; when they do, they are thought to indicate a degree of cardiac insufficiency and a reduction of the reserve capacity of the heart (150). HICKAM et al. (151) established that variations in stroke volume and cardiac output correspond to changes in emotional stresses. STEVENSON et al. (152) related them to some of the symptoms of neurocirculatory asthenia. The possible importance of such alterations in cardiac function to patients with already damaged hearts has not been assessed.

Arrhythmias, including paroxysmal atrial tachycardia, extrasystoles, atrial fibrillation, and even the more serious paroxysmal ventricular tachycardia may occur in association with stress of individuals who have no other detectable evidence of heart disease (153). Ordinarily, when there are changes in the pattern of the ECG during stressful situations, the assumption is made that there is a disturbance of cardiac nutrition. In the study of STEVENSON et al. (154), 19 patients displayed changes in *ST* segments or *T* waves to a degree considered significant, when exercise was performed during a period of stress. The same exercise on a day of relative security and relaxation produced less change in the ECG, or none at all. In all but one of the 19, it was possible to produce ECG changes during an interview covering pertinent problems and without exercise or conscious anticipation of muscular effort. This information is in keeping with the general concept that man and animals during stress, may react with their cardiovascular apparatus as if they were about to engage in strenuous muscular activity without any actual awareness of anticipating exercise (155). Although the functional changes may be quickly reversible, the possibility that repeated or sustained stress situations may lead to irreversible changes—as it was shown in our animal experiments—must be taken into consideration (156). The question, whether or not such functional abnormalities resulting from stress contribute to the development of morphologic lesions of the heart muscle, cannot be answered, however, on the basis of the data in hand. One may put forward the working hypothesis that cardiac necroses and some related cardiovascular disease, in a broad aspect, are the end-products of altered reactivity of body processes in their response to changes in intrinsic and extrinsic environmental influences. Final clinical evidence to support such notions is still lacking, but, as it was seen during the discussions of the present review, several experimental findings tend to support this view.

On the other hand, information as to precisely what circulatory patterns and cardiac activities are subject to influence from neural, neurohumoral, and endocrine centers – which pathways also participate in adaptation reactions in general – is still only fragmentary, but it tends to indicate that the cerebral cortex and the hypothalamus must be considered along with the pituitary

and adrenals as potentially controlling cardiovascular responses (157). The influence of the cerebral cortex upon the cardiovascular system is documented by anatomical, physiological and psychological data. The cortical areas that control cardiac activities are located in the anterior half of the brain and include the tip of the frontal lobe, the orbital cortex, the motor and premotor cortex, the anterior part of the temporal lobe, the insula and the cingulata gyrus (158). Above the medulla oblongata, the region which appears to be more concerned with cardiovascular control than any other, is the hypothalamus.

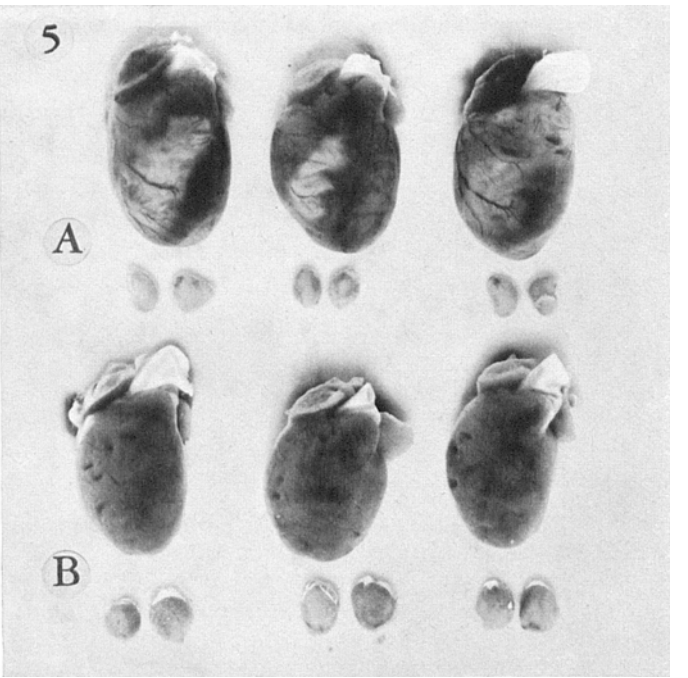

Fig. 5. *The participation of the adrenals at the development of cross-resistance. A:* Macroscopically visible large patches of cardiac necroses (white area) in the fluorocortisol plus Na-acetate-sensitized rats, as elicited with corn oil feeding. The corresponding adrenals are atrophic owing to the corticoid treatment. *B:* Note the absence of cardiac necroses, and the presence of adrenal enlargement, in the animals treated similarly but adapted to forced restraint (Ref. 137).

