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Received September 9, 1957. P.S.E.B.M., 1957, v96.

Humoral Conditioning for Production of Acute, Massive Myocardial Necroses by Neuromuscular Exertion.* (23523)

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Previous experiments have shown that 2-methyl-9(α)-chlorocortisol (Me-Cl-COL), administered in combination with either basic or acid phosphates, results in acute, massive myocardial necroses in the rat(1). The possible relationships between this experimental lesion and the cardiac infarcts of man have not yet been studied. Since it is well known that neuromuscular effort is likely to precipitate myocardial infarction in predisposed people, the question arose whether this would also be the case in rats sensitized by threshold amounts of Me-Cl-COL and phosphate.

Materials and methods. Eighty female Sprague-Dawley rats, with an average initial body-weight of 101 g (range: 95-110 g), were subdivided into 4 equal groups, as indicated in Table I. Me-Cl-COL† was administered subcutaneously, in the form of its acetate, as a microcrystal suspension of 50 μg in 0.2 ml of water, once daily. NaH_2PO_4 was given by stomach tube, as a 15% aqueous solution, at the dose of 2 ml, twice daily. Neuromuscular strain was induced by maintaining the rats on a board with adhesive tape, for a period of 17 hours, starting 78 hours after the initiation of the Me-Cl-COL and NaH_2PO_4 treatment. The animals of all 4 groups were killed with chloroform, 5 hours after the release of the restrained rats. The hearts and the kidneys of half of the animals in each group were fixed in Susa solution for subsequent staining with hematoxylin-eosin, and those of the other half in neutral formalin for the subsequent demonstration of calcium deposits by v Kossa's silver nitrate stain. For both of these purposes the tissues were embedded in paraffin.

Results. The principal results of these experiments are summarized in Table I.

Upon naked-eye inspection at autopsy, the most striking change was the presence of large, light-yellow patches throughout the myocardium in all the animals of Group IV (Fig. 1). Similar, though less extensive lesions were also seen in 20% of the rats in Groups II and III, but not in Group I.

TABLE I. Humoral Conditioning for Production of Acute, Massive Myocardial Necroses by Neuromuscular Exertion.

Group	Treatment	Myocardial lesions Incidence	Myocardial lesions Severity*	Nephrocalcinosis Incidence	Nephrocalcinosis Severity*	Mortality (%)
I	Me-Cl-COL	0	0	0	0	0
II	" + Restraint	20	.3	0	0	0
III	" + NaH_2PO_4	20	.4	100	2.0	0
IV	" + Restraint + NaH_2PO_4	100	2.6	100	2.0	50

* Severity of the lesions was assessed both macro- and microscopically, in terms of an arbitrary scale of 0-3; figures in this column are the means of these readings.

* Supported in part by a grant from the Gustavus and Louise Pfeiffer Research Foundation and by a Grant from the Muscular Dystrophy Association of Canada.

† Generously supplied by The Upjohn Co.

Histologically, the yellowish patches proved to consist of necrotic cardiac muscle, partly infiltrated by polymorphonuclear leukocytes and monocytes (Fig. 2). The histogenesis of

