

THE CHEMICAL
PREVENTION
OF
Cardiac
Necroses

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Preface

Cardiac necrosis is the most common cause of death in man. It may present itself in many forms, and most of its varieties are traditionally considered to be quite unrelated. The massive cardiac infarct caused by acute thrombosis of a coronary vessel surely appears to have little in common with such lesions as the necrotizing myocarditis of diphtheria, typhus or other infectious diseases, the "spotty myolysis" that occurs in certain viral infections, endomyocardial fibrosis, hypokalemic cardiopathy, Fiedler's "isolated myocarditis," and the "nonspecific chronic myocarditis" that eventually develops in everybody who lives long enough. Indeed, it would be difficult to imagine a group of maladies more dissimilar than these as regards their etiology, clinical course, and morphologic characteristics. Yet, they all have one feature in common: necrosis of cardiac muscle fibers which are replaced first by inflammatory cells and eventually by scar tissue.

Experimental medicine has brought to light an equally impressive list of necrotizing cardiopathies which likewise appear to be quite unrelated to each other. Deficiencies in various essential nutrients (e.g., potassium, magnesium, or vitamin-E), intoxications (e.g., with certain steroid hormones, sterols of the vitamin-D group, cardiac glycosides, proteases, carbon monoxide, or histamine) as well as numerous infections and hypersensitivity reactions can—at least under certain experimental conditions—produce necrotic and inflammatory foci in the myocardium.

Some years ago, we observed that a type of coronary sclerosis (often complicated by thrombosis) occurs in experimental animals simultaneously treated with desoxycorticosterone and dietary supplements of sodium chloride. Similar lesions were

induced by NaCl in the hearts of rats chronically exposed to the stress of cold. However, in rats maintained on small doses of cortical extract, adrenalectomy protected the heart against these injurious effects of NaCl plus cold. It was assumed, therefore, that the excessive endogenous secretion of corticoids (such as occurs during exposure to stress) may be of pathogenetic importance here. An increase in adrenocortical activity is an integral part of the General Adaptation Syndrome. Without this physiologic adrenocortical response, the body could not resist the effects of damaging agents. Yet, in the presence of an excess of NaCl, endogenous corticoids can become pathogenic. This was one of the first observations that led us to formulate the concept of the "diseases of adaptation," which postulates that adaptive hormonal reactions may, under certain conditions, derail and become pathogenic. These findings also drew our attention to the fact that *hormones, even without themselves producing disease, can so condition the body's response to normally inoffensive agents (here, NaCl) that morbid changes result.*

A few months ago, a rather unexpected, new observation of this kind was made in our laboratory. We found that rats rapidly develop fatal cardiac necroses followed by myocarditis, if they are simultaneously treated with normally innoxious amounts of various corticoids and certain sodium salts (e.g., NaH_2PO_4 , Na_2SO_4 , or NaClO_4). Salts of all cations other than sodium were ineffective in such experiments. It might have been thought, therefore, that Na is the essential pathogen, but curiously, NaCl proved to be devoid of cardiotoxic effects under these conditions. In fact, the cardiac lesions normally produced by corticoids plus NaH_2PO_4 , Na_2SO_4 , or NaClO_4 were largely suppressed by simultaneous NaCl administration. MgCl_2 and KCl were even more effective in protecting the heart against this kind of damage. It was concluded that electrolytes can condition (sensitize or desensitize) the cardiac muscle for the production of structural changes by corticoids and vice versa.

Then, we learned that, in the corticoid-conditioned rat, even mere exposure to nonspecific stressors (neuromuscular exertion,

PREFACE

v

traumatic shock, hot or cold baths) can elicit focal myocardial necroses with inflammation. This type of cardiac damage, as well as a number of other experimental cardiopathies (e.g., the myocardial necroses and inflammations caused by the intravenous injection of proteolytic enzymes or by combined treatment with vitamin-D derivatives and NaH_2PO_4) could also be prevented by the prophylactic administration of MgCl_2 or KCl. Thus, it gradually became evident that electrolytes, steroids, and stress all play important conditioning roles in the development of cardiopathies elicited by the most diverse agents.

Though this monograph is mainly concerned with cardiac diseases, it should be kept in mind that treatment with corticoids and electrolytes is often accompanied by morbid lesions outside the heart. For example, depending upon experimental conditions, there may be cramps, necroses, and inflammation in skeletal muscles, cerebral edema, hepatic necroses, or nephrocalcinosis. Interestingly, all these extracardiac effects of the electrolyte-steroid treatment can also be prevented by KCl or MgCl_2 . Evidently, the possibility of conditioning by corticoids for the pathogenic effects of certain electrolytes is not limited to the diseases of the heart.

Many isolated clinical and experimental observations on cardiac necroses are now scattered throughout the world literature. The object of this monograph will be to coordinate these data, in the light of newly acquired knowledge about the electrolyte-steroid-cardiopathies. It is hoped that such a systematization of our knowledge will help us to obtain a better insight into the complex *relationships between electrolytes, steroids, and stress*, which we believe to be fundamental for the understanding and prevention of many diseases.

A great deal of work is now under way on the chemical production and prevention of cardiac necroses. Since we wanted to make this volume as up-to-date as possible, we have included, in the galley-proofs, many of our hitherto unpublished observations that were made while this volume was in press. These, as well as publications from other laboratories that came to our attention after submission of the manuscript, are desig-

nated by reference numbers followed by letters. This made it possible to insert these last-minute additions in the proper alphabetic position of the bibliographic list (e.g., Büchner 48a, after Büchner 48), instead of having to attach a separate addendum to the bibliography.

The experimental work which forms the basis of this monograph was made possible through the financial assistance of Gustavus and Louise Pfeiffer Research Foundation; National Heart Institute (Grant No. H-3688), U. S. Public Health Service; National Research Council of Canada (Consolidated Grant No. 11); The Squibb Institute for Medical Research; Geigy Pharmaceuticals; Schering Corporation Limited; The Lilly Research Laboratories; Lederle Laboratories Division, American Cyanamid Company; and The Upjohn Company.

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HANS SELYE

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Contents

CHAPTER	PAGE
TABLES	ix
GLOSSARY	2
1 HISTORICAL INTRODUCTION	3
2 PATHOGENS AND CONDITIONING FACTORS OF CARDIAC NECROSES	17
Electrolytes	17
Hormones	54
Vitamins	90
Cardiac Glycosides and Their Aglycones	100
Other Chemical Compounds and Food Constituents . .	101
Physical Agents, Including Surgical Interventions . .	111
Psychic and Nervous Stimuli	118
Microbes and Their Toxins	123
Hypersensitivity	125
Spontaneous Diseases	126
Various Other Factors	139
3 THEORIES	150
4 OUTLOOK	160
5 SUMMARY AND CONCLUSIONS	167
REFERENCES	172
INDEX	195

Tables

TABLE	PAGE
1. Production of ESCN by Various Na-Salts	20
2. Attempted Production of ESCN by Salts of Cations Other Than Na	25
3. Attempted Inhibition of ESCN by Various Na-Salts	27
4. Inhibition of the Na_2HPO_4 ESCN by Various Chlorides	33
5. Inhibition of Na_2SO_4^- and NaClO_4^- -ESCN by Various Mg- and K-Salts	35
6. Inhibition of ESCN by Various Mg- and K-Salts	37
7. Intramolecular Antagonism Between Na and K	39
8. Quantitative Relationships in the Synergism Between Various Sensitizing Electrolytes	40
9. Quantitative Relationships in the Synergism Between Various Desensitizing Electrolytes	41
10. Toxicity of Various Steroids in Rats Sensitized with NaH_2PO_4	66
11. Conditioning by Various Electrolytes for the Toxic Actions of DHT	96
12. Importance of Conditioning by Electrolytes During Nervous Stress (Vagotomy, Motor Denervation)	120
13. Importance of Conditioning by Electrolytes During Nervous Stress (Restraint)	122
14. Effect of Various Natural Foods upon the ESCN	142
15. Induction of Cardiac Necroses by Various Stressors, in Rats Conditioned with Me-Cl-COL	146

The Chemical Prevention of

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Glossary

This Glossary is designed only to define the sense in which certain technical terms and abbreviations are used in this book.

Activating anion. Anion (e.g., PO_4 , SO_4 , ClO_4), which activates Na^+ so that the resulting salt sensitizes for the production of an ESCN.

COL. Cortisol or hydrocortisone.

Conditioning. The establishment of conditions which enhance or inhibit the production of a change. E.g., Me-Cl-COL conditions the myocardium for the production of necroses by NaH_2PO_4 .

Desensitizing electrolytes. Electrolytes which desensitize the cardiac muscle for the production of an ESCN.

DOC. Desoxycorticosterone.

ESCH. Electrolyte-Steroid-Cardiopathy characterized by Hyalinization in the walls of coronary arteries and the myocardium itself. This lesion is most readily induced by an excess of NaCl , after conditioning by mineralocorticoids.

ESCN. Electrolyte-Steroid-Cardiopathy characterized by Necroses. This change is induced, for example, by an excess of Na_2HPO_4 , NaSO_4 , or NaClO_4 , after sensitization with corticoids.

G.A.S. General Adaptation Syndrome.

Hyalinosis. A condition characterized by excessive deposition of hyalin.

Infarct. Tissue necrosis caused by interference with the blood supply. It is usually caused by acute and complete occlusion of an artery (e.g., by a thrombus). However, even chronic, partial occlusion of a coronary artery (e.g., by atherosclerosis), though normally well tolerated, can probably cause cardiac infarcts at times of stress when the blood requirements of the heart are suddenly increased and the normal adaptive vasodilatation becomes impossible.

Infarctoid cardiopathy. Infarct-like, large circumscribed patches of cardiac necrosis, which tend to develop suddenly, especially during stress, but are not due to organic obstructions in the coronary arteries.

Me-Cl-COL. 2α -methyl- 9α -chlorocortisol.

Sensitizing electrolytes. Electrolytes which sensitize the cardiac muscle for the production of an ESCN.

Toxic cardiac necrosis. Necrotic regions in the heart, induced by exogenous or endogenous, toxic chemicals. E.g., the ESCN.

Vitamin-D-electrolyte myocarditis. An acute, purulent myocarditis induced by treatment with certain electrolytes (e.g., NaH_2PO_4), after conditioning with sterols of the vitamin-D group.

Historical Introduction

In describing the way our knowledge of a subject has developed, we usually begin with the first formulation of the basic idea and then follow its evolution in time. The process is comparable to that of describing the path of a river, beginning at its source. Thoughts, like rivers, almost always have several sources, but in general, the tributaries manifestly tend to converge in one direction, right from the start. In such cases, it is logical to follow the course of the flow, beginning from the principal source and mentioning the tributary streams as we go along.

The development of a lake poses an entirely different problem. Here, the picture does not tend to develop gradually; the tributaries run in different directions and seem to be quite unrelated to each other until the very end, when they suddenly become one. In this case, it is difficult to decide where to begin the description; it is not possible to build up the picture step-wise, systematically.

We meet this same problem when we attempt to present the historical evolution of knowledge about those cardiopathies that form the subject of this monograph. Our present views about them have developed from a multitude of apparently quite unrelated observations whose fundamental interdependence became evident only in retrospect, after they were re-evaluated from a novel point of view.

There are three principal fields from which important data were gathered for this re-evaluation: (1) the concept of "physiologically balanced salt solutions"; (2) the pathology of the diverse "toxic cardiopathies" that are produced by biochemical

means; and (3) the concept of nonspecific stress and of the "conditioning" by hormones for nonhormonal pathogens. In the following historical survey, we shall first deal with each of these approaches separately and then attempt to synthesize them into a unified concept that can act as a guide through the subsequent chapters of this volume.

1. The Concept of Physiologically Balanced Salt Solutions. It has long been known that, in addition to their nonspecific effects as regulators of pH, osmotic pressure, etc., certain salts exert specific biologic actions; these largely depend upon equilibria between the various types of electrolytes. From about 1880 to 1895, such ionic interactions were extensively studied in comparatively simple physicochemical and biologic systems: the development of electric phenomena in collodion membranes, the precipitation of proteins (or of colloidal lecithin solutions), and the permeability of erythrocytes *in vitro*. With regard to many of their effects upon these targets, the anions can be roughly arranged in a series of increasing potency, thus: $\text{SO}_4 < \text{Cl} < \text{Br} < \text{NO}_3 < \text{SCN} < \text{I}$, and the cations, thus: $\text{Li} < \text{Na} < \text{Cs} < \text{Rb} < \text{K}$. This type of activity gradation is also manifest in other biologic phenomena, for example, in the effect of electrolytes upon the potassium-induced contractions of muscles or upon the fermentation of yeast. The position of the ions in this series is allegedly due to their progressively increasing effects upon the arrangement of colloidal particles on surfaces or upon enzyme systems; it corresponds to what Hofmeister (166) called the "lyotrope series."

A few years later, and quite independently, several very important papers were published on an apparently quite unrelated subject, the electrolyte requirements of sea-urchin eggs. Herbst (156) had shown that if any of the constituents of sea water is omitted, the larvae of this species can no longer develop. From this fact, he drew the conclusion that each constituent of sea water is indispensable for the development of sea-urchin embryos. However, later, Loeb (214) showed, in his classical experiments on the eggs of *Fundulus* (which normally develop in sea water), that this conclusion is incorrect, because: (1) the eggs died very rapidly in a pure NaCl-

solution (in which the Na was of the same concentration as in sea water), while they could live indefinitely when a small amount of Ca was added to the NaCl; and (2) the eggs developed normally in distilled water, which proved that neither Na nor Ca was in itself indispensable for their development. These experiments, and others on the eggs of sea urchins and on jellyfish, led Loeb (214) to the following important conclusion:

It seems to me that my experiments necessitate the introduction of a new conception, namely, that of **physiologically balanced salt solutions**. By this I mean salt solutions which contain such ions, and in such proportions, as to completely annihilate the poisonous effects which each constituent would have if it were alone in solution.

As far as I am aware, the term, as well as the concept of "physiologically balanced salt solutions," originated with this statement.

The importance of ionic interactions for the function of the cardiac muscle *in vitro* was also recognized as early as the end of the nineteenth century, when Ringer, Locke, and, later, Tyrode developed the perfusion fluids that now bear their names. For the fundamental principles that govern the pharmacologic interactions between inorganic ions, the reader is referred to an excellent and comparatively recent monograph (77). It is not yet fully possible to appraise the relationships between such *in vitro* effects and those ionic interactions which, *in vivo*, determine the heart's sensitivity to the production of the Electrolyte (NaCl) plus Steroid (DOC)-induced Cardiopathy, characterized by Hyalinosis, a type of change to which we now refer as the **ESCH**. Still, it is highly probable that in all these cases regulatory influences upon membrane permeability, as well as upon intracellular electric and enzymatic phenomena, are of importance.

2. Toxic Cardiac Necrosis and Myocarditis. In 1899, a German physician, Fiedler, described an "acute interstitial myocarditis" characterized by focal or diffuse necrosis of myocardial fibers, subsequently followed by inflammation and scar-formation. Fiedler was apparently unaware that, during the preceding year, Steffen (369) had described the same disease under the name of "acute focal myocarditis." However, both investiga-

tors agreed that this lesion is "isolated," in that it is a separate disease, not merely a manifestation of other systemic maladies, such as diphtheria, typhus, etc., which notoriously tend to produce myocarditis.

Lewitzky (206), in a doctoral thesis submitted to the University of St. Petersburg (Leningrad) in 1904, reported that **digitalis** extracts produced myocardial necroses in laboratory animals. The object of his study was to show that intoxication with cardiac glycosides can produce structural alterations in the heart. Hence, although these myocardial necroses were "isolated" (in that they were unaccompanied by important structural lesions outside the heart) and were associated with secondary inflammatory phenomena, the Russian investigator did not consider their possible relationship to Fiedler's myocarditis or to any other spontaneous cardiac disease.

During this same year—and quite independently of Fiedler's and Lewitzky's observations—several investigators (86, 98, 414) reported that, in rabbits, intravenous injections of **adrenaline** produced generalized arterial calcification with focal myocardial necroses and inflammation.

As soon as highly potent, irradiated ergosterol preparations became available, in 1928, we observed that intoxication with such sterols of the vitamin-D group also produces a generalized arterial calcification with focal calcium deposition and necrosis, in the cardiac muscle tissue (317). However, at that time, we failed even to consider the possibility of any relationship between these changes and the aforementioned findings, which were unknown to us.

In 1934, Büchner and Lucadou (49) found that, in rabbits, forced **muscular exercise** (in a revolving drum) can produce focal necroses and polymorphonuclear infiltration in the hearts, with electrocardiogram (ECG) changes similar to those seen in coronary infarction. Since these lesions were aggravated by a preceding hemorrhage, they have been ascribed specifically to relative tissue anoxia. Possible connections between this type of myocardial lesion and Fiedler's myocarditis, as well as the focal lesions induced in the heart by cardiac glycosides, adrenaline, or vitamin-D derivatives, have not been envisaged.

In 1937, Schrader *et al.* (311) made the highly important observation that in rats kept on potassium-deficient diets multiple foci of necrosis, calcification, and inflammation develop in the myocardium. These lesions could be prevented by the addition of K to the deficient diets; hence they were naturally interpreted as the specific consequences of K-deficiency. It is hardly surprising that Schrader and his colleagues neglected to consider any etiologic relationship between the nutritional lesion that they had discovered and the necrotizing cardiopathies produced by other agents.

In retrospect it is evident, however, that all the cardiac lesions that we have just surveyed (as well as many others that will be considered later) have certain salient common features: (1) morphologically, they are characterized by focal necrosis with invasion of the damaged muscle tissue by inflammatory cells; (2) unlike the true cardiac infarct, this necrosis is not due to acute vascular obstruction but presumably to biochemical changes in the myocardium. None of the earlier authors stressed these similarities. Every investigator approached the problem from an entirely different point of view and was evidently unaware of the relevant literature published by laboratories other than his own. Fiedler's myocarditis, the pharmacology of digitalis, the effects of adrenaline overdosage, the toxicology of vitamin-D derivatives, the cardiovascular effects of muscular work, and the essentiality of K as a nutrient are topics so far removed from each other that no investigator interested in any one of them could be expected to be well informed about the literature in all these fields.

It must be admitted, furthermore, that the principal structural characteristics (necrosis, calcification, inflammation) of these lesions, as well as their extent, position, and speed of development, vary somewhat from case to case. Still, pathology furnishes many examples of lesions that are caused by different agents and yet ultimately develop through a common, final pathway. The adrenal enlargement induced by heat, cold, infections, or trauma is a case in point, since, in the final analysis, it is always due to increased adrenocorticotropic hormone (ACTH) secretion. Conversely, pathology has also taught us

that one and the same agent may cause lesions of essentially different appearance, depending upon the dose or route of administration, the stage at which the reaction of the body is examined, variations in individual disease susceptibility, etc. Phthisis of the lungs, Pott's disease, lupus vulgaris, and miliary tuberculosis are all indubitably caused by the same microorganism, and yet their manifestations are quite dissimilar. It is perhaps not altogether unwarranted to suspect, therefore, that at least some among the isolated, focal, necrotizing cardiopathies may be due to fundamentally related biochemical mechanisms.

3. The Concept of Nonspecific Stress and of the "Conditioning" by Hormones for Nonhormonal Pathogens. According to the concept of the "diseases of adaptation," an excess of corticoids could be expected to produce morbid changes in organs that are particularly affected by systemic stress. Hence, as soon as adequate amounts of pure synthetic corticoids became available we wanted to determine whether structural lesions would be produced in the cardiovascular system by such hormones.

In 1940, we noted that chronic treatment with desoxycorticosterone (DOC) produces marked cardiac and renal hypertrophy, at least in male rats (318). However, there appeared to be no very specific pathologic changes in these enlarged hearts.

Considerable progress was made in this field during 1942. It occurred to Durlacher *et al.* (73) that the loss of K induced by DOC might be the immediate cause of such overdosage effects, for by then it had become known that mineralocorticoids cause hypokalemia and that K-deficient diets also increase renal size. In agreement with their expectations, these authors found that, in rats, the renal hypertrophy caused by **DOC can be inhibited by K-supplements.** The heart was not examined.

During the same year, we found that newly hatched birds are extremely sensitive to mineralocorticoids. For example, in very young chicks, small doses of **DOC** produce marked cardiac hypertrophy, nephrosclerosis, hypertension, and, eventually, fatal cardiac failure (with generalized edema, ascites, peri-

cardial fluid accumulation, cyanosis, and severe dyspnea). We were of the opinion that dietary factors might be responsible for this great sensitivity, because the chicks were kept on a ration comparatively rich in NaCl and also different in many other respects from that consumed by relatively DOC-resistant laboratory animals (320).

These experiments showed: (1) that overdosage with a pure synthetic mineralocorticoid can produce similes of the mesenchymal diseases of man; (2) that the production of such maladies depends at least as much upon "conditioning factors" (diet, species-sensitivity) as upon the absolute amount of hormone in the body.

Still during this same year, Darrow and Miller (66) claimed that, in addition to cardiac hypertrophy, **treatment with DOC alone causes minute myocardial necroses in the rat**. We have not been able to confirm this claim in otherwise untreated normal rats. However, the cardiac lesions that developed in the rats of Darrow and Miller could not be distinguished histologically from those characteristic of K-deficiency. Furthermore, in these DOC-treated animals, the kalemia was subnormal and dietary KCl supplements protected against the production of the cardiopathy. Consequently, these lesions were ascribed to the K-deficit induced by the mineralocorticoid and were thought to be identical with the well-known hypokalemic cardiopathy. Neither in this, nor in a later paper from the same laboratory (65), was there any suggestion of a possible relationship between this cardiopathy and that which occurs in association with nephrosclerosis and generalized mesenchymal disease in the chick. It was claimed, however, that dietary NaCl-supplements do not significantly alter the incidence and severity of the DOC-induced cardiac necroses (66).

In 1943, we verified our hypothesis that dietary NaCl could act as a conditioning agent for DOC in birds. We found that, in newly hatched chicks, large amounts of NaCl alone suffice to cause generalized tissue edema and nephrosclerosis, with concomitant cardiovascular changes. However, when DOC was simultaneously administered, even minute amounts of NaCl became highly effective in producing these same lesions. Equi-

molecular doses of KCl did not exhibit such actions, nor did they inhibit the sensitizing effect of NaCl in DOC-treated birds (359).

Later during this same year we finally succeeded in producing fatal cardiovascular damage with DOC, in mammals. When 1% NaCl was substituted for drinking water, even the otherwise resistant rat responded to DOC with typical hyalinizing myocarditis, periarteritis nodosa, nephrosclerosis, and hypertension (351). This change was an Electrolyte (NaCl) plus Steroid (DOC)-induced Cardiopathy, characterized by Hyalinization, the type of change to which we now refer as the ESCH.*

This hyalinizing cardiopathy resembles certain types of rheumatic carditis, and the extracardiac lesions (periarteritis nodosa, nephrosclerosis, and malignant hypertension), which accompany this change in the DOC-treated rats, also have their counterparts in clinical pathology. Because of these similarities to spontaneous diseases of man, the syndrome of mineralocorticoid overdosage stimulated a great many investigations during the subsequent years (see section entitled Electrolytes). Unfortunately, at the time in question, most investigators failed to distinguish clearly between the ESCH and the necrotizing, hypokalemic types of cardiopathy. As we shall see, the latter are not usually aggravated by NaCl and can be readily prevented by dietary supplements of KCl or MgCl₂.

Many of the apparently quite contradictory observations published during the last 15 years can be traced to this confusion. For example, after we had shown that dietary supplements of NaCl sensitize the rat for the production of the ESCH, Cannon and his colleagues (52, 285) believed they had demonstrated that NaCl also aggravates the myocardial necroses characteristic of severe K-deficiency. However, these investigators substituted MgCl₂ as a "filler" for NaCl in their control rats

* In clinical pathology, the term "hyalin" is often used to designate any kind of material that is homogeneous, "glassy," and tingible with eosin and other acid dyes. Some pathologists carefully differentiate hyalin from "fibrinoid" on the basis of staining reactions, particularly because only the latter is tingible with characteristic fibrin stains. Yet, it is admitted that fibrinoid degeneration can gradually develop into hyalin, so that the line of demarcation between the two is rather indistinct. It should be clearly stated, therefore, that we are using the word hyalin here in its more general sense.

because, at that time, the prophylactic effect of $MgCl_2$ was not yet known. It is very probable, therefore, that in this case, the aggravation of the myocardial necroses was unwittingly produced by substituting $NaCl$ for an effective inhibitor of hypokalemic cardiac necroses, namely, for $MgCl_2$.

In 1957, discovery of the Electrolyte-Steroid-Cardiopathy with Necroses (instead of hyalinization), the ESCN, greatly helped to clarify the fundamental difference between the hyalinizing and the necrotizing types of cardiopathy. It became evident that, under suitable conditions, the same steroids can predispose the rat for the production of either kind of cardiac lesion, but different electrolytes are necessary to elicit one or the other type of change.

Contrary to earlier claims, we found that even heavy overdosage with corticoids does not, in itself, produce cardiac necroses, but this treatment conditions the rat so that the subsequent administration of certain Na-salts (e.g., phosphates, sulfates, perchlorate) elicits massive focal myocardial necroses with subsequent inflammatory infiltration of the affected areas. $NaCl$ does not elicit this change in steroid-conditioned rats, nor does unilateral nephrectomy sensitize them. On the other hand, $MgCl_2$ or KCl is highly effective in protecting the heart against the production of necroses by combined treatment with potent corticoids and sensitizing Na-salts. Furthermore, the ESCN is not accompanied by periarteritis nodosa and nephrosclerosis.

By contrast, the ESCH is characterized by extensive hyalinization of the myocardium, accompanied by periarteritis nodosa and nephrosclerosis. The development of these lesions, under the influence of corticoids, is greatly enhanced by unilateral nephrectomy and $NaCl$. Furthermore, the intensity of the changes produced by corticoids plus $NaCl$ is only slightly affected by the concurrent administration of $MgCl_2$ or KCl (327, 352).*

* The essential difference between the ESCN and the ESCH is further illustrated by certain recent experiments. We found that if equivalent amounts of Na are given in the drinking water to unilaterally nephrectomized rats treated daily with DOC (5 mg of the acetate/day during 50 days), $NaCl$ causes hyalinosis, with periarteritis nodosa of the mesenteric vessels and the heart, as well as nephrosclerosis (in agreement with our earlier observations), while Na_2HPO_4 , Na_2SO_4 , and $NaClO_4$ produce cardiac necroses and a high mortality.

From the clinical point of view, perhaps one of the most interesting aspects of the ESCN is its dependence upon non-specific systemic stress (341a, 343c). It has been shown in a variety of experimental animals that after pretreatment with certain highly active corticoids, exposure to a variety of stressor agents elicits massive focal myocardial necroses, followed by inflammation. These changes are still more readily obtained in animals pretreated with, in themselves ineffective, small doses of corticoids plus sensitizing Na-salts (e.g., sodium phosphates); but curiously, during stress even NaCl enhances the conditioning action of corticoids (342). This precipitating effect of stress may explain why, under suitable experimental conditions, so many essentially different agents have been found to produce cardiac necroses (352).

4. Synthesis and Evaluation of the Results. We have seen that focal myocardial necroses, followed by inflammation, can occur in man, either as an apparently separate disease (Fiedler's myocarditis) or as part of systemic infections (e.g., in diphtheria). A review of the literature has shown, furthermore, that cardiac glycosides, vitamin-D derivatives, adrenaline, K-deficiency, forced muscular exercise, etc., that is, a number of apparently quite unrelated agents can elicit essentially similar lesions in the myocardium of experimental animals. Following pretreatment with in themselves ineffective doses of certain corticoids, similar cardiac lesions are even more easily elicited by noxious agents, presumably as a result of their nonspecific stressor effect.

After conditioning with such corticoids, myocardial lesions are also produced with great regularity by certain Na-salts,

rate but no manifestations of hyalinosis. In rats not subjected to unilateral nephrectomy but otherwise similarly treated, the results were essentially the same, although NaCl produced much less pronounced hyalinosis. Somewhat unexpectedly, Na_2SO_4 caused a greater mortality and more acute cardiac necroses in intact than in partially nephrectomized rats. Conversely, Na_2HPO_4 produced a greater mortality (presumably owing to intense nephrocalcinosis) though not more cardiac necroses, after partial nephrectomy. The apparent protective effect exerted under these conditions by unilateral nephrectomy against Na_2SO_4 remains unexplained. In any event, it is obvious that the sensitization to DOC by Na-salts is both qualitatively and quantitatively influenced by the anion to which the Na is attached (342).

but the character of the resulting lesions depends largely upon the anion. When NaCl is given, following conditioning with corticoids, the resulting change is the **ESCH**, characterized mainly by hyalinization and periarteritis nodosa of the cardiac vessels, while other Na-salts (e.g., the phosphates, sulfates, and perchlorate) induce a necrotizing cardiopathy, the **ESCN**. The latter change, unlike the former, is readily prevented by the prophylactic administration of KCl or MgCl₂.

The fact that, under suitable conditions, so many agents can produce an ESCN suggests that the lesion is largely nonspecific. This view is further supported by the observation that **MgCl₂ and KCl can protect the myocardium against the necrotizing effects of so many agents.** The cardiac necrosis produced by the intravenous injection of a proteolytic enzyme (e.g., papain) is presumably due to the direct effects of the protease upon the myocardial fibers, yet even this change is subject to regulation by steroids and electrolytes. Pretreatment with corticoids or Na-phosphate facilitates, while prophylactic administration of MgCl₂ or KCl prevents, the production of myocardial necroses even by such proteolytic enzymes (343).

The well-known fact that **cardiac glycosides can improve the efficiency of the myocardium after it has been damaged in many different ways**, also implies that a multitude of pathogens impair the heart, by virtue of some nonspecific effect upon a single, digitalis-sensitive mechanism.

With the aid of special stains that we have recently perfected in the Institute of Experimental Medicine and Surgery, it was possible to demonstrate the accumulation of a strongly **fuchsinophilic material** that eventually displaces all other elements within the cardiac muscle fibers and results in necrosis. Usually, only individual fibers or fiber segments are affected by this change, and, in this event, the lesion heals without causing inflammation or leaving a permanent trace. However, when many adjacent fibers are thus affected and the lesion assumes a "critical size," healing is possible only after the damaged tissue debris is removed by inflammatory cells and replaced by a connective-tissue scar. This change is also largely nonspecific; it can be produced by a variety of agents, especially in suitably

conditioned animals. Since the initial stages of fuchsinophilic degeneration cannot be detected by the usual histologic techniques, they would not be noticed on routine autopsy material. It is possible that this fuchsinophilic degeneration may be the morphologic expression of the kind of nonspecific cardiac damage that is highly subject to regulation by steroids or electrolytes, and perhaps also by cardiac glycosides. The so-called "chronic myocarditis," or myocardial fibrosis characteristic of old age, is largely the consequence of arteriosclerosis, yet, at least in part, it may also be related to this nonspecific exhaustion of the myocardium.

All these observations suggested that there may be some common pathway in the mechanism through which various agents can produce, first necrosis, then inflammation, and finally fibrosis, in the heart muscle.

These considerations led us to undertake a series of experiments on the participation of electrolytes and corticoids in the production of myocardial necroses and myocarditis. The extra-cardiac effects of treatment with these agents will be mentioned only incidentally in this volume, but we shall see that corticoids can condition the reactivity of various tissues to the potentially damaging effects of certain electrolyte-shifts. Thus, depending upon the kind of corticoid and electrolyte used, it is possible to produce nephrocalcinosis, nephrosclerosis, periarteritis nodosa, hepatic necroses, and hepatitis by combined treatment with steroids and inorganic salts, while other electrolytes prevent the development of these same changes. Much further work will be necessary before the clinical implications of all these findings will be fully elucidated.

Since the discovery of the ESCN, less than a year ago, more than 30,000 rats were used in this Institute for experiments designed to clarify certain aspects of this subject. It is evident that the complete evaluation of this enormous mass of material poses almost insuperable problems and many of our present hypotheses will undoubtedly have to be abandoned in the light of future research. However, basic and clinical research on the ESCN has already begun in many centers throughout the world and it is felt that a general survey of the relevant litera-

ture and of our many, hitherto unpublished, observations is needed now, even if many of our interpretations must meanwhile be regarded as tentative.

* * *

List of Electrolytes

The following salts were used in all the original experiments described in this monograph.

NAME	FORMULA	MOLECULAR WEIGHT	MANUFACTURER
Ammonium bisulfate	NH ₄ HSO ₄	115.11	Merck
Ammonium chloride	NH ₄ Cl	53.50	Nichols
Ammonium phosphate, dibasic	(NH ₄) ₂ HPO ₄	132.06	Fisher
Ammonium phosphate, monobasic	NH ₄ H ₂ PO ₄	115.04	Merck
Aluminum sulfate (approx. 18H ₂ O)	Al ₂ (SO ₄) ₃	666.41	B.D.H.
Calcium chloride, anhydrous	CaCl ₂	110.99	Fisher
Calcium phosphate, monobasic	CaH ₄ (PO ₄) ₂ ·H ₂ O	252.07	Fisher
Lithium phosphate	Li ₃ PO ₄ ·½H ₂ O	124.81	Anachemia
Lithium sulfate	Li ₂ SO ₄ ·H ₂ O	127.96	Fisher
Manganese chloride	MnCl ₂ ·4H ₂ O	197.91	Fisher
Manganese sulfate	MnSO ₄ ·H ₂ O	169.02	Fisher
Magnesium acetate	Mg(OOC·CH ₃) ₂ ·4H ₂ O	214.47	Fisher
Magnesium biphosphate	MgH ₄ (PO ₄) ₂ ·3H ₂ O	272.36	Fisher
Magnesium chloride	MgCl ₂ ·6H ₂ O	203.33	Merck
Magnesium nitrate	Mg(NO ₃) ₂ ·6H ₂ O	256.43	Fisher
Magnesium perchlorate, anhydrous	Mg(ClO ₄) ₂	223.23	Fisher
Magnesium sulfate	MgSO ₄ ·7H ₂ O	246.49	Fisher
Potassium acetate	KOOC·CH ₃	98.14	Merck
Potassium bisulfate	KHSO ₄	136.17	Fisher
Potassium chloride	KCl	74.55	Fisher
Potassium nitrate	KNO ₃	101.10	General Chem.
Potassium perchlorate	KClO ₄	138.55	Fisher
Potassium phosphate, dibasic	K ₂ HPO ₄ ·8H ₂ O	228.17	Brickman
Potassium phosphate, monobasic	KH ₂ PO ₄	136.09	Fisher
Rubidium chloride	RbCl	120.94	Anachemia
Rubidium perchlorate	RbClO ₄	184.93	Anachemia

NAME	FORMULA	MOLECULAR WEIGHT	MANUFACTURER
Sodium acetate	NaOOC·CH ₃ ·3H ₂ O	136.09	Merck
Sodium bicarbonate	NaHCO ₃	84.00	Merck
Sodium bisulfate	NaHSO ₄ ·H ₂ O	138.08	Fisher
Sodium bisulfite	NaHSO ₃	104.07	Merck
Sodium carbonate	Na ₂ CO ₃	106.00	Anachemia
Sodium chloride, anhydrous	NaCl	58.45	Brickman
Sodium citrate	Na ₃ C ₆ H ₅ O ₇ ·2H ₂ O	294.12	Merck
Sodium hexameta- phosphate	(NaPO ₃) ₆	(611.8 approx.)	Anachemia
Sodium hydroxide	NaOH	40.01	Merck
Sodium hypophosphate	Na ₄ P ₂ O ₆ ·10H ₂ O	430.11	Delta
Sodium hypophosphite	NaH ₂ PO ₂ ·H ₂ O	105.99	Fisher
Sodium lactate	Na-Lactate·2H ₂ O	(112.07)	Fisher
Sodium nitrate	NaNO ₃	85.00	B.D.H.
Sodium perchlorate	NaClO ₄ ·H ₂ O	140.46	Fisher
Sodium permanganate	NaMnO ₄ ·3H ₂ O	195.98	Fisher
Sodium phosphate, di- basic anhydrous	Na ₂ HPO ₄	141.98	Baker
Sodium phosphate, monobasic	NaH ₂ PO ₄ ·H ₂ O	137.99	Fisher
Sodium phosphate, tribasic	Na ₃ PO ₄ ·12H ₂ O	380.20	Merck
Sodium phosphite, dibasic	Na ₂ HPO ₃ ·5H ₂ O	216.06	Delta
Sodium phosphite, monobasic	NaH ₂ PO ₃ ·5H ₂ O	196.00	Delta
Sodium potassium phosphate	NaKHPO ₄	284.19	Delta
Sodium pyrophosphate	Na ₄ P ₂ O ₇ ·10H ₂ O	446.11	Mallinckrodt
Sodium sulfate, anhydrous	Na ₂ SO ₄	142.06	Merck
Sodium sulfite	Na ₂ SO ₃	126.06	General Chem.
Sodium tartrate	Na ₂ C ₄ H ₄ O ₆ ·2H ₂ O	230.09	Fisher
Sodium urate	Na ₂ C ₅ H ₂ N ₄ O ₃ ·H ₂ O	230.11	Anachemia

2

Pathogens and Conditioning Factors of Cardiac Necroses

This section will deal with the various pathogens that produce cardiac necroses, and the conditioning factors that determine the sensitivity of the heart to the necrotizing actions of the former. A conjoint discussion of these two types of agents is almost unavoidable, since a conditioning factor may become the decisive pathogen, under certain conditions, and, conversely, a subthreshold dose of a pathogen may condition the heart for an otherwise ineffective amount of another agent. As the ESCN is the principal topic of this monograph, electrolytes, steroids (e.g., steroid hormones and their derivatives), and sterols (e.g., vitamin-D derivatives and cardiac glycosides) necessarily occupy key positions in this survey.

A. ELECTROLYTES

Sensitizing Electrolytes

The ESCN was first observed in rats conditioned by injections of a highly active synthetic corticoid, 2α -methyl- 9α -chlorocortisol (Me-Cl-COL), and simultaneously given large amounts of NaH_2PO_4 by stomach tube. On the other hand, even fatal doses of the steroid or the phosphate alone failed to produce myocardial necroses (327, 352). As soon as these basic facts were established, it became evident that an electrolyte (NaH_2PO_4) can specifically sensitize or "condition" the cardiac muscle for the toxic effect of a steroid (Me-Cl-COL) or vice versa.

Our next task was to establish which property or part of the NaH_2PO_4 molecule is effective: the acidity, the anion, the cation, or a combination of these.

Role of the pH in the Production of the ESCN

In rats conditioned by Me-Cl-COL, both NaH_2PO_4 and Na_2HPO_4 (as well as neutral mixtures of both these salts) proved to be highly active in eliciting an ESCN. It was assumed, therefore, that this infarctoid cardiopathy is not due merely to changes in *pH* that might be induced either by the acid or by the basic phosphate (355).

Role of the Anion in the Production of the ESCN

Inactivity of NaCl. Our next task was to determine whether PO_4 is the active moiety in the Na-phosphates. When NaH_2PO_4 and NaCl were given in equimolecular amounts to rats conditioned by Me-Cl-COL, only the former salt caused cardiac necroses. The inactivity of NaCl led us to conclude that, for the production of the ESCN, the phosphate ion is the essential part of NaH_2PO_4 (355), but as we shall see, this is not entirely correct, because Na is likewise indispensable.

Activity of Various NaPO-Salts. Subsequently, it has also been possible to produce similar cardiac lesions by combined treatment with Me-Cl-COL and other inorganic phosphorus compounds, such as: NaH_2PO_3 , Na_2HPO_3 , NaH_2PO_2 , $\text{Na}_4\text{P}_2\text{O}_6$, $\text{Na}_4\text{P}_2\text{O}_7$, and $(\text{NaPO}_3)_6$. These salts may be partly metabolized into orthophosphates; still, it is noteworthy that phosphorus can produce myocardial necrosis when it is administered in such diverse forms (329).

Among all these phosphorus salts, only $\text{Na}_4\text{P}_2\text{O}_7$ and $(\text{NaPO}_3)_6$ share with the Na-orthophosphates the property of producing pronounced nephrocalcinosis concurrently with the cardiopathy. This observation gave us the first hint that the ESCN is not merely a consequence of renal calcification (329).

Other Na-Salts. At this point of our investigation, it appeared that the phosphate ion (or one of its close derivatives) is indispensable for the sensitization of the heart to the necrotizing action of Me-Cl-COL. However, since apart from the phos-

phates we had examined only NaCl, it seemed imperative to determine the efficacy of many other anions before reaching a definite conclusion. Consequently, a large variety of organic and inorganic ions were tested, with the aid of a **standardized experimental technique**, always in the form of their Na-salts and in concentrations that permitted direct comparisons between equimolecular amounts.

For this purpose, 440 female Sprague-Dawley rats, with a mean initial body-weight of 100 g (range: 90–110 g), were subdivided into 44 equal groups and treated as follows:

Me-Cl-COL was given in the form of a microcrystal suspension of its acetate, at the daily dose of 100 μg in 0.2 ml of water, subcutaneously.

The individual dose of all **electrolytes** (the amount indicated in Table 1) was administered in 5 ml of water, twice daily, by stomach tube, in all instances.

The duration of all these experiments was 12 days.

The diagnosis of **cardiac necroses**, **nephrocalcinosis**, and **hepatic necroses** was made with the aid of a dissecting loupe at autopsy. The lesions were graded on the basis of this examination, in an arbitrary scale of 0–3, and the means of these findings (with standard errors) are listed in Table 1, together with the percentual mortality rate. In doubtful cases, the diagnosis was checked on histologic sections, but minute lesions detectable only under the microscope were disregarded in the tabulated means, although they will be considered in our evaluation of these data.