The extensive evidence which supports this statement had its origin in the work of KARPLUS and KREIDL (159). However, in spite of the considerable amount of work done in this field, the physiology of the hypothalamic areas which influence cardiovascular function is rather obscure. For example, according to the views adopted by GELLHORN (160). The hypothalamus can be functionally divided into a rostral "parasympathetic" portion and a caudal "sympathetic" area. Others, however, claim that such distinction cannot be made and there is a complex hypothalamic mechanism of cardiac control that goes into action during the display of aggressive or defensive behavior (9, 157). Obviously much more work is needed in order to understand the role of the nervous and neuroendocrine systems in the cardiovascular adjustment reactions activated by emotional and physical stresses.

In summary it may be simply stated that the participation of higher neural and neuroendocrine structures in adaptive cardiovascular regulation is suggested by the following basic observations: (a) cardiovascular changes resulting from anticipation of exercise, of eating or of an emotional situation (161); (b) experimentally induced cardiovascular changes, such as those following injection of adrenaline and noradrenaline, do not mimic functional cardiovascular changes typical of stress (162); (c) the latency of the cardiovascular response to stress is too short to result from purely hormonal mechanisms (163). Unfortunately, no data are available as yet concerning the influence of the higher neural centers upon the development of the necrotizing cardiopathies.

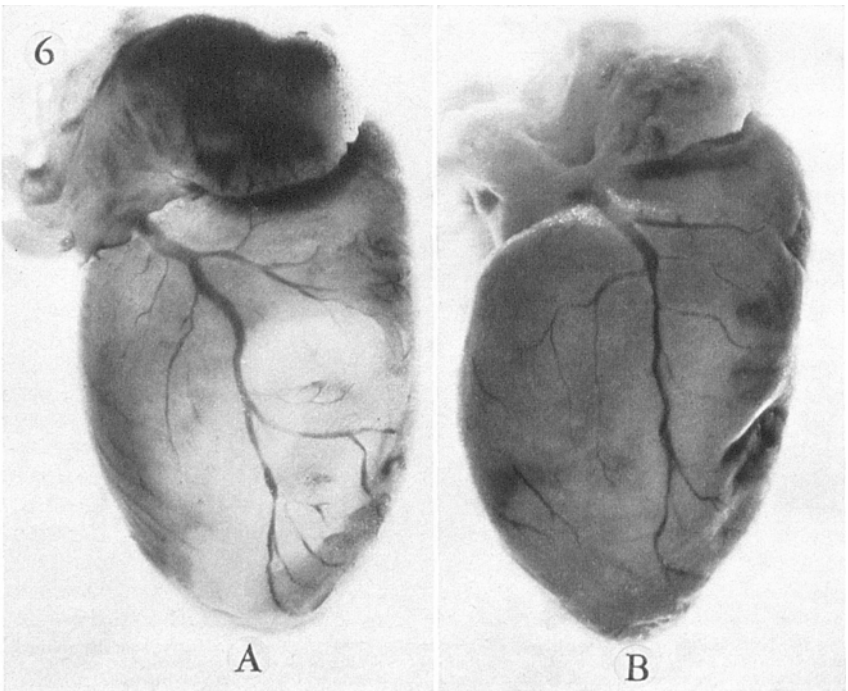

Fig. 6. *Prevention of cardiac necroses by chlorpromazine. A:* Large patches of cardiac necroses in a fluorocortisol plus Na-acetate pretreated rat, as elicited with the stressor action of immobilization. *B:* Note the absence of cardiac lesions in the rat similarly treated as that shown in fig. 6/A, but, in addition, injected with chlorpromazine. (Ref. 193.)

As another important point in the mechanism of cardiac necroses, the possible *dual actions of corticoids* may be considered. Among the sensitizing agents, corticoids (that is, Me-Cl-COL, F-COL, DOC, cortisol, and triamcinolone) appeared to be particularly active in the production of cardiac necroses with various potentially cardiotoxic factors. The administration of a combination of both mineralo- and glucocorticoids, or of a single compound possessing both these activities (e. g., Me-Cl-COL, F-COL) is the most effective in this respect. Among the halogenated corticoids tested, only triamcinolone (a pure glucocorticoid) failed to condition the cardiac muscle to the toxic effect of Na-salts. However, this hormone was found to be especially active in the

production of "spotty myolysis", when given simultaneously with noradrenaline to intact or adrenalectomized animals. It was also observed that following suitable pretreatment with corticoids otherwise innocuous agents may become cardiotoxic. For example, after pretreatment with Me-Cl-COL, pentamethylentetrazol, Na-arsenate, or diisopropylfluorophosphate all consistently elicited cardiac necroses in the rat, although none of these compounds nor the corticoid showed any cardiotoxic properties when given alone (14).