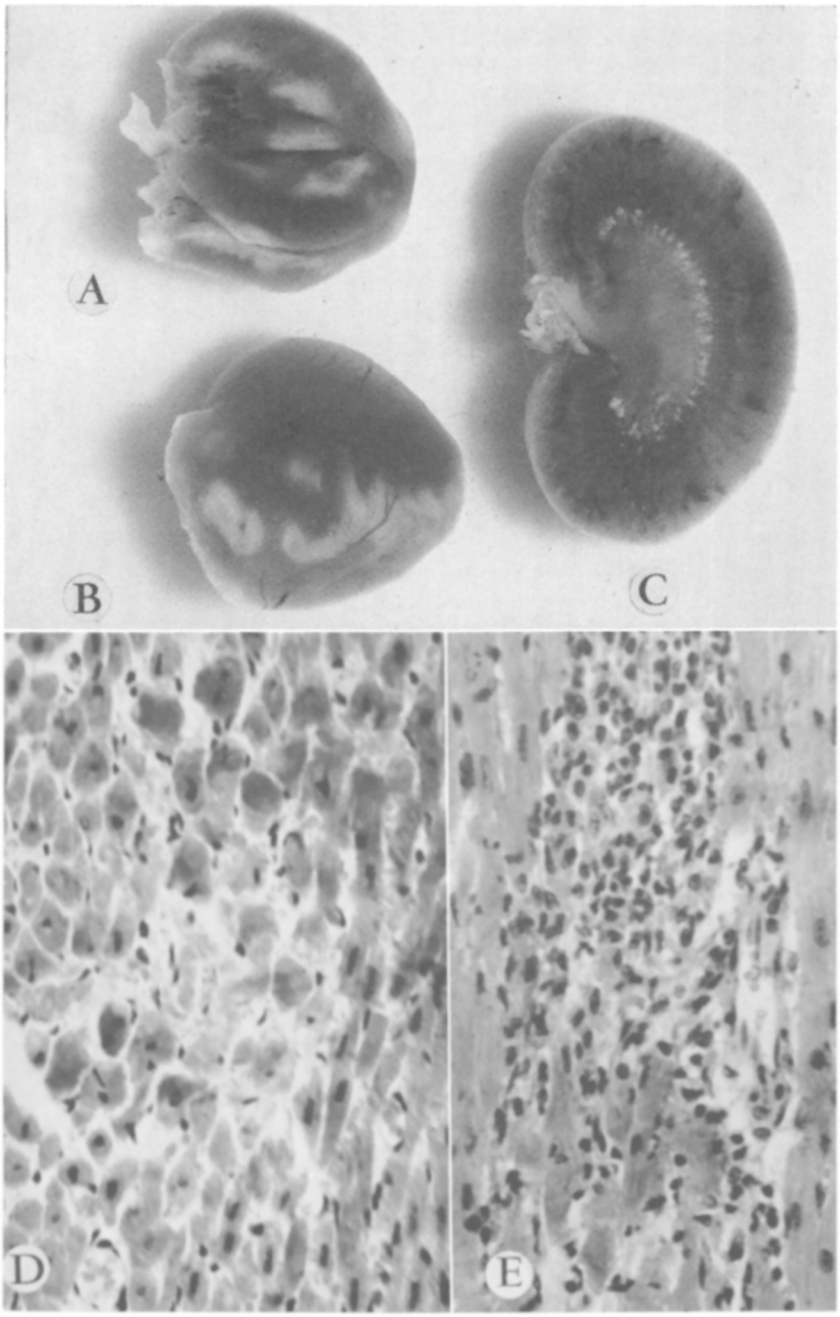

FIG. 1. Characteristic organ changes in a rat of Group IV. A. Cut surface of heart showing multiple large myocardial necroses in wall of ventricle and in papillary muscles as they appear to the naked eye. B. Similar infarcts underneath external surface of the same heart. C. Cut surface of kidney showing white spots of nephrocalcinosis at the cortico-medullary junction. D. Small focus of myocardial necrosis. Some of the affected muscle fibers stain particularly dark with eosin, others are pale and in the process of dissolution (× 320). E. A similar myocardial focus infiltrated with polymorphonuclear leukocytes and monocytes (× 320).

these lesions will be discussed in detail elsewhere; suffice it to mention here that, although histochemically demonstrable, fine granules of calcium were visible in certain areas of the myocardium, there appeared to be no close relationship between these and the necrotic areas. Indeed, most of the focal necroses contained no histochemically demonstrable calcium.

Nephrocalcinosis occurs readily in rats treated with mineralocorticoids and phosphates(2). Accordingly, this change was pronounced in Groups III and IV of the present series, but absent in Groups I and II, in which Me-Cl-COL was given without excess phosphate. There appeared to be no obvious relationship, however, between intensity of the nephrocalcinosis and the myocardial necroses; the latter were evident in 20% of the rats, both in Groups II and III, although in the former there was no nephrocalcinosis, while in the latter pronounced renal calcification was detectable in every animal.

Deaths occurred only in the animals in Group IV and were preceded by signs of cardiac failure, particularly dyspnea and pronounced cyanosis.

Discussion. Our earlier investigations have shown that even intense nephrocalcinosis, if produced by excess phosphate alone, does not cause myocardial necrosis(1). A lack of relationship between intensity of renal calcification and the cardiac changes is also apparent in the observations reported here. It is clear, furthermore, that Me-Cl-COL alone does not produce either myocardial or renal lesions, but merely "conditions" the organism for the production of such changes by an excess of NaH_2PO_4. It is also evident that, in rats maximally sensitized for the production of myocardial necrosis by conjoint treatment with Me-Cl-COL plus NaH_2PO_4 (and, to a lesser extent, in those sensitized only by Me-Cl-COL), the neuromuscular exertion consequent to forced restraint elicits acute, massive myocardial necroses. It remains to be seen whether the muscular effort or the frustration of forced restraint is most important in the production of these infarct-like changes; in any event, presumably, increased cardiac work during effort is a decisive factor. It is dubious whether the myocardial lesions are true infarcts; they are so acute that it is impossible to determine by histological means whether the death of muscle fibers is due to a primary metabolic derangement in the myocardium, or the secondary result of insufficient blood-supply; indeed, both factors may play a part.

Summary. Following pretreatment with 2-methyl-9(α)-chlorocortisol (Me-Cl-COL), a brief period of neuromuscular effort (induced by force restraint) can elicit acute, massive myocardial necroses in the rat. When NaH_2PO_4 was administered in addition to Me-Cl-COL during the pretreatment period, such changes occurred in 100% of the experimental animals, during or immediately after a period of forced restraint.

Addendum: Since this manscript went to press, it has been possible to show that combined treatment with cortisol and NaH_2PO_4 produces similar massive myocardial necroses in the rhesus monkey. These findings will be published in detail elsewhere; they are mentioned here only because they demonstrate that the principal natural glucocorticoid is also effective and that the primate responds like the rat in this respect.

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Received September 10, 1957. P.S.E.B.M., 1957, v96.