In order to avoid unnecessary repetition, let us point out here that, unless otherwise stated, this standard experimental technique was rigorously followed in all the experiments that are tabulated in this monograph. That is, each group, in any of our tables, is composed of at least 10 female Sprague-Dawley rats with a mean body-weight of 100 g (range: 90–110 g); Me-Cl-COL was invariably given at the daily dose of 100 μg and the individual dose of the electrolytes (whether one or several salts were given), indicated in the tables, was administered in 5 ml (occasionally in 2 ml) of water, twice daily, in the manner just outlined, during 12 days.

The electrolytes used for this work were all "Reagent" grade of purity, except for the Na-lactate (which was available as a 50% syrup) and the Na-hexametaphosphate (which, though a highly purified preparation, contained an undetermined amount of lower molecular metaphosphates). On page 15, will be found a list of the electrolyte preparations employed in these experiments.

Table 1 indicates that not only phosphates and their immediate derivatives but many other Na-salts can produce cardiac necroses in Me-Cl-COL-conditioned rats. The incidence and severity of these lesions would have been even greater if the histologic findings had been taken as a basis for the grading, because necrosis of occasional myocardial fibers or even small necrotic foci involving several fibers are often visible under the microscope, even in rats in which no cardiac change was detectable with the dissecting loupe. Such microscopic evidence of miliary necroses was found, for example, in all of the animals treated with NaHSO_3 (Group 27), Na_2CO_3 (Group 36), and Na-urate (Group 42), despite the almost uniformly negative autopsy findings. However, there are always occasional necrotic

TABLE 1
Production of ESCN by Various Na-Salts

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	H_2O (5 ml)	—	0	0	0	0
2	NaCl	1	0	0	0	0
3	"	2	0	0	0	0
4	"	3	0	0	0	20
5	NaClO_4	$\frac{1}{2}$	0	0	0	0
6	"	1	1.9 ± 0.28	0	0.6 ± 0.33	80
7	"	2	1.6 ± 0.25	0	0	100
8	NaH_2PO_4	$\frac{1}{2}$	0.1 ± 0.10	0.3 ± 0.15	0	20
9	"	1	1.0 ± 0.34	1.1 ± 0.32	0	50
10	"	2	1.8 ± 0.32	2.6 ± 0.23	0	100
11	Na_2HPO_4	$\frac{1}{2}$	1.1 ± 0.44	1.8 ± 0.32	0	40
12	"	1	1.6 ± 0.50	1.9 ± 0.30	0.3 ± 0.30	60
13	"	2	1.5 ± 0.32	2.1 ± 0.27	0	100
14	Na_4PO_4	1	1.9 ± 0.28	2.3 ± 0.25	0.1 ± 0.10	90
15	$\text{Na}_4\text{P}_2\text{O}_7$	$\frac{1}{4}$	1.2 ± 0.41	1.4 ± 0.30	0	30
16	Na_2HPO_3	$\frac{1}{2}$	0.6 ± 0.40	0.2 ± 0.20	0.1 ± 0.10	20
17	NaH_2PO_3	1	2.7 ± 0.30	0.1 ± 0.10	1.6 ± 0.32	90
18	NaH_2PO_2	1	0.4 ± 0.30	0	0	0
19	$\text{Na}_4\text{P}_2\text{O}_6$	$\frac{1}{4}$	0	0	0	0
20	(NaPO_3) ₆	$\frac{1}{6}\dagger$	2.0 ± 0.45	2.3 ± 0.20	0.2 ± 0.20	70
21	NaHSO_4	$\frac{1}{2}$	0	0	0	10
22	"	1	1.1 ± 0.40	0	0.5 ± 0.30	50
23	"	2	1.4 ± 0.30	0	0.2 ± 0.20	90

TABLE 1—(Continued)

Production of ESCN by Various Na-Salts—(Continued)

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
24	Na ₂ SO ₄	½	0.6 ± 0.32	0	0.3 ± 0.20	20
25	"	1	2.1 ± 0.35	0	1.3 ± 0.45	80
26	"	2	2.7 ± 0.35	0	1.2 ± 0.30	100
27	NaHSO ₄	1	0	0	0	10
28	Na ₂ SO ₃	1	2.7 ± 0.20	0	1.6 ± 0.32	100
29	NaMnO ₄	1	0	0	0	0
30	NaNO ₃	½	0	0	0	0
31	"	1	0	0	0	0
32	"	2	0	0	0	10
33	NaHCO ₃	½	0	0	0	0
34	"	1	0	0	0	0
35	"	2	0.2 ± 0.20	0	0.1 ± 0.10	40
36	Na ₂ CO ₃	1	0.3 ± 0.30	0.1 ± 0.10	0.3 ± 0.30	10
37	NaOOC-CH ₃	½	0	0	0	0
38	"	1	0	0	0	10
39	"	2	0.3 ± 0.30	0	0	40
40	Na-lactate	1	0	0	0	0
41	Na-citrate	1	0	0	0	0
42	Na-urate	1	0.3 ± 0.30	0	0	10
43	Na-tartrate	1	1.5 ± 0.45	0	1.2 ± 0.32	60
44	NaOH	½	0	0	0	100

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) in all groups, during the 12 days of this experiment.

† ½ mM of the compound was administered instead of the theoretically required ½ mM, because our preparation contained some lower molecular phosphates, in addition to the hexametaphosphate.

fibers in the heart, although these are readily detectable only by the use of special stains. Furthermore, in the Me-Cl-COL-pre-treated rat, various stressors tend to increase this disseminated fiber-necrosis and they may even produce larger miliary necrotic foci, some of which can be seen on fresh specimens, especially with the dissecting loupe. It is for these reasons that the lesions that are only detectable microscopically have not been tabulated. Indeed, for safety's sake, it is best to disregard even occasional, minute, macroscopic lesions, if we want to distinguish the salts that have a definite, specific necrotizing potency.

from those whose action is primarily due to their nonspecific stressor effect. Such a distinction is all the more desirable because individual fiber-necroses, and even the most minute, miliary necrotic foci, tend to disappear without leaving a trace; hence these lesions are not comparable in their nosologic significance to the "infarctoid," large patches of necrosis that give rise to inflammation and, eventually, to a permanent scar. With this in mind, the cardiac necroses of grade 1.0 and more are emphasized by bold face numerals in Table 1, since only these severe lesions are considered to be definitely indicative of noteworthy specific (not stress-induced) sensitization.

The major conclusions that may be drawn from the data in Table 1 are the following:

1. At all dose levels, up to 3 mM, NaCl is singularly ineffective in sensitizing the heart for the production of acute myocardial necroses by Me-Cl-COL (Groups 2-4).
2. NaClO_4 is highly effective in this respect at dose levels of 1 or 2 mM (Groups 6 and 7). In view of what we have just said about NaCl, it is clear that neither Na nor Cl, as such, is the decisive sensitizing factor in NaClO_4 .
3. All the three **Na-orthophosphates** are effective. Their activity is roughly proportional to the Na-content, in that NaH_2PO_4 (Groups 8-10), Na_2HPO_4 (Groups 11-13), and Na_3PO_4 (Group 14) exhibited increasing potency in the order mentioned. Apparently, 1 mEq of PO_4 can activate several mEq of Na.
4. The activity of all other phosphorus compounds listed in Table 1 (Groups 14-20) has been established previously, at higher dose levels (329). The present experiments were performed merely to determine the relative potencies of these salts when they are all administered in quantities containing the same amount (1 mEq) of Na. We note that, under such circumstances, NaH_2PO_3 and $(\text{NaPO}_3)_6$ are decidedly more active than the other compounds of this group.
5. The **Na-sulfates and sulfites** (Groups 21-28) are approximately as active as the corresponding phosphorus compounds. Here again, 1 mEq of the anion (SO_4 or SO_3) can activate more than 1 mEq of Na.

6. **Na-permanganate** (Group 29) and **Na-nitrate** (Groups 30-32) are inactive.

7. All the organic Na-salts (Groups 33-42) were virtually inactive at the dose levels tested, although, quite unexpectedly, some rats treated with Na-tartrate (Group 43) showed pronounced myocardial necroses. In several experiments in which we attempted to confirm this result, the Na-tartrate gave quite inconstant results in that it usually elicited no obvious change but occasionally produced extremely widespread myocardial necroses. It is conceivable that the activity of some among the organic Na-salts depends upon a highly variable, stress-conditioned, metabolic transformation into more potent Na-compounds.

8. It was of special interest to determine the possible activity of the free base **NaOH** in order to see whether Na when not attached to a salt-forming anion would be particularly effective. The alkalinity of such solutions precludes their use at high concentrations and, even at the $\frac{1}{2}$ mM dose level, the mortality was 100% (Group 44). However, several of the rats survived treatment for 5 to 6 days and during this time no myocardial necroses occurred. Although NaOH may have some inherent potency, the free base is evidently not more effective than some of its most potent salts, since the latter (e.g., Na_2HPO_4 or $\text{Na}_4\text{P}_2\text{O}_7$) exhibited definite effects at comparable dose levels, even in individual animals that died after one week of treatment.

9. The **extracardiac effects** of electrolyte-steroid treatment are not our principal concern here; yet, it is worth mentioning that the production by Me-Cl-COL plus sensitizing electrolytes of lesions in the heart, kidney, and liver does not run parallel. Only phosphates and their close derivatives produce significant amounts of nephrocalcinosis, while hepatic necrosis is induced by a larger variety of salts and particularly by the Na-sulfates, Na_2SO_3 , NaH_2PO_3 , NaClO_4 , and Na-tartrate.

10. An additional experiment in which all 44 groups of Table 1 were repeated without Me-Cl-COL conditioning yielded entirely negative results as regards the production of cardiac or extracardiac lesions (except for slight nephrocalcinosis in rats

given high doses of phosphates). Evidently, the steroid conditioning is indispensable for the production of these changes by all the Na-salts tested.

Our principal general conclusion from all these observations is that the morbid changes produced by electrolytes in Me-Cl-COL-conditioned rats do not depend merely upon the number of Na-atoms introduced into the body, but also upon the simultaneous presence of certain "activating" anions.

Role of the Cation in the Production of the ESCN

Salts of Cations Other Than Na. Since so many Na-salts proved to be inactive, the question arose whether the cation plays any role in the production of the ESCN or whether this lesion (as well as the hepatic and renal changes that may accompany it) depends merely upon the combined effect of the corticoid and the "activating" anion. KH_2PO_4 (unlike NaH_2PO_4) does not produce an ESCN in the Me-Cl-COL-sensitized rat (249). However, to determine whether Na is indispensable, additional experiments were performed using **phosphates, sulfates, and perchlorates of various cations other than Na.** The results of these investigations are summarized in Table 2. (For Experimental Materials and Techniques, see p. 19.)

It is evident that, unlike the corresponding Na-salts, none of these 18 compounds elicited the typical picture of the ESCN in rats suitably conditioned with Me-Cl-COL. This is all the more noteworthy because we purposely employed phosphates, sulfates, and perchlorates, that is, salts of anions that are highly effective in activating the ESCN-producing effect of Na. It is true that histologic examination did reveal minor cardiac lesions (increase of isolated fiber-necroses and, occasionally, even minute, miliary necrotic foci in which several adjacent fibers became necrotic) but, as we have already explained, such slight myocardial damage occurs quite frequently in Me-Cl-COL-conditioned rats, during exposure to stress. Since several of the salts employed in this experiment were definitely toxic—as shown by the mortality rates—these minor lesions were probably nonspecific stress effects. In any event, none of the phos-

phates, sulfates, or perchlorates of this series showed any activity even remotely comparable to that of the corresponding Na-salts. This finding indicates that Na is indispensable for the production of a typical ESCN.

TABLE 2
Attempted Production of ESCN by Salts of Cations Other Than Na

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	MgH ₄ (PO ₄) ₂	1	0.1 ± 0.10	0.3 ± 0.20	0	10
2	CaH ₄ (PO ₄) ₂	1	0	0	0	0
3	KH ₂ PO ₄	1	0	0	0	20
4	K ₂ HPO ₄	1	0	0	0	10
5	NH ₄ H ₂ PO ₄	1	0	0.1 ± 0.10	0	0
6	(NH ₄) ₂ HPO ₄	1	0	0.1 ± 0.10	0	40
7	Li ₃ PO ₄	1	0	0	0	100
8	MgSO ₄	1	0	0	0	0
9	KHSO ₄	1	0	0	0	20
10	NH ₄ HSO ₄	1	0	0	0	20
11	Al ₂ (SO ₄) ₃	1	0	0	0	100
12	Li ₂ SO ₄	1	0	0	0	100
13	MnSO ₄	1	0	0.6 ± 0.35	0.6 ± 0.40	100
14	Rb ₂ SO ₄	1	0	0	0	100
15	RbHSO ₄	1	0	0	0	100
16	Mg(ClO ₄) ₂	1	0	0	0	100
17	KClO ₄	1	0	0	0	70
18	RbClO ₄	1	0	0	0	100

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) in all groups, during the 12 days of this experiment.

On the other hand, some of the usual extracardiac accompaniments of the ESCN were elicited by salts of cations other than Na. For example, MnSO₄ produced definite nephrocalcinosis and hepatic necrosis in the Me-Cl-COL-conditioned animals. In control experiments (not tabulated here) on rats that did not receive simultaneous steroid treatment, MnSO₄ failed to produce such lesions. The conditioning by steroids of extracardiac structures for the potentially toxic effects of electrolytes will be the subject of a separate investigation. It should be mentioned here, however, that even the nephrocalcinosis pro-

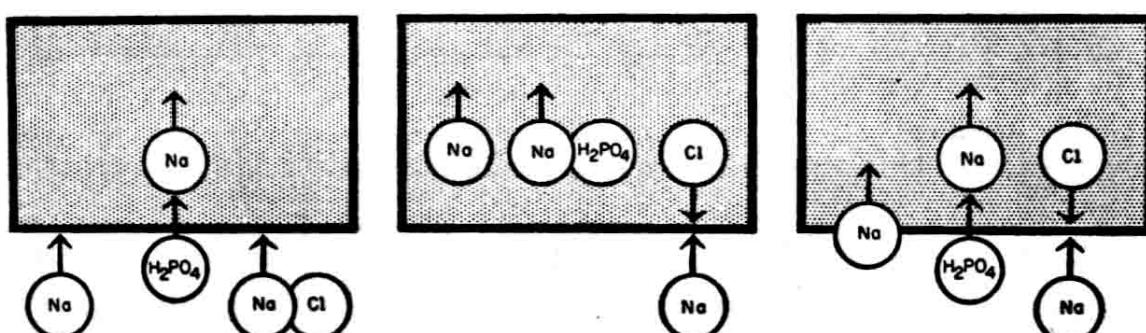
duced by Na-phosphates in corticoid-conditioned rats is largely dependent upon Na, since the other phosphates listed in Table 2 were singularly ineffective in this respect also.

Desensitizing Electrolytes

Role of the Anion in the Prevention of the ESCN

Inhibition of ESCN by Na-Salts. The experiments described in the preceding pages have shown that Na occupies a central position in the production of the ESCN and that certain anions, especially PO_4 , SO_4 , and ClO_4 , sensitize the heart for the cardio-toxic actions of this cation. After these facts were established the question arose whether anions that do not sensitize, for example, Cl, are merely inert or whether they actively inhibit the efficacy of Na. The original discovery that in the Me-Cl-COL-treated rat Na_2HPO_4 did, while NaCl in equimolecular amounts did not, induce cardiac necroses is equally compatible with three alternative hypotheses:

1. That Na is inherently harmless and becomes toxic in Na_2HPO_4 only because of a sensitization exerted by the phos-



Schematic illustration of the three alternative hypotheses. The boxes represent the myocardial fibers. The necrotizing activity of the electrolytes is indicated by their ability to penetrate the cell under various conditions. **First alternative (left):** Na (with or without Cl) is inactive; H_2PO_4 is necessary to activate it. **Second alternative (middle):** Na is inherently active (with or without H_2PO_4) but Cl can prevent its cardio-toxicity. **Third alternative (right):** Na is moderately cardiotoxic; its damaging effect is positively enhanced by H_2PO_4 and counteracted by Cl.

phate ion, while Cl is inert and hence cannot activate Na in NaCl.

2. That Na is inherently cardiotoxic, but its damaging effect is nullified by a positive neutralizing action of the chloride ion, while phosphate is inert.

3. That Na is moderately cardiotoxic, but its effect can be actively influenced by anions, in both directions, i.e., phosphate accentuates, while chloride inhibits, its toxicity. These three possibilities are schematically illustrated in the preceding figure.

Here, the toxicity of Na, expressed by its entrance into the cell (square), is assumed to be modified by H_2PO_4 or Cl. However, the same three possibilities would exist even if the toxicity of Na should not prove to depend merely upon its entrance into cells.

TABLE 3
Attempted Inhibition of ESCN by Various Na-Salts

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	None	—	2.1 ± 0.20	2.1 ± 0.30	0.5 ± 0.25	80
2	NaCl	½	1.2 ± 0.20	0.6 ± 0.30	0	50
3	Na-acetate	½	2.0 ± 0.25	2.4 ± 0.32	0.8 ± 0.32	80
4	NaHCO ₃	½	2.2 ± 0.20	2.4 ± 0.32	0.6 ± 0.30	100
5	Na-urate	½	2.4 ± 0.22	1.6 ± 0.25	0.9 ± 0.40	90
6	NaNO ₃	½	1.8 ± 0.30	1.3 ± 0.32	0	90
7	NaMnO ₄	½	†	†	†	100
8	Na-lactate	½	2.0 ± 0.35	2.0 ± 0.30	1.1 ± 0.35	100
9	Na-citrate	½	1.8 ± 0.28	2.0 ± 0.25	1.5 ± 0.32	80
10	Na ₂ SO ₄	½	2.5 ± 0.20	1.9 ± 0.25	0.9 ± 0.45	90
11	NaClO ₄	½	2.3 ± 0.25	0.5 ± 0.30	0.2 ± 0.20	90

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) and Na₂HPO₄ (1 mM, twice daily) in all groups, during the 12 days of this experiment.

† All animals died during first three days of treatment, before lesions could have developed.

Our first observations suggested that the Cl-ion exerts an active, inhibitory role, since, in rats treated with Me-Cl-COL plus NaH₂PO₄, the incidence of myocardial necroses (and incidentally also of nephrocalcinosis) was definitely diminished by

the concurrent administration of NH_4Cl , CaCl_2 , or even NaCl (348). The desensitizing effect of NaCl is particularly instructive, because, if Na is inherently toxic in itself, the Cl , given as NaCl , must have counteracted the toxicity not only of the Na in NaH_2PO_4 but also of the Na attached to the Cl . This view was further confirmed by experiments in which Me-Cl-COL-treated rats received either NaClO_4 (338) or Na_2SO_4 (336). In these animals, nephrocalcinosis was absent or minimal, but the ESCN was often accompanied by severe hepatic necroses, and here, the NaCl protected not only against the cardiac but also against the hepatic changes.

In order to confirm and extend these observations, systematic studies were performed on rats treated with a series of Na-salts in addition to Me-Cl-COL plus Na_2HPO_4 . These experiments are summarized in Table 3. (For Experimental Materials and Techniques, see p. 19.)

Among all the salts tested, only NaCl exerted a statistically significant protective action. This inhibition by one Na-salt of cardiac necroses produced by other Na-salts offers the most convincing proof of the active role played by anions.

Role of the Cation in the Prevention of the ESCN

By way of an introduction to this problem, let us briefly survey the prevention of cardiac necroses by cations that are normally present in the food. The prophylactic effect of these normal dietary constituents is best demonstrated by the consequences that ensue when animals are deprived of these cations.

Production of Cardiac Necroses by K-Deficiency. It has long been known that rats kept on K-deficient diets eventually develop a syndrome characterized by more or less extensive necroses (followed by cellular infiltration) in the myocardium and skeletal muscles; this is often accompanied by degenerative phenomena and sometimes by calcification in the kidney (51, 104, 134, 244, 311, 366, 386). Essentially similar changes have been observed in pigs (386), mice (207), and dogs (366), kept on K-deficient diets. There is some evidence that K-deficiency may also produce such lesions in man. For example, a patient with K-depletion due to chronic diarrhea died during the in-

travenous infusion of glucose (which notoriously decreases blood potassium). Autopsy revealed focal myocardial necroses, myocarditis, and hydropic degeneration of the renal tubules—a syndrome quite similar to that seen in animals kept on K-deficient diets (274).

Electron-microscopic studies revealed that, prior to the development of necroses, K-deficiency produces swelling and disintegration of cardiac mitochondria in the rat (277b).

It was at first claimed that these dietary myocardial necroses are actually due to a combined deficiency of K and vitamin-B₆ (386), but this contention has not been substantiated. Subsequent workers regularly succeeded in eliciting the cardiac changes with diets deficient only in K, not in vitamins. It had also been claimed that the cardiac and skeletal muscle necroses, normally produced by K-deficiency in the rat, can be prevented by simultaneous vitamin-B₁-deficiency (104). This finding is difficult to interpret, because vitamin-B₁-deficiency, in itself, tends to produce myocardial necroses. It is less unexpected that concurrent treatment with DOC (a mineralocorticoid known to cause hypokalemia) further aggravates the cardiac lesions that normally develop in rats kept on K-deficient diets (65).

In K-depleted animals, Na tends to replace K in the composition of various organs, and particularly of the muscle (85, 152, 244). Hence, it was of interest to determine **whether the cardiac and renal manifestations of K-depletion could be influenced by varying the Na-content of the diet.**

It is difficult to interpret the results of the early experiments on the influence of Na upon the production of myocardial necroses by K-deficient diets, because the role of other anions and cations was invariably disregarded. Not until quite recently has it been recognized that the anion to which Na is attached exerts a decisive influence upon the activity of the latter and that the presence of other cations (particularly of Mg) can greatly influence the consequences of variations in the proportion of K to Na in the diet. Early investigators who were unaware of these facts drew general conclusions concerning "the role of sodium" in the production of hypokalemic cardiac

necroses from experiments in which Na was administered only in the form of one of its salts, without controlling the participation of the anion. Indeed, sometimes, in diets designed to show the effects of simultaneous Na- and K-deprivation, Mg-salts of high anti-ESCN activity were substituted for Na-salts (to keep the total mineral-intake constant). So little thought was given to the possible participation of other ions in the production of dietary myocardial necroses that some workers merely listed the Na- and K-concentration of the diet, without even recording the other constituents of their salt mixtures.

In the first experimental series of this type, rats were given different amounts of Na and/or K, supplied as bicarbonates, "at the expense of the ration." Here, the myocardial necroses became progressively more severe as the Na-content of K-deficient diets was raised (244). As we have seen, in the ESCN, the effects of readily exchangeable, organic anions are very erratic.

In another investigation, "variations in either the potassium- or sodium-intake were made by adding known amounts of either cation to an otherwise basic diet." No mention was made of the form in which these cations were given nor of the incidence of cardiac lesions. Still, these observations led to the general conclusion that myocardial necroses occur in rats kept on diets low in K and normal or high in Na, but not in animals fed rations low in both K and Na. Incidentally, in this study, the depressor effect of K-deprivation was also prevented by simultaneous Na-deficiency (108). To explain these findings, it was assumed that only in the event of Na-deficiency is enough K retained by the tissues to prevent cardiac damage.

Another group of workers claimed that the administration of excess NaCl aggravates the myocardial necroses characteristic of severe K-deficiency. However, these authors, unaware of the prophylactic effect of Mg-salts, substituted MgCl₂ for NaCl in their control rats. Therefore—unless the hypokalemic cardiopathy differs essentially from the ESCN—it is very probable that, in this case, the aggravation of the myocardial necroses was unwittingly produced by the substitution of NaCl (a mild anti-ESCN agent) for MgCl₂ which is a much more effective inhibitor of cardiac necroses (52, 285).

In this connection, it is of interest that in some respects Mg and K can mutually substitute for each other, while Na_2HPO_4 aggravates both K- and Mg-deficiency. We found that when rats are kept on a virtually K-free diet that also contains only mere minimal maintenance levels of Mg, there develop cardiac necroses which can be prevented both by KCl and by MgCl_2 administration. On the other hand, Na_2HPO_4 (unlike equivalent amounts of NaCl) rapidly provokes the development of severe cardiac necroses, nephrocalcinosis, and muscular cramps before this diet, in itself, produces any obvious morbid changes. The particularly severe K- and/or Mg-deficiency syndrome induced by Na_2HPO_4 -supplements, in animals on this diet, can also be prevented by either KCl or MgCl_2 . These observations highlight the importance of PO_4^- and Mg-ions in the development of the syndrome usually ascribed to K-deficiency (343b).

NaClO_4 and Na_2SO_4 also aggravate the K-deficiency syndrome under similar circumstances and, here again, the induction of cardiac necroses, nephrocalcinosis, and muscular cramps by the Na-salts can be prevented by either KCl or MgCl_2 . Hence, here, the effect of sensitizing and desensitizing electrolytes is essentially the same as in the typical ESCN. The fact that Me-Cl-COL produces particularly severe and acute cardiac necroses in rats maintained on a K-deficient diet and that these changes are likewise prevented by MgCl_2 as well as by KCl further emphasizes that steroid-electrolyte equilibria can play a decisive role in the pathogenesis and prophylaxis of changes in various organs, produced in diverse ways (342).

Production of Cardiac Necroses by Mg-Deficiency. In the first studies on the production of Mg-deficiency, it was noted that rats kept on a low-Mg diet exhibit, among other derangements, vasodilatation and changes in the rhythm of the heart (195). Subsequently, cardiac changes (variously described as "myocardial degeneration," calcification, fibrosis, necrosis, or inflammatory infiltration), sometimes with nephrocalcinosis and hepatic necrosis, have been noted repeatedly in rats (19, 41, 60, 130, 217), in rabbits (19), in dogs (373), and in cattle (253), on Mg-deficient diets. In all these respects, the ESCN, which—depending upon the type of electrolyte used—may be accom-

panied by nephrocalcinosis and hepatic necroses, strikingly resembles the manifestations of K- or Mg-deficiency.

In connection with the effect of Mg upon the cardiovascular system, it is especially interesting that in rats (a species notoriously resistant to the production of atheromatosis), subintimal, sudanophilic, lipid depositions can be produced in the aorta and the cardiac valves by feeding a high cholesterol, low-Mg-diet. There appears to be an antagonistic interaction between Mg and cholesterol. On diets containing threshold amounts of Mg, dietary cholesterol supplements precipitate the manifestations of Mg-deficiency (hyperexcitability, hyperemia of the ears, nephrocalcinosis, hypomagnesemia), while excess administration of Mg prevents the production of atheromatosis by cholesterol (150, 150a, 394a, 395). The allegedly beneficial effect of Mg-theobromine-oleate in clinical arteriosclerosis (112a, 185a) requires confirmation.

Inhibition of ESCN by Various Chlorides. It has already been briefly mentioned that NaCl slightly inhibits the morbid changes that are produced in Me-Cl-COL-conditioned rats by simultaneous treatment with other Na-salts (particularly the phosphates, sulfates, and perchlorate). However, in this respect, equivalent amounts of KCl or MgCl₂ are far more effective than NaCl (333, 337, 338, 353). These facts were thought to be incompatible with the first among the three possible hypotheses outlined in the preceding section, namely, that the Cl-ion is inert and that the failure of NaCl to produce myocardial necroses, when given with Me-Cl-COL, is due exclusively to the fact that this anion (unlike PO₄, SO₄, or ClO₄) fails to endow Na with toxic properties in such tests.

The first comparative experiments with other electrolytes clearly showed, furthermore, that the cation is likewise of importance, since certain chlorides proved to be far more effective than others in preventing the ESCN. In particular, KCl and MgCl₂ were most active, NH₄Cl and CaCl₂ exhibited a moderate activity, while NaCl was least effective, in this respect. The nature of this desensitizing action is still obscure, but since even the forced oral administration of water gave some protection against the ESCN, the possibility had to be considered that

both water and the chlorides might act merely by increasing the urinary excretion of toxic electrolytes (348).

Another study was then performed under standard conditions (see p. 19) that permit direct comparisons between equimolecular amounts of various chlorides, regarding their ability to inhibit an ESCN produced by Na_2HPO_4 . The results are summarized in Table 4.

TABLE 4
Inhibition of the Na_2HPO_4 -ESCN by Various Chlorides

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	None	—	3.0 ± 0	2.1 ± 0.32	0.6 ± 0.30	100
2	NaCl	$\frac{1}{2}$	1.3 ± 0.30	0.7 ± 0.25	0	50
3	KCl	$\frac{1}{2}$	0	0.2 ± 0.20	0	0
4	MgCl_2	$\frac{1}{2}$	0	0	0	0
5	CaCl_2	$\frac{1}{2}$	1.0 ± 0.25	0.8 ± 0.30	0	30
6	NH_4Cl	$\frac{1}{2}$	1.5 ± 0.25	1.4 ± 0.25	0	60
7	RbCl	$\frac{1}{2}$	0	0	0	50
8	MnCl_2	$\frac{1}{2}$	0.1 ± 0.10	0.3 ± 0.20	0	10

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 $\mu\text{g}/\text{day}$) and Na_2HPO_4 (1 mM twice daily) in all groups, during the 12 days of this experiment.

It will be noted that the cardiac effect of Na_2HPO_4 was totally nullified by KCl (Group 3), MgCl_2 (Group 4), and RbCl (Group 7). There was only slight nephrocalcinosis in a few of the rats in Group 3 and none in Groups 4 and 7. The comparatively high mortality in the last-mentioned group was not due to the ESCN (or any accompanying renal and hepatic changes) but to the inherent toxicity of rubidium. MnCl_2 (Group 8) is likewise highly active, while the other chlorides exhibited only a moderate anti-ESCN effect.

Because of the comparatively high standard errors, it is not possible to establish the exact quantitative relationships between sensitizing and desensitizing electrolytes on the basis of this experiment. Still, our observations show that:

1. In Me-Cl-COL-conditioned rats, the production of an ESCN (with the accompanying renal and hepatic changes) by

1 mM of Na_2HPO_4 can be inhibited by $\frac{1}{2}$ mM of several chlorides.

2. The various chlorides tested are not equally effective in this respect; those of K, Mg, Rb, and Mn are considerably more active than those of Na, Ca, and NH_4 .

3. The administration of 2 mEq of Na, in a form activated by HPO_4 , can be inactivated by $\frac{1}{2}$ mEq of K, Mg, or Rb, administered in the form of their chlorides. Even the chlorides of the other cations exhibit a definite (though less pronounced) desensitizing action against phosphate-activated Na, when given in this same proportion of 1:4.

Earlier experiments suggested that the desensitizing effect of KCl , MgCl_2 and, to a lesser extent, of NaCl is also manifest in Me-Cl-COL-conditioned rats in which an ESCN is produced by Na_2SO_4 (337) or NaClO_4 (338), instead of Na_2HPO_4 . Hence, the phenomenon of desensitization does not depend upon interference with any specific effect of the phosphate-ion. To permit direct comparisons with the data in Table 4, another experiment was performed in which the anti-ESCN effect of $\frac{1}{2}$ mM of NaCl , KCl , or MgCl_2 was titrated against 1 mM of Na_2SO_4 or NaClO_4 . The observations are summarized in Table 5. (For Experimental Materials and Techniques, see p. 19.)

Comparative evaluation of the data in Tables 4 and 5 shows that:

1. In producing an ESCN, 1 mM of Na_2HPO_4 is approximately equivalent to 1 mM of either Na_2SO_4 or NaClO_4 .

2. Whichever of these three sensitizing electrolytes is used, $\frac{1}{2}$ mM of NaCl reduces the severity of the cardiac necroses by about 50%.

3. The ESCN-producing effect of 1 mM of Na_2SO_4 is totally inhibited by $\frac{1}{2}$ mM of KCl , MgCl_2 , or KHSO_4 , while MgSO_4 offers no protection.

4. The ESCN-producing effect of 1 mM of NaClO_4 is completely, or almost completely, inhibited by $\frac{1}{2}$ mM of KCl , MgCl_2 , or KClO_4 , while $\text{Mg}(\text{ClO}_4)_2$ offers no protection.

As a general conclusion, it may be said that the ESCN produced with any of these three salts is inhibited or abolished by NaCl , KCl , MgCl_2 , KHSO_4 , or KClO_4 , while MgSO_4 and

TABLE 5
Inhibition of Na_2SO_4 - and NaClO_4 -ESCN by Various Mg- and K-Salts

Group	Treatment *	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	Na_2SO_4 (1 mM)	2.5 ± 0.20	0.1 ± 0.1	0.5 ± 0.20	90
2	Na_2SO_4 (1 mM) + NaCl ($\frac{1}{2}$ mM)	1.3 ± 0.32	0	0	50
3	Na_2SO_4 (1 mM) + KCl ($\frac{1}{2}$ mM)	0	0	0	0
4	Na_2SO_4 (1 mM) + MgCl_2 ($\frac{1}{2}$ mM)	0	0	0	0
5	Na_2SO_4 (1 mM) + KHSO_4 ($\frac{1}{2}$ mM)	0	0	0	0
6	Na_2SO_4 (1 mM) + MgSO_4 ($\frac{1}{2}$ mM)	2.5 ± 0.20	0	1.5 ± 0.32	90
7	NaClO_4 (1 mM)	2.4 ± 0.25	0.4 ± 0.20	1.5 ± 0.30	90
8	NaClO_4 (1 mM) + NaCl ($\frac{1}{2}$ mM)	1.4 ± 0.25	0	0.9 ± 0.28	90
9	NaClO_4 (1 mM) + KCl ($\frac{1}{2}$ mM)	0	0	0.1 ± 0.10	50
10	NaClO_4 (1 mM) + MgCl_2 ($\frac{1}{2}$ mM)	0.2 ± 0.20	0	0.2 ± 0.20	10
11	NaClO_4 (1 mM) + KClO_4 ($\frac{1}{2}$ mM)	0	0	0	40
12	NaClO_4 (1 mM) + $\text{Mg}(\text{ClO}_4)_2$ ($\frac{1}{2}$ mM)	1.6 ± 0.30	0	0.1 ± 0.10	100

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with an initial body-weight of 100 g) received Me-Cl-COL (100 $\mu\text{g}/\text{day}$) in all groups, during the 12 days of this experiment.

$Mg(ClO_4)_2$ exhibit no such anti-ESCN effect. It is particularly noteworthy that the sensitizing effect of Na_2SO_4 can be nullified by $KHSO_4$ and that of $NaClO_4$ by $KClO_4$. Apparently, even when K is attached to an anion that can activate Na (SO_4^- or ClO_4^-), the protective potency of the resulting K-salt is not abolished, while Mg, administered as the sulfate or perchlorate, is ineffective. This distinction between K- and Mg-salts will be discussed further in more detail.

The mere fact that some chlorides have a greater anti-ESCN effect than NaCl is still compatible with the assumption that the cation plays no active part in the phenomenon of desensitization. When attached to Na, the Cl might be assumed to lose much of its anti-ESCN potency, owing to the opposite effect of the Na. However, the chlorides of cations other than Na also differ among themselves in the intensity of their anti-ESCN effects. As our earlier experiments have shown (cf. Table 2), cations other than Na never sensitize the Me-Cl-COL-treated rat for the production of an ESCN—even if these cations are attached to the most potent, activating anions (e.g., PO_4^- , SO_4^- , or ClO_4^-). These findings strongly suggest that **both the anion and the cation play active parts in the phenomenon of desensitization.**

Since $MgCl_2$ and KCl proved to be the most potent desensitizing salts—at least among the comparatively nontoxic chlorides—we then continued to examine which Mg- and K-salts other than chlorides could also inhibit the ESCN.

Inhibition of ESCN by Various Mg- and K-Salts Other Than Chlorides. Our first orientating experiments have shown that, in rats treated with Me-Cl-COL plus NaH_2PO_4 , the development of myocardial necroses and nephrocalcinosis can be inhibited, not only by the chloride, but also by the acetate, bisulfate, and sulfate of K (348). It was therefore decided to perform additional experiments under conditions that permit direct comparisons between equimolecular amounts of various K- and Mg-salts, other than the chlorides, as regards their ability to inhibit an ESCN produced by Na_2HPO_4 . The design of these experiments was the same as in the earlier series (cf. p. 19); the results are summarized in Table 6.

TABLE 6

Inhibition of ESCN by Various Mg- and K-Salts

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	None	—	2.4 ± 0.20	2.4 ± 0.25	0.5 ± 0.25	90
2	KCl	½	0	0.1 ± 0.10	0	0
3	MgCl ₂	½	0	0	0	0
4	KOOC·CH ₃	½	0.3 ± 0.20	1.1 ± 0.20	0	10
5	Mg(OOC·CH ₃) ₂	½	2.0 ± 0.20	2.1 ± 0.22	0.6 ± 0.25	80
6	KNO ₃	½	0	0.8 ± 0.20	0	10
7	Mg(NO ₃) ₂	½	0.6 ± 0.25	0.1 ± 0.10	0.4 ± 0.30	70
8	KHSO ₄	½	0.2 ± 0.10	1.3 ± 0.20	0	0
9	MgSO ₄	½	2.8 ± 0.15	1.6 ± 0.28	0.2 ± 0.20	90
10	KH ₂ PO ₄	½	0.2 ± 0.20	2.4 ± 0.20	0	10
11	MgH ₄ (PO ₄) ₂	½	2.5 ± 0.25	2.9 ± 0.10	0	100
12	KClO ₄	½	1.5 ± 0.28	0.9 ± 0.30	0	50
13	Mg(ClO ₄) ₂	½	2.8 ± 0.10	1.4 ± 0.28	1.2 ± 0.25	100

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) and Na₂HPO₄ (1 mM twice daily) in all groups, during the 12 days of this experiment.

These findings show that:

1. The ESCN (as well as the accompanying nephrocalcinosi s) can be inhibited, not only by KCl, but by a variety of other K-salts, although the chloride and nitrate appear to be the most effective.

2. MgCl₂ is about as potent as KCl, since ½ mM of either chloride inhibits the effect of 1 mM of Na₂HPO₄ in this experimental arrangement. However, all the other Mg-salts are definitely less potent than the corresponding K-salts. Presumably, K, Mg, Cl, and perhaps also NO₃ all possess inherent anti-ESCN effects, but among the cations, K is distinctly more potent than Mg. As a result of this, all K-salts are more effective than the corresponding Mg-salts, with the exception of MgCl₂. The exceptional activity of the latter is presumably due to the fact that ½ mM of MgCl₂ contains twice as much Cl as does the same amount of KCl; this greater amount of desensitizing anion may compensate for the comparatively low efficacy of the Mg.

3. When Mg is attached to anions capable of activating the ESCN-producing effect of Na-salts, its anti-ESCN effect is considerably diminished. This is shown by the high incidence of cardiac necroses in the groups which, in addition to Na_2HPO_4 , were treated with MgSO_4 (Group 9), $\text{MgH}_4(\text{PO}_4)_2$ (Group 11), or $\text{Mg}(\text{ClO}_4)_2$ (Group 13). In this connection, let us also recall the low protective effect of MgSO_4 against Na_2SO_4 (Table 5, Group 6), and of $\text{Mg}(\text{ClO}_4)_2$ against NaClO_4 (see Table 5, Group 12).

4. The nephrocalcinotic effect of Na_2HPO_4 was again more or less markedly inhibited by all the K-salts (particularly by KCl) except KH_2PO_4 . Presumably, in the latter salt, the beneficial effect of K was largely counteracted by the nephrocalcinotic action of PO_4 . MgCl_2 was also highly effective in preventing nephrocalcinosis, but the other Mg-salts (again with the notable exception of the nitrate) were virtually ineffective in this respect. In general, it is somewhat more difficult to inhibit the nephrocalcinosis than the ESCN under these conditions.

5. Since Na_2HPO_4 is not particularly hepatotoxic, the protective effect of these various electrolytes against hepatic necroses is not clearly demonstrable in this experimental series; yet it is perhaps significant that, apart from the controls (Group 1), only rats treated with Mg-salts showed necrosis of the liver.

Our next problem was to investigate whether Na and K can antagonize each other, even when both cations are part of the same molecule.

Intramolecular Antagonisms Between Na and K. We saw that NaH_2PO_4 sensitizes the heart for the production of an ESCN by Me-Cl-COL, while various K-salts exert an opposite effect. The question then arose whether K incorporated into the NaH_2PO_4 molecule would abolish the sensitizing effect of the latter to the same degree as does KH_2PO_4 . For this purpose, an experiment was carried out, in Me-Cl-COL-conditioned rats, in which the effect of KH_2PO_4 plus NaH_2PO_4 was compared with that of NaKHPO_4 . The design of this experiment was again the same as that of the other studies of this series (cf. p. 19), and the results are summarized in Table 7.

TABLE 7
Intramolecular Antagonism Between Na and K

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	NaH ₂ PO ₄	1	1.1 ± 0.38	1.9 ± 0.28	0.1 ± 0.10	50
2	NaH ₂ PO ₄ + KH ₂ PO ₄	1 each	0	2.4 ± 0.17	0	0
3	NaKHPO ₄	1	0	2.0 ± 0.20	0	0

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) in all groups, during the 12 days of this experiment.

It is evident that the substitution of K for one hydrogen atom in the NaH₂PO₄ molecule completely deprived the salt of its ability to sensitize the tissues to the toxic actions of Me-Cl-COL.

Quantitative Relationships

In the preceding pages, we repeatedly called attention to the existence of strictly quantitative relationships between sensitizing and desensitizing salts in the production of tissue-lesions by Me-Cl-COL. In order to obtain additional information on this subject, an extensive study was then performed, again under the usual standard experimental conditions (see p. 19). The results are summarized in Tables 8 and 9.

The data in Table 8 deal with quantitative relationships in the synergism between various sensitizing electrolytes.

This experiment shows that:

1. The ESCN-producing effect of 1 mM of NaH₂PO₄ (Group 1), NaHSO₄ (Group 2), or NaClO₄ (Group 3) can be duplicated by giving ½ mM of each of any two among these salts (Groups 4–6), or ⅓ mM of each of the three compounds (Group 7).