On the other hand, studies on the interactions between steroid hormones did not provide any evidence to show that the sensitizing action of one steroid could be prevented by another (122). Yet, the many antagonisms between steroids in other respects and the observation that pretreatment with stressor agents as well as the condition resulting from pregnancy offers considerable protection against most of the cardiopathies studied suggest that research along these lines may be profitable. Interestingly, the cross-resistance of the heart induced by stressors could not be duplicated by the concurrent injection of F-COL, triamcinolone, DOC, or ACTH, but in the adrenalectomized animals a combined administration of both mineralo- and glucocorticoids (i. e., DOC plus triamcinolone) proved to be the most effective in restoring the adaptability of the heart muscle. Some preliminary observations showed, furthermore, that a pretreatment with comparatively small amounts of DOC and, to a lesser extent, even with ACTH is moderately effective in protecting the heart against various cardiotoxic agents (164). Hence, it is still possible that some hitherto unexplored dual action of corticoids plays a role as mediator in the cross-resistance phenomenon.

A possible dual action of corticoids has been suggested by TANZ (165) who showed that small doses (1 μg/ml) of cortisone tend to restore the amplitude of contractions to control levels in the isolated heart preparation, while "toxic" doses (40 μg/ml) often result in abnormal contractile pattern. According to our own experimental observations (166–172) cortisol exerts a somewhat similar dual action on peripheral nerve regeneration and on the development of muscle atrophy. More precisely, these experiments indicated that the beneficial or adverse effect of cortisol administration is largely dependent on the amounts injected daily. A dose level of cortisol was demonstrated to significantly facilitate the recovery of sensory and motor function, and through enhancement of the nerve regeneration, to beneficially alter the final degree of muscle atrophy. Compared with this therapeutically active dose, smaller quantities proved to be ineffective, while a larger dose even exerted an opposite effect (i. e., it delayed the rate of recovery of nerve function and subsequently increased the degree of atrophy in the triceps surae muscle). The dual action of other hormones than corticoids is also established. For example, in subtotally pancreatectomized rats, early treatment with estrogens produces a biphasic effect: the incidence and severity of diabetes is first increased, but later reduced or even definitely suppressed. Thus, these and similar experiments revealed that estrogens can either exacerbate or ameliorate diabetes. Small amounts of these hormones usually aggravate diabetes, while the administration of larger doses may decrease hyperglycemia and insulin needs (173). The mechanism of this dual action of estrogens is obscure. The protective action is probably due to the stimulation of beta cell growth in the islets of LANGERHANS and consequently to increased insulin production.

Such dual action of hormones may have a basically important role in the variability of results obtained at different laboratories and in different sizes of animals. It may explain furthermore, why some clinicians obtained beneficial results from the administration of corticoids to patients with cardiac disease (e. g., cardiac infarcts), while others were unable to confirm these findings (174). Interestingly, studies on the cardiotoxic activity of a highly active synthetic corticoid, F-COL, showed that this hormone in a concentration of 0.5–1.0 μg/ml results in a positive inotropic action, an increased uptake of intracellular Na and loss of K. In a concentration of 10–20 μg/ml, F-COL gives rise to a negative ionotropic action, loss of intracellular Na and increased uptake of K. Small doses of this corticoid result in partial recovery of failing heart preparations, whereas larger doses added to the "normally" functionnig heart bring about failure quite rapidly. This latter functional alteration was found to be accompanied by morphologic abnormalities of the myocardium (175).

It would be, of course, impossible to analyze separately, here, each of the factors that possibly alter the synthesis and metabolism of corticoids, or even to enumerate simply the experimental and clinical findings showing the great many alterations in electrolyte-balance, metabolic, enzymatic and other vital activities, consequent to administration of corticoids. It is important, however, to mention that there are observations suggesting a direct effect of corticoids upon the cardiac tissue. The first intimating that the secretion from the adrenal cortex directly affects cardiac behavior was published in 1926 by ROGOFF and STEWARD (175), who noted a diminution in heart rate due to adrenal insufficiency. With the availability of cortisone and its use as therapeutic agent, reports were published by HENCH et al. (177), PERERA et al. (178), SOMMERVILLE (179) and others, describing a return to normal in the ECG of patients being treated with cortisone for adrenal insufficiency. On the other hand, the first observation showing that organic cardiovascular lesions can be regularly produced by DOC was published by SELYE as early as 1940 (180).

In 1951, ABRAMS and HARRIS (181) reported ECG changes in rabbits following the administration of cortisone, and concluded that this was the result of a direct action upon the heart. Later HOFFMANN (182) perfused isolated guinea pig and frog hearts with cortisone and observed with low concentrations (1–10 μg/ml) a positive inotropic action. This finding was confirmed by EMELE and BONNYCASTLE (183) using the hypodynamic cat papillary preparation. In reports of other workers, however, only a negative inotropic action is mentioned as elicited by cortisone on the rabbit LANGENDORFF preparation (184–186). Apparently, this can be explained by the high doses usually employed in the experiments quoted, because LACROIX and LEUSEN (187) reported a depression in myocardial oxygen consumption following large doses of cortisone.