2. On the other hand, under these conditions, the renal effect of 1 mM of NaH₂PO₄ cannot be duplicated by the electrolyte mixtures, since only the phosphate exhibits marked nephro-calcinotic actions.

TABLE 8
Quantitative Relationships in the Synergism Between Various Sensitizing Electrolytes

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	NaH ₂ PO ₄	1	2.3 ± 0.20	2.4 ± 0.35	0.5 ± 0.45	60
2	NaHSO ₄	1	2.3 ± 0.20	0	0.4 ± 0.40	100
3	NaClO ₄	1	2.6 ± 0.15	0	1.0 ± 0.35	100
4	NaH ₂ PO ₄ + NaHSO ₄	½ each	2.7 ± 0.15	1.1 ± 0.30	1.2 ± 0.30	100
5	NaH ₂ PO ₄ + NaClO ₄	½ each	3.0 ± 0	1.5 ± 0.25	1.2 ± 0.35	100
6	NaHSO ₄ + NaClO ₄	½ each	2.7 ± 0.20	0	0.9 ± 0.30	90
7	NaH ₂ PO ₄ + NaHSO ₄ + NaClO ₄	⅓ each	2.0 ± 0.30	0.4 ± 0.20	1.1 ± 0.25	100

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) in all groups, during the 12 days of this experiment.

The hepatic necrosis was too variable, under the above conditions, to permit any definite conclusions concerning the hepatotoxic actions of the electrolyte combinations.

The data in Table 9 deal with quantitative relationships in the synergism between various desensitizing electrolytes.

TABLE 9
Quantitative Relationships in the Synergism Between Various Desensitizing Electrolytes

Group	Treatment *	mM	Cardiac Necrosis	Nephro-calcinosis	Hepatic Necrosis	Mortality (%)
1	None	—	1.5 ± 0.20	1.3 ± 0.30	0.9 ± 0.35	70
2	KCl	1/8	1.1 ± 0.25	1.2 ± 0.32	1.5 ± 0.32	30
3	KCl	1/4	0.6 ± 0.20	0.8 ± 0.25	0	20
4	KCl	1/2	0	0.1 ± 0.10	0	0
5	MgCl ₂	1/8	1.8 ± 0.25	1.1 ± 0.25	0.5 ± 0.30	70
6	MgCl ₂	1/4	0.7 ± 0.20	0.4 ± 0.30	0	30
7	MgCl ₂	1/2	0	0.1 ± 0.10	0	0
8	KCl + MgCl ₂	1/16 each	1.5 ± 0.22	1.8 ± 0.22	0	40
9	KCl + MgCl ₂	1/8 each	0.9 ± 0.25	0.5 ± 0.30	0	30
10	KCl + MgCl ₂	1/4 each	0	0.1 ± 0.10	0	0

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (100 µg/day) and Na₂HPO₄ (1 mM twice daily) in all groups, during the 12 days of this experiment.

Here, both KCl and MgCl₂ were assayed at dose levels ranging from 1/8 mM to 1/2 mM. The experiment shows that:

1. Equimolecular amounts of KCl and MgCl₂ are almost exactly equivalent in their anti-ESCN potency.
2. 1/4 mM is the smallest amount of either KCl or MgCl₂ that can noticeably inhibit the ESCN-producing action of 1 mM of Na₂HPO₄.
3. When KCl and MgCl₂ are given in combination, their anti-ESCN effects are summated.
4. Larger doses of KCl or MgCl₂ (singly or in combination) are needed for the inhibition of nephrocalcinosis than for the prevention of the ESCN.

No definite conclusions can be drawn as regards hepatic necrosis, because of the comparatively low hepatotoxic effect of Na_2HPO_4 .

Site of Interaction Between Sensitizing and Desensitizing Electrolytes

In all our studies on the influence of electrolytes upon the development of the ESCN, the salts were administered orally, by stomach tube; hence it seemed of fundamental importance to establish whether the antagonism between sensitizing and desensitizing salts could be due merely to interactions between them, within the alimentary tract itself. Some of the sensitizing salts are readily precipitated by their antagonists; therefore, their pharmacologic inactivation could have been ascribed to the formation of insoluble compounds that are simply not absorbed. Indeed, the production of insoluble (or at least inabsorbable) compounds within the intestinal tract cannot be excluded *a priori*, even in the case of salt mixtures that do not form precipitates *in vitro*.

We therefore proceeded to examine whether oral administration of MgCl_2 or KCl can prevent the development of an ESCN, in rats sensitized by parenterally administered NaH_2PO_4 . Of course, the large amounts of NaH_2PO_4 that are required for the production of cardiac necroses and nephrocalcinosis cannot be injected subcutaneously, intravenously, or intraperitoneally. However, it was noted in rats that if a large subcutaneous air bubble is prepared and increasing concentrations of irritants are injected into its lumen, the wall of the resulting "granuloma-pouch" becomes unusually resistant to the necrotizing effects of very hypertonic solutions. Hence, we injected the requisite amount of Na-phosphate (a neutral mixture of NaH_2PO_4 and Na_2HPO_4) into subcutaneous granuloma-pouches of Me-Cl-COL-treated rats that simultaneously received either MgCl_2 or KCl , by mouth. Under these conditions, both MgCl_2 and KCl still exerted their customary prophylactic effect (333).

These experiments furnish definite proof that the desensitizing salts do not act by merely inhibiting the absorption of phos-

phate through some immediate local interaction with the latter in the gastrointestinal tract itself. Similar experiments have not yet been performed with other combinations of sensitizing and desensitizing salts, but at least the principle of a postabsorptive systemic interaction between them has been definitely established.

Histologic Characteristics of the ESCN

The most characteristic histologic feature of the ESCN is the development of massive patches of myocardial necrosis. Any part of the heart may be affected, but the right ventricle, the auricles, and the subendocardial layers of both ventricles are sites of predilection. In the left ventricle, the papillary muscles and the region near the apex of the heart are most commonly involved. The necrosis appears to be the result of a primary change in the myocardial fibers themselves, since these show the earliest lesions. It is in this respect that the "infarctoid cardiopathy" produced by corticoids and electrolytes differs most markedly from the classical cardiac infarct that results from acute obstruction in the coronary vessels.

The earliest detectable change is the appearance of a strongly fuchsinophilic material in the sarcoplasm between the myofibrils.* This change usually begins in the immediate vicin-

* For the demonstration of the fuchsinophilic material, we (261a) developed the following technique: (1) Fix, for 48 hours, in 10% formaldehyde solution neutralized by calcium carbonate; (2) Dehydrate in dioxane; (3) Embed in paraffin; (4) Deparaffinize in xylol; (5) Two changes of alcohol 95%; (6) A few seconds in alcohol 70% and in alcohol 50%; (7) Wash in running water, 5 minutes; (8) Rinse in distilled water; (9) Stain 15 minutes in **solution A** [10 ml of cresyl truly violet solution (stock solution = 1 g in 500 ml distilled water, filter after 1 hour); 40 ml distilled water + 0.2 ml oxalic acid 1%]. Solution prepared on day of use; (10) Rinse in running water, 10 minutes; (11) Mordant 15 minutes in **solution B** [phosphotungstic acid 1%]; (12) Rinse in running water, not more than 5 minutes; (13) Stain 20 minutes (rat heart) or 30 minutes (monkey heart) in **solution C**, moving slides frequently [20 ml of acid fuchsin 0.01%; 15 ml of orange G 0.01%; 15 ml of methyl green 0.01% + 0.2 ml of oxalic acid 1%]. In this laboratory, 1% stock solutions in distilled water are maintained, and diluted where required on the day of use. All dyes used in **solutions A** and **C** are obtained from Chroma-Gesellschaft, Schmid and Co., Stuttgart-Unterürkheim; (14) Rinse in glacial acetic acid 0.5%; (15) Dehydrate in alcohol 70% and 2 changes absolute alcohol; (16) Clear in xylol and mount in balsam (or any synthetic medium).

ity of nuclei and then tends to spread, so that ever larger portions of a muscle fiber are transformed into a more or less hyaline, strongly fuchsinophilic mass. At this stage, the rest of the muscle fiber, including its nucleus, may still retain a histologically normal appearance. As the lesion progresses further, the nucleus becomes indistinct and eventually disappears, while an entire segment of the muscle fiber, still sharply delimited by sarcolemma and intercalated discs, is completely transformed into a hyaline, fuchsinophilic tube.

As we have said previously, if only isolated muscle fibers or fiber segments are affected, the lesion heals without leaving a scar. Apparently, such small particles of necrotic tissue can be absorbed without causing any discontinuity in the tissue, because the adjacent muscle fibers merely join together and fill the gap. The fuchsinophilic material appears to be characteristic only of the initial stages of cardiac damage; it disappears completely from muscle fibers that have totally disintegrated and are in the process of being absorbed.

Interestingly, the skeletal musculature of the rat is normally tingible with our fuchsin stain; in this respect, it differs from the normal heart musculature. However, in normal skeletal muscle, the fuchsinophilia is never as intense and homogeneous as it is in cardiac muscle fibers affected by electrolyte-steroid treatment (342). Incidentally, this normal fuchsinophilia of skeletal muscle is not markedly influenced by the oral administration of KCl or MgCl₂, nor does muscular exercise exert a noticeable influence upon it (344).

Among other degenerative changes that tend to occur in the early stages of the ESCN, extensive calcium deposition in the affected myocardial fibers is the most common. Granules of calcium salts (tingible with von Kóssa's method) are often detectable, even in muscle fibers that still retain their cross striation and whose nucleus does not exhibit any manifest abnormality. It would appear, therefore, that calcium deposition is not necessarily the consequence of necrosis, although it occurs most commonly in necrobiotic or frankly necrotic fibers. Extensive calcification of the affected region is most common in animals in which the ESCN is produced with Na-phosphates,

yet it also occurs quite frequently when other sensitizing Na-salts are used.

Noteworthy accumulations of **sudanophilic lipids** have not been seen, either in the necrotic areas or in other parts of the myocardium and its vessels, during the development of ESCN.

The necrosis must reach a certain "critical size" before it will heal by scar-formation, like an infarct. When this size is reached, the focus is rapidly invaded by **inflammatory cells** (mainly, histiocytes and polymorphonuclear leukocytes, with an occasional eosinophil or plasma cell) and the necrotic fibers are absorbed. After this the inflammatory granuloma is gradually replaced by mature, fibrous connective tissue and becomes a **permanent scar**. Sometimes, a comparatively thin scar in the wall of the right ventricle gives rise to formation of an aneurysm, while extensive subendocardial scarring may endow the lesion with morphologic characteristics typical of endomyocardial fibrosis, as illustrated in Figs. 17, 18 (341b).

It is especially characteristic of the ESCN that **neither the coronary vessels nor the valves are primarily affected**, although they may become secondarily involved, if extensive regions of the surrounding muscle tissue undergo necrosis.

Functional Corollaries of the ESCN

Electrocardiographic Changes

The ECG was registered—using the three standard leads—in rats treated with Me-Cl-COL and NaH_2PO_4 , under the usual conditions of experimentation for the induction of the ESCN. The most conspicuous changes observed were: a decrease of the heart rate with prolongation of the PR and QT (QU) intervals and a lowering of the T waves. All these ECG-anomalies became evident as early as two days after initiation of the treatment, that is, long before the appearance of the massive cardiac necroses. However, after seven days, when large patches of ESCN appeared, the ECG began to reveal arrhythmias and conduction defects. Me-Cl-COL or NaH_2PO_4 , when given separately, did not alter the normal ECG picture (417).

While the administration of KCl or MgCl₂ completely protected the myocardium against the morphologic lesions, it only partially prevented the development of the ECG-disturbances (417a).

Blood Pressure Variations

DOC-Hypertension. Many investigators have studied the influence of various electrolytes upon the pressor actions of corticoids. That **DOC-hypertension**, as well as the associated ESCH (with periarteritis and nephrosclerosis), is aggravated by Na-salts is, by now, a well-established fact which need not be discussed here (323). Let us merely mention a few, less well-known interactions between corticoids and the pressor effects of electrolytes.

An adequate K-intake is essential for the development and persistence of DOC-induced hypertension in the rat, but an excess of K does not potentiate the pressor effect of this corticoid (292).

DOC is also unable to normalize the reduced blood pressure of rats kept on a K-deficient diet. Nevertheless, in such animals, both **cortisone and ACTH** can usually elevate the blood pressure towards normal, without altering the blood level of K (109).

The curative effect of cortisone upon the hypotension of K-deficiency is, apparently, not due to an augmentation of the vascular responsiveness to pressor substances. Rats kept on K-deficient diets still respond to adrenaline and angiotonin (294).

The "metacorticoid hypertension" that occurs after temporary overdosage with DOC is not influenced even by drastic restrictions in Na- or K-intake (129).

In rats in which **renal hypertension** is produced (either by a figure-of-8 ligature around the kidney or by DOC), the blood pressure can be lowered by withdrawal of K from the diet. In this case, cortisone still induces a prompt pressor effect, although the hypokalemia persists (295). Indeed, under certain experimental conditions, the pressor action of cortisone is actually increased by K-depletion (293).

All these data show that the pressor effects of corticoids are largely dependent upon the conditioning effects of both Na and K. In view of what we have learned about the ESCN, it would be most desirable to determine the relative vasopressor potencies of various Na-salts (e.g., the chloride, sulfate, phosphate, and perchlorate) in corticoid-conditioned animals. Similar studies with Mg-salts would likewise be instructive.

Blood Pressure Variations in the ESCN. In rats treated with NaH_2PO_4 plus Me-Cl-COL, there was a slight initial hypertension not significantly greater than that induced by Me-Cl-COL alone. NaH_2PO_4 alone did not alter the blood pressure in these experiments. However, in the animals that received the combined electrolyte-steroid treatment, the blood pressure fell below normal, several days before death from myocardial necroses (16). Here, the ante-mortem hypotension was presumably due to heart failure induced by the myocardial necroses. There is no evidence that the ESCN is preceded by any pronounced hypertensive episodes.

In Vitro Studies

In the course of his classical studies on the biochemistry of muscle contraction, Szent-Györgyi (376) noted that DOC-like digitalis compounds—abolishes the so-called “staircase phenomenon of Bowditch” (a sign of muscular weakness that tends to develop in hearts kept *in vitro*).

It has been claimed, furthermore, that, under certain conditions, **cortisone** and **progesterone** exert a negative inotropic action on the heart (30, 298). In connection with electrolyte-steroid interrelations, certain observations on the isolated, perfused rabbit heart are especially interesting. In this preparation, cortisone produces arrhythmias and a diminution of the coronary flow; addition of K to the perfused organ increases its cortisone resistance, while withdrawal of K exerts an opposite effect (3, 30). Presumably, the antagonism between certain corticoids and K takes place in the cardiac muscle itself and does not depend upon the maintenance of vascular or nervous connections between the heart and the rest of the body. However this supposition is based only upon the observation of cer-

tain functional changes; we have no evidence that the same is true of the ESCN.

Extensive studies have been performed on the effects of halocorticoids upon the behavior of cardiac muscle *in vitro*. **9-F-COL** (9 α -fluorocortisol) exerts a positive inotropic action and, at the same time, increases the uptake of radioactive Na by the isolated cat papillary muscle (378). Curiously, 9-F-COL produces the same kind of inotropic response in the isolated toad heart as does lanatoside-C, strophanthin-G, digoxin, or an excess of calcium ions. The response includes a marked and sustained increase in work-output, efficiency, and oxidative metabolism, but there is no apparent change in the rate of metabolic energy liberation. This suggests that all these agents bring about their inotropic response through an effect upon energy utilization rather than energy production (258). It is interesting that a corticoid can so precisely mimic the response produced by cardiac glycosides and aglycones, as well as by ionic changes. In cardiac muscle, 9-F-COL increases Na-uptake, and the cardiac glycosides increase K-loss; in either case, the resulting, changed Na:K ratio may be intimately associated with the inotropic response. Perhaps this change is concerned with the orientation of K-ions about the actin-myosin complex, as outlined by Szent-Györgyi (376). But these alterations in ionic distribution may also be aftereffects of changes in the actomyosin threads and the polymerization of actin (258).

In vitro observations on the effects of steroids upon functional and chemical changes induced in the myocardium by the electrolytes that affect the ESCN would now be most informative. These observations are likely to give us important information about the fundamental mechanism of this kind of conditioning and about the possible relationships between the actions of the steroid hormones and the cardiac aglycones.

Chemical Corollaries of the ESCN

Electrolytes. In rats treated with DOC alone, there is an increase in the Na- and a decrease in the K-concentration of both cardiac and skeletal muscle (66). If DOC-treated rats are

kept on a K-deficient diet, these changes tend to be even more severe (65).

In relation to the ESCN, the distribution of Na, K, and inorganic PO₄ was studied in the serum, abdominal muscles, and heart of the rat. A significant increase in the Na-concentration of the heart was noted, following treatment with either NaH₂PO₄ or Me-Cl-COL; this rise was even more marked after combined treatment with both these agents. The K-concentration was sometimes decreased in the heart and always in the skeletal muscles of rats treated with NaH₂PO₄ and/or Me-Cl-COL. On the other hand, there was no significant change in the inorganic PO₄-content of the heart during any of these treatments (74). More recent work of the same investigators showed that, under similar circumstances, the Mg-content is greatly decreased in the heart, while the Ca-content is markedly increased in the heart and decreased in the serum.

It would be premature to speculate upon the biochemical mechanism through which electrolyte-steroid treatment can produce myocardial necroses. In view of the experiments just mentioned, it is possible, however, that the combined treatment with Me-Cl-COL plus certain Na-salts facilitates the entry of Na into the heart and thereby produces cell damage. In this connection, it is noteworthy that creatine apparently occurs in the heart as the dipotassium salt of phosphocreatine (227). A number of independent investigations showed, furthermore, that the maintenance of a normal balance between K, Mg, Na, and PO₄, within the cardiac muscle, is of paramount physiologic import (85, 376). Furthermore, in man, the K-content of the myocardium is decreased in spontaneously infarcted areas (114a), and similar observations have been made after ligation of coronary branches in dogs (175).

Cholesterol and Lipoproteins. The pathologic cholesterol-lipoprotein blood levels that are often seen in patients with myocardial infarction, can be restored toward normal by folliculoid hormones. Testoids exert an inverse effect and may even produce abnormal lipoprotein patterns, in patients who have previously been found to be free of such anomalies (18). The behavior of the blood lipids during the ESCN has not yet

been examined, but oral administration of fats increases the sensitivity of the heart for the production of an ESCN (see p. 109).

Extracardiac Lesions That May Be Associated with the ESCN

Renal Lesions. As stated earlier in this monograph, the **ESCH** (e.g., after DOC treatment of rats sensitized by unilateral nephrectomy and an excess of NaCl) is accompanied by renal lesions that, in the initial stages, resemble nephrosis and later assume the character of a malignant, hyalinizing nephrosclerosis (323).

On the other hand, the renal changes associated with the **ESCN** vary according to the type of electrolyte used for sensitization. After treatment with various phosphates, nephrocalcinosis occurs, presumably because, in animals conditioned with corticoids, the phosphate ion tends to precipitate out with calcium during the process of its renal elimination. Occasionally, nephrocalcinosis may also occur in animals treated with NaClO_4 (338), perhaps owing to the precipitation of insoluble calcium perchlorate. However, there is no direct parallelism between the degree of nephrocalcinosis and the severity of the cardiac necroses; several steroids that can condition for the production of nephrocalcinosis (e.g., folliculoids, testoids, DOC) are totally inert or, at most, only very slightly effective in producing an ESCN. Still, it is remarkable that the salts that protect against the ESCN (e.g., MgCl_2 , KCl) also prevent the formation of the accompanying nephrocalcinosis.

Hepatic Lesions. It is evident from Table 1 that although hepatic necroses may occur in association with the ESCN, they are not an obligatory accompaniment of the cardiac necroses. For example, NaH_2PO_4 is highly effective in producing myocardial necroses when given to Me-Cl-COL-treated rats, but hardly ever causes any liver damage. On the other hand, Na_2HPO_4 and Na_3PO_4 (see Table 1), as well as the sulfates (337) and perchlorate (338) of Na, exhibit a much greater tendency to induce toxic necroses in the liver.

Other Lesions. It is not within the scope of this book to present a detailed discussion of the extracardiac corollaries of the ESCN; besides, up to now we have not studied these as carefully as the cardiac lesions themselves. However, further investigations along these lines promise to be rewarding, because it seems that steroids can condition various organs rather selectively to the production of pathologic changes by Na-salts. This is not only true of the kidney and liver; under certain circumstances in the steroid-conditioned rats, Na-salts may produce muscular cramps (338), brain edema, hemorrhagic edema of the lungs, and diverse other changes (342).

Summary

The following are the principal results of all our experiments concerning the sensitizing and desensitizing effects of electrolytes, in the Me-Cl-COL-conditioned rat:

1. Only Na-salts are active in producing an ESCN.
2. Not all Na-salts permit the production of an ESCN. Sulfates, phosphates, and perchlorate are particularly active, while the chloride and several other organic and inorganic salts are ineffective.
3. The production of an ESCN by sensitizing Na-salts can be prevented by a variety of chlorides. NaCl is only weakly (though definitely) effective in this respect, while KCl and MgCl₂ are the most effective among the relatively nontoxic chlorides that we have tested.
4. When given in various forms, the anti-ESCN action of K is greater than that of Mg, but KCl and MgCl₂ are about equally active, presumably because the latter salt contains twice as much Cl as does the former.
5. A number of K-salts other than the chlorides likewise exhibit considerable anti-ESCN activity, while the corresponding Mg-salts are less active or actually inert.
6. The facts just mentioned appear to substantiate the view that both the cation and the anion play important roles in the production, as well as in the prevention, of the ESCN. Though Na is indispensable, its activity can be greatly enhanced by certain anions (e.g., phosphates, sulfates, perchlorate) and

diminished by others (e.g., chloride). Conversely, several cations (particularly, K and Mg) exhibit anti-ESCN effects that can be enhanced by certain anions (particularly, chloride).

7. The ESCN-producing effect of various sensitizing electrolytes can be summated when subthreshold amounts of two or more of these salts are given simultaneously.

8. The anti-ESCN effect of various electrolytes can be summated when subthreshold amounts of two or more of these salts are given simultaneously.

9. The actions of pro- and anti-ESCN cations can neutralize each other when both types of cations are attached to the same activating anion (e.g., phosphate). Hence, NaKHPO₄, unlike NaH₂PO₄, possesses no pro-ESCN effect. This demonstrates the existence of an intramolecular antagonism between Na and K.

10. There exist strictly quantitative relationships between sensitizing and desensitizing electrolytes in that $\frac{1}{4}$ to $\frac{1}{2}$ mM of KCl or MgCl₂ is the threshold amount necessary to produce a just significant inhibition of an ESCN induced by 1 mM of Na₂HPO₄.

11. One activating anion can activate several ions of Na, since the ESCN-producing activity of NaH₂PO₄, Na₂HPO₄, and Na₃PO₄ increases in the order in which the salts are here listed.

12. Extracardiac lesions may accompany the ESCN. For example, if cardiac necroses are produced in Me-Cl-COL-conditioned rats, with one of the Na-phosphates, there results a marked nephrocalcinosis, while Na-sulfates and perchlorate produce little, if any, renal damage but tend to induce hepatic necrosis. These extracardiac actions, like the ESCN, can, in turn, be inhibited by the simultaneous administration of certain desensitizing electrolytes, particularly KCl and MgCl₂.

13. The possibility had to be considered that sensitizing and desensitizing electrolytes might inactivate each other, owing to chemical reactions that take place immediately after these salts are introduced into the gastrointestinal tract. It has been found, however, that the oral administration of desensitizing salts counteracts the effect of sensitizing electrolytes, even if the latter are injected parenterally.

14. The histologic features characteristic of the ESCN have been described in detail. Special emphasis has been placed upon "fuchsinophilic degeneration." This change tends to affect individual muscle fibers or fiber segments even in normal hearts, and becomes widespread, during the development of the ESCN in certain regions, just before microscopically visible necrotic foci appear. Among other products indicative of cell degeneration, **calcium deposits** are especially common. Individual necrotic muscle fibers or even miliary microscopic foci of necrosis may be absorbed without leaving a scar; hence these lesions are functionally much less important than the "infarctoid cardiopathy," which induces permanent damage. Probably the main reason for the impossibility of producing massive, eventually fatal, cardiac necroses with DOC or other corticoids, when these are given alone, is that, without sensitization by electrolytes, the steroids at the most cause only occasional, isolated, minute islands of necrosis, in which the muscle fibers are rapidly absorbed without leaving a detectable scar. Only after suitable electrolyte treatment is there a tendency for these lesions to spread and coalesce into massive infarctlike areas.

15. The most conspicuous **electrocardiographic manifestations of the ESCN** are: a decrease of the heart rate with prolongation of the PR and QT (QU) intervals and a lowering of the P waves. All these ECG-anomalies are evident after about 48 hours of corticoid-electrolyte treatment, that is, long before the appearance of microscopically visible manifestations of the ESCN. Later, when massive infarctoid necroses develop, the ECG also reveals arrhythmias and conduction defects.

16. NaH_2PO_4 alone does not alter the **blood pressure** significantly. The pressor effect of NaH_2PO_4 plus Me-Cl-COL is inconspicuous and not significantly greater than that exhibited by Me-Cl-COL alone. However, several days prior to death from ESCN, the blood pressure falls below normal, presumably owing to heart failure induced by the myocardial necroses.

17. The many **similarities between the actions of corticoids and cardiac glycosides** have been surveyed with special reference to the dependence of the cardiac actions of such compounds upon changes in Na- and K-metabolism.

B. HORMONES

Steroids

Anatomic Changes Induced by Corticoids in the Heart

Cardiac Hypertrophy. Functional changes in the cardiovascular system were noted in the first Addisonians treated with DOC. In these patients congestive heart failure sometimes developed, with roentgenologically demonstrable dilatation of the heart and a tendency to edema formation (95, 123, 235, 236, 387-389, 409). However, in such cases, cardiac failure was attributed merely to the additional burden on the heart caused by an increase in the volume of circulating fluid that results from the mineralocorticoid actions of this hormone (95).

Following another line of thought, soon after adequate amounts of DOC became available, we wanted to test our theory of the "diseases of adaptation" with this first synthetic cortical hormone. According to our concept, an excess of corticoids could be expected to produce morbid changes in organs that are particularly affected by systemic stress. We found that, in male rats, chronic treatment with DOC produces marked cardiac and renal hypertrophy. In females, these effects are less conspicuous, unless the animals are simultaneously treated with testosterone (318).

As regards the kidney, Durlacher *et al.* (73) first confirmed these findings, and then proceeded to explore the possibility of inhibiting such DOC-overdosage effects by the addition of KCl to the drinking water. They suspected that the loss of potassium induced by the mineralocorticoid might be the immediate cause of such overdosage effects, because it was already known at that time that DOC causes hypokalemia and that K-deficient diets increase renal size. In agreement with their expectations, these authors found that, in rats, the renal hypertrophy caused by DOC can be inhibited by K-supplements. This was the first clear-cut demonstration of the inhibition by K of a morbid change caused by mineralocorticoid overdosage.

At the same time, we also tried to follow up our observations on the production by DOC of cardiac and renal hypertrophy, but all our efforts to produce severe cardiac or renal disease with this hormone failed, until we began to use newly hatched chicks as experimental animals. In these, DOC overdosage produced not only marked cardiac hypertrophy but also typical nephrosclerosis, with an increase in blood-pressure, generalized edema, ascites, pericardial fluid accumulation, cyanosis, and severe dyspnea. We did not know whether the extraordinary efficacy of DOC in the chick was due to a special sensitivity of this species or to the fact that these birds received a diet that was comparatively rich in NaCl and essentially different in many other respects also from that of our laboratory mammals. We merely concluded that "it is perhaps not too far-fetched to suspect adrenocortical involvement as the causative agent in nephrosclerotic hypertension" (320). These experiments showed that:

1. Overdosage with a pure, synthetic mineralocorticoid can produce similes of the mesenchymal diseases of man.
2. The production of such diseases depends at least as much upon "conditioning factors" (genetic predisposition, diet) as upon the amount of hormone in the body.

Cardiac Necroses Without Coronary Occlusion. In the first experiment on the prevention by K of DOC-overdosage changes (73), the heart was not examined. However, soon after this, it was reported (65, 66) that, in addition to the cardiac hypertrophy, DOC sometimes causes minute myocardial necroses in the rat. These changes were accompanied by hypokalemia and, as regards their histologic appearance, they could not be distinguished from the cardiac lesions that are produced by K-deficient diets. Furthermore, 1.5% KCl, given as drinking fluid, prevented these lesions. Therefore, it was deduced that "these experiments seem conclusive that deficit of potassium is the central feature of the cardiac lesions produced by prolonged injections of desoxycorticosterone acetate" (66). However, this conclusion was reached without examining the possible prophylactic effect of electrolytes other than K-salts. To see whether Na would accentuate the K-deficiency in a few rats

(number not stated), NaCl (amount not stated) was added to the drinking water, but the incidence and severity of the cardiac lesions were allegedly not influenced thereby (66).

The same investigators also observed cardiac necroses in one diseased cat (admittedly, "very sick from an infection") but not in healthy dogs. Even in the rats, cardiac lesions were visible only under the microscope and apparently they were so mild that they did not interfere with the well-being of the animals. Indeed, even prolonged treatment with DOC, for over one month, did not succeed in producing massive, fatal myocardial lesions or even consistent histologic evidence of necrosis in rats (66).

Disseminated, small foci of myocardial necrosis were also noted in a patient who received DOC and a diet low in K because of Addison's disease (121). It is very probable, however, that here, the cardiopathy was principally due to K-deficiency, because the patient received an amount of DOC barely sufficient for maintenance and, besides, this corticoid is among the least effective in producing myocardial necrosis, even after optimal conditioning with electrolytes.

The important claim that hypokalemic, myocardial necroses can be produced with a mineralocorticoid *alone* has been widely quoted in the literature. But it is significant that in the many intervening years, it has not been possible to confirm these observations by large-scale experimentation, either in the rat or in any other species, as long as the animals are kept on adequate diets. Now that we know that NaCl tends to inhibit the production of myocardial necroses by corticoids, even after optimal conditioning, it is understandable that in all our work on the production of hyalinizing myocarditis with DOC plus NaCl, such cardiac lesions hardly ever occurred (323). However, even in animals not given NaCl supplements, we have never been able to reproduce these changes (357), although we have administered amounts of DOC equal to, or far in excess of, those given by the earlier workers (66). It is difficult to understand, therefore, how DOC in itself could have produced such lesions in the hands of some experimenters, unless they unwittingly exposed their animals to stress or employed diets

that specifically sensitized the myocardium for the development of necroses. Still, the lesions that allegedly have been produced with DOC alone are probably related in their pathogenesis to the acute, fatal infarctoid cardiopathy that is regularly elicited by some corticoids, in rats simultaneously treated with certain sodium salts.

In any event, the production of myocardial necroses by DOC proved far too erratic to act as a test object for the analysis of the mechanism through which steroids act upon the structure of the myocardium. Hence, the steroid-induced cardiac necroses were not subjected to a systematic study until 15 years later, when the intense conditioning effect of certain Na-salts was discovered.

Cardiac Necroses Caused by Coronary Occlusion. Many investigations have dealt with the effect of corticoids upon the healing of the cardiac necroses that are produced by coronary occlusion, and with the possibility of eliciting coronary occlusion and true cardiac infarcts by treatment with such steroids.

It has been claimed that, in dogs in which myocardial infarcts were produced by ligation of coronary vessels, cortisone decreases the immediate mortality rate and the fibrosis in the infarcted area, while it increases vascularization of the scar. Hence, it was thought that cortisone might be useful in the treatment of myocardial infarction in man (114, 176a, 177, 178). However, re-examination of these findings, under essentially similar experimental conditions, led to the conclusion that cortisone exerts no beneficial influence upon such lesions; in fact, it tends to delay the early resorption of necrotic tissue (153) and it is now fairly well established that neither cortisone nor ACTH affects the healing of experimental infarcts significantly (56, 169).

In commenting on this work, an editorial in the *Journal of the American Medical Association* recommended special caution in the use of glucocorticoids for the treatment of myocardial infarcts, because, by producing retention of Na and water, these compounds increase the load on the heart and in addition tend to produce hypertension, as well as a tendency towards thrombosis (9). Still, some workers (113a, 113b)

continue to recommend cortisone for the treatment of myocardial infarction.

There is also ample evidence that ACTH and glucocorticoids tend to increase the coagulability of the blood and may occasionally be the cause of thromboembolic complications in man (31, 58, 94, 300). On the other hand, the addition of minute amounts of cortisol to hypertonic dextrose solutions used for intravenous infusion diminishes the danger of thrombophlebitis (278). This effect of the glucocorticoid, however, is probably due merely to its topical antiphlogistic action.

True cardiac infarcts occur even less frequently than do thromboembolic complications of peripheral vessels, in patients treated with ACTH or glucocorticoids. In a case of eosinophilic leukemia, myocardial infarction occurred during ACTH treatment, but there is no proof that the hormone was responsible, especially since infarcts are not uncommon in this disease (90). In another patient, subendocardial infarction, with lesions very similar to those of the ESCN, was observed during ACTH treatment (196); several additional instances of coronary thrombosis or embolism in patients treated with ACTH have been reported (40). Such complications are allegedly most common in patients with previously elevated serum cholesterol levels; this created "the impression of a causal relationship between the pre-existing elevated level of serum cholesterol and the thromboembolic phenomena" (4). Occasionally, cardiac infarcts have also been seen after treatment with Δ^1 -cortisone (prednisone) for rheumatoid arthritis (35, 63).

On the other hand, in a series of 86 patients with myocardial infarction, ACTH allegedly proved beneficial in combating the early symptoms of shock, although it did not exert any striking effect upon the healing of the cardiac lesions themselves (10). Δ^1 -cortisone has likewise been recommended for the treatment of patients with cardiac insufficiency due to myocardial infarction, mainly because the hormone acts as a potent diuretic (24).

It is noteworthy in this connection that, although ACTH and glucocorticoids have often been found useful in the treatment of rheumatic carditis, they may occasionally precipitate heart failure. The reason for this is not yet clear, but salt and water

retention presumably plays an important part here (383). Conversely, ACTH has sometimes been found to be beneficial in cases of congestive heart failure presumably due to chronic rheumatic affections (21). In one case, ACTH was given to a patient who had received heparin after a cardiac infarct, but fatal hemorrhagic necrosis of the adrenals developed, owing to an excessive corticotrophic stimulation (252).

ACTH has also been recommended for the therapy of cardiac arrhythmias and particularly of heart block, when these are due to inflammation of the atrioventricular node or the bundle of His (283).

Finally, it is interesting to note that typical Fiedler's myocarditis has occurred in an acromegalic (38), although there was no proof of an etiologic relationship between the two diseases.

This brief review of the literature shows that clinical medicine has not yet furnished any conclusive evidence that ACTH and glucocorticoids can participate in the production of healing of cardiac infarcts. The great variability in the reported results is probably due to the difficulty of appraising the important part played by conditioning factors in individual patients.

Anatomic Changes Induced by Corticoids and Electrolytes in the Heart

The Electrolyte-Steroid-Cardiopathy with Hyalinization (ESCH). While the previously mentioned experiments on the production of cardiac hypertrophy and myocardial necroses with DOC were under way, it was found that an essentially different type of lesion develops in animals simultaneously treated with DOC and NaCl.

The suspicion that the diet, and particularly its NaCl content, might have something to do with the unusual DOC-sensitivity of chicks (320) led us to explore the possibility that the cardiotoxic actions of steroids might largely depend upon conditioning by dietary means. A series of earlier experiments had shown that we must distinguish between unconditional and conditional hormone actions: the former are the immediate results of a hormone excess and are relatively independent of

other stimuli, while the latter are conditional upon the simultaneous activity of other concurrently applied agents. It is often difficult or impossible to obtain such conditional actions by either the hormone or the sensitizing agent alone, although simultaneous treatment with the hormone and its specific sensitizer is eminently effective (322, 345). In such instances, it is immaterial whether we say that the hormone conditions the effect of the nonhormonal stimulus or vice versa, since both factors are necessary to obtain a full response.

To verify whether, in birds, NaCl could act as a conditioning agent for DOC, the experiments on the chick were repeated, but this time the DOC and NaCl were given either alone or in combination. It was found that large amounts of NaCl can cause generalized tissue edema and nephrosclerosis with the concomitant cardiovascular changes, even in otherwise untreated chicks, but the effect of DOC is greatly potentiated by the concurrent administration of small amounts of NaCl that are in themselves inactive. Equimolecular doses of KCl do not exhibit this conditioning action, nor do they inhibit the sensitizing effect of NaCl in DOC-treated birds (359).

We then proceeded to explore the possibility of producing fatal cardiovascular damage in mammals, with DOC plus NaCl. When 1% NaCl was substituted for drinking water, even the otherwise resistant rat responded to the mineralocorticoid with typical hyalinizing myocarditis (ESCH), periarteritis nodosa, nephrosclerosis, and hypertension (351). Comparison of the syndrome thus produced with that occasionally elicited by DOC alone showed them to be essentially different: the former is characterized by hyalinosis (hyaline degeneration of cardiac muscle, hyalinization of coronary and other vessels, as well as of the renal glomeruli); the latter, by focal necrosis of the myocardium (with secondary infiltration by histiocytes and leukocytes), without hyaline deposits in the heart or in any other part of the circulatory system (see figs. 1-8).

The finding that combined treatment with DOC and NaCl can produce an experimental simile of a malignant hypertensive disease stimulated extensive experimentation to determine whether it is the Na- or the Cl-ion of NaCl that sensitizes the

heart for the production of hyalinizing lesions by DOC. Rats sensitized by unilateral nephrectomy received various electrolytes in equimolecular concentrations. All salts were given daily by gavage, to avoid any accidental variations of their intake such as occur, owing to individual differences in voluntary food or fluid consumption, when drugs are mixed with the diet or dissolved in the drinking water.

Under these rigorously controlled experimental conditions, it could be established that severe ESCH (with the accompanying nephrosclerosis and periarteritis) occurs in DOC-treated rats, not only after the administration of NaCl, but also when Na is given in the form of Na_2SO_4 or NaHCO_3 . Other chlorides—particularly NH_4Cl , CaCl_2 and, to a lesser extent, KCl and MgCl_2 —far from sensitizing the circulatory system, actually inhibit the production of hyalinizing cardiovascular lesions, in rats treated with otherwise highly effective doses of DOC plus NaCl (347).

The incidence of the nephrosclerosis, after treatment with DOC plus NaCl, was, in this respect, not markedly affected by KCl or K-acetate. In any event, these K-salts were not nearly as effective as were equimolecular amounts of NH_4Cl , $(\text{NH}_4)_2\text{SO}_4$, NH_4NO_3 , MgCl_2 , or CaCl_2 . Therefore, this inhibition could not be ascribed to a specific antagonism between K and Na; it may have been due simply to the Na-diuretic action of various electrolytes. Since the potent protective action of NH_4Cl and CaCl_2 against nephrosclerosis and periarteritis was shared by $(\text{NH}_4)_2\text{SO}_4$ and NH_4NO_3 , this extracardiac effect was ascribed to the "acidifying" property of these electrolytes, that is, to their ability to form an excess of acid-producing anions within the organism. In the case of NH_4Cl , $(\text{NH}_4)_2\text{SO}_4$, and NH_4NO_3 , the NH_4 -ion is neutralized by being transformed into urea, thus leaving an excess of inorganic acid. With CaCl_2 and MgCl_2 , the comparatively low absorption rate of Ca and Mg, as well as their ready excretion into the intestine, is said to achieve the same end result, because it also leaves an excess of Cl-ions to form HCl in the body (347). Since we have not actually determined the rate at which Ca and Mg are absorbed from, or excreted into, the intestine, it was impossible to reach any defi-

nite conclusion concerning the mechanism through which these salts act, but in any event the nephrosclerotic effect of DOC-plus-NaCl-treatment was shown to be markedly inhibited by these so-called "acidifying salts," while (unlike the cardiovascular damage) it is not significantly affected by K-salts. Furthermore, blood electrolyte determinations definitely proved that nephrosclerosis can be produced by treatment with DOC plus NaCl, even when K-salts are given simultaneously in amounts sufficient to prevent the hypokalemia (347).

This inactivity of K-salts is in sharp contrast with their potent prophylactic effect against the necrotizing cardiopathy that is produced by DOC, under certain experimental conditions. The ESCH elicited by combined treatment with DOC plus NaCl occupies an intermediate position, in that its incidence and severity are definitely, but only slightly, reduced by K. Failure to distinguish between the effects of K upon the various manifestations of DOC-overdosage has led to considerable confusion in the literature, because most investigators merely concluded from their observations that K is, or is not, a potent prophylactic agent against "DOC-intoxication," without specifying which target organ served as a basis for their conclusions.

For example, one group of investigators produced disseminated myocardial necroses in rats that received DOC while kept on K-deficient diets. As might have been expected, in this case, K was eminently effective in preventing the development of the lesions. Although the authors emphasized that the myocardial changes were of the hypokalemic type, no distinction was made between these necroses and the hyalinizing myocarditis (with nephrosclerosis and periarteritis) produced by DOC, in rats not sensitized by K-deficient diets but by NaCl and unilateral nephrectomy. Hence, the experiments were thought to prove that the hyalinizing lesions must also have resulted from K-deficiency (275). This, despite the well-known fact that rats kept on K-deficient diets develop cardiac necroses but never periarteritis nor nephrosclerosis with hyalinization.

Another group of investigators (183, 184) reported that, in unilaterally nephrectomized rats in which a typical hyalinizing myocarditis was produced by DOC plus NaCl, the K-concentration of the cardiac muscle was diminished in proportion to the severity of the histologic changes. The ESCH-type of myocarditis was considerably diminished, but could not be abolished, by KCl. Here, no mention was made of renal

changes; hence, it is impossible to say whether the nephrosclerotic effect of DOC-plus-NaCl-treatment remained uninfluenced by the KCl-supplement as it did in our experiments. Still, it was concluded—without emphasizing that only the heart had been examined—that K protects against the toxic effects of DOC.

Yet, another investigator (14) found that, in rats treated with DOC plus NaCl (without unilateral nephrectomy), a dietary excess of KCl prevented the development of cardiac hypertrophy and mesenteric periarteritis nodosa but did not affect the renal changes elicited under these conditions.

In rats in which a relative renal insufficiency was created by treatment with anti-rat-kidney serum (instead of unilateral nephrectomy), DOC plus NaCl intensified the nephritic process and produced hypertension with cardiac hypertrophy. A diet virtually free of Na diminished these actions of DOC. On the other hand, "the addition of KCl to the drinking water of rats receiving DOC and NaCl tended to correct the depression of the level of potassium in the serum, but had no effect upon the hypertension in nephritic animals nor upon the anatomic lesions" (189). This is in agreement with the observation that, in mice, the renal effects of DOC-overdosage are allegedly also resistant to KCl treatment (230).

A repetition of our comparative studies on the effect of KCl and NH₄Cl upon the hyalinosis syndrome induced in unilaterally nephrectomized rats by DOC plus NaCl, confirmed that NH₄Cl is incomparably more effective than KCl in preventing nephrosclerosis and mesenteric periarteritis nodosa. Under the conditions of this particular experiment, the myocarditis was not sufficiently intense to permit any conclusions as regards its inhibition by KCl, but NH₄Cl completely prevented the cardiac lesions (284). These findings re-emphasize the need for caution in drawing any conclusions concerning the "central position" of K in this syndrome merely on the basis of its partial suppression by KCl-supplements.

In connection with the cardiotoxic effects of corticoids, it is also of interest that DOC produces severe ECG changes in rabbits only when it is given in combination with NaCl. Additional treatment with minute amounts of intravenous KCl corrects these ECG changes. On the other hand, in NaCl-treated rabbits, cortisone produces only minimal ECG changes, and even these are unlike those of animals treated with DOC plus NaCl. Curiously, when cortisone is given to DOC- and DOC-plus-NaCl-treated animals, the ECG changes tend to be inhibited, although the survival time is shortened (141).

In rats in which a myocardial injury is produced by burning a small area of the cardiac surface, treatment with DOC

diminishes, while KCl aggravates, the severity of the resulting ECG changes (50). It is doubtful whether these findings have any direct bearing upon the interpretation of the electrolyte-steroid-cardiopathies.

Conclusion. It is essential to distinguish between two types of cardiac lesions that can be produced with DOC:

1. **Myocardial necroses (ESCN and related conditions)** with cardiac hypertrophy, but without hyaline deposition in the heart, periarteritis nodosa, or nephrosclerosis. This change is readily prevented by KCl and, to a lesser extent, by NaCl.

2. **Hyalinizing myocarditis (ESCH)** also with cardiac hypertrophy. Here, myocardial necroses are absent or inconspicuous, but there is much hyalinization in the cardiac muscle and in the coronary arteries. This syndrome is associated with malignant nephrosclerosis and periarteritis nodosa throughout the body, particularly in the mesenteric area. NaCl (especially when combined with unilateral nephrectomy) greatly sensitizes for the production of this hyalinosis. KCl only moderately diminishes the cardiac changes, as well as the accompanying periarteritis, and does not prevent the nephrosclerosis. In any event, in this hyalinosis syndrome, certain "acidifying salts"—and particularly NH₄Cl—are much more effective as prophylactic agents than are K-salts.

The Electrolyte-Steroid-Cardiopathy with Necrosis (ESCN). As previously stated, the typical, massive, fatal myocardial necroses characteristic of the ESCN can most readily be produced by the concurrent administration of some corticoids and certain Na-salts, particularly the phosphates, sulfates, and perchlorate. Among these electrolytes, the sensitizing action of NaH₂PO₄ was the first to be discovered; hence, most of the available data concerning this type of steroid-electrolyte-interaction were obtained in animals treated with various steroids and sensitized by the oral administration of this phosphate.

Among the many steroids that have been tested in this manner up to now, Me-Cl-COL proved to be the most active. However, 2 α -methyl-9 α -fluorocortisol (Me-F-COL) and the corresponding nonmethylated steroids (9 α -chlorocortisol and 9 α -

fluorocortisol) are likewise very effective in this respect (327, 331, 349, 357). All these compounds are rich in both glucocorticoid and mineralocorticoid potency. Another halogenated corticoid, triamcinolone (Δ^1 -9 α -fluoro-16-hydroxycortisol), which is highly potent as a glucocorticoid but possesses little or no mineralocorticoid activity, proved to be totally ineffective in producing an ESCN (340). On the other hand, cortisone, a glucocorticoid with some mineralocorticoid activity, is at least as cardiotoxic as is DOC, although the latter is much more mineralocorticoid than is the former (330, 357, 358).

It is also noteworthy that, in rats sensitized with NaH_2PO_4 , the ability of various steroids to produce cardiac necroses does not run strictly parallel with their capacity to cause nephrocalcinosis. For example, DOC greatly sensitizes the rat for the production of renal calcification by NaH_2PO_4 , but not to the induction of myocardial necroses (330, 340).

In order to facilitate comparisons between these various pharmacologic actions and the chemical structure of steroids, our results are summarized in Table 10, which is based, in part, upon previous publications (331, 340, 349, 357) and, in part, upon numerous, hitherto unpublished observations.

All the experiments that are summarized in Table 10 were performed on Sprague-Dawley rats, with a mean initial body-weight of 100 g (range: 90–110 g). During the experiment, the animals were fed exclusively on "Purina Fox Chow," and received tap water to drink. Every dose level of each steroid was tested on groups of at least 10, and in many cases up to 40, rats, as follows:

The steroids were given subcutaneously, in the form of microcrystal suspensions, the daily dose (indicated in the table) being suspended in 0.2 ml of water.

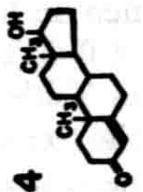
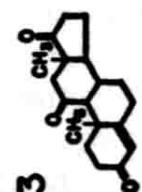
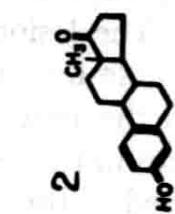
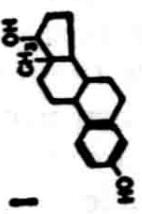
NaH_2PO_4 was administered at the dose of 300 mg, in 4 ml of water, twice daily, by stomach tube.

The duration of each of these experiments was 12 days.

The diagnosis of **cardiac necroses** and **nephrocalcinosis** was first made with the aid of a dissecting loupe at autopsy and, in doubtful cases, verified on histologic sections. The lesions were graded in an arbitrary scale of 0–3, and the means of these findings (with standard errors) are listed in Table 10, together with the percentual mortality rate. Since none of the steroids produce necroses in the liver of rats sensitized with NaH_2PO_4 , hepatic changes are not listed in this table.

TABLE 10
Toxicity of Various Steroids in Rats Sensitized with NaH₂PO₄

Structure	Name *	Dose (μ g)	Cardiac Necrosis	Nephro- calciosis	Mortality (%)
C₁₈ and C₁₉ Compounds					
1	$\Delta^{1,3,5}$ -estratriene-3,17 β -diol ESTRADIOL (Schering)	500 5000	0 0.6 ± 0.26	2.5 ± 0.32 1.7 ± 0.53	60 60
2	$\Delta^{1,3,5}$ -estratriene-3-ol-17-one ESTRONE (Schering)	100 1000 5000	0 0 0	2.1 ± 0.30 2.6 ± 0.28 2.5 ± 0.32	0 0 0
3	Δ^4 -androstene-3,11,17-trione ADRENOSTERONE (Farmitalia)	1000	0	1.0 ± 0.15	0
4	Δ^4 -androstene-3-one-17 β -ol TESTOSTERONE (Schering)	100 1000 5000	0 0 0	2.2 ± 0.28 2.3 ± 0.32 2.3 ± 0.30	0 0 0



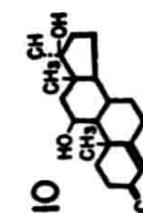
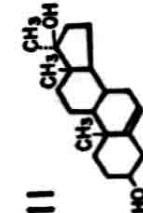
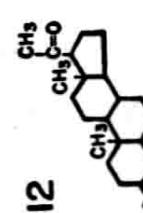
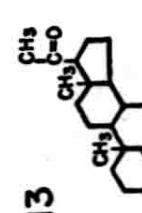
5	Δ^4 -androstene-3,11,17-trione-4-chlor	0	0	0.9 \pm 0.14	0
	4-CHLORO-ADRENOSTERONE	1000	0		
	(Farmitalia)				
6	Δ^5 -androstene-3 β -ol-17-one				
	DEHYDRO-ISO-ANDROSTERONE	3000	0	1.7 \pm 0.37	10
		5000	0	2.0 \pm 0.28	40
7	Δ^4 -androstene-3-one-4-chloro-17 β -ol-17-acetate				
	4-CHLORO-TESTOSTERONE ACETATE	1000	0	0.8 \pm 0.17	0
	(Schering)				
8	17α -methyl-androstan-3 β ,11 β ,17 β -triol				
	METHYLANDROSTANETRIOL	100	0	2.1 \pm 0.28	0
		1000	0	2.2 \pm 0.25	0
		5000	0	2.3 \pm 0.30	0
67					

C₂₀ Compounds

9	17α -methyl- Δ^4 -androstene-3-one-17 β -ol	2000	0	1.7 \pm 0.30	0
	METHYLTESTOSTERONE	3000	0.9 \pm 0.48	2.3 \pm 0.28	0
	(Schering)	5000	0	2.5 \pm 0.17	10

* In addition to the steroids listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received NaH₂PO₄ (300 mg twice daily) in all groups, during the 12 days of this experiment.

TABLE 10—(Continued)
Toxicity of Various Steroids in Rats Sensitized with NaH₂PO₄—(Continued)

Structure	Name *	Dose (μ g)	Cardiac Necrosis	Nephro- calcinosi	Mortality (%)
	17 α -methyl- Δ^4 -androstene-3-one-11 β ,17 β -diol			2.4 ± 0.28	0
	11 β -HYDROXY-METHYLTESTOSTERONE	100 1000 5000	0 0 0	2.1 ± 0.30 2.0 ± 0.35	0 10
	17 α -methyl- Δ^5 -androstene-3 β ,17 β -diol				
	METHYLANDROSTENEDIOL (MAD)	3000 5000	0 0	2.8 ± 0.14 2.7 ± 0.20	0 20
	(Ciba)				
	C₂₁ Pregnanes				
	pregnane-3,20-dione PREGNANEDIONE	1000 2000 5000	0 0 0	2.3 ± 0.20 2.2 ± 0.28 2.2 ± 0.24	0 0 0
	(Schering)				
	C₂₁ Δ⁴ Pregnanes				
	Δ ⁴ -pregnen-3,20-dione PROGESTERONE	2000 5000	0 0	1.7 ± 0.28 1.6 ± 0.35	0 0
	(Ciba)				

14		Δ^4 -pregnene-3,11,20-trione	0	0	1.8 ± 0.30	0
		11-KETOPROGESTERONE (Squibb)	500	0	1.0 ± 0.22	0
			1000	0	1.7 ± 0.28	0
			2000	0		
15		Δ^4 -pregnene-3,20-dione-17 α -ol-acetate 17-ACETOXY-PROGESTERONE (Upjohn)	100	0	2.4 ± 0.32	0
			1000	0	2.3 ± 0.35	0
			5000	0	2.1 ± 0.28	10
16		Δ^4 -pregnene-3,20-dione-21-ol-21-acetate DESOXYCORTICOSTERONE ACETATE (DOC-Ac) (Schering)	10	0	2.0 ± 0.30	0
			100	0	2.5 ± 0.35	0
			500	0	2.8 ± 0.20	10
			2000	0.7 ± 0.47	2.8 ± 0.16	50
			5000	0.5 ± 0.37	2.8 ± 0.16	22
17		Δ^4 -pregnene-3,20-dione-17 α ,21-diol-21-acetate Cpd"S"-ACETATE, DESOXYCORTISOL ACETATE (Pfizer)	2000	0	1.8 ± 0.25	0
			5000	0	1.6 ± 0.17	0
18		Δ^4 -pregnene-3,20-dione-11 β ,17 α ,21-triol- 21-acetate CORTISOL (COL) ACETATE HYDROCORTISONE ACETATE (Schering)	2000	0	0.5 ± 0.23	0
			5000	0.2 ± 0.25	1.1 ± 0.23	30

TABLE 10—(Continued)
Toxicity of Various Steroids in Rats Sensitized with NaH₂PO₄—(Continued)

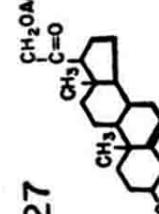
Structure	Name *	Dose (μ g)	Cardiac Necrosis	Nephro- calciosis	Mortality (%)
19	Δ^4 -pregnenene-3,11,20-trione-17 α ,21-diol-21-acetate				
	CORTISONE (CON) ACETATE (Schering)	2000 5000	0.7 \pm 0.3 1.1 \pm 0.31	1.8 \pm 0.36 1.3 \pm 0.30	20 30
	 C_{21} Δ^4-Pregnene-Halo				
20	Δ^4 -pregnenene-3,11,20-trione-9 α -bromine BROMOXOPROGESTERONE (BOP) (Squibb)	5000	1.5 \pm 0.5	3.0 \pm 0	60
21	Δ^4 -pregnenene-3,20-dione-9 α -fluoro-11 β -ol 9α-FLUORO-11β-HYDROXYPROGESTERONE (Squibb)	5000	2.9 \pm 0.1	2.5 \pm 0.17	100
22	Δ^4 -pregnenene-3,20-dione-11 β -ol-12 α -bromine 12α-BROMO-11β-HYDROXYPROGESTERONE (Squibb)	100	0	1.5 \pm 0.22	0

23		Δ^4 -pregnene-3,20-dione-9 α -chloro-11 β ,17 α ,21-triol-21-acetate	100	0	2.3 ± 0.26	0
		9α-CHLOROCORTISOL (Cl-COL) ACETATE	100	2.5 ± 0.26	2.9 ± 0.10	70
		(Squibb)	500	2.2 ± 0.41	2.2 ± 0.18	100
			1000	2.5 ± 0.30	2.3 ± 0.14	100
24		Δ^4 -pregnene-3,20-dione-9 α -fluoro-11 β ,17 α ,21-triol-21-acetate	10	0	1.4 ± 0.26	0
		9α-FLUOROCORTISOL (F-COL) ACETATE	100	2.0 ± 0.41	2.3 ± 0.26	70
		(Squibb)	500	1.4 ± 0.46	1.8 ± 0.23	87
			1000	2.8 ± 0.14	2.0 ± 0.30	100
25		Δ^4 -pregnene-3,20-dione-9 α -fluoro-11 β ,16 α ,17 α ,21-tetrol	100	0	1.4 ± 0.26	0
		16α-HYDROXY-9α-FLUOROCORTISOL	500	0.8 ± 0.35	1.2 ± 0.35	80
		(Squibb)	5000	1.1 ± 0.40	1.4 ± 0.33	100

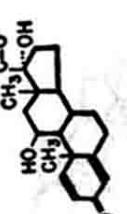
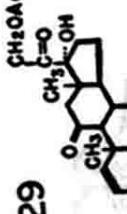
C₂₁ Δ^5-Pregnanes						
26		Δ^5 -pregnene-3 β -ol-20-one PREGNENEOLONE	5000	0	1.6 ± 0.28	0
		(Schering)				

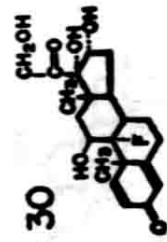
TABLE 10—(Continued)

Toxicity of Various Steroids in Rats Sensitized with NaH_2PO_4 —(Continued)

Structure	Name *	Dose (μg)	Cardiac Necrosis	Nephro- calcinosis	Mortality (%)
27		Δ^5 -pregnen-3 β ,21-diol-20-one-21-acetate ACETOXYPREGNENEOLONE (AOP) (Schering)	5000	0	1.6 ± 0.33

C₂₁ $\Delta^{1,4}$ -Pregnadienes and Their Halogenated Derivatives

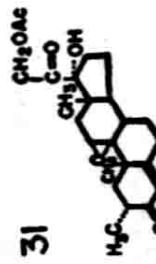
28		$\Delta^{1,4}$ -pregnadiene-3,20-dione-11 β ,17 α ,21-triol- 21-acetate Δ^1-CORTISOL (Δ^1-COL) ACETATE PREDNISOLONE ACETATE (Schering)	500 2000 5000	0 0.8 ± 0.36 0.8 ± 0.31	1.1 ± 0.18 1.7 ± 0.33 1.8 ± 0.24
29		$\Delta^{1,4}$ -pregnadiene-3,11,20-trione-17 α ,21-diol- 21-acetate Δ^1-CORTISONE (Δ^1-CON) ACETATE PREDNISONE ACETATE (Schering)	500 2000 5000	0 0.8 ± 0.33 0.3 ± 0.33	1.9 ± 0.20 2.3 ± 0.20 1.4 ± 0.40



$\Delta^1,4$ -pregnadiene-3,20-dione-9 α -fluoro-
11 β ,16 α ,17 α ,21-tetrol
TRIAMCINOLONE, Δ^1 -9F,16-OH-COL
(Squibb)

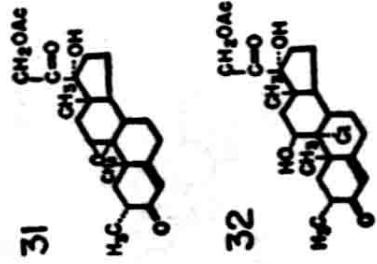
	$\Delta^1,4$ -pregnadiene-3,20-dione-9 α -fluoro- 11 β ,16 α ,17 α ,21-tetrol TRIAMCINOLONE, Δ^1-9F,16-OH-COL (Squibb)	100	0	1.2 ± 0.30	0
		500	0	1.3 ± 0.27	50
		2000	0	1.6 ± 0.26	90
		5000	0	1.5 ± 0.25	100

C₂₂ 2-Me- Δ^4 -Pregnenes and Their Halo Derivatives



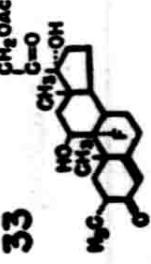
2 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -oxido-
17 α ,21-diol-21-acetate
(Upjohn)

	2 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -oxido- 17 α ,21-diol-21-acetate (Upjohn)	5000	0	1.4 ± 0.26	0



2 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -chloro-
11 β ,17 α ,21-triol-21-acetate
2 α -METHYL-9 α -CHLOROCORTISOL
(Me-Cl-COL) ACETATE
(Upjohn)

	2 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -chloro- 11 β ,17 α ,21-triol-21-acetate 2α-METHYL-9α-FLUOROCORTISOL (Me-F-COL) ACETATE (Upjohn)	10	2.4 ± 0.27	2.4 ± 0.22	75
		100	2.7 ± 0.22	2.4 ± 0.22	90
		500	2.0 ± 0.37	1.5 ± 0.18	100
		1000	2.5 ± 0.27	2.9 ± 0.10	100

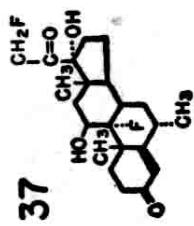


2 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -fluoro-
11 β ,17 α ,21-triol-21-acetate
2 α -METHYL-9 α -FLUOROCORTISOL
(Me-F-COL) ACETATE
(Upjohn)

TABLE 10—(Continued)

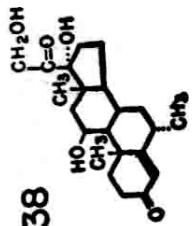
Toxicity of Various Steroids in Rats Sensitized with NaH₂PO₄—(Continued)

Structure	Name *	Dose (μ g)	Cardiac Necrosis	Nephro- calciosis	Mortality (%)
C₂₂ 6Me-Δ^4-Pregnanes and Their Halogenated Derivatives					
34		6 α -methyl- Δ^4 -pregnene-3,20-dione-11 β -ol 6α-METHYL-11β-HYDROXYPROGESTERONE (Upjohn)	1000 5000	0 0	2.1 ± 0.27 1.2 ± 0.30
35		6 α -methyl- Δ^4 -pregnene-3,11,20-trione 6α-METHYL-11-KETOPROGESTERONE (Upjohn)	1000 5000	0 0	1.1 ± 0.27 1.6 ± 0.25
36		6 α -methyl- Δ^4 -pregnene-3,20-dione-11 β ,17 α -diol 6α-METHYL-21-DESOXYCORTISOL (Upjohn)	1000	0	1.1 ± 0.30



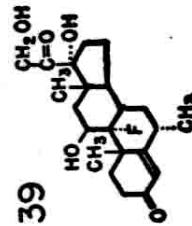
**6 α -methyl- Δ^4 -pregnene-3,20-dione-9 α ,21-difluoro-11 β ,17 α -diol
(Upjohn)**

1000 0 1.0 ± 0.26 100



**6 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -fluoro-11 β ,17 α ,21-triol
6 α -METHYLCORTISOL (6-Me-COL)
"MEDROL"**

100 0 2.2 ± 0.28
1000 0 2.7 ± 0.25
5000 0 1.1 ± 0.37
100 0 1.0



**6 α -methyl- Δ^4 -pregnene-3,20-dione-9 α -FLUOROCORTISOL,
6 α -METHYL-9 α -FLUORO-MEDROL
(6-Me-9-F-COL) "9 α -FLUORO-MEDROL"
(Upjohn)**

100 0 2.2 ± 0.10
1000 0 2.8 ± 0.10
 0.9 ± 0.31 70
 2.2 ± 0.25 100

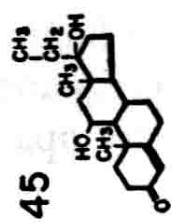
C₂₂ 6Me- $\Delta^{1,4}$ -Pregnadienes and Their Halogenated Derivatives



1000 0 1.4 ± 0.22 80

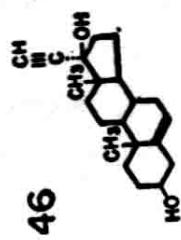
TABLE 10—(Continued)
Toxicity of Various Steroids in Rats Sensitized with NaH₂PO₄—(Continued)

Structure	Name •	Dose (μ g)	Cardiac Necrosis	Nephro- calcinosis	Mortality (%)
41		1000	0	1.2 ± 0.25	100
C₂₁ 17-Epi Compounds					
76		5000	0	2.1 ± 0.28	10
42		5000	0	1.3 ± 0.30	0
43		5000	0	1.3 ± 0.30	0
44		5000	0	1.3 ± 0.20	0



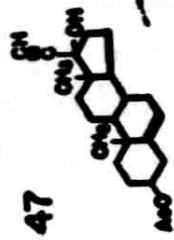
17 α -ethynyl- Δ^4 -androstene-3-one-11 β ,17 β -diol
(Upjohn)

1000 0 1.2 ± 0.25 0



17 α -ethynyl- Δ^5 -androstene-3 β ,17 β -diol
ETHINYLANDROSTENEDIOL
(Horner)

5000 0 2.7 ± 0.14 0



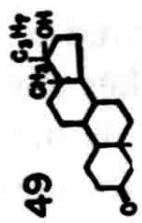
17 α -ethynyl- Δ^5 -androstene-3 β ,17 β -diol-3-acetate
ETHINYLANDROSTENEDIOL ACETATE
(Horner)

5000 0 2.9 ± 0.10 25



17 α -ethynyl- Δ^4 -androstene-3-one-17 β -ol
ETHINYLTESTOSTERONE, ETHISTERONE
(Frosst)

5000 0 1.1 ± 0.28 0



17 α -propyl-19-nor-etiocholane-3-one-17 β -ol
PROPYLDIHYDRONORTESTOSTERONE
(Searle)

5000 0 1.8 ± 0.20 0

In evaluating the data, we must keep in mind that each steroid was also assayed (at the highest dose listed in Table 10) in rats not conditioned by NaH_2PO_4 , but the results of these tests were uniformly negative. It may be said, therefore, that under our experimental conditions **none of the steroids so far examined could be shown to produce cardiac necroses without electrolyte-conditioning.**

Nephrocalcinosis is only incidentally mentioned in this table, as it has no direct bearing upon the development of cardiac necroses; yet it should be stated that there was no renal calcification in the rats treated with any of these various steroids alone.

Treatment with NaH_2PO_4 alone also consistently failed to produce cardiac necroses, but it produced nephrocalcinosis of the grade 1.6 ± 0.17 , in a group of 40 rats.

If these control values are kept in mind as a standard for comparison, the following among the data in Table 10 appear to be worthy of special comment.

None of the **C₁₈, C₁₉, and C₂₀** compounds exhibited any noteworthy ability to produce cardiac necroses. However, *estradiol* (No. 1) caused a high mortality, and both this compound and *estrone* (No. 2) increased the severity of the nephrocalcinosis. *Adrenosterone* (No. 3), as well as *4-chloro-androsterone* (No. 5) and *4-chloro-testosterone* (No. 7), possibly diminished the nephrocalcinosis and showed no toxicity. This antinephrocalcinotic potency is not due to the very weak testoid actions of these steroids, because the much more "androgenic" *testosterone* (No. 4), *dehydro-iso-androsterone* (No. 6), *methyltestosterone* (No. 9), and *methylandrostenediol* (No. 11) actually aggravated the nephrocalcinosis, especially at high dose levels, as did also *methylandstanetriol* (No. 8) and *11β-hydroxy-methyltestosterone* (No. 10).

The only pregnane derivative in this series, *pregnanedione* (No. 12), failed to cause cardiac necroses or mortality, but it appeared to have increased the nephrocalcinosis. This finding is rather unexpected and should be verified, because pregnanedione is not known to possess any physiologic activity apart from its anesthetic effect.

Among the Δ^4 -pregnenes, *DOC** (No. 16) was, if anything, somewhat less cardiotoxic than *cortisone* (No. 19), while the effect of *cortisol* (No. 18) was virtually negligible. It is noteworthy in this connection that, despite this low ESCN-producing activity of cortisol plus NaH_2PO_4 , rats pretreated with these two agents are highly susceptible to the production of acute, myocardial necroses by subsequent exposure to stress (330, 358), as we shall see later. *Progesterone* (No. 13), *11-ketoprogesterone* (No. 14), *17-acetoxypregnsterone* (No. 15), and *Reichstein's "Compound S"* (No. 17) were devoid of cardio-toxic potency.

Nephrocalcinosis was markedly aggravated by *DOC* and (especially at low dose levels) slightly inhibited by some of the glucocorticoids of this series. It is noteworthy that when high doses of glucocorticoids are given, the nephrocalcinosis is almost completely localized in a narrow band at the cortico-medullary junction, but, in this zone, tends to be extremely severe.

Among the halogenated Δ^4 -pregnenes (without methyl substitution), *9\alpha*-fluoro-*11\beta*-hydroxypregnsterone (No. 21), *9\alpha*-chlorocortisol (No. 23), and *9\alpha*-fluorocortisol (No. 24) were most effective in eliciting the ESCN. The data available do not suffice to draw any conclusion concerning the relative cardio-toxicity of these three compounds, but *bromoxopregnsterone* (No. 20) and *16\alpha*-hydroxy-*9\alpha*-fluorocortisol (No. 25), though also very effective, were somewhat less potent. It is difficult to appraise the activity of *12\alpha*-bromo-*11\beta*-hydroxypregnsterone (No. 22) beyond the fact that it does not belong among the most active halocorticoids, because we did not have enough of this compound to test it at higher dose levels.

In this series, the nephrocalcinotic potency of the steroids again roughly paralleled their known mineralocorticoid activity.

Both Δ^5 -pregnenes, *pregnenolone* (No. 26) and *acetoxypregnolone* (No. 27), were devoid of cardiotoxic and nephro-

* For the sake of simplicity, I shall refer only to the parent compounds in this discussion, but Table 10 indicates whether the steroid was tested as such or in the form of an ester.

calcinotic activity at the high dose level at which they were tested.

None of the $\Delta^{1,4}$ -pregnadienes or their halogenated derivatives (Nos. 28, 29, 30) exhibited much cardiotoxic activity. It is especially remarkable that *triamcinolone* (No. 30)—a highly active glucocorticoid with virtually no mineralocorticoid potency—is completely ineffective in this respect, in the electrolyte-conditioned rat. We shall have more to say about this in discussing the relationships between the cardiotoxic and the gluco- or mineralocorticoid potencies of steroids.

The nephrocalcinotic effect of this group of compounds was too variable to allow definite conclusions, but the singular tendency of glucocorticoids to concentrate calcification in a narrow corticomedullary strip was again very evident, especially in the case of triamcinolone.

The most active cardiotoxic and nephrocalcinotic steroids were discovered among the group of the 2-methyl- Δ^4 -pregnenes and their halogenated derivatives. In both these respects, *Me-Cl-COL* (No. 32) is the most effective steroid known, but *Me-F-COL* (No. 33) is almost as effective. On the other hand, the closely related *epoxy compound* (No. 31) is totally inert.

All the 6-methyl- Δ^4 -pregnenes and their halogenated derivatives (Nos. 34–39), as well as the corresponding 6-methyl- $\Delta^{1,4}$ -pregnadienes (Nos. 40, 41), are devoid of cardiotoxic activity.

At certain dose levels 6-*Me-COL* (No. 38) and 6-*Me-F-COL* (No. 39) appeared to aggravate the nephrocalcinosis; most of the other compounds seemed to exert a slight protective effect, but these changes were not statistically significant.

All the 17-*epi*(α)-ethyl, ethinyl, and propyl derivatives proved to be completely devoid of cardiotoxic activity, even at the very high dose level (5,000 $\mu\text{g}/\text{day}$) at which they were tested, but some of them (e.g., Nos. 42, 46, 47) appeared to aggravate the nephrocalcinosis.

Very little is known as yet about interactions between steroids in the production of the ESCN. All the steroid hormones that we found to be highly effective in producing this cardiopathy are potent corticoids. However, from the observations mentioned so far, it was not possible to ascertain

whether the cardiotoxic effect is more closely related to the mineralocorticoid or to the glucocorticoid action. Probably, both types of activity are important. In experiments in which neither high doses of triamcinolone (a pure glucocorticoid) nor of DOC (a pure mineralocorticoid) produced any marked degree of cardiopathy in NaH_2PO_4 -sensitized rats, combined treatment with small doses of both these steroids sufficed to induce pronounced and extensive cardiac necroses (340). It would appear, therefore, that the concurrent action of mineralo- and glucocorticoids is most effective in conditioning the cardiac muscle to the necrotizing action of electrolytes.

This view received support from subsequent investigations, which showed that a number of glucocorticoids [6 α -methyl-21-fluoro-11 β ,17 α -dihydroxy- $\Delta^{1,4}$ -pregnadiene-3,20-dione; 6 α -methyl-9 α ,21-difluoro-11 β ,17 α -dihydroxy- $\Delta^{1,4}$ -pregnadiene-3,20-dione; 6 α -methyl-21-desoxy-cortisol; 6 α -methyl-9 α ,21-difluoro-21-desoxy-cortisol; 6 α -methyl-cortisol (Medrol); Δ^1 -fluoro-16-hydroxy-cortisol (triamcinolone)] can produce a severe ESCN in rats pretreated with otherwise virtually inactive doses of DOC plus NaH_2PO_4 . On the other hand, estradiol and methyl-testosterone failed to potentiate the cardiotoxic effect of DOC. Apparently, many, if not all, glucocorticoids have the ability to activate the ESCN-producing effect of mineralocorticoids in the NaH_2PO_4 -sensitized rat, although without simultaneous treatment with DOC these compounds are inactive in this respect despite NaH_2PO_4 sensitization (17a).

We do not yet have any direct evidence to show that the production of an ESCN by one steroid could be prevented by another. Yet the many antagonisms between steroids in other respects and the fact that pregnancy offers considerable protection against this type of cardiopathy suggest that research along these lines may be profitable.

Hypophysectomy and ACTH

Since hypophysectomy prevents the ESCH normally produced by DOC in unilaterally nephrectomized rats conditioned by NaCl-supplements (321), it is of interest that treatment

with Me-Cl-COL plus NaH_2PO_4 can produce an ESCN, even in hypophysectomized rats (342). On the other hand, it has been claimed that the production of myocardial necroses by Me-Cl-COL or DOC, in bilaterally nephrectomized rats deprived of water, is prevented by hypophysectomy (29). However, perhaps under these conditions, the hypophysectomized animals did not survive long enough for the development of detectable cardiac lesions.

In all the experiments reported in the section on steroids, the ESCN was produced with high doses of synthetic corticoids; the most active of these are not known to occur under natural conditions in the body. Therefore, it was of particular importance to establish whether the adrenal cortex can secrete sufficient amounts of the kind of corticoid that conditions for the production of such myocardial changes.

In order to answer this question, an experiment was performed under the usual conditions, except that ACTH was substituted for the synthetic corticoids. Twenty female Sprague-Dawley rats (with a mean body-weight of 100 g, and given 300 mg of NaH_2PO_4 , twice daily) received 50 I.U. of ACTH, in 0.2 ml of sesame oil, twice daily, subcutaneously during 12 days. The mean grade of cardiac necrosis was 1.5 ± 0.3 (nephrocalcinosis: 1.6 ± 0.33 ; mortality: 40%). From this, we concluded that the adrenal cortex is capable of producing amounts of cardiotoxic corticoids sufficient to induce an ESCN in rats suitably conditioned with activating Na-salts (357).

A rather unexpected series of observations has been made recently on one-year-old Sprague-Dawley rats of both sexes, which received comparatively small amounts of ACTH (0.33 I.U./100 g of body-weight/day) during a period of 7 weeks. In the females, there developed an extremely pronounced, calcifying arteriosclerosis of virtually the entire vascular system. At the same time, there were thromboses in the coronaries, and multiple cardiac infarcts. In the males, the lesions were entirely different and consisted mainly of periarteritis nodosa and renal calculi. The authors were careful to point out that most of these animals were "discard breeders," which fact ". . . focuses attention on the stress of repeated pregnancy in

these animals as a sensitizing factor in the subsequent development of arteriosclerosis." They state furthermore, ". . . if, as Selye believes, the stresses of life are channeled through the pituitary-adrenal system, stress may conceivably be an important determinant in human arteriosclerosis." This view appears to find support in the authors' preliminary experiments ". . . on the effect of exposure to cold and heat [which] suggest that stressful situations other than exogenous administration of ACTH will also induce arteriosclerosis in these discard breeders" (405).

Innumerable observations have been made during the past 15 years on rats treated with ACTH for various purposes, yet no such severe cardiovascular lesions were seen, even after the administration of much higher doses of the hormone. Hence, these observations require confirmation. But, as our experiments on the ESCN have shown, the cardiovascular effects of ACTH are highly subject to conditioning influences; therefore, it is not impossible that some seemingly incidental factors (diet, previous stress experiences, latent disease) might have played a role also in the experiments on discard breeders.

Vasopressin

Focal, usually subendocardial, necroses may occur in the hearts of vasopressin-treated cats. At the same time, vasopressin often produces ECG changes and degenerative lesions in the cerebral cortex. Histologically, the myocardial necroses produced by vasopressin resemble those of digitalis poisoning, and it was thought that both types are due to a diminution of the coronary blood flow. However, these lesions are difficult to produce with vasopressin, allegedly because in order to obtain a positive result the dose of the hormone must be large, the time interval between succeeding injections must be optimal, and the animal must be old (68).

Vasopressin also greatly increases the incidence of the focal, myocardial lesions that are normally produced in rabbits by Pearce's virus III (266, 268). It has been observed, furthermore, that this hormone can precipitate an ESCN in rats pre-

treated with Me-Cl-COL (342) or with, in themselves inactive, low doses of Me-Cl-COL plus NaH_2PO_4 (356). These necroses may well be a result of the nonspecific stressor effect of the vasopressor principle.

Adrenalectomy and Adrenergic Hormones

Adrenalectomy does not prevent the production of the ESCN in the rat treated with Me-Cl-COL plus Na_2HPO_4 (342). Of course, this merely proves that living adrenal tissue is not necessary for the production of this lesion, since Me-Cl-COL substitutes for both the gluco- and mineralocorticoid activity of the suprarenals. It is more significant that even the myocardial necroses normally produced by heat, cold, adrenaline, and noradrenaline failed to be significantly affected by adrenalectomy, in rats maintained solely with triamcinolone ($500\mu\text{g}/\text{day}$). Triamcinolone is a pure glucocorticoid that fails to condition for the production of cardiac necroses by sensitizing Na-salts; hence, it is evident that neither exogenous nor endogenous mineralocorticoids are indispensable for the production of necrotic foci in the myocardium by the stressors just mentioned (342).

After simultaneous adrenalectomy and nephrectomy, injection of parathyroid extracts still produces myocardial necroses. Since, under these latter conditions, exogenous corticoids did not substantially aggravate the cardiac injury, it was concluded that there is no direct synergism between the parathyroid and corticoid hormones (202).

The repeated intravenous injection of adrenaline is a standard procedure for the production of arterial calcification in the rabbit. Many investigators who used this technique also found focal, myocardial necroses, with inflammatory infiltrates (86, 87, 98, 146, 182, 268, 271, 414). Cardiac necroses, accompanied by ECG changes, can likewise be produced in cats by the intravenous infusion of adrenaline solutions (393).

In a patient with asthma, long-term treatment with adrenaline resulted in a fatal myocardial lesion that appeared to have been identical with Fiedler's myocarditis (107). However, in

this case, there is no proof of an etiologic relationship between the adrenaline injections and the myocarditis. Since morbid lesions in the heart occur only quite exceptionally as a result of adrenaline treatment in man, it is probable that, at the most, the hormone may have played a conditioning role here.

Many other observations also suggest that the cardiotoxic effect of adrenaline—like that of corticoids—probably depends upon a “conditioning” for the effects of other potentially pathogenic stimuli. For example, in rabbits treated with adrenaline, the incidence of myocardial necroses and myocarditis is greatly augmented by the concurrent administration of caffeine, sparteine, or other cardiac stimulants (100, 107, 146). The earliest studies that suggested some such synergism between adrenaline and other agents were based on the observation that the cardiac damage caused by infection with typhoid bacilli is greatly enhanced by the concurrent administration of adrenaline, in rabbits (182). More recently, similar observations were made on rabbits inoculated with Pearce’s virus III (268) or treated with an allegedly specific “adrenaline sensitizer” extracted from microbes (360–362).

Myocarditis occurs quite commonly in rabbits, as a spontaneous disease, probably owing to a dormant infection (p. 137); hence, it is not impossible that whenever adrenaline alone was thought to have caused myocardial necroses and inflammation in this species, the hormone merely conditioned the heart for the potentially pathogenic effect of a latent infection.

Various pressor adrenaline derivatives, e.g., ephedrine, have been recommended for the therapy of coronary shock after myocardial infarction in man (5, 289a, 393a). Yet, the potentially cardiotoxic actions of adrenaline and its analogues must be kept in mind, especially when these substances are used in patients with pre-existent cardiac damage. In the rabbit, ephedrine (like adrenaline) can also produce cardiac necroses, although, allegedly, the myocardial lesions induced in this species by transection of the depressor nerves are somewhat lessened by concurrent treatment with ephedrine (243).

In rats sensitized by, in themselves ineffective, low doses of Me-Cl-COL plus NaH_2PO_4 , concurrent administration of adren-

aline or noradrenaline precipitates the development of the ESCN (356). As we shall see later (p. 147), Me-Cl-COL alone suffices to condition the heart for the necrotizing effect of these adrenergic hormones. It remains to be shown whether this cardiotoxic action is due to a specific property of the adrenergic hormones or merely to their stressor effect. On the other hand, the production of myocardial necroses by adrenaline (without concurrent corticoid treatment) is not significantly altered by NaClO_4 , Na_2SO_4 , or Na_2HPO_4 . Evidently, the electrolytes that are most active in conditioning the cardiac muscle for the toxic effects of Me-Cl-COL are inert in this respect (344).

We shall see later that repeated blood-letting, which lowers the blood pressure (and thereby presumably decreases the cardiac load), can protect the heart against necroses produced by various means. Here, let us merely mention that the myocardial necroses normally produced by adrenaline and noradrenaline are likewise prevented by blood-letting (342).

Insulin

According to some investigators, focal necroses in the heart and skeletal musculature occur after the induction of insulin shock in rabbits (240, 377) and in rats (160). These structural alterations are often associated with ECG changes, degenerative lesions in the central nervous system, and focal necroses in the liver. However, other extensive studies (140) failed to reveal any evidence of myocardial necrosis in rabbits that had been treated chronically with small doses, or acutely with shock-producing amounts, of insulin, although ECG changes were very prominent. This apparent contradiction between the findings of different investigators may also be due to the fact that certain breeds of rabbits bear dormant infections that can lead to myocardial necrosis and inflammation during exposure to certain stressors.

There is much more convincing evidence that myocardial lesions—quite similar to those seen in K-deficient animals—can occur in patients with diabetic acidosis (290). In this instance, the focal necroses with round-cell infiltration may be due to

hypokalemia (which often occurs in diabetic acidosis as a consequence of dehydration), an insufficient exogenous supply of K, the diuretic and dilution effects of intravenous glucose and saline therapy, or the K-fixing effect of insulin.