The already discussed results of TANZ (165, 175) may be quoted as evidence of the protective or normalizing action of small amounts of cortisone on the whole isolated cat heart preparation and histologic preservation on the papillary muscle preparation. This action is not surprising in view of the fact that adrenal insufficiency is often characterized by cardiac impairment. Moreover, the protective action of certain glucocorticoids on skeletal muscle has been demonstrated by BAJUSZ and SELYE (188), and NASMYTH (189) was able to show that a perfusion of small amounts of cortisone through isolated

rat hearts (taken from animals that had been adrenalectomized 72 hours previously) causes a slight increase in the amplitude of contractions. SOLOMON et al. (190) demonstrated, furthermore, that the addition of corticosterone to the heart-lung preparation of adrenalectomized rats restored cardiac work capacity. Several studies on dogs also showed this "normalizing" ability of glucocorticoids on the heart. For instance, NAHAS (191) observed that the administration of corticol will prevent the onset of acute acidotic heart failure and GROSSFIELD et al. (192) using adrenalectomized dogs, have been able to demonstrate the disappearance of asystoles following the injection of certain glucocorticoids.

These results tend to support the belief that certain naturally occurring corticoids (especially glucocorticoids) are necessary for normal cardiac function by virtue of a direct effect upon the myocardium.

Miscellaneous factors in the pathogenesis of cardiac necroses. – It was already pointed out on the previous pages that corticoids may influence cardiac metabolism directly, or indirectly, by altering the ionic equilibrium via the kidneys.

It was shown that an antimineralocorticoid steroid-spirolactone ("Aldactone") offers considerable protection against the induction of cardiac necroses normally produced by stress in rats sensitized by F-COL plus Na-acetate (8). This finding may suggest that an increased mineralocorticoid activity upon the kidney is involved. It should be considered, furthermore, that stress, through increasing vasopressin secretion, is a proper antidiuretic agent and, thus, may also contribute in this way to the misregulation of water and electrolyte balance.

At any rate, whenever the mineralocorticoid activity increases – which in turn enhances the secretion of K and the retention of Na and Cl – we would expect that the kidney immediately balances the changes induced in order to keep the body composition normal. Our observations suggest, however, that in certain conditions (e. g., during, or consequent to severe stresses) the kidney may not do this, indicating that it has lost its adaptive ability to maintain or restore selective function and that the physiological stimuli to the kidney are not operating in a proper manner. Interestingly, exposure to stressors does not elicit the typical necrotizing cardiac lesions in the electrolyte plus steroid conditioned rat following nephrectomy. Moreover, pretreatment with restraint markedly inhibits the development of the uremic cardiopathy normally produced by bilateral nephrectomy, even if sensitizing amounts of Na_2HPO_4 are administered (193). It may be concluded, therefore, that the presence of the kidneys is not necessary for the cardiac necrosis eliciting actions of stress. However, it is equally possible that the phenomenon of cross-resistance does not depend upon the presence or absence of renal tissue.

It was also observed that exposure to stressors elicit cardiac necroses even in adrenalectomized animals sensitized by Na-salts while maintained on small amounts of corticoids (8). This finding suggests the participation of some extra-adrenal mechanisms. In fact, the experiments with neuroleptic phenothiazine derivatives pointed out the importance of certain neural pathways in the mechanism through which various stressors either elicit cardiac lesions or induce cross-resistance of the heart (139).

As a final conclusion we may say that our investigations suggest that there may be some common mechanism through which various agents influence

the heart muscle, thereby producing necroses, inflammation and/or calcification. The observations that certain factors uniformly sensitize, while others desensitize the myocardium for the production of structural lesions by a great variety of agents could be interpreted in this manner. The experiments and related data summarized in this review not only reveal the existence of principal interactions between certain factors (especially dietary electrolytes) that basically alter the disease-susceptibility of the heart muscle, but also suggest the directions in which future research could be extended.