Thyroid Hormone

It was noted more than 35 years ago that scattered areas of myocardial necrosis, with round-cell infiltration, appear in rats fed large doses of desiccated thyroid (146). However, these lesions are inconstant and they never assume macroscopically visible proportions. Using carmine as a vital stain, it was possible to demonstrate the presence of many phagocytes and histiocytes, throughout the cardiac stroma of these animals. In the hearts that showed particularly severe myocarditis, some of the muscle fibers also tended to stain diffusely pink with carmine, in areas where the cross striations became indistinct. Sodium iodide (10 mg/day, subcutaneously, for 10 days) produced similar lesions, even in thyroidectomized rats; hence, it was thought that the cardiotoxic effect of the desiccated thyroid might have been due to its inorganic iodine content. The early electron-microscope manifestations of this kind of cardiac lesion have been studied in triiodothyronine-treated rats (277a).

In the rabbit, heavy overdosage with desiccated thyroid also produces focal, myocardial necroses (with secondary histiocytic infiltration and fibrosis) very similar to those of the ESCN. This effect is allegedly further enhanced by transection of the depressor nerves. Therefore, the cardiotoxic effect was attributed to the nonspecific action of cardiac overwork rather than to any specific effect of thyroxin (243).

An excellent review of the whole literature on the production of disseminated myocardial necroses by thyroid hormone overdosage has been presented by Dearing *et al.* (69). As these authors point out, even severe hyperthyroidism (induced by thyroid extract or thyroxin) only rarely causes focal myocardial lesions in the cat. Yet, even in this species, overdosage with thyroxin sensitizes the heart to the production of necroses by otherwise ineffective doses of digitalis. Here again, we are

apparently dealing with the conditioning effect of a hormone, although occasionally thyroxin alone suffices to elicit such changes in the cat (147a).

Exposure to various stressors (cold, quadriplegia induced by motor nerve transection, noradrenaline, forced restraint) failed to induce infarctoid, massive myocardial necroses (344) in rats pretreated with thyroxin. We mention this because, following pretreatment with Me-Cl-COL (or with, in themselves, inactive amounts of Me-Cl-COL plus Na_2HPO_4), the same stressors are highly effective in eliciting the ESCN-type of lesion. Oral administration of corn oil or glucose, which sensitizes for the development of the ESCN, is likewise unable significantly to aggravate the production of myocardial necroses by thyroxin (344).

In man, disseminated cardiac necroses, with inflammation, have been observed repeatedly in association with colloid or hyperthyroid goiter (91, 122, 205, 407). However, in no instance has it been possible to demonstrate that the thyroid disease was actually the cause of the myocardial change. A systematic reinvestigation of the subject has led to the conclusion that, in patients with hyperthyroidism, it is common to find "apparently swollen fibers with indistinct striations, but myocarditis or myocardial necroses are comparatively rare" (408).

In one patient, Fiedler's myocarditis was associated with a simple colloid goiter; at the same time, necroses, with surrounding gliosis, appeared in the central nervous system (225). But, of course, it was impossible to verify whether the three lesions were causally interrelated.

The mechanism through which thyroid hormone can sometimes produce structural lesions in the heart is not yet known. It is interesting, however, that, in young, growing rats, thyroxin-feeding increases the Mg-requirements. At the same time, the oxidative-phosphorylation efficiency of cardiac mitochondria is decreased and there develop typical signs of Mg-deficiency, which can be prevented by dietary supplements of Mg (395a). Following Mg-deprivation, the oxidative phosphorylation of cardiac mitochondria is also rapidly impaired (394). The metabolism of cardiac tissue seems to be peculiarly sensitive to

Mg-deprivation and to thyroxin. It is possible that the protection offered by $MgCl_2$ and KCl against various types of cardiac necroses depends upon an inhibition of some metabolic defect related to this impairment of oxidative phosphorylation. (For the effects of thyroparathyroidectomy, see the next section.)

Parathyroid Hormone

The ESCN produced by combined treatment with Me-Cl-COL plus NaH_2PO_4 is not prevented by removal of the thyroparathyroid apparatus in the rat. However, after **thyroparathyroidectomy** (with or without substitutive thyroxin treatment) or **parathyroidectomy**, the individual cardiac lesions tend to be smaller and more disseminated than under ordinary conditions and the large necrotic patches of the ESCN are rare. This suggests that parathyroid hormone has a conditioning influence in the ESCN, but is not an obligatory prerequisite for its development (342).

It has been claimed, however, that in the parathyroprival rat, bilateral nephrectomy no longer produces the usual uremic, myocardial necroses (201, 202). Since bilateral nephrectomy greatly stimulates parathyroid hormone secretion (319), it was concluded that the myocardial necroses characteristic of uremia are the secondary consequences of hyperparathyroidism. However, in Me-Cl-COL-pretreated, bilaterally nephrectomized rats, we were unable to prevent the development of cardiac necroses, either by thyroidectomy or by thyroparathyroidectomy (342).

Acute heavy overdosage with **parathyroid extract** produces a syndrome of generalized soft-tissue calcification, not unlike that induced by intoxication with vitamin-D derivatives (to be discussed later).

In rats simultaneously treated with parathyroid hormone and NaH_2PO_4 , there develops not only calcification but often also focal necrosis without calcification, in the myocardium. These lesions—just as those of the ESCN—can be prevented by the simultaneous administration of $MgCl_2$ or KCl. However, in animals that are not sensitized to parathyroid hormone by

NaH_2PO_4 -supplements, MgCl_2 and KCl are extremely toxic and do not exert any obvious protective effect upon the production of cardiac lesions by parathyroid hormone. Presumably, the Mg- and K-salts do not protect so much against parathyroid hormone itself, but rather against the damage that is normally induced by concurrent NaH_2PO_4 treatment. It had been thought at first that perhaps, here, MgCl_2 and KCl act merely by virtue of some local interaction with phosphates, which would prevent the absorption of the latter from the intestine. However, this hypothesis has been invalidated by the observation that even when NaH_2PO_4 is given subcutaneously (by the granuloma-pouch technique) to the parathyroid-hormone-treated rat, the concurrent oral administration of MgCl_2 and KCl still exerts a protective influence (335).

C. VITAMINS

Vitamin-D Derivatives

Vitamin-D Derivatives Alone. Almost 30 years ago it was noted that, in rats, certain sterols of the vitamin-D group can produce not only arteriosclerosis but also necrosis with calcification of cardiac muscle fibers (316, 317). On the basis of the purely histologic studies made at that time, it was impossible to decide whether, in this case, the myocardial calcification is the cause or the result of the necrosis. However, as we have seen, calcification of cardiac muscle fibers also occurs in the ESCN in which the necrosis is produced by steroids that possess no specific soft-tissue calcifying properties.

Vitamin-D Derivatives plus Stress. It has been claimed that, in rats chronically treated with irradiated ergosterol, the production of coronary sclerosis is enhanced by repeated periods of forced muscular exercise (276, 309). In connection with the role played by stress in the production of the ESCN, this could be of great interest. Our own preliminary experiments revealed a noteworthy aggravation of the vitamin-D-intoxication syndrome in rats exposed to brief periods of acute,

sublethal stress (produced by cold, heat, trauma, starvation, forced restraint).

Vitamin-D Derivatives plus NaH_2PO_4 . In view of the important role played by dietary NaH_2PO_4 -supplements in the ESCN, we wished to determine the possible effect of this salt upon the myocardial changes induced by vitamin-D derivatives. One of these, dihydrotachysterol (DHT), normally produces calcification and necrosis of the cardiac muscle in rats, without stimulating any significant local inflammatory reaction. However, if rats given DHT simultaneously receive dietary supplements of NaH_2PO_4 , the character of the cardiac lesions changes and an acute, suppurative myocarditis results. We thought, at first, that perhaps this change is merely due to an aggravation of the DHT-effect, rather than to a qualitative alteration of the response to DHT. However, unless NaH_2PO_4 is administered at the same time, even fatal doses of DHT (or of vitamin-D₃) produce only calcinosis without inflammation (328).

More recently, generalized soft-tissue calcification with myocardial necrosis and myocarditis, eventually resulting in congestive heart failure, has also been observed in rhesus monkeys that accidentally received a diet exceedingly rich in vitamin-D, calcium, and phosphorus (187a).

Like the typical ESCN, the acute arteriosclerosis (338a), as well as the diffuse myocarditis, normally produced in rats by DHT plus NaH_2PO_4 , can be prevented by the simultaneous administration of KCl or MgCl_2 (334, 354).

On the other hand, concurrent treatment with Me-Cl-COL greatly aggravates the cardiac lesions produced by NaH_2PO_4 plus DHT in the rat (328), mouse, rabbit, dog, and hamster (342). It is especially noteworthy, however, that 1 mEq or more of K or Mg (given as the chloride) is required to protect the heart against 1 mEq of Na (given as NaH_2PO_4) in the DHT-conditioned rats; while, in Me-Cl-COL-sensitized animals, one-eighth to one-fourth of this dose of K or Mg is sufficient to accomplish the same result (342). These quantitative relationships have not yet been worked out as regards the inhibition by MgCl_2 and KCl of the cardiopathy normally produced by concurrent treatment with Me-Cl-COL, NaH_2PO_4 plus DHT.

Under our standard experimental conditions, the production of a necrotizing myocarditis by combined treatment with DHT and NaH_2PO_4 is not significantly aggravated by pure *glucocorticoids* or *mineralocorticoids* alone, but stress (e.g., cold) or combined treatment with pure glucocorticoids and mineralocorticoids exerts a pronounced sensitizing effect. Thus, DHT (25 μg) plus NaH_2PO_4 (1 mM), given twice daily in the usual manner during seven days, caused no cardiac necroses, in rats with a mean initial body-weight of 100 g. Simultaneous treatment with DOC (1 mg of the acetate/day), triamcinolone (300 $\mu\text{g}/\text{day}$), Medrol (300 $\mu\text{g}/\text{day}$), or 6α -methyl-21-desoxy-cortisol (300 $\mu\text{g}/\text{day}$) was likewise ineffective, but, at the same dose levels, combined treatment with DOC and triamcinolone, Medrol, or 6α -methyl-21-desoxy-cortisol produced pronounced cardiac necroses and myocarditis. Similar treatment with DHT plus NaH_2PO_4 plus COL (1 mg of the acetate/day) was likewise highly effective (342). Similar observations were made in rats conditioned with DHT plus NaClO_4 instead of DHT plus NaH_2PO_4 , under otherwise identical circumstances (344).

In rats given Me-Cl-COL (50 $\mu\text{g}/\text{day}$) plus DHT (50 $\mu\text{g}/\text{day}$), NaClO_4 (1 mM twice daily) produced much more pronounced cardiac necrosis and calcification than did equimolecular amounts of NaH_2PO_4 , Na_2HPO_4 , NaHSO_4 , or Na_2SO_4 , while other Na-salts (NaCl , NaNO_3 , NaHCO_3 , Na-acetate or Na-lactate) were virtually ineffective. The fact that tissue calcification due to DHT can be greatly aggravated by phosphates has long been known and has always been ascribed to the rather specific effect exerted by the vitamin-D group upon phosphate metabolism. It is noteworthy, however, that in rats simultaneously treated with Me-Cl-COL, the perchlorate should be even more efficacious (342). In a similarly conducted experiment with salts other than those of Na, Ca-acetate and $\text{CaH}_4(\text{PO}_4)_2$ proved to be most effective in producing cardiac lesions. K_2HPO_4 was moderately effective, while $\text{MgH}_4(\text{PO}_4)_2$, KH_2PO_4 , $(\text{NH}_4)_2\text{HPO}_4$, MgSO_4 , KHSO_4 , NH_4HSO_4 , KClO_4 , $\text{Mg}(\text{ClO}_4)_2$, and K-acetate were inert. Thus, in the DHT plus Me-Cl-COL-conditioned rat, we again see that both the anion and the cation

participate in the production of cardiac lesions. For example, NaClO_4 is highly active, while KClO_4 is inert, and the Na-phosphates are much more effective than the K-phosphates or the acid Mg-phosphate (344).

We have already seen that, in the ESCN, myocardial necroses occur without any morphologic evidence of a vascular obstruction. It is in this respect that the ESCN differs most markedly from the usual spontaneous cardiac infarct of man. It must be kept in mind, however, that the development of all cardiac infarcts depends primarily upon the relationship between the metabolic requirements and the blood supply of the heart. Hence, combined treatment with active Na-salts and corticoids might act by inducing potentially dangerous metabolic changes within the myocardium, so that even the physiologic, normally well-tolerated, variations in its blood supply may result in necroses. In this case, the precipitating effect of stress could be due either to an additional increase in the metabolic demands of the cardiac muscle or to temporary variations in its blood supply that are not reflected in any detectable structural change within the coronary vessels. If this concept were correct, the ESCN might help to clarify the pathogenesis of those cardiac infarcts of man that are unaccompanied by acute vascular obstruction.

All our experiments concerning the ESCN were performed on healthy young animals with normal cardiac vessels, while spontaneous infarcts tend to occur with the greatest frequency in middle-aged or older men, in whom even a moderate degree of coronary sclerosis may well act as a predisposing factor for metabolic changes similar to those induced by electrolytes plus corticoids.

We thought that in order to elucidate this problem, it would be useful, first, to produce a moderate amount of coronary sclerosis and hardening (for instance, by pretreatment with DHT) and then, to determine whether such an "artificial aging" of the arterial system can sensitize the heart to the necrotizing effect of subsequent treatment with electrolytes and corticoids. Overdosage with DHT tends to cause rather diffuse sclerosis of the entire coronary system. Consequently, if our hypothesis were

correct, it would be expected that after DHT-pretreatment, the administration of electrolytes plus corticoids would affect the myocardium more markedly and cause necroses not only at the usual sites of predilection (the atria, the right ventricle, and the subendocardial layers of both ventricles).

To verify this hypothesis, albino rats were pretreated with DHT, during 10 days, so as to produce mild narrowing and calcification of the coronary arteries. After this, no further treatment was given until all the animals had recovered, as judged by their growth and clinical appearance. Then, combined treatment with NaH_2PO_4 plus Me-Cl-COL was initiated at a dose level that, in non-pretreated animals, caused only occasional microscopic foci of myocardial necrosis, localized in the areas of predilection. It was found that, in the DHT-pretreated rat, this dose level of NaH_2PO_4 plus Me-Cl-COL produces particularly extensive, macroscopically visible patches of necrosis throughout the heart. This finding appeared to support our hypothesis, but quite unexpectedly it was also noted that after sensitization with DHT, intense, proliferative, and eventually obstructive changes develop in all parts of the coronary tree during NaH_2PO_4 plus Me-Cl-COL treatment (341). The mechanism of this vascular sensitization is not yet clear, but these observations suggest that the electrolyte-steroid effect is not necessarily limited to the cardiac muscle itself but may also participate in the production of obstructive coronary lesions (see figs. 13, 14).

Subsequently, it has been shown that the arteriosclerosis produced by Me-Cl-COL plus NaH_2PO_4 , in rats sensitized by a previous short-term treatment with DHT, can also be inhibited both by KCl and MgCl_2 , even if these salts are administered only during the period of Me-Cl-COL plus NaH_2PO_4 treatment (334) (see figs. 15, 16).

In connection with this experimental syndrome of coronary lesions and cardiac necroses, it is interesting to speculate on the possibility that, in man, coronary thrombosis may occasionally also be a result, rather than a consequence, of cardiac necrosis. In our experiments on rats pretreated with DHT (as in patients who have reached an age in which coronary infarcts are common), the cardiac vessels were already affected at the time that

necrosis was produced. Hence, it is possible that endothelial damage and a slowing of the circulation through the sclerotic vessels acted as contributing factors for the production of thrombosis in areas that became necrotic owing to subsequent Me-Cl-COL plus NaH_2PO_4 treatment. Is it not conceivable that in an elderly person, in whom the coronaries are somewhat similarly affected, the production of cardiac necrosis due to biochemical changes in the heart muscle may secondarily result in a thrombosis of the affected area?

Conditioning for DHT-Toxicity by Various Electrolytes. Our next concern was to verify whether electrolytes other than Na-phosphate could likewise produce purulent myocarditis in DHT-conditioned rats.

For this purpose, an additional series of experiments was performed on 330 rats, subdivided into 33 equal groups and treated with 1 mM of various electrolytes mixed with 25 μg of DHT in 2 ml of water, twice daily by stomach tube, during 12 days, as outlined in Table 11. In this case, the cardiac lesions were graded on the basis of histologic examination of slides stained with von Kóssa's technique for the demonstration of calcium. In Table 11, the column "Cardiac Lesions" gives the means arrived at by combining the readings for calcification and myocarditis (both estimated in arbitrary scales of 0-3), while in the columns "Aortal Calcification" and "Nephrocalcinosis," only macroscopically visible calcium deposits were taken into consideration.

It is evident that this small dose of DHT produced no detectable change in itself, and that, with very few exceptions, only phosphates produced noteworthy cardiac lesions, aortal calcification, or nephrocalcinosis in the DHT-conditioned animals. The most noteworthy exception to this generalization is: that NaClO_4 (Group 9) also produced definite myocardial calcification, myocarditis, and aortal calcification. Essentially the same was true of all the calcium salts that were not immediately fatal under these circumstances (Groups 30, 31, and 33), except that they caused virtually pure tissue-calcification without inflammation. The animals treated with calcium nitrate (Group 32) died too soon for any definite conclusions to be made. Curiously, in the rats treated with Mg-biphosphate (Group 21), the nephrocalcinosis was quite predominantly localized in

the renal papillae; in those given CaCl_2 or Ca -acetate (Groups 30 and 31), in the renal cortex; and in those given Na-phosphates (Groups 5 and 6) or NaClO_4 (Group 9), at the cortico-medullary junction and in the renal cortex.

TABLE 11
Conditioning by Various Electrolytes for the Toxic Actions of DHT

Group	Treatment *	Cardiac Lesions	Aortal Calcification	Nephro-calcinosis	Mortality (%)
1	None	0	0	0	0
2	NaCl	0	0	0	0
3	$\text{NaOOC}\cdot\text{CH}_3$	0	0	0	0
4	NaNO_3	0	0	0	10
5	NaH_2PO_4	1.8 ± 0.30	1.0 ± 0.28	2.7 ± 0.10	20
6	Na_2HPO_4	0.9 ± 0.35	0.9 ± 0.25	1.4 ± 0.28	20
7	NaHSO_4	0.1 ± 0.10	0	0.1 ± 0.10	20
8	Na_2SO_4	0	0	0	10
9	NaClO_4	0.6 ± 0.39	1.0 ± 0.30	0.2 ± 0.20	10
10	KCl	0	0	0	0
11	$\text{KOOC}\cdot\text{CH}_3$	0	0	0	0
12	KNO_3	0	0	0	0
13	KH_2PO_4	1.7 ± 0.35	0.9 ± 0.37	2.0 ± 0.35	20
14	K_2HPO_4	1.6 ± 0.37	0	2.1 ± 0.25	100
15	KHSO_4	0.1 ± 0.10	0	0.3 ± 0.30	20
16	K_2SO_4	0	0	0	50
17	KClO_4	0	0	0	0
18	MgCl_2	0	0	0	20
19	$\text{Mg}(\text{OOC}\cdot\text{CH}_3)_2$	0	0	1.1 ± 0.38	20
20	$\text{Mg}(\text{NO}_3)_2$	0.1 ± 0.10	0	0	100
21	$\text{MgH}_4(\text{PO}_4)_2$	0.7 ± 0.20	0	1.5 ± 0.35	30
22	MgSO_4	0	0	0	0
23	$\text{Mg}(\text{ClO}_4)_2$	0.2 ± 0.15	0	0	100
24	NH_4Cl	0	0	0	0
25	$\text{NH}_4\text{OOC}\cdot\text{CH}_3$	0	0	0	0
26	NH_4NO_3	0	0	0.2 ± 0.15	20
27	$\text{NH}_4\text{H}_2\text{PO}_4$	0.1 ± 0.10	0	1.4 ± 0.15	30
28	NH_4HSO_4	0	0	0.1 ± 0.10	70
29	NH_4ClO_4	0	0	0	70
30	CaCl_2	0.6 ± 0.27	0	0.5 ± 0.30	90
31	$\text{Ca}(\text{OOC}\cdot\text{CH}_3)_2$	1.5 ± 0.37	0.9 ± 0.32	2.1 ± 0.28	20
32	$\text{Ca}(\text{NO}_3)_2$	0	0	0	100
33	$\text{CaH}_4(\text{PO}_4)_2$	0.8 ± 0.39	0.1 ± 0.10	1.3 ± 0.30	60

* In addition to 1 mM, twice daily, of each salt listed in this column, the rats (Sprague-Dawley females with a mean initial body-weight of 100 g) received 25 μg , twice daily, of DHT in all groups during the 12 days of this experiment.

As a general conclusion, it may be deduced from these observations that the electrolytes that proved to be most potent in producing an ESCN in corticoid-conditioned rats are not necessarily effective in causing morbid changes after treatment with DHT. This fact suggests a fundamental difference in the mechanism through which corticoids, on the one hand, and sterols of the vitamin-D group, on the other, exert their conditioning effects.

Vitamin-B₁

Several authors reviewed the myocardial changes that occur in the course of vitamin-B₁ deficiency in various species (105, 372).

Among silver foxes bred on fur farms, there sometimes develops a peculiar nutritional disease, "Chastek paralysis" (a counterpart of Wernicke's hemorrhagic polioencephalitis), which is accompanied by focal necroses in the liver and myocardium. Since dietary supplements of thiamine readily prevent such outbreaks, the malady has been considered to be a form of B₁-avitaminosis (89).

Multiple myocardial necroses (in one case sufficiently large to become macroscopically visible) have also occurred among thiamine-deficient pigs. These cardiac foci were first infiltrated by polymorphonuclear and mononuclear cells; later, they healed with scar-formation. No cardiac lesions were observed in a large number of pigs that died as a result of other vitamin deficiencies or of inanition; hence, the myocardial necroses were ascribed specifically to the lack of thiamine, although no changes were found in the nervous system (105, 410).

Focal myocardial necroses may also develop during vitamin-B₁ deficiency in the monkey (289), dog (282, 372), rat (13, 221), and in man (402). In several of these species, the cardiac lesions of B₁-deficiency are accompanied by ECG changes and by focal necroses in the skeletal musculature. In the dog, there may be flaccid paralysis of the neck muscles, similar to that seen in this species during hypokalemia. However, all these changes are quite inconstant, hence, their occurrence may well depend upon the simultaneous action of condi-

tioning factors. For example, one investigator, who found no myocardial changes in severely thiamine-deficient rats, claimed that, under his conditions of experimentation, the myocardial necroses of K-deficiency could be actually prevented by simultaneous vitamin-B₁-deprivation. Curiously, the renal lesions and skeletal-muscle necroses, characteristic of K-deficiency, did occur, even in rats concurrently deprived of thiamine (104).

Choline

Myocardial changes have long been known to occur in choline-deficient rats (80). However, the first investigators did not realize that the presence of certain dietary fats is important for the production of such lesions by choline-deficiency.

The fatty degeneration of the liver, characteristic of choline-deficiency, is notoriously aggravated by an increased fat intake. In the course of a study on the relationship between dietary fatty acids and fatty liver production, it was observed that on a synthetic, choline-free diet that contains 35% ethyl laurate almost all rats died within a week and exhibited histologic signs of myocardial necrosis and inflammation (371). These changes do not occur if choline, betaine, or methionine is added to such diets. The myocardial changes of choline-deficiency are very reminiscent of those produced by K-deficient diets, but the two types of lesions differ essentially, because in choline-deficient rats: (1) the K-content of the myocardium is not decreased, and (2) dietary K-supplements do not prevent the cardiopathy (188).

A systematic re-examination of this subject showed that, in choline-deficient rats, myocardial necrosis is preceded by the deposition of stainable fat droplets in the myocardial fibers. Cardiac damage can develop, even on fat-free, choline-deficient diets, but fatty acid supplements sensitize for it. In this respect, lauric acid is especially effective, while tricaprin, tricaprylin, trimyristin, and tripalmitin are less potent. Among the naturally occurring fats, beef fat and lard produced more cardiac damage in choline-deficient rats than did corn or coconut oil. Although renal necroses often occur in choline-deficient rats,

they do not appear to be the cause of the myocardial damage, since cardiac necroses may occur in animals with essentially normal kidneys (406).

Cardiac and hepatic necrosis can also be produced in mice, by varying the protein, fat, and choline content in rather complex diets. The brief abstract in which these findings were described gives few details, but it is evident that, here, the necrosis occurred only after from two to ten months of treatment (406a).

The possible relationships between the myocardial necroses produced by choline-deficiency and the ESCN have not yet been adequately investigated. However, as shall be discussed (p. 109), oral administration of fat-supplements aggravates the ESCN. In view of this, it would be interesting to see whether steroids and electrolytes can modify the effect of choline-deficiency upon the heart, and, conversely, whether choline has any influence upon the development of the ESCN (see also Acetylcholine, p. 102).

Other Vitamins

Focal necroses of myocardial fibers have also been found in vitamin-C deficient guinea pigs (234).

In vitamin-E deficient rats, cardiac necroses with fibrosis and pigment deposition occur quite commonly but somewhat later than in the skeletal musculature (229).

As we shall see (p. 110), sulfaguanidine or succinylsulfathiazole can produce myocardial necroses in rats and mice on certain synthetic diets. Recent investigations suggest that the addition of either vitamin-E or vitamin-K (62, 71) to such diets prevents the production of these cardiac lesions in mice. This would suggest that at least some degree of deficiency in both vitamin-E and vitamin-K is necessary in order to condition the myocardium for the production of necroses by these sulfa-compounds (71).

On the other hand, the myocardial necroses and hemorrhages produced in mice by large amounts of dicumarol could be prevented only by vitamin-K, not by vitamin-E (70).

D. CARDIAC GLYCOSIDES AND THEIR AGLYCONES

Myocardial Necroses Following Intoxication with Digitalis and Related Compounds. Probably one of the first, if not the first, observation concerning the experimental production of toxic cardiac necroses is contained in the doctoral thesis of A. Lewitzky (206). This author treated a number of rabbits, dogs, and cats with large amounts of digitalis extracts and observed myocardial necroses with secondary inflammatory phenomena. The findings of this Russian investigator have been subsequently confirmed and extended by numerous authors, using a variety of extracts or purified cardiac glycosides, in the cat (20a, 45, 69, 161, 191, 209, 210, 392, 400) and dog (171, 197). One investigator specifically commented on the absence of focal myocardial necroses in cardiac patients treated with heavy doses of digitalis (197), but it has been alleged that actual infarcts have sometimes been produced by digitalis in man (79).

There is no uniformity of opinion regarding the mechanism through which cardiac glycosides produce morphologic changes in the heart. In any event, here, as in the ESCN, anatomic evidence of a coronary occlusion has never been seen.

Relationships Between Corticoids, Potassium, and Cardiac Aglycones. Steroid hormones and cardiac aglycones are similar, not only in their chemical structure, but also as regards their pharmacologic actions. We have already mentioned that cardiac glycosides and aglycones elicit chemical and functional changes in the papillary muscle of cats, *in vitro*, which are strikingly similar to those produced by 9 α -fluorocortisol (258, 378). Furthermore, several synthetic steroid alkylamines exert important antiaccelerator and antiarrhythmic effects upon the heart (125, 126, 228, 307).

It has also been claimed (though this requires confirmation) that cardiac glycosides can protect the intact cat against K-poisoning, lower the plasma-K level, and prolong life after adrenalectomy (418).

It is interesting in this connection that, in cats, even therapeutic doses of digitalis significantly increase the intracellular K- and water-content of the cardiac muscle but reduce the chloride and extracellular water-concentration. On the basis of these findings, it has been suggested that, in cardiac failure, the beneficial effects of digitalis may be brought about, in part, by a corticoidlike action upon the myocardium, whereby K is maintained within the cell and cell hydration is improved (32).

On the other hand, in the rat, the cardiac necroses and ECG-changes that develop on K-deficient diets are allegedly not influenced by digitalis (289b).

A review of the rather extensive literature on the role of K in the mechanism of digitalis actions (219) revealed several relevant facts: (1) orally administered K temporarily abolished the ECG manifestations of digitalis intoxication in patients, (2) various procedures that cause a loss of K increase sensitivity to digitalis, (3) the failing heart is depleted of K, and (4) the normal, in contrast with the failing, heart is comparatively resistant to digitalis intoxication. Stimulated by these earlier observations, it was then shown that DOC decreases the threshold of digitalis toxicity in patients, presumably as a result of the K-depletion induced by this steroid (219, 220).

E. OTHER CHEMICAL COMPOUNDS AND FOOD CONSTITUENTS

Since electrolyte-steroid-cardiopathies are the principal topic of this monograph, special sections have been devoted to the Electrolytes (p. 17), the Steroids (p. 54), the Vitamins, with particular reference to the sterols of the vitamin-D group (p. 90), and the Cardiac Glycosides which also contain the steroid nucleus (p. 100). However, many other drugs and food constituents can produce focal myocardial necroses, at least under certain experimental conditions. Virtually nothing is known about the mechanism through which these latter agents affect the cardiac muscle, but preliminary studies with a few such compounds have convinced us that the production of cardiac necroses by almost any means is likely to be influenced—at

least to some extent—by those factors (steroids, electrolytes, stress) that determine the development of the typical ESCN. Hence, a critical survey of the widely scattered data in the relevant literature may be of assistance as a guide to the future experimental elucidation of this field.

At the present time, it would hardly be possible to give a rational structure to such a review; therefore, in the following pages, we shall merely survey the literature on the production of myocardial necroses by chemical means, in the alphabetic order of the agents that were employed.

Acetylcholine. In dogs, daily infusions of large quantities of acetylcholine caused thromboses in the coronary arteries, accompanied by multiple infarcts and thromboses in other organs (142). Although these findings were thought to suggest the participation of cholinergic factors in the genesis of cardiac infarcts, the thromboses in these dogs may have been merely due to the constant intravenous infusions. No control experiments were done to check this point, nor was there any evidence of a specific effect upon the heart, since so many other organs were similarly affected.

Arsenic. Myocardial necrosis with inflammation (often claimed to resemble Fiedler's myocarditis) has repeatedly been observed in syphilitic patients who received treatment with various organic arsenicals (42, 75, 259, 380). The rather extensive clinical literature on this subject has been surveyed elsewhere (42). Suffice it to point out here that in such cases the cardiac lesions have variously been ascribed to syphilis, the exfoliative dermatitis that the arsenicals often produce, or to a direct action of the arsenicals themselves.

Using large doses of arsphenamine in rats, we succeeded in producing typical focal myocardial necroses without any complicating skin lesions. It is evident, therefore, that the arsenicals themselves can induce myocardial changes of this type. Our preliminary experiments suggest, furthermore, that the cardiac lesions produced by threshold doses of arsphenamine can be aggravated by Me-Cl-COL or Na_2HPO_4 and inhibited by KCl or MgCl_2 (344).

Azide. In rats given large amounts of sodium azide, myocardial necroses appear, in association with necrotic and degenerative lesions in the brain (160).

Barium. Intravenous administration of barium chloride, in doses thought to produce cardiac anoxia, sensitize the rabbit for the production of focal myocardial lesions by inoculation with Pearce's virus III (268). It may be questioned whether in such experiments the effect of barium is actually the result of anoxia. As we have repeatedly pointed out in this monograph, various potentially cardiotoxic agents (including Pearce's virus III) tend to produce myocardial necroses more readily in animals exposed to systemic stressors: it remains to be seen whether all stressors act by diminishing the oxygenation of the heart.

Carbohydrates. In rats treated with subthreshold amounts of Me-Cl-COL plus NaH_2PO_4 , oral administration of glucose can precipitate a typical ESCN; it also aggravates the accompanying nephrocalcinosis (348). Carbohydrate ingestion tends to cause hypokalemia; this may play an important role here.

Carbon Monoxide. In rabbits, carbon monoxide poisoning produces multiple, focal myocardial necroses. These are accompanied by changes which led to the conclusion that CO damages the heart merely by producing anoxemia. Forced muscular exercise (in a revolving drum) intensifies both the ECG changes and the cardiac necroses, in the CO-intoxicated rabbit (57, 393).

In man, the production of myocardial necroses by CO or coal gas has often been reported, especially because of its forensic importance. These are sometimes accompanied by hemorrhage, calcification, and—if the patient lives long enough—secondary inflammatory infiltration of the affected area. Usually, the necrotic foci are comparatively small, but occasionally, large infarctlike necrotic patches have been observed (37, 116, 157, 158, 174, 192–194, 382).

Cholesterol. The voluminous literature on experimental cholesterol atherosclerosis and its possible bearing upon the

cardiovascular diseases of man have been the subject of an extensive review (199). Although the coronary arteries are frequently affected in rabbits with cholesterol atheromatosis, cardiac necroses—and particularly, true cardiac infarcts—are uncommon.

Nothing is known as yet about the possible influence of cholesterol upon the typical ESCN or about the possibility of modifying cholesterol atheromatosis by the steroids that prove particularly effective in regulating the development of an ESCN (for the effect of Mg, see p. 32).

Data on the cardiotoxic actions of other fats and lipoproteins (some of which contain cholesterol) are discussed under Lipids (p. 108) and Choline (p. 98).

Dicumarol. In mice, large doses of dicumarol can produce myocardial necroses with hemorrhages and inflammation. As previously stated (p. 99), these lesions can be prevented by vitamin-K (70).

Dinitrophenol. Focal myocardial necroses, accompanied by hepatic and renal lesions, have been observed in a patient who died of accidental dinitrophenol intoxication (280). Similar necroses with round-cell infiltrations have also been noted in the hearts of rats poisoned with dinitrophenol (160), but under our experimental conditions we have not been able to confirm this (344).

Enzymes. Extensive focal myocardial necroses can be produced in rabbits by a single intravenous injection of certain proteolytic enzymes, particularly papain, trypsin, ficin, and crude streptokinase. The distribution of these lesions is very similar to that in the ESCN: the foci occur most frequently in the atria, the subendocardial layers of both ventricles, and in the wall of the right ventricle. Within the affected areas, Anitschkow-myocytes and multinucleated giant cells are commonly observed; therefore, certain pathogenic relationships have been suspected between these lesions and spontaneous collagen diseases, such as rheumatic fever and periarteritis nodosa. Occasionally, there is also calcification in the necrotic foci. The skeletal musculature (especially the diaphragm) is

likewise commonly affected. Similar changes have been produced with papain in rats and mice, but not in chickens or guinea pigs. It was thought unlikely that these enzyme-necroses could be related to the hypokalemic myocardiopathy, because the K-concentration of the blood is not significantly affected in rabbits that receive a dose of papain sufficient to produce marked myocardial lesions (186).

Similar focal myocardial necroses have also been produced in a high percentage of rabbits, guinea pigs, and mice given a single intravenous injection of crystalline streptococcal proteinase (187). This finding is of particular interest because of the well-known association between rheumatic fever and antecedent streptococcal infections; it allegedly "suggests the possibility that specific streptococcal products may be directly implicated in the pathogenesis of the anatomical changes present in rheumatic heart disease."

In dogs, focal myocarditis, with interstitial mitral valvulitis, was produced by intravenous injections of papain, but essentially similar changes occur in animals with temporary or permanent arteriovenous fistulae; hence, it was concluded that "the effects of the papain may be due to direct enzymatic action on the cardiac structures or to nonspecific cardiovascular stress." However, in dogs in which arteriovenous fistulae were produced or amphetamine was injected, for the production of stress, a subsequent papain injection did not result in a significantly greater incidence or severity of cardiac lesions than it did in nonstressed controls (264).

We have performed systematic studies with papain on female Sprague-Dawley rats, under our usual experimental conditions for studies on the ESCN. This work showed that **Me-Cl-COL** and/or Na_2HPO_4 greatly sensitize the myocardium to the production of necroses by a single, subsequent intravenous injection of papain extract. On the other hand, MgCl_2 and **KCl** are extremely effective in protecting the heart against this type of enzymatic damage. It is significant that the hepatic necroses and renal changes that also occur in rats, following massive intravenous injections of papain, are quite similarly influenced by **Me-Cl-COL**, Na_2HPO_4 , MgCl_2 , and **KCl** (343). It is gen-

erally assumed—although perhaps not definitely proved—that proteolytic enzymes, such as papain, produce necroses by acting directly upon the tissue proteins. If this is so, the observations just described would imply that the humoral agents that we employed can even modify the susceptibility of tissues to proteolysis, *in vivo*.

In rats kept either on Mg- or on K-deficient diets for one week, the production of myocardial necroses by the intravenous injection of papain extract is greatly aggravated. This sensitizing effect of the K-deficient diet can be abolished by supplements of not only K but also of $MgCl_2$, and that of the Mg-deficient diet, not only by Mg but also by KCl (343d).

Like the typical ESCN-changes, the myocardial necroses produced by intravenous administration of papain are largely inhibited by preceding repeated hemorrhages, and enhanced by injections of noradrenaline. It is to be assumed that a decrease or increase in the cardiac load produced by hemorrhage and noradrenaline, respectively, is responsible for this change in the sensitivity of the myocardium to the action of the enzymes (344).

It has been noted, furthermore, that in rats exposed to the severe stress of prolonged restraint (strapping to a board), papain produces particularly severe cardiac necroses (17). Therefore, the previously mentioned, negative findings of Parker *et al.* (264) may have been due to the fact that these authors employed comparatively mild stressors.

Ethanol. There appears to be some similarity between Fiedler's myocarditis and the cardiopathy that tends to develop in chronic alcoholics (38, 39).

In order to establish the effect of ethanol upon the ESCN, an experiment was performed on 20 female Sprague-Dawley rats, with a mean initial body-weight of 97 g. All animals were treated with Me-Cl-COL (100 μ g./day) plus Na_2HPO_4 (1 mM twice daily). In addition, 10 of these rats received 1 ml of 50% ethanol, twice daily, by stomach tube, together with the Na_2HPO_4 . The experiment was terminated after 6 days. By this time, none of the controls had shown any sign of myo-

cardial damage, while 50% of the rats that received ethanol had severe (grade: 1.0 ± 0.30) myocardial necroses. It remains to be seen, however, whether experiments such as these have any bearing upon the "alcoholic cardiopathy" of man.

Fluorine. In the rat, large doses of Na-fluoroacetate produce focal myocardial necroses, in association with lesions in the cerebral cortex. This was ascribed to the antienzymatic action of the compound (159, 160). In connection with the ESCN, it is noteworthy that the production of cardiac necrosis by Na-fluoroacetate, in rats, is greatly aggravated by pretreatment with Me-Cl-COL (p. 147).

The histologically demonstrable succinic dehydrogenase activity disappears from the necrotic areas of the heart, in rats intoxicated with Na-fluoroacetate (396). It remains to be seen, however, whether this change in enzymatic activity is the cause or the consequence of the necroses.

Gum Acacia. Intravenous injection of gum acacia greatly enhances the production of focal myocardial lesions by Pearce's virus III, in rabbits (266, 268). However, there is no evidence that this gum could not produce myocardial damage in itself; besides, its influence upon virus-infected rabbits may merely be due to a nonspecific stressor effect.

Histamine. Many investigators found that, in rabbits, severe intoxication with histamine can produce multiple myocardial necroses concurrently with ECG changes and hepatic necroses (155, 237, 238, 379, 393). Most of the authors who observed this phenomenon ascribed especial significance to it because of the important role played by histamine in certain hypersensitivity reactions and in shock. However, all these investigators were apparently unaware of the fact that so many earlier workers obtained similar lesions by a variety of other agents, so that the response to histamine may well be a wholly nonspecific stress effect.

Iodine. In the section on the thyroid (p. 87), we have already mentioned that subcutaneous injections of NaI can pro-

duce myocarditic changes in rats (146), but this conclusion was based on a very small experimental series and has not yet been confirmed. On the other hand, Na-monoiodoacetate (an enzyme-poison that interferes with lactic-acid production in muscle) rather consistently produces focal, myocardial hemorrhages and severe ECG changes, in the rabbit (299).

Lead. In man, chronic lead poisoning may produce a cardiopathy that is apparently related to the lesions of the ESCN (359a).

Lipids. It has long been suspected that the fat-content of the diet plays an important role in the development of various experimental and spontaneous cardiovascular diseases (136). Allegedly, even typical focal myocarditis can be produced by high-fat diets, at least in certain strains of mice (363). Some pertinent data have already been mentioned under the headings Choline (p. 98) and Cholesterol (p. 49).

The extensive studies of Gofman (119) led him to conclude that an elevation of lipoproteins of the S_r 0-12, 12-20, 20-100, and 100-400 classes in the serum is associated with an increased risk of myocardial infarction in man. He believes that the dietary management of coronary disease and the prophylaxis of myocardial infarction through nutritional means must primarily aim at lowering these lipoprotein levels. It appears that animal fat contains some factor that provokes elevation in the serum levels of S_r 0-12 and 12-20 class lipoproteins, but there is no valid evidence to substantiate the views expressed by some investigators, that vegetable oils depress these same lipoproteins. Restriction of dietary carbohydrate, on the other hand, can provoke a marked fall in the serum level of the S_r 20-100 and 100-400 lipoprotein classes. It is thought that the beneficial effect of caloric restriction and weight reduction can be largely explained on the basis of the alteration in animal fat and carbohydrate intake (119). These investigations further highlighted the important role played by fats in the pathogenesis of cardiovascular disease.

In dogs fed a high-fat diet for 8 weeks or longer and then

subjected to a standard (surgical or chemical) experimental renal injury, there develops an acute polyarteritis, often associated with focal necroses in the myocardium (167, 168).

Experiments on rats indicate that the degree of myocardial necrosis and nephrocalcinosis normally produced by combined treatment with Me-Cl-COL and Na₂HPO₄ can be considerably increased by the oral administration of various plant or animal fats, but it remains uninfluenced by mineral oil (336). It is evident, therefore, that the dietary fat-intake greatly sensitizes the heart to the production of an ESCN. However, in this respect, the various fats that have been tested so far are approximately equal in activity, except the mineral oil, which is unabsorbable and was merely used as a control substance.