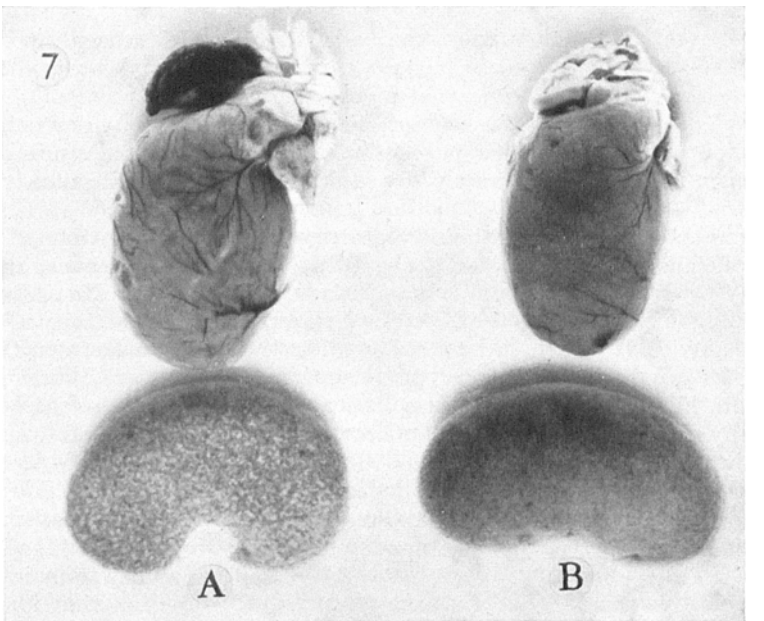

Fig. 7. *Prevention of coronary sclerosis and nephrocalcinosis by forced restraint.* – *A:* Macroscopic view of coronary sclerosis (white line in the middle of the heart) and nephrocalcinosis in a rat treated with DHT plus Ca-acetate. *B:* Note normal appearance of the heart and only a slight degree of renal calcification in a rat treated similarly to that shown on the previous picture (A), but in addition this animal was gradually adapted to forced restraint.

The importance of the ionic equilibrium. – On the previous pages, observations were already discussed in length, which showed that K-deficiency is not the only factor in the pathogenesis of experimental cardiopathies induced by the chemical means. Yet, NICKERSON et al. (194) recently concluded that the ESCN, normally produced by combined administration of Me-Cl-COL plus Na_2SO_4, is simply due to K-loss through diarrhea. This conclusion was based on results obtained by electrolyte determinations of the blood and cardiac muscle and, indeed, we can enumerate many additional facts that furnish almost incontrovertible evidence in support of the thesis that K is the decisive pathogenic factor in the electrolyte-steroid cardiopathies. For example: (a) mineralocorticoids, which cause loss of K, are indispensable for the production of ESCN; their effect is enhanced by Na, a known antagonist of K; (b) the ESCN can be duplicated by feeding a K-deficient diet, even without

treatment with corticoids, Na-salts, or stressors; (c) the classical ESCN (produced by corticoids plus Na-salts), like the structurally similar lesions induced by dietary K-deficiency, can be prevented by the oral administration of K-salts; (d) acute stress, which causes a pronounced sudden loss of K, can precipitate electrolyte-steroid cardiopathies as well as other types of experimental cardiac necroses and this effect can also be prevented by dietary K-supplements; (e) in man, hypokalemia resulting from various diseases is frequently associated with cardiac necroses that resemble the ESCN. On the

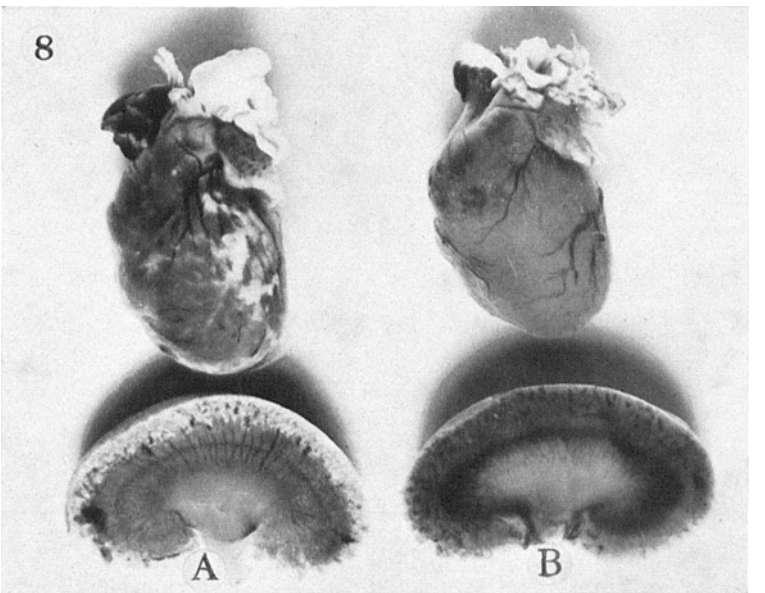

Fig. 8. *The effect of gradual muscular exercise on the development of severe calcifying cardiac and renal lesions. A:* Typical macroscopic appearance of the calcifying cardiopathy and cortical nephrosclerosis in a rat treated with fluorocortisol plus Ca-acetate. *B:* Prevention of the cardiac and renal lesions by pretreatment with gradual muscular exercise.

other hand, there are a number of other findings indicating that K alone is not the only decisive pathogenic factor. For example: (a) in the corticoid conditioned rat, an ESCN can also be elicited by salts that have no cathartic action (e. g., phosphates, perchlorate); (b) subcutaneous administration of these sensitizing Na-salts is likewise effective in this respect; (c) indeed, even mere exposure to stress, without any electrolyte pretreatment, produces an ESCN type of cardiac lesion after corticoid conditioning; (d) the ESCN can be prevented not only by K-salts, but also by $MgCl_2$ as well as by chlorides of other cations; (e) cardiac necroses induced by K-deficient diets respond as well to prophylactic treatment with $MgCl_2$ or to other chlorides as to K-salts themselves; (c) pretreatment with stressors – which certainly causes loss of K – significantly protects against the induction of an ESCN.

The experiments discussed in this paper revealed that the *metabolic cardiac necroses* (*including the electrolyte-steroid cardiopathies*) *are characterized precisely by the fact that they depend upon complex anion-cation interactions*, not upon a

single alteration in the electrolyte-balance. Nevertheless, the observations that Mg, Na and Cl all play an active role in the pathogenesis of these cardiac lesions do not indicate that the participation of K is not equally important in this regard. In fact, several recent publications have supplied additional evidence in support of this view.

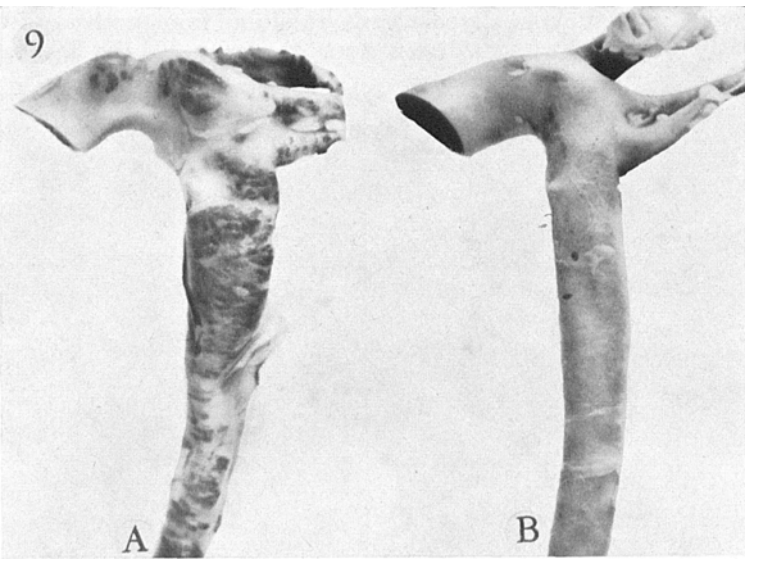

Fig. 9. *Effect of forced immobilization on the development of Mönckeberg sclerosis.* – *A:* Heavily calcified aorta of a rat treated with large doses of DHT. *B:* Prevention of this MÖNCKEBERG-type of arteriosclerosis by pretreatment with forced immobilization (Ref. 133).

Namely, certain observations suggest that a K-servomechanism regulates cardiac work and that K-efflux from the heart is augmented when the cardiac work-load and heart rate are increased. In coronary disease, myocardial intracellular K-loss is markedly accentuated by ischemia, and extra-cellular K is excessively elevated, since it is not washed away rapidly owing to poor blood-flow. Not only myocardial ischemia, but various stressors (muscular work, adrenaline, cold), all deplete myocardial K and increase coronary venous K. These and many cognate observations were taken to mean that K occupies a pivotal position in the physiology and pathology of the myocarddium (195). The precise role of Mg in cardiac physiology and pathology is even less understood. In vitro observations suggest that heart muscle transaminase is activated by Mg-ions (196). It has been suggested, furthermore, on the basis of indirect evidence that Mg might be involved in certain vitally important defensive actions of cardiac enzymes, particularly those of mitochondria (58, 71). But how these effects may be related to the pathogenesis of structural lesions remains unknown. Although $MgCl_2$ can replace K-salts in the prophylaxis of various experimental cardiopathies and even the sensitizing action of K-deficiency can be abolished by $MgCl_2$, nothing is known about the mechanism through which it exerts these effects. Actually, our observations do not prove that the Mg-ions, as such, play an important role,