Malononitrile. In the rat, malononitrile can produce focal myocardial necroses. These are usually associated with severe degenerative and necrotizing lesions in the cerebral cortex, the corpus striatum, the corpus callosum, the optic tracts, and the hippocampus (160).

Pentamethylenetetrazol. Multiple myocardial necroses (with severe ECG-changes) can be produced in rabbits by toxic doses of pentamethylenetetrazol (240). In the rat, we have not been able to confirm this even when just sublethal doses of the compound were administered (344).

Peptone. During severe peptone shock, multiple myocardial necroses tend to develop in rabbits. These lesions were found to be very similar to those elicited by histamine, anaphylactic shock, or severe pulmonary embolism. It was, therefore "suggested that, in all these four conditions myocardial ischemia, accompanying acute *cor pulmonale*, is responsible for the injury" (155). The fact that so many other agents produce similar cardiac changes has not been taken into account.

Plasmocid. Multiple necroses—not only in the myocardium but also in skeletal muscle—occur quite frequently in rats treated with high doses of plasmocid [8-(3-diethylaminopropylamino)-6-methoxyquinoline] (160). In the necrotic areas

so produced, the histochemically demonstrable succinic dehydrogenase activity is reduced (396).

Curiously, the myocardial necroses produced by plasmocid do not appear to obey the laws that govern the actions of most other cardiotoxic agents that we have discussed in this volume. For example, it is extremely difficult, if not impossible, to influence the effect of plasmocid upon the heart by NaH_2PO_4 , Na_2HPO_4 , ME-Cl-COL, noradrenaline, or hemorrhage (344).

Selenium. The myocardial necroses that occur in rats kept on a vitamin-E- and cysteine-deficient diet can be prevented by extraordinarily low doses (13.3 $\mu\text{g}/\text{day}$) of Na-selenite. In the prevention of these lesions, selenium is far more effective than either vitamin-E or cysteine (314).

Sodium Polyanetholsulfonate. This compound, also known as "Liquoid," can produce myocardial necroses concurrently with other manifestations of the generalized Shwartzman phenomenon. The substance also increases the ability of bacterial toxins to produce a generalized Shwartzman phenomenon (131).

Sulfur. Cutaneous infections have been observed in many patients who died of Fiedler's myocarditis. In one of these, the dermatitis was due to indiscriminate treatment with a sulfur-containing ointment (233). In this case, it seemed rather probable that the myocarditis was the direct or indirect consequence of the sulfur treatment.

Interstitial myocarditis—sometimes with focal myocardial necroses and calcification—has also been observed after treatment with sulfaguanidine (sulfanilylguanidine) or succinyl-sulfathiazole in the mouse, rat, and man (12, 61, 62, 110, 200). In rats, this type of carditis is usually accompanied by hypertension, renal injury, and arterial calcification. Like the ESCH, the sulfa-syndrome is aggravated by an excess of NaCl and can be largely prevented by NH_4Cl . It would seem, therefore, that this type of lesion is partly due to renal insufficiency and is more closely related to the ESCH than to the ESCN. However, as previously stated (p. 99), the sulfa-necroses can also be prevented by dietary supplements of vitamins E and K.

F. PHYSICAL AGENTS, INCLUDING SURGICAL INTERVENTIONS

Interventions on the Cardiovascular System

A number of surgical procedures have been devised for the production of myocardial infarction by direct interference with the blood supply of the heart. The lesions so produced are not directly related to the toxic myocardial necroses that form the main subject of this monograph. However, we must at least briefly consider simple infarcts, because the changes elicited by mechanical interference with the cardiac blood supply furnish suitable control material for the evaluation of the chemically induced necroses.

Ligation of Coronary Branches. When the left circumflex coronary artery of dogs is ligated close to its origin, a large infarct develops in the posterior papillary muscle and the posterolateral portion of the left ventricle. Because of the rather uniform and predictable size and position of such infarcts, they are well suited for the study of factors that influence the course of myocardial necroses in general (176). Using this experimental technique, it was found that, within the first 60 to 90 minutes after vascular obstruction, about 10% of the ionic-K is lost from the infarcted tissue. By the end of 12 hours, the intracellular K-concentration falls nearly to the extracellular level of this ion. Histochemical studies showed, furthermore, that normally, K is distributed evenly throughout the cardiac muscle fiber, without any obvious relation to intracellular structures. About 12 hours after the vascular occlusion, virtually no K is histochemically demonstrable in the myocardial fibers (175). Here, the loss of tissue-K is evidently the consequence of cellular death, yet, as nutritional experiments have shown, K-deficiency can also be the cause of cardiac necrosis.

Embolization of Coronary Vessels. In order to obtain multiple, focal myocardial necroses, air or suspensions of small particles (oil, starch) have been injected intravenously in rabbits. Of course, under these conditions, infarcts also occur in

extracardiac tissues, particularly in the lung, where they are first carried from the intravenous injection site (397). If larger particles (e.g., 1.9–2.8 mm glass beads) are injected intravenously in rabbits or cats, the particles cannot pass through the pulmonary capillaries and, hence, a direct obstruction of coronary branches is excluded. Yet, even then, multiple myocardial necroses occur, as judged by the infarctlike ECG changes that ensue, and by actual histologic observation. In this case, the necroses are most commonly situated in the right ventricle; they have been ascribed to a sudden increase in the load upon this part of the heart, which results from the pulmonary embolisms (239). Multiple myocardial necroses also occur in rabbits in which pulmonary embolisms are produced by the intravenous injection of either lycopodium spores or air. Here, the ECG pattern is similar to that found in acute *cor pulmonale* (154). It is likewise possible to produce myocardial infarction by direct embolization of the coronary arteries (in open-chest dogs) with plastic beads suspended in methylcellulose (6).

Direct Trauma to the Cardiac Muscle. Cardiac necroses can also be produced in circumscribed areas, quite independently of the blood supply, by the topical application of toxic agents (silver nitrate, ethanol) to the heart (53) or by electrocautery (368), for example, in open-chest dogs.

The fact that interventions on the cardiovascular system may predispose the heart for the production of focal necroses by other agents has already been mentioned. For example, in rabbits infected with Pearce's virus III, a preceding cardiac puncture greatly augments the incidence of necrotic and inflammatory changes that are normally produced by this microorganism (266).

Special Surgical Intervention Outside the Cardiovascular System

We have already mentioned that unilateral nephrectomy sensitizes the rat to the production of an ESCH by mineralocorticoids (351), and that partial destruction of the kidney may induce cardiac necroses in dogs kept on high-fat diets (167, 168) or in rats treated with certain sulfa-drugs (200). On the

other hand, the ESCN produced by Me-Cl-COL plus NaH_2PO_4 is not significantly modified by unilateral nephrectomy (342).

Complete bilateral nephrectomy tends to produce myocardial necroses in the rat (29, 201, 202), but the lesions so produced are inconstant and rarely severe, presumably because the animals die too soon. However, after pretreatment with mineralocorticoids the survival time of bilaterally nephrectomized rats is significantly prolonged (350) and then, particularly widespread myocardial necroses develop quite constantly (29, 201, 202).

In rats concurrently treated with Me-Cl-COL plus NaH_2PO_4 , complete bilateral nephrectomy did not produce especially severe myocardial necroses, perhaps because phosphate is very toxic for uremic rats and shortens their survival so that they die before structural lesions can develop (356). As we have seen (p. 89), the production of cardiac necroses by complete nephrectomy is allegedly prevented by parathyroidectomy (201, 202), but this claim requires confirmation.

The particularly acute renal hypertension that can be produced in dogs by constriction of both renal arteries is usually accompanied by multiple hemorrhages and necroses in the cardiovascular system (120). The myocardial lesions so induced can be prevented by rutin, allegedly because of the stabilizing effect of this compound on the ground substance of the arterioles and of the precapillary sheath (149).

An extensive, partial hepatectomy (in which about 75% of all the liver is removed) does not significantly alter the production of either the ESCN or of the hepatic necroses normally induced, in rats, by combined treatment with 100 $\mu\text{g}/\text{day}$ of Me-Cl-COL and 1 mM of Na_2HPO_4 , Na_2SO_4 , or NaClO_4 (342).

In rats in which the pylorus is ligated and a permanent gastric fistula is produced, cardiac necroses develop quite often though not regularly (346). Here, the loss of K through the gastric juice and the alkalosis that result after this operation may be responsible for the cardiac damage. Such metabolic changes may also explain why even a temporary obstruction of the pylorus precipitates massive myocardial necroses, in rats pretreated with Me-Cl-COL plus NaH_2PO_4 (332). Yet, in all

in these cases the nonspecific, systemic stressor effect of the eliciting procedures probably also plays an important part.

Systemic Trauma

It is a well-known fact that, in man, coronary thrombosis can be precipitated by postoperative shock (26, 67). Of course, this is also true of many other somatic and even psychic factors that can induce shock (323), and we shall have more to say about this in the section on stress (p. 143).

In rats treated with Me-Cl-COL alone (344) or with sub-threshold amounts of Me-Cl-COL plus NaH_2PO_4 (356), the development of the ESCN has been precipitated by multiple bone fractures or crushing of the intestines.

Temperature Variations (Including Burns)

After extensive skin burns, focal necrosis of the myocardium with secondary histiocytic infiltration (often accompanied by skeletal muscle necroses, hepatitis, and brain edema) has been observed in rabbits (92, 145) and in man (415, 416).

In rats pretreated with Me-Cl-COL (344) or with sub-threshold doses of Me-Cl-COL plus NaH_2PO_4 (356), it was possible to precipitate extensive myocardial necroses by comparatively short immersion in hot or ice-cold water. It is highly probable that in most of these instances, as in systemic traumatic injuries, nonspecific stress was of pathogenic importance.

Hemorrhage

Myocardial necroses, with secondary inflammation and ECG changes, may occur in rabbits, following severe loss of blood (49). As a consequence of acute or chronic hemorrhage due to various causes, disseminated myocardial necroses—especially in the subendocardial layers of the heart—have been repeatedly observed in man also, especially when there was a pre-existing coronary sclerosis (263). These cases again illustrate the fact that a latent insufficiency in the cardiac blood supply may predispose to the subsequent production of necroses by stressors.

Yet, hemorrhage appears to be singularly ineffective in producing cardiac necrosis in Me-Cl-COL-conditioned rats (see

p. 147). This unexpected fact has been largely clarified by certain recent observations (342) which showed that repeated blood-letting actually protects the rat against the production of cardiac necroses by Me-Cl-COL plus NaH_2PO_4 , noradrenaline, or noradrenaline plus Me-Cl-COL. This protective effect was ascribed to the fall in blood pressure caused by the hemorrhage. The suppurating myocarditis and myocardial necrosis normally elicited by combined treatment with DHT plus NaH_2PO_4 can likewise be prevented by repeated blood-letting (344). Presumably, the resulting decrease in aortic pressure diminishes cardiac work, and thereby renders the heart-muscle fibers less susceptible to the damaging effect of necrotizing agents. These observations may also explain some apparently paradoxical, earlier findings, which showed that comparatively mild stressors (e.g., cold baths or exercise) are more liable to produce cardiac necroses than are agents that cause severe shock (e.g., sublethal hemorrhage or high spinal-cord transection).

Hypoxia

Many of the agents that we have discussed in the preceding pages (systemic trauma, extreme variations in temperature, burns, hemorrhage) are severe stressors that tend to cause shock and, consequently, tissue anoxia. Therefore, it was of considerable importance to establish whether lack of oxygen can, in itself, produce myocardial necroses.

In animal experiments designed to clarify this point, hypoxia was produced by reducing the atmospheric pressure or by adding large amounts of nitrogen to the air. Multiple, focal myocardial necroses (often in association with necroses in skeletal muscle, the liver, and the central nervous system) can be produced in this manner in rabbits (48a, 377), guinea pigs (222, 223), cats (133), and rats (159). In cholesterol-fed rabbits, hypoxia is especially effective in producing predominantly sub-endocardial, myocardial necroses (257).

In predisposed patients, anginal pain can be elicited at will when hypoxia is produced by rebreathing the expired air for a few minutes (296). In Germany, systematic investigations on the pathologic anatomy of "acute high-altitude death" ("akuter

Höhentod") were undertaken on aviators whose oxygen equipment failed during bombing missions. In most of these men, degenerative changes, hyalinization, and edematous imbibition of cardiac muscle fibers were quite common, but actual focal necroses did not occur, presumably because of the short time-lapse between the onset of hypoxia and death (256).

Extensive electron-microscope studies revealed that the anoxic necroses—like those due to K-deficiency—are preceded by swelling and disintegration of the cardiac mitochondria, in rabbits (241a, 249a, 249b).

Muscular Exercise

The fact that sudden muscular exertion can precipitate cardiac infarcts, especially in predisposed middle-aged or older men, is too well known to deserve special attention here. However, allegedly, even in healthy young rabbits, forced muscular exercise (in a revolving drum) can produce ECG changes similar to those seen in human coronary infarction, as well as necrosis of occasional muscle fibers, with regenerative phenomena and polymorphonuclear infiltration. Such changes are more common in rabbits previously subjected to severe hemorrhage and they have consequently been ascribed to relative tissue anoxia (49, 93).

Similar lesions also occur in rabbits frightened by strong acoustic stimuli; hence, Fanfani (93) considered the possibility that cardiac necroses may be an inherent part of the General Adaptation Syndrome (G.A.S.). However, since he was unable to detect other obvious manifestations of the stress syndrome (e.g., reduction of adrenocortical lipids), he subsequently rejected this interpretation. As shall be discussed, stress produces severe morphologic changes in the heart only in the presence of certain conditioning factors; hence, it would not be correct to say that focal myocardial necroses are an integral part of the G.A.S. It is difficult to imagine, however, that, in rabbits forced to perform extremely severe muscular exercise or exposed to considerable nervous irritation, such sensitive indicators of stress as the adrenocortical stimulation could have been totally lacking.

We have seen that ingestion of excess cholesterol greatly sensitizes the rabbit to the production of myocardial necroses by forced muscular exercise (257). In this connection, let us also call attention again to the observations which showed that, in rats, the cardiovascular damage (arterial calcification and scar-formation in the myocardium) produced by overdosage with irradiated ergosterol is aggravated by repeated periods of muscular exercise in a revolving drum (276, 309). The effect of muscular exertion upon the ESCN is discussed elsewhere (see pp. 145-147).

Orthostatic Collapse

If rabbits are strapped to a board in the vertical position with the head pointing upward, they soon enter into a shock-like state, the "orthostatic collapse." In this condition, focal myocardial necroses (usually with severe ECG changes and hepatic necroses) develop with considerable regularity (237, 238, 367, 379). It has been generally assumed that this type of cardiac damage is primarily due to a relative anoxia: in the orthostatic position, the heart must pump against gravity towards the head, and the oxygen requirements for this work-increase are allegedly difficult to meet under such conditions.

Restraint

Orthostatic restraint appears to be particularly effective in producing myocardial necroses; yet, such cardiac lesions do occur even when rabbits are strapped to a board in the prone or supine position (237, 393).

In the rat, we failed to produce myocardial necroses by brief restraint in the horizontal position, although this procedure was highly effective in precipitating an ESCN after pretreatment with Me-Cl-COL alone (344) or with subthreshold doses of Me-Cl-COL plus NaH_2PO_4 , both in rats (352, 356), and in rhesus monkeys (358).

Even pretreatment with less active steroids (such as cortisol or DOC) in combination with NaH_2PO_4 sensitizes the rat (330) and rhesus monkey (358) to the production of myocardial necroses by restraint.

By very prolonged restraint it is also possible to produce marked myocardial necroses, both in rats (330, 352) and in monkeys (358), after sensitization with Me-Cl-COL or cortisol alone (that is, without sensitization by electrolytes).

Electroshock

After repeated faradization, rats occasionally develop microscopic foci of myocardial necrosis; these have been interpreted as infarcts, although they are never associated with any evidence of a coronary lesion (162). "This seemed to suggest that circulatory changes in the smaller and smallest branches of the coronary system might be responsible for the primary injury to the muscle fibers which eventually led to more extensive muscular damage and replacement of the damaged areas of muscle by connective tissue" (163). The possibility of a direct effect upon the cardiac muscle has not been considered.

Subsequent, systematic investigations in guinea pigs showed that if even a comparatively weak electric current is led directly through the cardiac region, it can produce multiple, focal myocardial necroses unaccompanied by detectable coronary damage. However, here, histochemical studies revealed a "trans-mineralization" that was held responsible for the lesions: the K-content diminished in the necrotic region and was greatly augmented in the immediately surrounding muscle fibers. At the same time, the necrotic tissue tended to accumulate granules of calcium (261). Incidentally, this same type of K-redistribution subsequently was found also in the heart of a patient who died of myocardial infarction. Here again, the necrotic area was depleted, while the surrounding muscle became unusually rich in histochemically demonstrable K (281).

In man, infarctlike cardiac necroses have also been observed as a result of accidental electrocution by contact with a high tension wire (261) or by lightning (381).

G. PSYCHIC AND NERVOUS STIMULI

In the preceding pages, we have mentioned many agents (forced muscular exercise, traumatic injuries, restraint, etc.)

that, in addition to their other effects, undoubtedly produced pain and emotional upset. Here, it is evidently quite impossible to separate the purely nervous and emotional from the somatic factors. However, fear produced by strong acoustic stimuli (93) or by transection of the depressor nerves (243) has also been shown to induce typical focal myocardial necroses, with secondary histiocytic invasion, in rabbits; in these instances, it is probable that the cardiac damage was primarily due to nervous influences.

In rats sensitized by Me-Cl-COL alone (344) or by threshold doses of Me-Cl-COL plus NaH_2PO_4 (356), quadriplegia (produced by transection of the motor nerves of all four extremities) and bilateral vagotomy proved to be highly effective, while spinal-cord transection was ineffective in precipitating an ESCN. The ineffectiveness of spinal-cord transection was difficult to explain, especially in view of the fact that so many stressors are capable of eliciting cardiac necroses in rats thus sensitized by steroids and electrolytes. Here we have a problem very similar to that which we have met in discussing the paradoxical fact that severe hemorrhage, far from eliciting myocardial infarcts, can actually prevent their occurrence in animals pretreated with normally effective amounts of Me-Cl-COL and NaH_2PO_4 (cf. p. 114). The comparative inefficacy of spinal-cord transection (like that of severe hemorrhage) may result from the fact that these agents produce a marked drop in peripheral resistance. The resulting diminution of cardiac work apparently renders the heart less susceptible to the damaging effect of necrotizing agents. In support of this view, it has been shown that a lumbar spinal-cord transection (which causes no marked drop in blood-pressure or body temperature) induces severe cardiac necroses, while a cervical spinal-cord transection (which produces much more pronounced stress, hypothermia, and hypotension) rarely if ever induces visible structural lesions in the myocardium of the rat (343e).

The question arose whether the production of cardiac necroses by nervous stimuli can also be prevented by KCl or MgCl_2 , especially if these electrolytes are applied only during the

period of stress. A special experiment was performed to verify this point on animals subjected to vagotomy or motor denervation of the extremities.

Eighty female Sprague-Dawley rats, with a mean initial body-weight of 101 g (range: 92–108 g), were subdivided into eight equal groups and treated with Me-Cl-COL (100 μ g in 0.2 ml of water/day, subcutaneously) and Na_2HPO_4 (2 mM in 2 ml of water, twice daily, by stomach tube), as indicated in Table 12. After 72 hours, bilateral vagotomy was performed in Groups 1–4, and quadriplegia was produced by transection of the motor nerves of all four extremities, in Groups 5–8. Also after 72 hours, Na-phosphate treatment was discontinued in some animals (Groups 2 and 6), while in others, 1 mM of KCl (Groups 3 and 7) or 1 mM of MgCl_2 (Groups 4 and 8) was added to the usual bidaily dose of NaH_2PO_4 . The Me-Cl-COL injections were continued until the termination of the experiment, 96 hours after the initiation of the Me-Cl-COL plus Na_2HPO_4 treatment (that is, 24 hours after the nerve transections). The results are summarized in Table 12 on the basis of the macroscopically visible changes.

TABLE 12

**Importance of Conditioning by Electrolytes During Nervous Stress
(Vagotomy, Motor Denervation)**

Group	Terminal Treatment *	Cardiac Necrosis	Nephro-calcinosis	Mortality (%)
1	Vagotomy	1.3 \pm 0.14	2.8 \pm 0.23	80
2	Vagotomy + Na_2HPO_4 withdrawal	0	0.7 \pm 0.33	20
3	Vagotomy + KCl	0.3 \pm 0.17	2.1 \pm 0.34	50
4	Vagotomy + MgCl_2	0.3 \pm 0.20	1.1 \pm 0.40	60
5	Motor denervation	1.3 \pm 0.17	2.3 \pm 0.28	20
6	Motor denervation + Na_2HPO_4 withdrawal	0.5 \pm 0.28	1.6 \pm 0.38	10
7	Motor denervation + KCl	0.5 \pm 0.28	2.1 \pm 0.30	10
8	Motor denervation + MgCl_2	0.3 \pm 0.23	2.1 \pm 0.30	10

* The animals of all groups received Me-Cl-COL (100 μ g/day) and Na_2HPO_4 (1 mM twice daily) throughout the 96-hour duration of the experiments. This column lists only the deviations from this basic procedure during the last 24 hours of observation (for details see text).

The rapid development of cardiac necroses and nephrocalcinosis under the influence of the nervous interventions (Groups 1 and 5) was confirmed. However, these lesions were mild, or absent, when either Na_2HPO_4 treatment was interrupted (Groups 2 and 6) or when, in addition to the usual amount of Na_2HPO_4 , KCl (Groups 3 and 7) or MgCl_2 (Groups 4 and 8) was administered during the terminal 24-hour-period of stress. No marked hepatic necrosis occurred in any of the groups in this experiment.

We may conclude from this experiment that:

1. Without sensitization with Na_2HPO_4 during stress, this short pretreatment with Me-Cl-COL plus Na_2HPO_4 did not suffice to condition the heart for the production of macroscopically detectable necroses by subsequent, strong nervous stimuli.
2. Such brief hormonal sensitization resulted in massive myocardial necrosis, when Na_2HPO_4 was given both before and after either kind of nerve injury.
3. Even in the latter case, the effect of Na_2HPO_4 could be abolished when KCl or MgCl_2 was administered during the period of stress.

We then proceeded to verify the importance of electrolyte conditioning during another type of nervous stress, namely, **forced restraint**. One hundred and forty female Sprague-Dawley rats, with a mean initial body-weight of 100 g (range: 94–108 g), were subdivided into seven equal groups and treated with Me-Cl-COL (100 μg in 0.2 ml of water/day, subcutaneously) and other agents, as indicated in Table 13. KCl and MgCl_2 were administered at the dose of $\frac{1}{2}$ mM in 2 ml of water, twice daily by stomach tube, throughout the experiment, in Groups 4 and 6 respectively. The animals of Groups 5 and 7 were given no KCl or MgCl_2 pretreatment, but during restraint, they received similar $\frac{1}{2}$ mM doses of these electrolytes, four times. Forced restraint was accomplished in Groups 2 to 7 by strapping the animals to wooden boards in the prone position for 17 hours, on the eleventh day of the experiment. The animals were killed 24 hours later. In this experiment the grades

of cardiac necroses listed in Table 13 are based on histologic examination of slides stained with our fuchsin technique.

TABLE 13

Importance of Conditioning by Electrolytes During Nervous Stress (Restraint)

Group	Treatment	Cardiac Necrosis	Mortality (%)
1	Me-Cl-COL	0	0
2	Restraint	1.0 ± 0	0
3	Me-Cl-COL + restraint	2.2 ± 0.10	30
4	Me-Cl-COL + restraint + KCl	1.1 ± 0.18	30
5	Me-Cl-COL + restraint + KCl (during stress only)	0.7 ± 0.17	20
6	Me-Cl-COL + restraint + MgCl ₂	0.6 ± 0.17	0
7	Me-Cl-COL + restraint + MgCl ₂ (during stress only)	0.4 ± 0.13	10

We note that:

1. Histologically detectable cardiac necroses were produced by this prolonged period of restraint, even without any special hormonal conditioning (Group 2).

2. After Me-Cl-COL pretreatment, the incidence of the necroses was considerably augmented (Group 3).

3. The intense cardiotoxic effect of restraint after Me-Cl-COL conditioning was diminished both by KCl and by MgCl₂, not only when these electrolytes were given during the entire conditioning period but even when they were administered only during stress.

On the basis of this experiment, it is not possible to state with certainty that pretreatment with electrolytes is unimportant. However, there can be no doubt that both pretreatment with KCl or MgCl₂ and intense treatment with these electrolytes during stress only (without any pretreatment) were highly effective in diminishing the cardiotoxic action of nervous stress. The mortality rate was not significantly influenced by either of these electrolytes, in this experimental arrangement, but even the animals that died (presumably owing to the stress of re-

straint or to the toxic effects of KCl and MgCl₂) showed no evidence of marked cardiac damage.

H. MICROBES AND THEIR TOXINS

It is well known that various acute, infectious diseases (diphtheria, typhoid, pneumonia, scarlet fever, influenza, measles, whooping cough, etc.) tend to produce myocarditis.

In typical, severe cases there is widespread necrosis—especially of the subendocardial regions—often accompanied, in the less affected areas, by interstitial edema and fatty degeneration of muscle fibers. In addition, there are usually smaller isolated foci of necrosis in which the muscle cells eventually disappear. This process corresponds to the so-called “dropping out of muscle fibers” or “spotty myolysis,” which gives the heart muscle a “moth-eaten” appearance—to use the rather descriptive terms employed by some investigators. If the patient survives, the damaged muscle tissue is gradually infiltrated by inflammatory cells (neutrophils, eosinophils, histiocytes, plasma cells), which, in turn, are eventually replaced by scar tissue.

In this respect, the morphogenesis of these lesions is somewhat reminiscent of the changes (necrosis followed by inflammation and, eventually, scar-formation) that take place in the purest type of anemic necrosis—the acute cardiac infarct. The only important difference is that in infectious and toxic myocarditis, the affected regions are less sharply demarcated than in infarcts and not restricted to individual vascular territories. Furthermore, in microbial or toxic myocarditis, degeneration, necrosis, and inflammation often overlap in the same region and one or the other type of response may predominate at any one time in different parts of the same heart, so that a clear distinction between a necrotic and an inflammatory stage is impossible (7, 46, 185, 251).

Most of the early investigators considered it to be self-evident that, in such cases, inflammation is a defense reaction against the topical damage caused by the pathogenic microorganisms or their toxins. However, as the study of the ESCN has shown, myocardial necroses produced by ionic disequilibria

also stimulate local inflammation, presumably as a response to toxic products liberated from the dying muscle.

Of course, this type of acute, necrotizing, infectious myocarditis must be clearly distinguished from the pyemic myocardial abscesses that are demonstrably due to the presence of microbial embolisms in the heart.

Because of the essential similarity among the necrotizing types of myocarditis produced by various infectious diseases, we may discuss them here conjointly. Necrotizing myocarditis is particularly common in patients who die of **diphtheria** (46, 83, 84, 124, 127, 185, 250, 399, 403, 404). Since the same type of lesion can be reproduced experimentally by the administration of **diphtheria toxin** in the horse (1), guinea pig (1, 137, 138), and rabbit (1, 138), the presence of living microbes is evidently not essential for its development.

In guinea pigs given large doses of diphtheria toxin, the muscle near the apex of the heart appears to be most frequently affected (137) and the histologically demonstrable oxidase granules disappear from the muscle fibers, even before any evidence of necrosis is detectable (138).

In rats, it is notoriously difficult to produce damage with diphtheria toxin, but when two injections are given at an interval of approximately one week, focal myocardial necroses, with round-cell infiltration, occur and the glycogen-content of the heart is greatly diminished (135).

In rabbits, a single intravenous injection of **meningococcal endotoxin** produced myocardial and valvular hemorrhages and cardiac muscle necroses (with calcification and round-cell infiltration of muscle fibers) in about 50% of the animals. This was accompanied by extensive changes in the coronary arteries (edema, fibrinoid degeneration) and, occasionally, by bilateral renal cortical necroses (43, 385).

Combined treatment with **streptolysin O** and material extracted from the skin lesions of rabbits with cutaneous streptococcal infections causes focal myocardial necroses in rabbits. From this, it was concluded that, when group A streptococci multiply in the skin, a material is produced that is capable of markedly enhancing the responsiveness of the rabbit to another

soluble streptococcal product that occurs in reduced culture filtrates. "The results presented here indicate that the active factor in the reduced filtrates is streptolysin O" (313). Rabbits subjected to a single pharyngeal infection with group A streptococci develop similar cardiac lesions, sometimes within 24 hours after inoculation. Occasionally, there are multinucleated giant cells and calcium deposits in the affected cardiac foci (118).

Focal myocardial necroses, with inflammatory phenomena, have also been seen in patients suffering from epidemic typhus (7, 185), syphilis (190, 233, 263), tuberculosis (190), scarlet fever (39, 185), scrub typhus (7), influenza (59, 97, 310), poliomyelitis (185), infectious mononucleosis (99a), Rocky Mountain spotted fever (7), measles (46), and in a variety of other virus infections of man (306) and experimental animals (151, 266-270).

In the following two sections, Hypersensitivity and Spontaneous Diseases, we shall discuss, among other things, a number of presumably related conditions in which bacteria or their products are responsible for the production of myocardial necroses.

I. HYPERSENSITIVITY

Several investigators have shown that focal myocardial necroses and myocarditis can readily be produced in rabbits, by repeated injections of various foreign proteins (e.g., horse-serum, egg-white), as one manifestation of a hypersensitivity response (11, 115, 154, 184a, 216, 238). Essentially similar changes have also been produced in this way, in dogs, cats, guinea pigs (216), mice (80a), and man (36a, 392a). The cardiac lesions are usually accompanied by more or less generalized periarteritis; sometimes, there is also nephritis, hepatic necrosis, and hyperplasia of the lymphatic system.

Rather similar lesions have also been produced in dogs and rabbits by "endocardiocytotoxic serum" (204) and, in rabbits, by repeated injections of various microbial products with or without adjuvants, e.g., hemolytic streptococci (254, 384), *E. coli* endotoxin (131), and meningococcal toxin (131, 384,

385). These lesions have variously been described as an "Arthus phenomenon" (76), "sequelae of anaphylactic shock" (154), and "a generalized Shwartzman reaction" (131, 312, 384, 385). In rabbits, the myocardial necroses occur with particular frequency in the right ventricle; there are usually concurrent lesions in the pulmonary vessels, and ECG changes similar to those found in acute *cor pulmonale*. Therefore, it was suggested that the myocardial ischemia accompanying acute *cor pulmonale* is the fundamental cause of the injury in the hypersensitivity type of myocardial necrosis of rabbits.

This view appears to have received further confirmation from the observation that similar myocardial necroses, with a predilection for the right ventricle, can be produced by the pulmonary embolization that results from the intravenous injection of lycopodium spores or air (154). This interpretation may be correct, but the author was apparently not aware that, in the rabbit, so many other agents also cause myocardial necroses with a predilection for the ventricle. It remains to be shown whether all these factors damage the heart by interfering with the pulmonary circulation.

In the rat, it is notoriously difficult to produce hypersensitivity reactions. Still, as stated previously, when two injections of diphtheria toxin are given at an interval of approximately one week, focal myocardial necroses, with round-cell infiltrations, occur even in this species (135).

Finally, it is of special interest in connection with what we shall have to say about the probable relationship between the ESCN and Fiedler's myocarditis, that features of hypersensitivity were prominent in several patients with the latter disease (38).

J. SPONTANEOUS DISEASES

The toxic myocardial necroses that develop under the influence of various chemical, physical, psychic, and infectious agents have been discussed in previous sections. At this point, we shall merely consider a few "spontaneous" diseases of man and animals that are of interest in connection with the ESCN and have not yet been considered under other headings.

Cardiac Infarcts in General

The typical cardiac infarcts that are due to acute occlusion of coronary arteries have been the subject of many excellent monographs (164, 246, 277), to which the reader may refer. In connection with the possible relationship between true cardiac infarcts and infarctoid cardiopathies such as the ESCN, it will suffice to say a few words here about: (1) cardiac infarcts without acute coronary obstruction; (2) cardiac infarcts due to acute atheromatosis or acute edema of the coronary vessels (in the absence of marked atheromatosis or thrombosis; (3) fuchsinophilic degeneration in spontaneous cardiac infarcts; and (4) the influence of Mg upon cardiac infarcts in man.

Cardiac Infarcts Without Acute Coronary Obstruction

It is generally known that, in a very large percentage of patients who suddenly die as a result of apparently typical cardiac infarction, even the most careful search fails to reveal any acute coronary occlusion. Since, as a rule, cardiac infarcts develop in middle-aged or older people, there is usually some evidence of chronic coronary atheromatosis; however, this is not necessarily more severe than in patients of the same age who do not suffer an acute heart attack (33, 39, 44, 132, 173, 231, 232, 262, 291, 368a, 411-413).

It is difficult to estimate the frequency of this condition, but, in several large and carefully examined series, about 30% of the myocardial infarcts occurred without evidence of recent coronary thrombosis (111, 248, 412, 413), although some investigators list the incidence as high as 59% (213) or as low as 16% (106).

It is also interesting that, in hearts in which there is no evidence of recent coronary occlusion, the infarcts are often situated in the subendocardial layers (248), where necrosis is also most common in the ESCN.

Furthermore, in a number of cases, autopsy revealed complete occlusion of one major coronary artery or primary branch, without evidence of infarction or even of angina pectoris (26, 27). Apparently, infarctlike, large patches of cardiac necrosis

can develop without acute coronary thrombosis and, conversely, complete occlusion of a major coronary artery—if it establishes itself slowly enough to permit the development of collaterals—does not necessarily result in a severe local deficiency of cardiac nutrition. Evidently, the induction of a myocardial infarct depends both on the nutritional supply and on the requirements of the myocardium.

According to prominent students of this field (26), the most important factors that decrease the nutritional supply to the heart are:

1. Narrowing and occlusion of the coronary arteries;
2. A fall in blood-pressure (e.g., in shock) or a low diastolic blood-pressure (e.g., aortic insufficiency);
3. Anoxia (anemia, congestive failure, pulmonary edema).

The factors that usually increase the work of the heart and consequently raise its nutritional requirements are:

1. Muscular effort;
2. Infection;
3. Arterial hypertension;
4. Cardiac hypertrophy;
5. Valvular stenosis and insufficiency;
6. Anoxia caused by pulmonary disease or anemia;
7. Tachycardia.

Cardiac Infarcts Due to Acute Atheromatosis or Acute Edema of the Coronary Vessels

The findings in a series of 300 young American soldiers (average age: 22.1 years), killed during the Korean war, presumably illustrate the effect upon the coronary circulation of the stress of battle. "In 77.3% of the cases, some gross evidence of coronary disease was demonstrated, that varied from minimal eccentric thickening to complete occlusion of one or more of the main coronary branches." . . . "The stress results in subendothelial fibroblastic proliferation, deposition of mucoid ground substance, and fragmentation of the internal elastic membrane. The accumulation and phagocytosis of certain plasma lipids in the plaques aggravates and hastens the disease process" (81). Of course, such observations cannot definitely prove a relationship between the vascular changes and the

stress of previous battle experiences, but, in view of the comparative rarity of such severe coronary lesions in very young men, a causal connection is not improbable.

Sometimes, fatal myocardial infarcts that are not due to coronary thromboses occur as a result of the sudden development of fat-free edema, in the subintimal layers of the cardiac arteries. This edema may virtually occlude the vascular lumen. It appears to occur with particular frequency in men under 45 years of age under the influence of some sudden exertion (34, 47, 241, 255). These observations are of special interest in connection with our finding that, in rats in which a mild coronary sclerosis has been produced by overdosage with vitamin-D derivatives, subsequent treatment with Me-Cl-COL plus NaH_2PO_4 can elicit this type of acute, occlusive, subintimal edema with multiple myocardial necroses (see p. 90).

Occurrence of Fuchsinophilic Degeneration in Spontaneous Cardiac Infarcts

There seem to exist transitional changes between the fuchsinophilic degeneration and the so-called "hydropic degeneration." In his classic treatise *Pathology of the Heart*, Gould (127), for example, illustrates what is obviously a segmental degeneration or necrosis (clearly delimited by intercalated discs). He labels it as a "hydropic change," although the affected portion—far from being swollen—is actually narrower than the rest of the same muscle fiber. Such a change is very reminiscent of fuchsinophilic degeneration, but, of course, it could not have been identified as such, since for this it would have been necessary to use a special staining technique, such as that described on page 43. In any event, using this stain, we have found (hitherto unpublished observations with Doctors Lemire and Renaud) that human cardiac muscle fibers rarely show the brilliant red color characteristic of the ESCN in the rat. Yet, definitely fuchsinophilic fibers are commonly observed in patients who have died of cardiac infarcts or acute cardiac failure due to other causes. A detailed report about these studies will be published later. Here, they are mentioned only to show that fuchsinophilic degeneration can occur not only in experimental animals but in man also.

Influence of Mg upon Cardiac Infarcts in Man

The Soviet investigator Peplia (272) was probably the first to recommend the oral administration of hypertonic $MgSO_4$ -solutions for the treatment of angina pectoris in general, and for the relief of pain after myocardial infarction in particular. Although it is difficult to draw any definite conclusions from his small series of patients, the author ascribed his apparently beneficial results to the anesthetic, analgesic, and antispasmodic effects of Mg-salts.

Almost at the same time and quite independently, a group of South-African physicians reported that "a dramatic clinical improvement results in many cases of coronary heart disease with parenteral administration of magnesium sulphate." These workers were careful to point out that they "can offer no reasons why magnesium sulphate administered parenterally in cases of degenerative heart disease should be efficacious," but they suspected that the vasodilating, analgesic, and lipemia-clearing effects of Mg might play important roles. In connection with the last-mentioned effect, it is noteworthy that the abnormal lipoprotein patterns that were demonstrated in some of their patients, prior to treatment, rapidly reverted to normal during $MgSO_4$ -therapy (226). These observations have recently given rise to much discussion in the South-African medical literature (4a, 9a, 227a, 380a), especially in connection with the alleged influence of Mg on blood-coagulation and stress (22a).

This same group of investigators claimed that coronary thrombosis is less common and the serum-Mg is higher (while the serum-cholesterol is lower) in the Bantus of Africa than in Europeans. Hence, it was thought that there may be some correlation between serum-Mg, serum-cholesterol, and the incidence of myocardial necrosis (23).

The South-African investigators administered $MgSO_4$, in the form of a 50% aqueous solution, at the dose of 0.5–2.0 ml, intramuscularly, first daily and then at increasingly greater intervals, but at the same time, "morphine and pethidine were given as required."

In commenting upon this work, the *British Medical Journal* points out, editorially, that the improvement of the patients treated by the South-African investigators "does not differ materially from that seen in many patients on bedrest only" and deplores the lack of control observations with comparable injections of other salts. Hence, "in the absence of confirmation of this work it is not possible to define the indications for magnesium sulphate therapy" (8).

It should also be kept in mind that, although we found $MgCl_2$ to be highly effective in protecting against the ESCN, other Mg-salts, including $MgSO_4$, were not very effective. Hence, on the basis of our experimental work, it would seem more appropriate to attempt treatment of angina pectoris and myocardial infarction by the oral administration of $MgCl_2$ and/or KCl.

In connection with our findings concerning the role of Na and K in the production of cardiac necroses by stress, other recent clinical observations are likewise of great interest. It was found that an intravenous infusion of Na-lactate (designed to decrease myocardial-K, in patients with anginal pain) produces ECG changes similar to those that develop on performance of a double two-step exercise test. At the same time, anginal pain is frequently elicited by the Na-lactate. The ischemic ECG-changes that are produced by exercise were augmented when the double two-step test was performed immediately after Na-lactate infusion. KCl acted inversely: it prevented the ischemic ECG-changes and increased exercise tolerance. In two patients with acute myocardial infarction, 30 mEq of KCl were given during the initial period of severe pain, and, in both, temporary relief occurred. "These observations indicate that the determining factor producing ischemic electro-cardiographic changes and anginal pain is not anoxia *per se*, but an acute alteration in myocardial potassium produced by ischemia. Factors which tend to provoke anginal attacks in patients with coronary disease, such as stress, anoxia, tachycardia, cold, food (glucose-insulin) and digitalis all share in common the effect of lowering myocardial and serum potassium" (136a).

Fiedler's Myocarditis

History. In 1888, Steffen (369) described a "focal acute myocarditis" that was "isolated," i.e., it was not associated with any disease of which it might have been a manifestation. He emphasized that, thereby, this myocardial lesion differs from that seen in diphtheria and other infectious diseases, in which the heart is only secondarily affected. During the following year—and apparently quite independently—Fiedler (96) published his classic monograph on "acute interstitial myocarditis," in which the clinical features of the disease now generally known as "Fiedler's myocarditis" were outlined in detail. Subsequently, the histologic characteristics of the cardiac lesion have been studied by several investigators (304, 315).

A summary of the now quite extensive literature that deals with this malady (185) indicates that apparently the first lesion, a rather nonspecific necrosis of myocardial fibers, is subsequently followed by inflammatory infiltration and, eventually, scar-formation. The lesions may be circumscribed foci of varying sizes, or they may take the form of a more diffuse myocarditis not unlike that which accompanies many acute infections. The subendocardial layers are often selectively affected, but this is by no means the rule. Even the isolated localization of morbid changes in the myocardium is not invariably characteristic of this condition, which is not necessarily a "primary" disease but may be secondary to eczema, intoxications, or infections.

Depending upon certain morphologic characteristics that are especially prominent in individual cases (giant-cell formation, spotty myolysis, fibroplasia, miliary distribution of necroses) or the course (acute, chronic, pernicious) or the presumed cause (intoxication, eczema, uremia) of the disease, essentially the same malady has been described under different names. The confusion in the terminology and evaluation of this malady is primarily due to the fact that most investigators who described relevant cases were not aware of the whole literature, and, therefore, coined names to emphasize characteristics that happened to be prominent in their particular cases.

The following is a list of the most commonly used designations for what we believe to have been essentially the same malady:

- Isolated myocarditis**, which may be acute, subacute, or chronic (55, 143, 180, 185, 208, 364, 365, 391).
- Acute isolated interstitial myocarditis** (315).
- Isolated diffuse myocarditis** (25).
- Fiedler's myocarditis** (59, 180, 185, 365).
- Gauley's cardiopathy** (149).
- Diffuse myocarditis** (304).
- Idiopathic, diffuse myocardial fibrosis in young men** (315a).
- Granulomatous myocarditis** (179, 185, 247).
- Isolated productive giant-cell myocarditis** (72).
- Toxic myocarditis** (107, 122).
- Subacute primary myocarditis** (113, 181).
- Myocarditis perniciosa** (28).
- Chronic primary myocarditis** (2).
- Chronic fibroplastic myocarditis** (398).
- Exhaustion necroses of the myocardium** (112).
- Endomyocardial fibrosis** (6a, 39, 88, 172).
- Endomyocardial necrosis** (370).
- Diffuse endomyocardial sclerosis** (224).
- Subendocardial necrosis** (170).
- Acute miliary infarction of the heart** (212).
- Acute toxic interstitial myocarditis** (233).
- Eczema myocarditis** (22).
- Uremic cardiopathy** (128).
- Spotty myolysis** (46).
- Myolytic cardiopathy of the newborn** (46).
- Coalescent areas of myocardial fibrosis** (26).

All these myocardial changes are obviously not identical; they differ, with respect to size, shape, and distribution, as well as to the speed of their development; they also vary according to the age of the patient and the concurrent development of lesions outside the heart. Although it was not possible in any of these cases to determine the evocative agent with certainty, it is highly probable that all these forms of myocarditis were not due to the same pathogen. Yet, the morbid changes described under this great variety of names have the following three basic characteristics in common:

1. Myocardial fiber necrosis is usually followed by inflammation and (if the patient lives long enough), eventually, by sclerosis.

2. The myocarditis is not due to the localization within the heart of demonstrable microbial colonies (in this respect, it differs from pyemic abscesses).

3. The myocardial lesion does not exhibit the characteristics of any specific systemic disease (e.g., rheumatic fever, tuberculosis, syphilis) of which it might be one manifestation.

In view of what we have learned about the ESCN, it is highly probable that a number of potential pathogens may produce myocardial necroses under suitable humoral conditions. It is possible, therefore, that Fiedler's myocarditis is also closely related to a variety of cardiac lesions of known etiology, for example, those of acute infections and intoxications and those produced by diverse physical agents (cf. previous sections). In all these, the morphologic and functional attributes of the heart lesion are essentially the same, but if the pathogen is known, we describe the disease accordingly (e.g., diphtheric, anoxic, arsenic myocarditis) and if it is unknown, we speak of Fiedler's myocarditis, idiopathic myocarditis, or use one of the other names in the list just given.

The great similarity between the ESCN and all these types of toxic cardiac necroses is rather evident. In view of this, it is well to keep in mind that endogenous corticoids, dietary electrolytes, stress, and the many other factors that have been shown to affect the course of the ESCN may also play a part in the various types of Fiedler's myocarditis that occur in man. We have already said that the development of cardiac necroses is primarily dependent upon the balance between the heart's requirements for oxygen and nutrients, on the one hand, and its blood-supply, on the other. Hence, some of these toxic myocardial necroses are probably also related to cardiac infarcts, at least to those that are not demonstrably due to any acute vascular obstruction. For example, in the presence of a slight, latent impairment in the cardiac blood-supply, normally well-tolerated metabolic changes (e.g., an excess of corticoids, electrolyte shifts) may suffice to produce infarctlike necroses. One of the most clear-cut instances of "toxic myocardial necroses"

is that produced by the intravenous injection of proteolytic enzymes (e.g., papain); yet we have seen that even this type of lesion is responsive to humoral conditioning factors in that it can be prevented or aggravated by appropriate treatment with corticoids or electrolytes (see p. 105). It is perhaps not too farfetched to assume, therefore, that the production of myocardial necroses produced by other drugs, bacteria, bacterial toxins, or allergens may likewise largely depend upon such conditioning factors.

Uremia

The typical uremic cardiopathy seems to be closely related to Fiedler's myocarditis, in that the lesions are focal and characterized by degenerative changes (hyalinization, calcification) with necrosis, followed by inflammatory infiltration (127, 128). Allegedly, this cardiopathy does not occur as commonly in ordinary obstructive uremia as in renal disease associated with a rise in blood pressure; hence, it has been thought that some renal toxin may be the causative agent (128). However, the fact that complete bilateral nephrectomy can reproduce similar changes in animals (see p. 113) does not appear to be compatible with this view. Two rather characteristic features of the uremic cardiopathy are its predilection for the subepicardial layers of the heart and its comparatively common association with pericarditis. However, subepicardial foci are not invariably predominant, nor are they always absent in other types of focal myocarditis.

Pulmonary Disease

Several investigators noted that focal myocardial necroses, with inflammation, occur with special frequency in patients suffering from various diseases of the lung (112, 279, 291, 401). It is very probable that, here—as in the experimental cardiac necroses elicited by pulmonary embolisms (154, 239)—an excess load upon the heart, and particularly upon its right ventricle, is of primary pathogenic importance (82). However, it must also be kept in mind that only bacteria and toxins coming from the lung can get into the coronary system without first having to filter through the pulmonary capillary net.

Skin Diseases

It has repeatedly been noted that various types of dermatitis may be associated with focal myocardial necroses and myocarditis (15, 22, 99, 233). Some investigators postulated that toxic metabolites produced in inflamed skin may play a specific role in this type of myocardial change, but there are few, if any, objective facts to substantiate this view.

Pancreatitis

Endomyocardial necrosis and pancreatitis, in association with numerous other manifestations of the stress syndrome, have been seen in a patient. It has been postulated that "the basic pattern of the pancreatic changes fits into the framework of the General Adaptation Syndrome" (370).

At that time it was not yet known that under certain humoral conditions, stress may also produce myocardial necroses; hence the possible relationship between the pancreatic changes and the heart lesions were not considered.

Nervous Diseases

More or less extensive, myocardial necroses, sometimes accompanied by focal inflammation of the "Fiedler's myocarditis" type, tend to occur in epileptic patients (139, 260, 273). These lesions are reminiscent of the experimental myocardial necroses produced by various convulsive drugs and by electroshock.

The comparatively common occurrence of myocarditis in Friedreich's ataxia also deserves to be mentioned in this connection (148, 236a, 392b).

More recently, a syndrome of "myocardial infarction with cerebral neurological manifestations" has been described (93a), but here it is doubtful whether the cerebral changes are causally related to the infarcts.

Status Thymicolumphaticus

The very existence of status thymicolumphaticus as a separate disease entity has not yet been fully established. Still,

many investigators, who performed careful autopsies on large series of children who died suddenly with a generalized enlargement of the thymicolumphatic system, claimed that in such patients there is usually an "idiopathic enlargement" of the heart, with miliary necroses and foci of round-cell infiltration in the myocardium. These infiltrates are sometimes only of microscopic dimensions, but they may be so diffuse and intense as to give a "thymus-like" appearance to important portions of the cardiac muscle. In one such case (147), streptococci could be isolated from the blood and spleen; yet, most investigators are inclined to regard these cardiac changes as an inherent part of the status thymicolumphaticus (22, 54, 218, 287, 288).

Myasthenia Gravis

"Lymphorrhages" (collections of lymphocytes) in various organs, and particularly in skeletal muscle, are common in myasthenia gravis. They have generally been ascribed to the well-known tendency for lymphatic and thymus tissue-proliferation in this disease. However, a review of the literature and a personal study of twelve cases of myasthenia gravis and/or thymoma led to the conclusion that, here, the cardiac muscle is not merely infiltrated by lymphocytes but that "myocardial necrosis with secondary inflammatory reaction is found to be an integral part of the pathology of myasthenia gravis." Furthermore, the skeletal muscle necroses—whose intensity roughly paralleled the severity of the myocarditis in this series—"may be of much greater severity than the usually reported 'lymphorrhages'" (242). In this group of patients, as well as in several other published cases, the myocardial lesions of myasthenia gravis bore a striking resemblance to those described as characteristic of Fiedler's myocarditis (20, 36, 117, 297, 301).

Spontaneous Diseases in Animals

It is particularly important to realize that toxic cardiac necroses, with secondary inflammatory changes reminiscent of Fiedler's myocarditis, can occur spontaneously in experimental animals and particularly in the rabbit. Estimates as to the frequency of this disease among laboratory rabbits vary, presuma-

bly because certain strains are more susceptible than others. However, most investigators agree that, in the vast majority of rabbit colonies, focal myocardial necroses with inflammation are extremely common and may assume epizootic proportions (93, 140, 215, 269). In some colonies, such myocardial lesions have been reported to occur in about 40% (254) or even 60% (93, 245) of the apparently normal rabbits. The etiology of these "spontaneous myocarditides" in rabbits is not yet clear, but the lesions have usually been ascribed to some latent infection with a microorganism, perhaps a virus that is difficult to identify. Occasionally, they have been described as "resembling Aschoff bodies" (215).

In any event, it is clear that the rabbit is not a particularly suitable test object for the study of toxic myocardial necroses. Yet, most of the earlier work on this subject was performed on rabbits, because in this species it is especially easy to produce myocardial lesions. Of course, usually, investigators who believed they had produced toxic myocarditis or myocardial necroses in rabbits by any one agent examined untreated controls and verified that, in these, the cardiac lesions were inconspicuous or, at least, much less pronounced than in the experimental animals. However, we now know that even nonspecific stress can render the latent, potentially cardiotoxic actions of various agents manifest. Hence, such seemingly well-controlled observations may still be misleading. Since, in the rabbit, the stressor effect of diverse agents can bring out the otherwise dormant tendency for myocardial necrosis, it is difficult to recognize agents that themselves produce such changes.

Similar lesions have also been observed in 33% of apparently normal, control mice. They have been called "Aschoffoid" to underscore their resemblance to the cardiac changes seen in patients with rheumatic fever (203). It seems that in certain strains of mice (e.g., the "yellow" strain) myocarditis is especially prevalent (363).

We used well over 30,000 female Sprague-Dawley rats for the work described in this monograph. All of these animals weighed approximately 100 g, when we obtained them from the Sprague-Dawley Farms (Madison, Wisconsin). We consider

the rat to be a suitable test-object for work on the ESCN, because we have never seen any spontaneous focal myocardial necroses or myocarditis among apparently healthy controls or among animals treated with steroids and/or electrolytes that do not possess cardiotoxic effects.

On the other hand, focal myocarditis was quite common among a small percentage of our rats that suffered from regional ileitis with hepatitis. The cause of this disease has not yet been definitely established, but *Paracolobactrum coliforme* and *Pasteurella pseudotuberculosis* could be cultured from the intestinal ganglia of the affected animals. At autopsy, this type of myocarditis can readily be distinguished from the ESCN, because the proliferation of granulomatous tissue is extremely abundant in the affected regions. Consequently, the myocarditic foci become prominent and hard, exhibiting the translucent, pearly grey color of proliferating granuloma tissue. In this respect, these lesions differ sharply from the atrophic, depressed, yellowish-white patches, characteristic of the ESCN. The myocarditis that accompanies regional ileitis also differs from the ESCN, in that necrotic muscle fibers are rare, while granuloma tissue is comparatively abundant, and in that the localization of the lesions does not show the predilection for the subendocardial layers that characterizes the ESCN. Besides, except in very early cases, the great enlargement and inflammation of the terminal ileum, as well as the associated hepatic changes, rarely leave any doubt about the diagnosis (286).

Among domestic animals, cardiac lesions similar to Fiedler's myocarditis appear with great frequency in cattle affected by foot-and-mouth disease or "aphthous fever" (185).

K. VARIOUS OTHER FACTORS

Age. We also performed experiments to determine the importance of the age factor in the production of the ESCN. Rats weighing 50, 100, 200, and 250 g, respectively, were given 50 µg of Me-Cl-COL and 300 mg of NaH₂PO₄ per 100 g body-weight. In this series, the older animals were definitely more susceptible

to the production of the ESCN and of nephrocalcinosis than the young.

The only rather constant difference in the appearance of the ESCN that could be attributed to age was the size and position of the foci. In the older rats, the myocardial lesions are usually small and rather evenly distributed throughout both ventricles, while in the younger animals (weighing 100 g or less) there is a characteristic predisposition for the localization of the necroses (predilection for the atria, the right ventricle—often near the origin of the pulmonary artery—and the subendocardial layers of both ventricles).

We found no myocardial or renal lesion in newborn rats whose mothers were treated with Me-Cl-COL plus NaH_2PO_4 , in amounts sufficient to produce severe myocardial necroses and nephrocalcinosis (342).

Sex. In our experience males and females are about equally sensitive to the production of the ESCN by the usual techniques. However, we have only exceptionally used males (rats, rabbits, monkeys), so that our material would not have permitted us to detect minor sex-differences in susceptibility.

Pregnancy. In pregnant rats, otherwise effective doses of Me-Cl-COL plus NaH_2PO_4 produce little or no myocardial necroses. The development of nephrocalcinosis is likewise inhibited by gestation, but not as completely as that of the ESCN (339).

It is interesting in this connection that, in dogs, pregnancy can also prevent the induction of polyarteritis and myocardial necroses by renal damage and a high-fat diet (168). Furthermore, during gestation, rats are unusually resistant to the production of cardiovascular calcification by DHT (326).

On the other hand, "puerperal myocarditis," a disease that appears to be similar to Fiedler's myocarditis, may occur in women during late pregnancy or the early puerperium (38).

Genetic Predisposition. The medical implications of all our observations on the ESCN are, of course, largely dependent upon the demonstration that the production of such cardiac necroses is not merely a species-specific reaction-type peculiar

to the rat—the experimental animal employed in all of the early experiments. However, similar cardiac lesions have also been produced by Me-Cl-COL plus NaH_2PO_4 , in the guinea pig, hamster, rabbit, and dog (302, 303).

Since the principal glucocorticoid of man is cortisol, it is especially noteworthy that extensive myocardial necroses can likewise be induced in primates (rhesus monkeys) by combined treatment with cortisol acetate and NaH_2PO_4 (358). This makes it probable that the cardiac muscle of man is also sensitive to this type of combined electrolyte-steroid action.

Complex Diets. The effect of various individual dietary factors (e.g., minerals, carbohydrates, fats) upon the ESCN has already been considered in the sections headed Electrolytes (p. 17) and Other Chemical Compounds and Food Constituents (p. 101). Therefore, we may limit ourselves here to the discussion of complex diets whose activity cannot be traced to any one ingredient.

It is well known that **overeating** predisposes for the formation of true cardiac infarcts in man. It is usually assumed that the resulting increase in body-weight puts an excessive load upon the heart and at the same time there may occur certain unfavorable changes in plasma lipids and lipoproteins.

However, chronic and severe **undernutrition** can also damage the cardiac muscle. In severely undernourished patients, a singular water imbibition of the peripheral parts of the cardiac muscle fibers ("Mantelödem," or "mantle edema"), as well as focal myocardial necroses, has been observed (211).

We have performed many experiments to determine the effect of various natural foods upon the course of the ESCN.

In all this work, we again used female Sprague-Dawley rats, with an average initial body-weight of 100 g (range: 93–110 g). All the animals were treated with Me-Cl-COL (50 $\mu\text{g}/\text{day}$) and NaH_2PO_4 (2 mM, twice daily, by stomach tube). In addition to controls kept on "Purina Fox Chow," we also had a group of partially starved controls that likewise received only "Purina," but in quantities so restricted that the body-weight was kept approximately as low as that of the most cachectic rats in the other groups (animals that lost more than 30% of their initial body-weight). This type of control was necessary to determine whether

malnutrition, in itself, could alter the course of the ESCN. All the animals were killed after 8 days of treatment, and the results are summarized in Table 14.

TABLE 14
Effect of Various Natural Foods upon the ESCN

Group	Treatment *	Cardiac Necrosis	Nephro-calcinosis	Mortality (%)
1	Purina (<i>ad libitum</i>)	0.2 ± 0.20	1.1 ± 0.40	10
2	Purina (restricted)	0	0.8 ± 0.37	30
3	Purina + 30% casein	0.5 ± 0.30	1.6 ± 0.25	10
4	Purina + 30% corn starch	1.9 ± 0.35	2.3 ± 0.30	50
5	Purina + 30% lard	2.2 ± 0.27	1.8 ± 0.37	90
6	Lentils (dried)	0.1 ± 0.10	1.9 ± 0.35	90
7	Rice (dried)	2.2 ± 0.17	0.7 ± 0.40	100
8	Beans (dried)	0.1 ± 0.10	1.2 ± 0.38	80
9	Peas (dried)	0.4 ± 0.35	1.6 ± 0.28	80
10	Corn (dried)	2.1 ± 0.28	1.9 ± 0.27	100
11	Potatoes (dried)	0.3 ± 0.25	1.2 ± 0.35	90
12	Lard (pork fat)	2.4 ± 0.25	0	100
13	Liver (horse)	0.2 ± 0.20	0.8 ± 0.40	20
14	Muscle (lean horse meat)	0.1 ± 0.10	0.4 ± 0.36	20
15	Kidney (horse)	0	0.2 ± 0.20	10
16	Spleen (horse)	0.2 ± 0.20	0.1 ± 0.10	10

* In addition to the treatments listed in this column, the rats (Sprague-Dawley females, with a mean initial body-weight of 100 g) received Me-Cl-COL (50 µg/day) and NaH₂PO₄ (2 mM twice daily) in all groups, during the 8 days of this experiment.

Some of the results of this experiment are difficult to interpret, because the rats did not take equal amounts of these various diets; furthermore, in certain groups, there was a high mortality that was due not to cardiac necroses but to malnutrition, diarrhea, and other complications. However, it is evident that severe restriction of the food-intake did not increase the severity of either the cardiac necroses or the nephrocalcinosis (cf. Groups 1 and 2). The effect of adding 30% casein to the basic Purina diet (Group 3) was not very striking, but when a similar amount of corn starch (Group 4) or lard (Group 5) was admixed with Purina, the incidence of myocardial necroses and of nephrocalinosis rose considerably above the control (Group

1) level. A similar severe accentuation of the cardiac and renal lesions was obtained by feeding rice (Group 7) and corn (Group 10), which are especially rich in carbohydrates. The lesions in the controls were so mild, in this short-term experiment, that a possible protective effect of the natural foods could not have been detected with certainty. Still, it is evident that none of the diets increased susceptibility to the ESCN as markedly as corn starch, corn, or lard. That the rats fed lard alone (Group 12) showed no nephrocalcinosis is merely due to the fact that they succumbed from severe cardiac necroses during the first few days of treatment, when nephrocalcinosis could not yet have developed.

Some of these natural foods contain both sensitizing (carbohydrates, fats) and desensitizing (K- and Mg-salts) ingredients. Hence, in order fully to evaluate experiments of this kind, it would have been necessary to make complete balance studies, taking into account the total amount of food ingested and the entire chemical composition of the diet. Furthermore, the data would have to be corrected for the nonspecific stressor effect of the rations, before we could draw any conclusions about specific sensitizing effects. Yet, the observations clearly show that the mixture of chemical compounds contained in certain natural foods can very considerably sensitize the myocardium to the production of the ESCN.

Stress. It is important to distinguish between the ESCN that is produced gradually by the persistent action of corticoids plus certain activating Na-salts and the sudden eliciting effect of stress, to which we have made repeated but only cursory reference up to now. To clarify the specificity of this eliciting mechanism, rats were briefly treated with small amounts of **Me-Cl-COL plus NaH₂PO₄**. Although this pretreatment produced little or no cardiac damage, subsequent exposure to the stress of neuromuscular effort (induced by strapping the rats to a board) immediately elicited severe and extensive cardiac necroses in all experimental animals. Indeed, even in rats pre-treated only with Me-Cl-COL (without NaH₂PO₄ supplements), such neuromuscular exertion occasionally produced cardiac lesions (352).

It might have been thought that, here, the neuromuscular exertion acts specifically, not merely through its stressor effect; but, in rats similarly sensitized with threshold doses of Me-Cl-COL plus NaH_2PO_4 , a high incidence of massive myocardial necroses could also be elicited by bilateral vagotomy, hot or cold baths, multiple bone fractures, crushing of intestines, quadriplegia (subsequent to transection of motor nerves), or toxic doses of adrenaline (356). Although all stressors were not equally effective in this respect, it is clear that the eliciting mechanism is largely nonspecific. The possibility of precipitating infarctlike, myocardial lesions by sudden exposure to stressors is of special interest in view of its obvious clinical implications.

It is significant that, in preparing the heart for the production of acute, infarctlike changes by subsequent exposure to a neuromuscular exertion, cortisol, a predominantly glucocorticoid compound, is more effective than DOC, a virtually pure mineralocorticoid (330).

We felt that the precipitating effect of stress could be most clearly demonstrated in rats **conditioned only by a corticoid**. The concurrent administration of Na-salts, unlike treatment with corticoids alone, always produces some cardiac necroses, so that, here, the difference between the stressed and the control animals can be, at best, one of degree. Besides, it is possible that stress itself might act largely through metabolic changes that make sensitizing Na-ions more readily available; in this event, the exogenous administration of such ions would merely obscure the results.

In view of these considerations, an extensive experimental series—to be reported in detail elsewhere (343a)—was performed under the following conditions:

Four hundred and eighty female Sprague-Dawley rats, with an initial body-weight of 100 g (range: 90–110 g) were divided into 48 equal groups, as shown in Table 15. During the experiment, the animals were fed exclusively on “Purina Fox Chow” and received tap water to drink. They were treated with various agents, in doses verified (by preliminary experiments) to be definitely damaging to rats of this sex, strain, and size. Some of these stressors were selected particularly because of contradictions in the literature concerning their ability to produce cardiac

necroses when these agents are administered without special conditioning. Half of the groups received, in addition to the various stressors, 500 µg of Me-Cl-COL, in the form of microcrystals of its acetate, in 0.2 ml of water, subcutaneously, once daily, during 10 days.

All stressors were applied during 24 hours only, between the eighth and ninth days of the experiment; in addition, the diphtherotoxin was also administered on the sixth day. Unless otherwise indicated, single interventions (e.g., spinal-cord transection) were performed at 4 P.M., on the eighth day, while double interventions (e.g., hemorrhage, injections of drugs) took place at 4 P.M. on the eighth, and 9 A.M. on the ninth, day. All drugs were injected subcutaneously. The stressors used were:

Cold bath (immersion in icy water at 1° C, for 3 minutes, twice);

Hot bath (immersion in water at 48° C, for 5 minutes, twice);

Muscular exercise (2½ hours in the morning and 3 hours in the afternoon, in a drum, 12 inches in diameter, revolving at 18 revolutions per minute);

Restraint (the animals were strapped to a board by adhesive tape, in the prone position, once during 17 hours);

Motor denervation of extremities (both cervical plexuses, as well as the femoral and sciatic nerves, were severed, like all other surgical operations, under ether anesthesia);

Spinal-cord transection (with a thermocautery, at the height of the seventh cervical vertebra);

Vagotomy (transection of both vagi, at the height of the thyroid);

Crushing of intestines (stomach, ileum, and cecum, each crushed three times with a hemostat);

Hemorrhage (removal of 3 ml of blood from the jugular vein, twice);

Adrenaline or noradrenaline (200 µg, in 0.2 ml of oil, twice);

Vasopressin (Pitressin, 10 I.U., in 1 ml of water, twice);

Pentamethylenetetrazol (Metrazol, 6 mg, in 0.2 ml of water, twice);

Diisopropylfluorophosphate (0.6 mg in 2 ml of oil, by stomach tube, twice);

Na-fluoroacetate (50 µg in 0.2 ml, of water, twice);

Na-iodoacetate (2.5 mg in 0.2 ml of water, twice);

Dinitrophenol (6.0 mg in 0.2 ml of water, twice);

Picrotoxin (0.2 mg in 0.2 ml of water, twice);

Na-arsenite (0.6 mg in 0.2 ml of water, twice);

Na-arsenate (2.5 mg in 0.2 ml of water, twice);

Digitoxin (750 µg in 0.2 ml of water, twice);

Diphtherotoxin (1:2.5 dilution in 0.9% NaCl; 0.5 ml, once on sixth day, 1 ml once on eighth day);

Pseudomonas aeruginosa infection (1:100 suspension in 0.9% NaCl [turbidity, 50] into a subcutaneously prepared air-pouch, once on sixth day).

The doses listed above were given to the Me-Cl-COL-treated groups. However, by the eighth day under the influence of this potent corticoid, the body-weight of the rats had dropped from 100 to 80 g, while that of the controls without pretreatment had risen to 120 g; to compensate for this difference, the dose of the stressors had to be adjusted accordingly, in these controls. Hence, the amounts of all drugs given to the animals not pretreated with Me-Cl-COL were higher, by one-half, than those given to the pretreated animals. The hemorrhage was similarly adjusted, in that one-third more blood was removed in the controls. No such correction was deemed necessary as regards heat, cold, muscular exercise, restraint, motor denervation, spinal-cord transection, vagotomy, or crushing of the intestines.

For further safety, two additional types of controls were used for each stressor agent, namely: "weight controls" (younger rats, whose mean body-weight, like that of the Me-Cl-COL-pretreated animals, was 80 g, at the time of exposure to stress), and "age controls" (animals of the same age as those of the principal experiment, but whose body-weight was diminished to 80 g by partial starvation). However, the findings in these additional weight and age controls were essentially the same as those in the animals that were not treated with Me-Cl-COL in the principal experiment; hence, they are not listed in Table 15.

TABLE 15

**Induction of Cardiac Necroses by Various Stressors, in Rats
Conditioned with Me-Cl-COL**

Group	Treatment	Cardiac Necrosis	Mortality (%)
1	None	0	0
2	None ± Me-Cl-COL	0	0
3	Cold bath	0	40
4	Cold bath + Me-Cl-COL	2.6 ± 0.23	0
5	Hot bath	0	0
6	Hot bath + Me-Cl-COL	1.3 ± 0.20	0
7	Muscular exercise	0	0
8	Muscular exercise + Me-Cl-COL	1.7 ± 0.36	10
9	Restraint	0.6 ± 0.20	0
10	Restraint + Me-Cl-COL	2.8 ± 0.10	10
11	Motor denervation of extremities	0	10
12	Motor denervation of extremities + Me-Cl-COL	1.0 ± 0.27	10
13	Spinal-cord transection	0	0
14	Spinal-cord transection + Me-Cl-COL	0.2 ± 0.15	20
15	Vagotomy	0	80
16	Vagotomy + Me-Cl-COL	1.7 ± 0.27	80

TABLE 15—(Continued)

Induction of Cardiac Necroses by Various Stressors, in Rats
Conditioned with Me-Cl-COL—(Continued)

Group	Treatment	Cardiac Necrosis	Mortality (%)
17	Crushing of intestines	0	0
18	Crushing of intestines + Me-Cl-COL	0.2 ± 0.15	20
19	Hemorrhage	0	20
20	Hemorrhage + Me-Cl-COL	0	50
21	Adrenaline	1.0 ± 0	0
22	Adrenaline + Me-Cl-COL	2.1 ± 0.32	0
23	Noradrenaline	0.4 ± 0.40	0
24	Noradrenaline + Me-Cl-COL	2.9 ± 0.10	0
25	Vasopressin	0	0
26	Vasopressin + Me-Cl-COL	1.5 ± 0.40	0
27	Pentamethylenetetrazol	0	0
28	Pentamethylenetetrazol + Me-Cl-COL	0.6 ± 0.40	0
29	Diisopropylfluorophosphate	0.4 ± 0.40	20
30	Diisopropylfluorophosphate + Me-Cl-COL	1.9 ± 0.32	30
31	Na-fluoroacetate	1.2 ± 0.20	0
32	Na-fluoroacetate + Me-Cl-COL	2.0 ± 0.10	0
33	Na-iodoacetate	0	0
34	Na-iodoacetate + Me-Cl-COL	0	0
35	Dinitrophenol	0	100
36	Dinitrophenol + Me-Cl-COL	0	20
37	Picrotoxin	0	0
38	Picrotoxin + Me-Cl-COL	0.8 ± 0.32	0
39	Na-arsenite	0.2 ± 0.20	0
40	Na-arsenite + Me-Cl-COL	0.6 ± 0.35	0
41	Na-arsenate	0	0
42	Na-arsenate + Me-Cl-COL	0.4 ± 0.27	0
43	Digitoxin	0	0
44	Digitoxin + Me-Cl-COL	0	0
45	Diphtherotoxin	0	0
46	Diphtherotoxin + Me-Cl-COL	0.2 ± 0.15	0
47	<i>Pseudomonas aeruginosa</i> infection	0.2 ± 0.27	40
48	<i>Pseudomonas aeruginosa</i> infection + Me-Cl-COL	1.0 ± 0.36	20

On the tenth day, all survivors were killed with chloroform; their hearts were fixed in formalin and stained with our fuchsin-technique. The results given in Table 15 are based upon the histologic findings. This is important, because, under these particular circumstances (Me-Cl-COL-conditioning and subsequent exposure to stressors), even

extensive necroses are often difficult to see by mere inspection with the dissecting loupe. The reason for this occasional indistinct macroscopic appearance of histologically advanced and extensive necroses is not clear. Perhaps the decomposition products that usually endow dead muscle fibers with a characteristic yellow color do not form rapidly, or perhaps they are too quickly removed, under certain conditions of experimentation. In any event, the possibility of a marked discrepancy between histologically detectable and macroscopically obvious necroses must always be kept in mind.

It is evident that Me-Cl-COL alone again failed to produce any cardiac necroses; however, it significantly increased the cardiotoxic effect of numerous, quite unrelated agents, particularly that of cold (Group 4) and hot (Group 6) baths, muscular exercise (Group 8), restraint (Group 10), motor denervation (Group 12), vagotomy (Group 16), adrenaline (Group 21), noradrenaline (Group 24), vasopressin (Group 26), diisopropylfluorophosphate (Group 30), Na-flucroacetate (Group 32), picrotoxin (Group 38), and *Pseudomonas aeruginosa* (Group 48). In many of the other groups, Me-Cl-COL likewise increased the incidence of cardiac necroses (Groups 18, 28, 40, 42, 46), but the difference between the corticoid-treated and the corresponding control groups was less striking and not statistically significant. In the remaining groups, Me-Cl-COL produced no necrotic foci but merely an increase in individual fiber necroses and fuchsinophilia; such minor effects have been disregarded in our grading.

Some of the agents may have failed to produce necroses merely because, at the dose-level tested, they did not produce sufficiently severe stress. Yet, excessive systemic damage is likewise unfavorable for the induction of myocardial necroses. During the circulatory collapse of shock, the pulse is so weak and the peripheral resistance so low that the heart's demands for oxygen and nutrients may decrease to a point where necroses fail to ensue, despite the severe derangement in cardiac metabolism induced by Me-Cl-COL. It is well known, that, for example, in "artificial hibernation" induced by cold or during cardiac arrest with K, the heart muscle has no great tendency to undergo necrosis, despite the failure of the coronary blood supply. (Cf. also prevention of ESCN by hemorrhage, p. 115.)

In any event, we may conclude from Table 15 that, after Me-Cl-COL conditioning, cardiac necroses can be induced by a great variety of essentially different agents; hence, this lesion is largely a nonspecific effect of stress.

The biochemical mechanism through which systemic stress thus predisposes the cardiac muscle to the production of necroses is not yet known. It is of considerable interest, however, that NaCl—which usually exerts a definite, though mild, desensitizing effect upon the production of an ESCN—greatly augments the sensitivity of the heart to the production of necroses by stressor agents, such as forced restraint (344). We are now engaged in a study of this singular phenomenon, but preliminary data suggest that, in the corticoid-conditioned rat, stress can so alter metabolism that even a normally inert, or actually desensitizing, Na-salt becomes an effective sensitizer.

Unlike steroids, such as Me-Cl-COL, the typical sensitizing electrolytes do not appear to induce any great predisposition for the production of cardiac necroses by stressors. At least, under standard conditions, the slight cardiac-necrosis producing effect of cold baths was not significantly aggravated by 1 mM twice daily of NaCl, NaClO₄, Na₂SO₄, or Na₂HPO₄ (342).

3

Theories

One of the greatest handicaps in the theoretic evaluation of the various myocardial necroses and inflammations was the lack of a coordinated review of the many scattered facts that touch upon this field. Clinicians who observed spontaneous necrotizing cardiopathies and experimenters who produced them in animals were, in general, unaware of each other's findings and consequently missed the common features in the lesions which they described. This state of affairs is hardly surprising, since a necrotizing cardiopathy was usually an incidental finding in studies dealing primarily with a great variety of unrelated topics, such as nutritional deficiencies, infectious diseases, anoxia, hypersensitivity reactions, and so forth. The lengthy list of references at the end of this monograph bears witness to the abundance of available data, but the individual facts did not fall into any orderly pattern that could have been surveyed and experimentally explored from a unified point of view. Perhaps the worst consequence of this lack of systematization was that those who attempted a theoretic evaluation were inclined to consider the particular pathogen that they studied to be the common denominator in all kinds of necrotizing cardiopathies.

These were the considerations that stimulated the compilation of the present monograph, in the hope that it might help in the formulation of a concept compatible with all the relevant data in the literature. It will not be necessary, here, to discuss every antiquated hypothesis; we shall merely say a few words about the principal theories that were proposed to explain the necrotizing cardiopathies, and, then, attempt to formulate a

more unified interpretation on the basis of our investigations concerning the ESCN.

Hypoxia

In support of the hypoxia theory, it has been pointed out that lowering of the atmospheric pressure greatly increases the incidence of the focal myocardial lesions that are produced by Pearce's virus No. III in the rabbit. Various procedures that allegedly cause cardiac anoxia indirectly (intravenous injections of barium chloride, adrenaline, vasopressin, or gum acacia) also increase the heart's susceptibility to this virus; on the other hand, agents that are said to produce cardiac damage without anoxia (chloroform anesthesia or intravenous injections of corn syrup, nicotinamide, digitalis, papaverine, or large volumes of saline) were found to be ineffective. The authors of this work (268) were apparently unaware of the fact that several of their "sensitizing procedures" had previously been shown to produce necrotizing myocarditis even without virus infection; hence, no controls were used to check this point. It is not clear, furthermore, how these workers established that only the procedures intended to produce cardiac hypoxia did, in fact, diminish the oxygen supply of the heart or that the agents meant to cause only cardiac strain did not cause hypoxia as well. On the basis of the published results, it is conceivable that the efficacy of the sensitizing agents used in these experiments depended upon the degree of systemic stress which they produced.

The previously reported production of myocardial necrosis and secondary inflammation by hemorrhage (49), forced muscular exercise (49, 93), orthostatic hypotension (238, 379), and electroshock (162) has also been ascribed to hypoxia. However, this interpretation is difficult to reconcile with the fact that, in our experience, even just sublethal loss of blood only exceptionally caused any myocardial necroses. Indeed, hemorrhage prevented the production of an ESCN in rats treated with Me-Cl-COL plus NaH_2PO_4 (Cf. p. 115).

According to a modification of the hypoxia theory, a temporary local disturbance in the cardiac blood supply (perhaps

owing to vasospasms) is considered to be the cause of the necrotizing myocarditis produced by a variety of agents, such as histamine, adrenaline, forced restraint, carbon monoxide, or vasopressin (68, 393). Still, in none of these cases has the oxygen tension in the cardiac blood been determined, and there is no actual proof that hypoxia, rather than any other biochemical change, was the cause of the lesions produced.

Some investigators believe that functional spasms of the coronary vessels may play a role in the production of myocardial necrosis by digitalis compounds (45, 197), while others assume that, here, "the blood supply may become relatively insufficient in proportion to the increased activity of the ventricles" (79). The fact that in the frog, unlike in mammals, digitalis intoxication does not produce focal necroses, has been thought to support the vascular theory, because, in the frog heart, there is no coronary circulation (171). It must be kept in mind, however, that amphibian tissues are unusually resistant to anoxia. Besides, in frogs, digitalis produces severe hyalinization of cardiac muscle fibers, although this does not terminate in necrosis. The hyalinization was ascribed to persistent cardiac muscle spasms; if this is so, these might well cause necrosis in the more sensitive heart tissue of mammals. Hence, the demonstration of definite morphologic changes in the cardiac muscle of digitalis-treated frogs may equally well be considered as an argument against the vascular theory, because here the change cannot be due to coronary spasms.

Severe lack of oxygen will certainly cause necrosis in the heart, as it does in any other tissue, but cellular death is the most nonspecific end result of any sufficiently severe biochemical derangement; hence, it does not seem justified to single out hypoxia as the final, common pathway of myocardial necroses, no matter how produced.

Excessive Cardiac Work

The mere physical strain of excessive cardiac work has also been considered as a possible common pathway in the production of myocardial necroses and myocarditis. For example, one group of investigators, who produced such lesions by combined

treatment with caffeine and adrenaline or by uranium nitrate, concluded that "mechanical strain is the direct cause of the myocarditic lesions," and that "these lesions are, in all probability, not due to a lack of nutrition of the muscle-fibers as a result of contraction of the coronary vessels, inasmuch as it has been shown that adrenaline does not cause a contraction of the coronary vessels" (101).

Infection

Since necrotizing myocarditis is particularly common in acute infectious diseases (e.g., diphtheria, typhus), it has been thought that all such cardiopathies are necessarily of infectious origin. This theory has been vigorously defended, despite overwhelming evidence to the contrary. Even such an outstanding authority in the field of the cardiovascular diseases as Mönckeberg (251) concluded (in the Henke and Lubarsch Handbook) that, as judged from his extensive survey of the literature, "all authors agree that the diffuse interstitial myocarditis is an infectious disease although, as Saltykow has emphasized, the bacteriologic findings are always negative." Brigden (38), another prominent student of cardiac disease, went even further in his recent St. Cyres Lecture. He categorically stated that the term "myocarditis should certainly be reserved for those conditions in which there is reasonable evidence of an infective origin."

Every inflammation of the heart muscle is, by definition, a myocarditis and, in the absence of any proof of microbial invasion, it hardly seems warranted to assume that the cardiac necroses produced by drugs result in inflammation only "by preparing the soil for bacterial infection" (101). It would be wholly unjustified, for example, to postulate that the polymorphonuclear and histiocytic infiltration of necrotic cardiac foci, in rats treated with Me-Cl-COL plus NaClO₄ or with DHT plus NaH₂PO₄, is not a myocarditis simply because it is not due to infection. The production of inflammation by chemical agents (e.g., croton oil, formalin) is a fully established fact, and there is no reason to doubt that endogenous chemical irritants produced in the cardiac muscle during necrosis could also give rise to true inflammation.

Hypersensitivity

It has been demonstrated that focal myocardial necroses and myocarditis can be produced in experimental animals by repeated injections of various foreign proteins, as a result of a hypersensitivity reaction (154, 216). Yet there is no basis for the belief, frequently expressed in the literature, that all, or even any considerable proportion of, the spontaneous and experimental necrotizing cardiopathies are local manifestations of immune reactions to bacterial or other exogenous toxins.

Metabolic Toxins

Many investigators thought that the necrotizing inflammations of the heart are due to some endogenous metabolic toxins that might be produced, for example, during hyperthyroidism (122) or in uremia (128). This is undoubtedly true, but the incrimination of a "metabolic toxin," without any evidence as to its origin or identity, is not a particularly illuminating hypothesis. The arbitrary character of such a vague concept is clearly illustrated by the view of one author (133), who came to the conclusion that even the cardiac lesions induced by lack of oxygen are due to some special metabolic toxins, the "*Mangelstoffwechselprodukte*." The proponents of the hypoxia theory could, of course, postulate with equal justification that even cardiac necroses caused by "metabolic toxins" are, in the final analysis, the results of tissue anoxia.

Stress, Steroids, and Electrolytes

Nonspecificity of Necrotizing Myocarditis. Our survey of the literature revealed that a surprisingly large number of microbial, chemical, and physical agents can produce myocardial necroses followed by inflammation. This fact suggested that the necrotizing cardiopathies may merely be due to non-specific stress. But this view is not easily reconciled with the observation that even just sublethal doses of most agents do not produce such cardiac lesions regularly. If the necrotizing cardiopathy were a truly nonspecific manifestation of stress, it should be possible to elicit it with all stressors, just as it is pos-

sible to produce the typical manifestations of the general adaptation syndrome (e.g., an ACTH discharge, adrenocortical hypertrophy, or thymicolumphatic involution) with all these agents. Actually, our survey shows that, although the experimental production of cardiac necroses by drugs goes back to the beginning of the present century and spontaneous necrotizing myocarditis had been observed in man much before that, the relevant literature is quite contradictory. The development of such lesions is extremely erratic; it appears to depend upon a large number of uncontrollable variables. Presumably, cardiac necrosis with inflammation is one of those consequences of nonspecific stress that are particularly dependent upon conditioning factors. The stressor effects of various agents and more or less ubiquitous, conditioning factors (e.g., dietary constituents), rather than any specific property of the eliciting pathogens, may represent the common factors in the causation of this cardiopathy.

Experiments based upon this concept demonstrated that, in suitably conditioned rats (e.g., in animals pretreated with Me-Cl-COL or, even better, with subthreshold amounts of Me-Cl-COL plus sensitizing Na-salts), a great variety of apparently quite unrelated agents (e.g., heat, cold, neuromuscular exertion, and many drugs) consistently produce a severe necrotizing cardiopathy. It is improbable that, in all these cases, the pathogenic mechanisms would be completely distinct and specific for each agent.