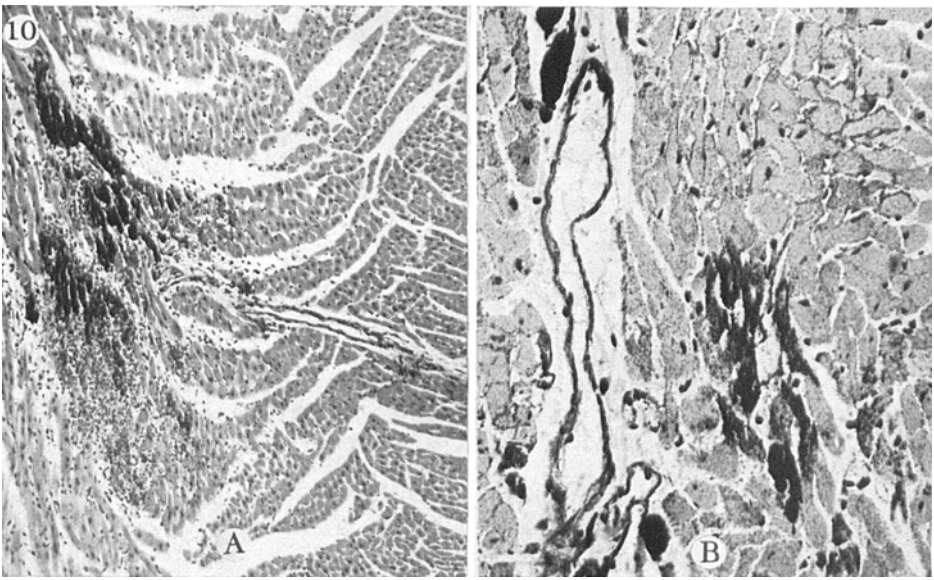

Fig. 10. *Failure to produce cross-resistance in adrenalectomized animals.* – *A* and *B:* Microscopic appearance of the typical DHT plus Na_2HPO_4-myocarditis with calcification of the myocardium and coronary vessels. This adrenalectomized rat was maintained with triamcinolone, and under these experimental conditions cross-resistance could not be induced with adaptation to stressor agents.

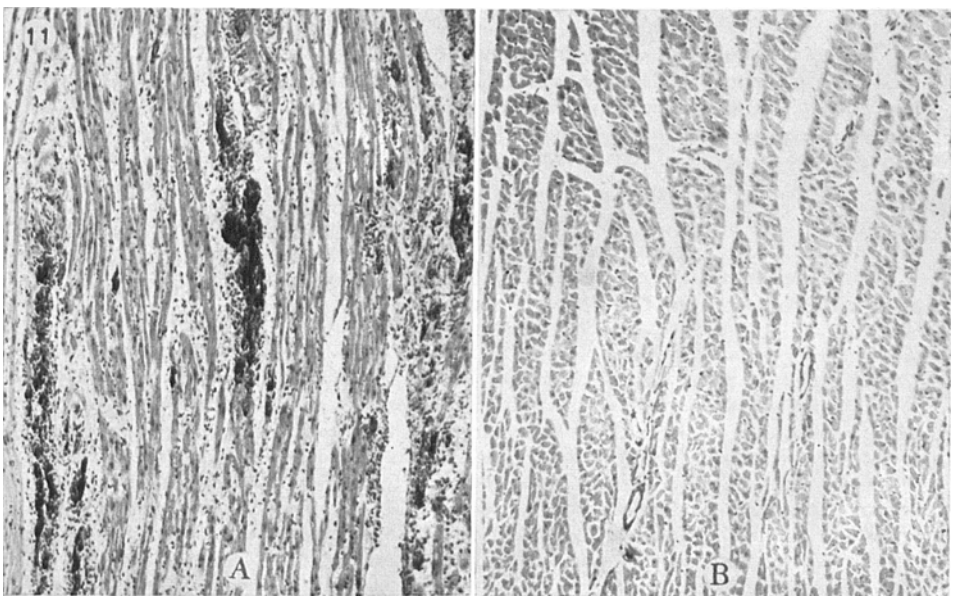

Fig. 11. *The importance of corticoids at the development of stress-induced cross-resistance of the heart muscle. A:* Severe cardiac lesions in an adrenalectomized rat maintained with desoxycorticosterone and treated with DHT plus Na_2HPO_4. – *B:* Prevention of cardiac lesions with pretreatment with forced restraint; this animal was also adrenalectomized, but received a maintenance therapy with both mineralo- plus glucocorticoids (desoxycorticosterone plus triamcinolone).

since Cl itself is an effective prophylactic agent. Hence, our findings are, to a certain extent, compatible with the assumption that $MgCl_2$ acts merely as a particularly suitable chloride donor.

Let us recall, here, that the damaging effect of Na is enhanced by the anions that are attached to it (PO_4, SO_4, ClO_4), but counteracted by Cl. Indirect evidence suggests that the Na-ion is inherently toxic when excessive quantities of it enter the myocardial cell and that its entry largely depends upon the presence of other ions. In this sense, the beneficial effect of K would be caused by displacement of Na, while that of Cl might be ascribed to displacement of the more cardiotoxic anions just mentioned (13). Thus, it seems that Na always is cardiotoxic if not attached to Cl or balanced by K, an assumption that highlights the importance of the ionic equilibrium of the organism is maintaining the integrity of the myocardium.

Finally, we note that there are observations indicating that increased cardiac work is a cardinal factor in cardiovascular pathology. Electrolyte changes seen in heart failure (Na and H_2O-retention, K-depletion) are also observable after muscular work. The changes involving K are of particular importance: when the gradient between intra- and extracellular K decreases, muscular contractions become impossible (197). The cardiac necrosis eliciting action of stressor agents, and of the more specifically cardioactive, adrenergic and thyroid hormones, may in the final analysis, act by increasing cardiac work and thereby augmenting the production of cardiotoxic electrolyte shifts or metabolites in the overstrained heart muscle.

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Summary

Experimental cardiopathies that are widely different in their histologic characteristics were studied in the albino rat. The main purpose of these comparative investigations was to determine the participation of various cations and anions (especially of K, Mg, Na and Cl) in the pathogenesis of metabolic cardiopathies that are induced by chemical means, but are not accompanied by histologically detectable changes of the coronary arteries.

It was observed that variations in dietary intake, not only of certain cations (K and Mg) but also of the anions (Cl and PO_4), play an important role in the pathogenesis of certain necrotizing cardiopathies as well as in the mechanism of adaptive reactions that basically alter the disease-susceptibility of the myocardium. It was also noted that most of the agents that are capable of inducing cardiac lesions through some biochemical mechanism are potentially acting pathogens, whose cardiotoxicity largely depends upon other factors or conditions: some of which (i. e., corticoids, Na-salts, dietary deficiencies

in K, Mg and Cl, sudden stress situations, age and coronary sclerosis) uniformly sensitize, while others (i. e., Cl-excess, Na-deficiency, adaptation to stressor agents and the condition produced by pregnancy) desensitize the myocardium to the production of cardiac lesions (necrosis, inflammation, calcification) by most diverse potentially pathogenic agents. On the other hand, the cardiac infarcts that can be produced by surgical occlusion of coronary arteries in the rat, differ basically in many respects from all metabolic cardiopathies studied. The latter are characterized precisely by the fact that they depend upon complex anion-cation interactions, not upon a single pathogen.

The importance of K, Mg, Na and Cl in the pathogenesis of cardiac necroses and the possible role of the ionic equilibrium in the production and prevention of necrotizing cardiac diseases are discussed on the basis of experimental studies performed by the author and of previous observations described by others.

Résumé

Nous avons étudié chez le rat diverses cardiopathies expérimentales à caractères histologiques différents. Ces études comparatives avaient pour objet d'évaluer le rôle de certains anions et cations (notament, le K, Mg, Na et le Cl) dans la pathogénèse des cardiopathies métaboliques provoquées par des agents chimiques mais en l'absence de toutes modifications histologiquement démontrables des artères coronaries.

Il fut observé que des variations du contenu en cations K et Mg ou encore en anions Cl et PO_4 dans la diète, jouent un rôle important dans la pathogénèse de certaines cardiopathies nécrosantes tout autant que dans le mécanisme fondamental des réactions adaptives qui modifient la susceptibilité du myocarde. Nous avons constanté en outre que la plupart des agents capaples d'induire des lésions cardiaques par un mécanisme biochimique ont un potentiel pathogène et que leurs effets cardiotoxiques dépendent d'autres facteurs ou conditions. Ainsi, les hormones corticoïdes, les sels de Na, les déficiences alimentaires en K, Mg et Cl, les stress aigus, l'âge et la sclérose des artères coronaires tiennent lieu d'agents sensibilisateurs alors qu'un excès en Cl, une déficience en Na, une adaptation aux agents stressants et la gestation désensibilisent le myocarde à la production de lésions cardiaques (nécrose, inflammation, calcification) par des agents à potentiels pathogènes les plus divers. Par ailleurs, les infarctus cardiaques provoqués par l'occlusion chirurgicale des artères coronaires chez le rat, montrent des différences fondamentales avec les cardiopathies métaboliques que nous avons étudiées. Ces derniers, en effet, out pour caractéristique de dépendre essentiellement d'une interaction entre les anions et les cations et n'ont pas un seul agent pathogène.

L'importance du K, Mg, Na et du Cl dans la pathogénèse des nécroses du myocard et le rôle possible de l'équilibre ionique dans la production et la prévention des maladies cardiaques de type nécrosant sont discutés sur la base des études expérimentales effectuée par l'auteur et de diverses observations décrites par l'auteur.

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Author's address:
Dr. med., Dr. phil. EÖRS BAJUSZ, Department of Pathology, University of Montreal, Faculty of Medicine, P. O. Box 6128, Montreal (Canada)