A Working Hypothesis. In view of the facts just mentioned, we assumed, as a working hypothesis, that nonspecific **stress** occupies a key position in the pathogenesis of the necrotizing cardiopathies, and that the latter could consequently be regarded as "diseases of adaptation" caused by some derailment of the General Adaptation Syndrome. Our observations on the ESCN suggest that, during stress, an **excessive production of corticoids or the undue activation of such steroids by certain electrolyte shifts** may produce irreversible metabolic derangements in the cardiac muscle fibers, and thereby induce necrosis.

The fuchsinophilic degeneration appears to be one of the earliest morphologically detectable manifestations of such bio-

chemical disturbances in the myocardium. Inflammation is a secondary consequence of this same derangement, and, hence, an integral part of the lesion. Since any sizeable focus of myocardial necrosis is secondarily invaded by inflammatory cells, it would only be misleading to distinguish sharply between cardiac necrosis and necrotizing myocarditis. Of course, inflammation may occur in the heart, as in any other organ, without preceding necrosis, but no matter how a necrotic focus is produced in the myocardium (e.g., by coronary occlusion, or thermocoagulation), even in the absence of any exogenous chemical or microbe, the dead tissue is destroyed and removed by inflammatory cells. We emphasize these points because they suggest that whatever may be learned about the pathogenesis and prevention of cardiac necroses will also be applicable to at least some types of myocarditis.

From our earlier work on stress and the diseases of adaptation, we concluded that "there begins to emerge a new and somewhat more complex pathology, in which the main objects of our studies are no longer individual 'pathogens,' but rather 'pathogenic situations'" (324). This concept has subsequently (325) helped us to come closer to the understanding of a variety of diseases (e.g., gastroduodenal ulcers, hypertension, nephrosclerosis, periarteritis nodosa, rheumatoid diseases), in which the interminable search for single, specific pathogens has, of necessity, been fruitless. These maladies are not due to any one causative factor, but to **pathogenic constellations** that can be induced in various ways. The findings reported in this volume suggest that this is also true of the necrotizing cardiopathies and of certain types of myocarditis.

As it stands today, our hypothesis has **two severe flaws**: first, we have seen that several stressors do not produce a necrotizing cardiopathy, even when lethal amounts are applied to rats optimally conditioned by corticoids and/or electrolytes; second, the postulated, common, metabolic derangement in the cardiac-muscle fiber, that we believe is induced by stress under certain conditions, has not yet been identified.

Our concept is not offered as a final solution, but, despite its admitted weaknesses, it seems to be the **working hypothesis**

most compatible with all the known facts. There is overwhelming evidence in support of the view that certain conditioning factors (corticoids, Na-salts) can predispose to the production of necrotizing cardiopathies by wholly unrelated stressors. That some agents, capable of producing severe stress, nevertheless fail to elicit pronounced myocardial necroses may be a promising lead for further investigations. For example, this fact suggests experimentation to verify whether there exist adaptive mechanisms (e.g., humoral factors, circulatory collapse with diminished cardiac work) that can protect the heart against necrosis when stress of a certain intensity is produced in a certain way. The same attitude must be taken with regard to the second point, namely, our present ignorance of the fundamental biochemical derangement that causes myocardial necrosis.

It would be gratuitous, at present, to elaborate a detailed biochemical theory of the necrotizing cardiopathies. It is obvious, from the data cited in this volume, that electrolyte shifts are important and it may be that the corticoids condition the cell by altering its affinity for certain ions—perhaps through changes in cell permeability. Whether the concurrent accumulation of fuchsinophilic substance is the cause or the consequence of damage we do not know, but it would certainly be rewarding to extract this material and to identify its properties. These are avenues for further research.

The only general conclusion that appears to be justified at present is that the necrotizing cardiopathy is largely, but not totally, nonspecific, as it can be produced by many, but not by all, stressors, in suitably conditioned animals. The concept of relative nonspecificity receives further support from the observation that certain factors sensitize (e.g., corticoids, Na-salts), while others desensitize (e.g., $MgCl_2$, KCl), the cardiac muscle for the production of necroses by a great variety of agents. All this suggests the existence of common elements in the pathogenesis of the necrotizing cardiopathies.

Relationship Between Necrotizing Myocarditis and True Cardiac Infarcts. Although manifestly similar in their morphologic appearance, the ESCN and other types of necrotizing myocarditis differ sharply from the true cardiac infarcts of

man, in that they cannot be traced to any histologically demonstrable vascular occlusion. Spasms in the larger branches of the coronary arterial system are also unlikely to be involved in the causation of the ESCN and related cardiopathies, because the necroses do not coincide with major vascular territories. However, as we have said before, the development of true cardiac infarcts depends primarily upon the relationship between the metabolic requirements of the heart and its blood supply; hence, combined treatment with corticoids and sensitizing Na-salts might act by inducing potentially dangerous metabolic changes within the myocardium, so that even normally well-tolerated physiologic variations in the blood supply may result in necroses. In this case, the precipitating effect of stress could be due either to an additional increase in the demand made upon the cardiac muscle or to temporary variations in the blood supply that are not reflected by any detectable structural change in the coronary vessels.

The question arises whether this type of biochemical conditioning could play a part in the pathogenesis of the cardiac infarcts that occur in man. We have seen (see p. 127) that in about 30% of all clinical cardiac infarcts even careful examination of the coronary vessels failed to reveal any evidence of an acute obstruction. In most of these cases, there is some atheromatosis, which may produce a partial occlusion or, at least, a rigidity of the vascular wall. Such changes could interfere with the vasodilatation necessary to supply increased amounts of blood to the heart, when its requirements for oxygen and nutrients suddenly rise (e.g., during neuromuscular stress). It is conceivable, therefore, that, at times of stress, this increase in demand could cause myocardial infarction, despite the absence of an acute coronary occlusion. Thus, the biochemical derangement that is produced by stress, corticoids, and electrolytes and that is all-important in the production of the ESCN, may also play a rôle in those cardiac infarcts of man that cannot be traced to coronary occlusion. This view is further substantiated by the observation that systemic stress can precipitate an ESCN in animals suitably conditioned by a

corticoid, just as it can cause cardiac infarcts in predisposed human beings.

If this interpretation is correct, the prophylactic measures effective in the treatment of the ESCN (e.g., KCl, MgCl₂) may also be beneficial in the prevention of certain cardiac infarcts.

4

Outlook

Now that we have painstakingly attempted to systematize all the available data concerning the necrotizing cardiopathies, it may be permissible to speculate a little about the probable scope and future of this field. To my mind, the most important outcome of work on the ESCN was the discovery of a highly effective humoral conditioning system, through which we can, at will, sensitize or desensitize the cardiac muscle to the production of necrotizing inflammation by a great many agents. It remains to be seen to what extent this new knowledge will be able to act as a guide for future research and, thereby, promote our understanding of basic problems in physiology and pathology. Yet, certain general implications already begin to take shape, and we should like to discuss these now in relation to four major areas of investigation that we believe to be particularly promising.

1. **Physiologic Chemistry of Cardiac Muscle.** Work on the ESCN has taught us that the influence of electrolytes upon the cardiac muscle can be decisively altered by conditioning with certain corticoids. Although, up to now, our attention was primarily directed towards the production and prevention of pathologic lesions in the heart, it is highly probable that similar interactions between corticoids and electrolytes also take place under physiologic conditions. Hence at this point it would appear to be promising to investigate the cardiac effects of near-normal blood levels of corticoids and of those electrolytes whose actions we found to be particularly dependent upon conditioning by cortical hormones. In order to understand the

underlying basic mechanisms, such investigations should be performed not only on entire animals but also *in vitro*. For example, it would be instructive to explore the effect of such hormone-electrolyte interactions upon the function and tissue metabolism of the isolated heart preparations.

In all future investigations of this type we shall have to keep in mind the hitherto largely neglected interdependence of cations and anions. It is difficult (except in small amounts, by iontophoresis) to administer anions and cations separately, yet we have seen how meaningless it is to speak merely of the actions of K, Na, Mg, PO₄, Cl, or SO₄, without taking into account the combinations in which these ions are made available to the tissues.

Up to now, the interactions between corticoids and inorganic elements occupied the center of our interest, but the organic constituents of the heart also deserve attention if we are to arrive at a more profound understanding of the fundamental mechanisms involved. This is suggested, for example, by the fact that interactions between electrolytes and steroids may result in fuchsinophilic degeneration and necrosis of the cytoplasm.

2. Pathologic Chemistry of Cardiac Failure. Despite the many studies that have dealt with this subject in the past, comparatively little is known about the chemical basis of cardiac failure. Why is it that, when the heart has to work under very adverse conditions, it usually adapts itself to the increased work requirements at first, but, eventually, this adaptability is exhausted and cardiac failure ensues?

The investigations of others have shown that the intracellular Na- and K-content of the aorta rises in animals in which renal or adrenocortical hypertension is produced in various ways. These electrolyte shifts were thought to play an important part in the altered peripheral vascular resistance that characterizes hypertension (390). The few chemical studies on the ESCN that have been performed so far indicate that important electrolyte shifts also accompany the cardiac insufficiency and necrosis produced by treatment with corticoids and certain Na-salts.

The histologically demonstrable accumulation of fuchsinophilic material suggests that rather specific changes in the organic constituents of the heart occur at a very early stage of cardiac failure. Now it will have to be determined whether these chemical changes represent causes or consequences of cardiac damage, and whether they are characteristic only of certain pathogens or are nonspecific phenomena that occur no matter how the cardiac muscle is overburdened.

3. Chemical Protection of the Heart Against Structural Damage. At first sight, it would seem highly improbable that any one substance could shield the cardiac-muscle fiber against damage produced by many fundamentally different agents. Yet, this is just what the observations on the ESCN have taught us. We saw, for example, that the myocardial necroses produced by corticoids, parathyroid extract, dihydrotachysterol, or various stressors can all be prevented by KCl or MgCl₂. It might be claimed that, in each of these cases, there is a final common pathway and that the effect of KCl and MgCl₂ always depends upon an inactivation of (exogenous or endogenous) sensitizing Na-salts. It is perhaps farfetched to invoke such a mechanism for the explanation of the inhibition, with KCl or MgCl₂, of the cardiac necroses normally produced by the intravenous injection of proteolytic enzymes. Presumably, proteases lyse cardiac muscle by virtue of a direct action, just as they attack protein solutions *in vitro*. Yet, as we have seen, KCl and MgCl₂ can protect the heart against necrosis due to intravenously injected papain; hence some largely nonspecific mechanism must be suspected.

Even the most conservative evaluation of these findings cannot fail to raise the hope that such a protection by electrolytes may also be effective in the prophylaxis of at least some among the cardiopathies of man. It is rather unlikely that all the manifold experimental cardiopathies should depend upon mechanisms that are wholly unrelated to the pathogenesis of the histologically similar cardiac diseases of man. Besides, a good deal of evidence suggests that certain clinical conditions are closely related to the type of experimental cardiopathy that can be prevented by KCl or MgCl₂. The cardiopathies that develop

in the course of acute infections can be so closely duplicated in animals by the intravenous injections of proteases that it would be difficult to reject the suggestion that the former are due to bacterial proteases (187). Besides, as we have seen, even the cardiotoxic effect of stress is effectively combated by KCl or MgCl₂, and few cardiologists would be inclined to deny that stress also plays an important part in the production of cardiac infarcts and certain other spontaneous cardiopathies of man.

The great efficacy of specific treatments for specific diseases, and the fact that so many maladies can be produced only by certain pathogens have somewhat blurred our vision for non-specific elements in pathogenesis and treatment. Yet, it is indisputable that such tissue lesions as necrosis and inflammation can be induced by many wholly unrelated agents, and that inflammation, be it caused by microbes, allergens, or chemical irritants, can be prevented by the same glucocorticoids. It may be difficult at first to see why different cardiotoxic agents should raise the Mg- and K-requirements of the body; yet, we know that stress, no matter how produced, raises corticoid requirements and causes death, unless the adrenal cortex can meet the situation by increased hormone secretion.

Finally, we might point out that **nonspecific therapy** can be effective, even in the particular field of cardiology with which we are concerned here. The cardiac glycosides—whose actions largely depend upon shifts in tissue-K-concentrations (32, 220, 265, 418)—increase cardiac efficiency when the heart is damaged in various ways, and both K (198, 220, 265, 305) and Mg (102, 103, 374, 375) are effective in combating cardiac arrhythmias due to diverse derangements.

The **cardiac-glycoside-like actions of corticoids** have already been discussed (p. 100), but, in connection with the subject under consideration here, it is worth mentioning that certain steroid derivatives also possess definite **antiaccelerator and antifibrillatory activity** (125, 126, 228, 307).

The mechanism through which KCl and MgCl₂ exert their **beneficial effects** is, meanwhile, difficult to assess. Mg-ions considerably increase the production of oxalacetate by the heart, presumably through their effect upon **cardiac transaminase**.

(144), and countless observations have shown that both Mg-ions (78, 102, 308) and K-ions (64, 165) are important for cardiac contraction in particular, and for the actions of various enzyme systems in general.

It is difficult to foretell which among the spontaneous cardiac diseases of man are most likely to be prevented or improved by KCl and MgCl₂. Only extensive, statistically evaluated clinical observations will be able to answer this question. Far-reaching speculations would not be warranted now, but, since clinical trials cannot be made at random, it seems appropriate to evaluate the probable applicability of this treatment in advance.

The spontaneous diseases of man that most closely resemble the ESCN are: the isolated myocarditis of Fiedler, the various types of necrotizing myocarditis that accompany acute infectious diseases (diphtheria, typhus, etc.) and certain "idiopathic" subendocardial necroses that are often diagnosed as infarcts. In all these maladies, we are dealing with more or less diffuse, often predominantly subendocardial, necroses followed by inflammation. The cardiac infarcts that tend to occur in the presence of moderate arteriosclerosis without acute coronary occlusion, may also be closely related in their pathogenic mechanism to the ESCN. This is made probable especially by what we have said about the importance of the relationship between the nutritional demands of the myocardium and its blood supply, particularly during stress. Hence, in all these conditions, treatment or prophylaxis with KCl and MgCl₂ may prove to be effective.

We have described a more or less gradual transition from fuchsinophilic degeneration of fiber segments to individual fiber necrosis and the eventual development of larger necrotic foci. In view of these findings, it would seem particularly desirable to conduct extensive observations on human pathologic material to determine the part played by fuchsinophilic degeneration and disseminated fiber necrosis, not readily detectable with the customary stains, in patients who died from cardiac failure due to various causes. In experimental animals, fuchsinophilic degeneration and fiber necrosis appear to be the

first and most nonspecific manifestations of cardiac damage; since these changes are also beneficially influenced by KCl and MgCl₂, it would be highly important to determine the possible role of these early lesions in clinical heart failure.

Obviously, such clinical trials would have to be carried out with the greatest caution, to avoid **possible toxic side-effects**. But both KCl and MgCl₂ have long been used in the treatment of various functional derangements (including cardiac arrhythmias), and there is no definite reason to believe that these salts would be more dangerous than any other new drug that could be recommended for the therapy or prophylaxis of structural changes in the myocardium. In our animal experiments, the toxic side-effects of both KCl and MgCl₂ were most manifest (and, incidentally, the beneficial actions least pronounced) when the salts were given in large amounts, at long intervals; hence, it is probably undesirable to flood the body suddenly with these electrolytes. A slow absorption could perhaps best be accomplished by the inclusion of the salts in **capsules that are slowly dissolved** at various levels of the gastrointestinal tract. Furthermore, since we have found that, in the treatment of the ESCN, the beneficial effects of KCl and MgCl₂ are **summated**, it may also be advantageous to give **mixtures of these salts** in order to obtain a maximal therapeutic effect while reducing the specific toxic actions of each component. It may be useful also to employ certain **Na-exchange rosins and chelating agents**, so as to combine the administration of excess Mg and K with a forced loss of Na. Finally, it will be remembered that although among the salts that we tested, KCl and MgCl₂ proved to be the most effective and least toxic, yet other chlorides also exhibited marked anti-ESCN effects. Hence, it is possible that, by suitable combination of KCl and MgCl₂ with various **other chlorides**, an even safer mixture could be prepared, because then, the required daily dose of each ingredient could be further reduced.

4. Physiology and Pathology of Extracardiac Actions. Since the ESCN and its clinical implications are the principal topics of this volume, we have somewhat neglected the extracardiac manifestations of steroid-electrolyte actions. Still, we

mentioned that nephrocalcinosis, hepatic necrosis, cerebral edema, cramps, and sometimes even actual necroses in skeletal muscle also occur when certain electrolytes are administered to corticoid-conditioned animals. These findings suggest that the interaction between steroids and electrolytes may have much more general implications in physiology and pathology than are implied by the ESCN itself. It is particularly noteworthy, therefore, that KCl and MgCl₂ can prevent, not only the cardiac manifestations of the damage produced by an excess of corticoids and certain Na-salts, but also all the extracardiac effects just mentioned.

Much further work will be necessary to clarify the fundamental mechanism through which electrolytes exert their corticoid-conditioned effects. It must be clearly stated that, at present, there is no evidence to prove that the same labile biochemical system that is so readily deranged by corticoids and electrolytes in animals also exists in man, or that the therapeutic measures that proved to be so highly effective in laboratory rodents would also be of value to patients. However, it is encouraging that, although most of our work was performed in the rat, the ESCN is not a species-specific phenomenon. We have confirmed our basic observations in various other species, all of which, including the primate, responded in essentially the same manner. That is as far as the experimental physician can go in preparing the field for a new approach to treatment, but the decisive proof of the applicability of these concepts in human pathology will have to be furnished by clinicians.

5

Summary and Conclusions

The object of this monograph—as stated in the Preface—is to coordinate the many, isolated observations on necrotizing cardiopathies in the light of newly acquired knowledge about the production and prevention of similar lesions in animals. It was hoped that such a systematization of our knowledge would help us to obtain a better insight into the complex relationships between electrolytes, steroids, and stress, which we believe to be fundamental for the understanding and prevention of these and many other diseases. An integrative review of several hundred publications does not readily lend itself to condensation in the form of a synopsis, but it may be helpful, in closing, to summarize what we consider to be the principal conclusions that can be derived from our own research.

1. The ESCN. Combined treatment with certain Electrolytes and Steroids produces a Cardiopathy characterized by Necroses, the “ESCN.” In this condition, multiple, massive, necrotic foci may occur anywhere within the myocardium, but they usually show a definite predilection for the right ventricle, the atria, and the subendocardial layers of both ventricles. The formation of the large, necrotic foci is usually preceded by a singular “fuchsinophilic degeneration” and the necrosis of scattered, individual muscle fibers. Such isolated necrotic fibers do not give rise to inflammation and are eventually absorbed without leaving a trace. However, if many adjacent fibers die and the affected focus reaches a “critical size,” it is invaded by phagocytic elements (mainly histiocytes and polymorphonuclear leukocytes) and heals by scar-formation, which leaves a permanent muscle defect.

2. Sensitizing Electrolytes. Of all the electrolytes examined, only certain Na-salts could produce an ESCN, following conditioning with steroids. Phosphates, sulfates, and perchlorate were particularly effective in this respect, while chlorides, nitrates, permanganate, and most of the organic Na-salts were inactive. We conclude that both the cation (Na) and the anion (PO_4 , SO_4 , ClO_4) possess sensitizing potency.

Although NaCl does not normally sensitize for the ESCN, it does acquire sensitizing properties during stress.

3. Desensitizing Electrolytes. Certain electrolytes not only failed to produce an ESCN, but actually prevented its development, when they were given simultaneously with sensitizing electrolytes to animals suitably conditioned with steroids. Among all the salts tested, KCl and MgCl_2 were the most potent anti-ESCN agents. K-salts other than the chloride (e.g., KHSO_4 , KClO_4 , KNO_3 , KH_2PO_4) and chlorides other than KCl (e.g., NH_4Cl , CaCl_2 , RbCl , MnCl_2 and, to some extent, even NaCl) also proved to be effective, but their prophylactic usefulness is limited because some of them are toxic, while others possess a comparatively low potency. We conclude that both the cation (K, Mg) and the anion (Cl) are endowed with desensitizing activity.

It has been found, furthermore, that when Na is given in the form of one of its sensitizing salts (e.g., as a phosphate, sulfate, or perchlorate), 4-8 mEq of Na can be inactivated by 1 mEq of K or Mg, given as the chlorides.

4. Steroids. Among all the steroids tested, only some corticoids proved to condition the heart for the production of the ESCN. Virtually pure glucocorticoids (e.g., triamcinolone) were ineffective and a pure mineralocorticoid, such as desoxycorticosterone (DOC), exhibited a comparatively low potency; on the other hand, mixtures of these two types of compounds, as well as some of the synthetic halocorticoids that possess both mineralo- and glucocorticoid activities, were highly effective. Of all the steroids tested up to now, 2α -methyl- 9α -chlorocortisol (Me-Cl-COL) possesses the highest potency as a conditioner for the production of the ESCN.

5. Sterols of the Vitamin-D Group. Certain sterols of the vitamin-D group (e.g., dihydrotachysterol, "DHT") can produce necrosis of myocardial fibers, presumably as a consequence of tissue calcification. However, even the extensive myocardial lesions produced by fatal doses of DHT do not stimulate any noteworthy local inflammatory response. If, on the other hand, DHT is given concurrently with NaH_2PO_4 , a purulent myocarditis results. The other Na-salts that are highly effective in producing an ESCN in animals conditioned by corticoids exhibited little, if any, tendency to produce myocarditis after pretreatment with DHT.

KCl and MgCl_2 can completely prevent the production of myocarditis by combined treatment with DHT plus NaH_2PO_4 . However, in this respect, 1 mEq or more of Mg or K is necessary to counteract the effect of 1 mEq of NaH_2PO_4 .

Hence, there appear to exist fundamental differences in the manner in which electrolytes affect the heart, following conditioning by corticoids on the one hand, and by sterols of the vitamin-D group on the other. Yet, in both types of cardiopathies, KCl and MgCl_2 exert marked protective actions.

6. Nonspecificity of the Cardiac Necroses. Numerous, earlier, isolated observations, as well as our extensive investigations on a homogeneous animal material, revealed that cardiac necroses can be produced by a variety of drugs, physical agents, allergens, and infections. However, a survey of the literature shows that only few agents produce such lesions consistently. In general, the results are highly variable and erratic, in that positive results obtained with a certain agent by one investigator could not be confirmed under the experimental conditions used by other workers. This inconsistency has variously been ascribed to latent infections, hypersensitivity, unidentified nutritional factors, or simply to the "poor condition" and hyper-susceptibility of certain strains of laboratory rodents.

On the basis of our literature survey, we are inclined to consider the so-called "isolated myocarditis" of Fiedler, certain forms of necrotizing myocarditis that occur in acute infectious diseases (diphtheria, typhus), and perhaps the cardiac infarcts that develop without acute coronary occlusion as the closest

clinical counterparts of the toxic necrotizing myocarditis that is produced by various agents in animals.

7. Stress and Conditioning as Nonspecific Factors in the Pathogenesis of Necrotizing Cardiopathies. The realization that so many essentially dissimilar factors can produce necrotizing myocarditis in experimental animals and man, as well as the great inconsistency of the results produced by the same pathogen in different circumstances, made the evaluation of these lesions rather difficult. It was noted, however, that, in animals conditioned by large doses of highly active corticoids (or, even better, with subthreshold amounts of corticoids and sensitizing Na-salts), a great variety of noxious agents (hot and cold baths, surgical trauma, adrenaline, neuromuscular exertion, vasopressin, Na-fluoroacetate) are all highly and consistently effective in producing a necrotizing myocarditis. This nonspecific activity was ascribed to the stressor action of the agents used. Presumably, there exists in the heart a particularly labile chemical system, which is easily deranged through some metabolic effect of stress, especially in the presence of intense hypercorticoidism and an excess of sensitizing Na-salts.

Thus, the relative nonspecificity of necrotizing myocarditis appears to find its explanation in the fact that a great many agents can elicit the metabolic derangements characteristic of stress (including hypercorticoidism) and that stress, corticoids, and dietary electrolytes influence the cardiotoxic effects of many otherwise unrelated agents. Differences in the diet, the stressor effect of the pathogens, and the stress-susceptibility of the experimental animals used may best explain the variability of the results obtained by earlier investigators, who were not aware of the important part played by such conditioning factors.

8. Outlook. One of the most striking results of these investigations was the demonstration that the production of necrotizing myocarditis by so many agents is uniformly influenced by corticoids and electrolytes. KCl and MgCl₂ prevent, not only the typical ESCN induced by corticoids and sensitizing Na-salts, but also the suppurative myocarditis that is normally

elicited by combined treatment with DHT plus NaH_2PO_4 , the necrotizing myocarditis that develops in corticoid-conditioned rats during exposure to various stressors, and even those cardiac necroses that occur (presumably as a result of a direct proteolytic action) following intravenous treatment with a protease.

These findings raise the hope that some of the spontaneous, necrotizing cardiopathies of man may also be beneficially influenced by KCl or MgCl_2 .

Now we shall have to analyze the metabolic consequences of steroid-electrolyte intoxication, both in the heart and in those extracardiac structures (skeletal muscles, kidney, liver, brain) that are profoundly influenced by such treatment. Yet, even the facts that have already been established suffice to show that the interactions between steroids and electrolytes have much more general implications in physiology and pathology than was hitherto suspected.

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Index

To facilitate the use of this index, block numerals (e.g., 12) refer to principal discussions of a subject and ordinary Roman numerals (e.g., 12) to all other parts of the text.

Greek letters (e.g., α , β , γ , δ , Δ), numbers which form part of indexed words, short connecting words (e.g., the, of, for, from, to, as) and bracketed remarks are neglected in determining the alphabetic position of entries.

When a "target organ" A is influenced by a stimulus B, this is indicated by an arrow pointing from B to A thus: $A \rightarrow B$, instead of the usual cumbersome entry: "A, effect of B upon." Conversely, the effect of A upon B is indicated by the entry: $B \leftarrow A$, while a general discussion of the interrelations between A and B is indexed thus: $A \leftrightharpoons B$. If two stimuli B and C act upon the same target organ A, this is indexed: $A \leftarrow B + C$ and $C \rightarrow A \leftarrow B$. If either B or C act alone, we write: $A \leftarrow B$, C as well as $B \rightarrow A$ and $C \rightarrow A$.

It is, of course, impossible to index highly complex interactions under each stimulus or target involved (and under all synonyms), but entries have been so selected that it will be rarely necessary to search for a specific item under more than two possible headings.

- Absorption of salts from intestine, 42
- Acetoxypregneneolone → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 72
- 17-Acetoxyprogesterone → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 69
- Acetylcholine → heart, 102
- Acromegaly → Fiedler's myocarditis, 59
- ACTH
 - blood coagulability, 58
 - blood pressure, 46
 - cardiac infarcts in man, 58
 - heart (arrhythmias) in man, 59
 - heart ← coronary vessel ligature, 57
 - heart ← NaH_2PO_4 , 82
 - heart ← pregnancy, 82
 - heart failure, 58, 59
 - kidney ← NaH_2PO_4 , 82
 - rheumatic carditis, 58
- "Activating" anions, 24
- "Acute high-altitude death," 115
- Acute isolated interstitial myocarditis, 5, 133

- Acute miliary infarction of the heart, 133
- Acute toxic interstitial myocarditis, 133
- Adrenalectomy
 - heart ← Me-Cl-COL + NaH_2PO_4 , 84
 - heart ← nephrectomy + parathyroid extract, 84
 - heart ← nephrectomy + parathyroid extract + corticoids, 84
 - mortality ← cardiac glycosides, 100
- Adrenaline
 - coronaries, 153
 - ECG, 84
 - heart, 6, 84, 147, 152
 - heart ← "adrenaline sensitizer," 85
 - heart ← blood-letting, 86
 - heart ← caffeine, 85
 - heart ← Me-Cl-COL, 147
 - heart ← Me-Cl-COL + NaH_2PO_4 , 85, 144
 - heart ← NaClO_4 , Na_2HPO_4 , Na_2SO_4 , 86

- Adrenaline—Continued
 → heart ← Pearce's virus III, 151
 → heart ← sparteine, 85
 → heart ← triamcinolone, 84
 → heart ← typhoid bacilli, 85
 "Adrenaline sensitizer" → heart ← adrenaline, 85
 Adrenosterone → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 66
 Africa, frequency of cardiac infarcts, 130
 Age
 → heart ← Me-Cl-COL + NaH_2PO_4 , 139
 → heart ← vasopressin, 83
 → nephrocalcinosis ← NaH_2PO_4 + Me-Cl-COL, 140
 Alcohol; *see* Ethanol
 "Alcoholic cardiopathy," 107
 Allergy → heart, 125
 $\text{Al}_2(\text{SO}_4)_3$ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25
 Amitotic division in heart, **Fig. 6**
 Ammonium; *see* NH_4^+
 Anaphylaxis → heart, 126
 Angina → K in heart in man, 131
 Anion in prevention of ESCN, 26
 Anions, "activating," 24
 Anitschkow-myocytes in heart ← enzymes, 104
 Anoxia → heart, 115
 Anti-rat-kidney serum → kidney ← DOC + NaCl, NaCl-deficiency, NaCl + KCl, 63
 Antiaccelerator steroid alkylamines, 100
 Antiaccelerator steroids, 163
 Antiarrhythmic alkylamines, 100
 Antidiuretic hormone; *see* Vasopressin
 Antifibrillatory steroids, 163
 Aorta
 ← DHT + Ca-acetate, CaCl_2 , $\text{CaH}_4(\text{PO}_4)_2$, $\text{Ca}(\text{NO}_3)_2$, K-acetate, KCl, KClO_4 , K_2HPO_4 , KH_2PO_4 , KHSO_4 , KNO_3 , K_2SO_4 , Mg-acetate, MgCl_2 , $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$, MgSO_4 , Na-acetate, NaCl, NaClO_4 , Na_2HPO_4 , NaH_2PO_4 , NaHSO_4 , NaNO_3 , Na_2SO_4 , NH_4 -acetate, NH_4Cl , NH_4ClO_4 , $\text{NH}_4\text{H}_2\text{PO}_4$, NH_4HSO_4 ,
 NH₄NO₃, 96
 ← DHT + NaH_2PO_4 + KCl, MgCl_2 , **Fig. 15**
 ← Mg-deficiency + cholesterol, 32
 "Aphthous fever"
 ⇌ Fiedler's myocarditis, 139
 → heart in cattle, 139
 Arrhythmias ← K, Mg, 163
 Arsenic
 → Fiedler's myocarditis, 102
 → heart, **102**
 Arsphenamine
 → heart, 102
 → heart ← Me-Cl-COL + KCl, MgCl_2 , 102
 Arteriosclerosis
 ← DHT + NaH_2PO_4 + KCl, MgCl_2 , 91
 ← Me-Cl-COL + NaH_2PO_4 + DHT + KCl, MgCl_2 , 94
 ← Mg-theobromine-oleate, 32
 "Arthus phenomenon" → heart, 126
 "Artificial aging" of coronary vessels, 93
 Aschoff bodies
 (spontaneous) in mice, 138
 in rabbits, 138
 Ascorbic acid; *see* Vitamin-C
 Atherosclerosis ← cholesterol, **103**
 Atheromatosis
 ← cholesterol, **103**
 ← cholesterol + Mg-deficiency, 32
 → cardiac infarcts, 128
 Azide → heart, 103
 Bacterial toxins → heart, **123**
 Barium → heart, 103
 → heart ← Pearce's virus III, 103, 151
 Beans → heart, nephrocalcinosis ← Me-Cl-COL + NaH_2PO_4 , 142
 Betaine → heart ← choline deficiency, 98
 Blood coagulability ← ACTH, corticoids, 58
 Blood-coagulation ← MgSO_4 , 130
 Blood-letting
 → heart, 147, 151
 → heart ← adrenaline, 86
 → heart ← DHT + NaH_2PO_4 , 115
 → heart ← Me-Cl-COL, 114, 147
 → heart ← Me-Cl-COL + NaH_2PO_4 , 114, 151

- Blood-letting—Continued
 → heart ← noradrenaline, 86
 → heart ← papain, 106
 → heart ← plasmocid, 110
- Blood pressure
 ← ACTH, cortisone, cortisone + K-deficiency, DOC, renal hypertension + K-deficiency, 46
 ← DOC in fowl, 8, 55
 ← DOC + NaCl, 10, 60
 ← Me-Cl-COL, Me-Cl-COL + NaH₂PO₄, 47
- Blood vessels ← Mg-deficiency, 31
- Bone fractures → heart ← Me-Cl-COL + NaH₂PO₄, 144
- “Bowditch’s staircase phenomenon,” 47
- Brain edema ← Me-Cl-COL + NaClO₄, 51
- 12α-Bromo-11β-hydroxyprogesterone
 → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 70
- Bromoxoprogesterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 70
- Burns → heart, 114
- Ca-acetate
 → aorta, heart, mortality, nephrocalcinosis ← DHT, 96
 → heart ← Me-Cl-COL + DHT, 92
- Ca in ESCN, 44
- Ca in heart
 ← electroshock, 118
 ← Me-Cl-COL + NaH₂PO₄, 49
 ← streptococci, 125
- Ca in serum ← Me-Cl-COL + NaH₂PO₄, 49
- CaCl₂
 → aorta, heart, mortality, nephrocalcinosis ← DHT, 96
 → heart ← DOC + uninephrectomy + NaCl, 61
 → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL + Na₂HPO₄, 96
 → kidney ← DOC + uninephrectomy + NaCl, 61
- Caffeine → heart ← adrenaline, 85
- CaH₄(PO₄)₂
 → aorta, heart, mortality, nephrocalcinosis ← DHT, 96
 → heart ← Me-Cl-COL + DHT, 92
 → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25
- Calcium; *see Ca*
- Ca(NO₃)₂ → aorta, heart, mortality, nephrocalcinosis ← DHT, 96
- Carbon monoxide, 152
 → ECG, heart, 103
 → heart ← exercise, 103
- Cardiac; *see Heart*
- Cardiac aglycones
 → heart, 100
 ⇌ corticoids, 100
- Cardiac failure, pathologic chemistry, 161
- Cardiac glycosides, 13, 14
 → heart, 100
 → heart ← K, 100
 → K in blood, 100
 → mortality ← adrenalectomy, 100
 ⇌ K-metabolism, 163
- Cardiac infarcts
 ← ACTH in man, 58
 ← age in man, 129
 ← atheromatosis, 128
 ← coronary edema, 128
 ← corticoids, 58
 ← glucocorticoids in man, 57
 ← Mg in man, 130
 → cholesterol in blood, 49
 → heart ← ephedrine, 85
 → K in blood in man, 131
 → K in heart, 111
 → K in heart in man, 49, 118, 131
 → lipoproteins in blood, 49, 108
 ⇌ coronary occlusion, 127
 ⇌ ESCN, 93, 157
 ⇌ Mg in blood in man, 130
 ⇌ necrotizing myocarditis, 157
 absent in coronary occlusion, 127
 among Africans, 130
 in man, 58, 127
 with fuchsinophilia in man, 129
 with “hydropic change,” 129
 without acute coronary obstruction, 127
- Cardiac necroses, theories, 150
- Cardiac necrosis
 as a cause of coronary thrombosis, 94
 toxic, 5
 without coronary occlusion, 55
- Cardiac puncture → heart ← Pearce's virus III, 112
- Cardiac work (theory)
 → ESCN, 152
 → heart, 152
- Cardiovascular surgery → heart, 111

- Casein → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
- Cations → prevention of ESCN, 28
- Cations → production of ESCN, 24
- Cerebral lesions → heart, 136
“Chastek paralysis,” 97
- Chelating agents → heart, 165
- 4-Chloro-adrenosterone → liver, mortality, nephrocalcinosis ← NaH₂PO₄, 67
- Chloroform → heart ← Pearce's virus III, 151
- 4-Chloro-testosterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 67
- Cholesterol
- aorta, atheromatosis ← Mg-deficiency, 32
 - atherosclerosis, 103
 - heart, 103
 - ← hypoxia, 115
 - ← Mg, 32
 - ← muscular exercise, 117
 - in blood
 - ← cardiac infarcts, 49
 - ↔ Mg in blood, 130
- Choline deficiency
- heart, 98
 - ← betaine, ethyl laurate, fatty acids, K, lipids, methionine, 98
 - K in heart, 98
 - kidney ← fatty acids, 98
 - lipids in heart, 98
 - liver, 98
- Chlorides → heart ← Me-Cl-COL, 32
- Chronic fibroplastic myocarditis, 133
- Chronic myocarditis, 14
- Chronic primary myocarditis, 133
- Chronology (*see also* Time relations), in production of ESCN, 120, 121, 122
- Cl-COL
- heart ← NaH₂PO₄, 65
 - heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 71
- Coalescent areas of myocardial fibrosis, 133
- Cold
- heart, 146
 - ← DHT, 91
 - ← Me-Cl-COL, 114, 146
 - ← Me-Cl-COL + NaH₂PO₄, 114, 144
 - ← thyroxin, 88
- Cold—Continued
- ← triamcinolone, 84
 - ← NaCl, NaClO₄, Na₂HPO₄, Na₂SO₄, 149
- Colloid goiter → Fiedler's myocarditis, 88
- Conditioning action of hormones, 8, 59, 144
“Conditioning factors,” 55
- Convulsions; *see* Muscles
- Corn → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
- Corn oil; *see* lipids
- Corn syrup → heart ← Pearce's virus No. III, 151
- Coronaries
- ← adrenaline, 153
 - ← DHT + NaH₂PO₄, Fig. 16
 - ← Me-Cl-COL + NaH₂PO₄ + DHT, 94, Figs. 13, 14
 - ← meningococcal endotoxin, 124
 - edema, 128
 - edema → cardiac infarcts, 128
 - embolization → heart, 111
 - in cardiac necrosis, 55
 - ligature → heart ← ACTH, cortisone, 57
 - ligature → K in heart, 111
 - ligature → K in heart in dog, 49
 - occlusion → heart, 57
 - occlusion ↔ cardiac infarcts, 127
 - occlusion without cardiac infarct, 127
 - thrombosis as a consequence of cardiac necrosis, 94
- Cor pulmonale*, 109, 126, 135
- Cor pulmonale* → ECG, 112
- Corticoids
- blood coagulability, 58
 - cardiac infarcts, 58
 - heart ← adrenalectomy + nephrectomy + parathyroid extract, 84
 - heart ← stress, 12
 - thrombosis, 57
 - ↔ cardiac aglycones, 100
 - ↔ cardiac glycosides → heart, 48
 - ↔ digitalis, 100
 - ↔ K → heart, 47
 - conditioning effect of, 144
- Cortisol
- heart ← DHT + NaClO₄, NaH₂PO₄, 92
 - heart ← NaH₂PO₄ + restraint, 144, Fig. 5

Cortisol—Continued

- heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 69
- liver, mortality, nephrocalcinoses ← NaH_2PO_4 , 69
- subendocardial necroses ← NaH_2PO_4 + restraint, **Fig. 8**
- Δ^1 -cortisol → heart, liver, mortality, nephrocalcinoses ← NaH_2PO_4 , 72

Cortisone

- blood pressure, 46
- blood pressure ← K-deficiency, 46
- heart ← coronary ligature, 57
- heart ← NaH_2PO_4 , 65
- heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 70
- in vitro* → heart, 47

Δ^1 -cortisone → heart, liver, mortality, nephrocalcinoses ← NaH_2PO_4 , 72

Cramps; see Muscles

“Critical size” of necrosis in ESCN, 13, 45

Definition

- of ESCH, 10
- of ESCN, 11
- of fibrinoid, 10
- of hyaline, 10

Dehydro-iso-androsterone → heart, liver, mortality, nephrocalcinoses → NaH_2PO_4 , 67

Depressor nerve severance

- heart, 119
- ← ephedrine, 85

Dermatitis → heart, 102

“Desensitizing electrolytes,” **26**

Desoxycortisol → heart, liver, mortality, nephrocalcinoses ← NaH_2PO_4 , 69

DHT

- aorta
- ← Ca-acetate, CaCl_2 , $\text{CaH}_4(\text{PO}_4)_2$, $\text{Ca}(\text{NO}_3)_2$, K-acetate, KCl , KClO_4 , K_2HPO_4 , KH_2PO_4 , KHSO_4 , KNO_3 , K_2SO_4 , Mg-acetate, MgCl_2 , $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$, MgSO_4 , Na-acetate, NaCl , NaClO_4 , Na_2HPO_4 , NaH_2PO_4 , 96
- ← NaH_2PO_4 + KCl , MgCl_2 , **Fig. 15**
- ← NaHSO_4 , NaNO_3 , Na_2SO_4 , NH_4 -acetate, NH_4Cl ,

DHT—Continued

- NH₄ClO₄, NH₄H₂PO₄, NH₄HSO₄, NH₄NO₃, 96
- arteriosclerosis
- ← Me-Cl-COL + NaH_2PO_4 + KCl , MgCl_2 , 94
- ← NaH_2PO_4 + KCl , MgCl_2 , **91**
- coronaries
- ← Me-Cl-COL + NaH_2PO_4 , **Figs. 13, 14**
- ← Me-Cl-COL + NaH_2PO_4 , 94
- ← NaH_2PO_4 , **Fig. 16**
- heart
- ← cold, 91
- ← cortisol + NaClO_4 , NaH_2PO_4 , 92
- ← DOC + NaClO_4 , NaH_2PO_4 , 92
- ← heat, 91
- ← K-acetate, KCl , KClO_4 , K_2HPO_4 , KH_2PO_4 , KHSO_4 , KNO_3 , K_2SO_4 , 96
- ← Me-Cl-COL + Ca-acetate, $\text{CaH}_4(\text{PO}_4)_2$, KClO_4 , K_2HPO_4 , KH_2PO_4 , KHSO_4 , $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, MgSO_4 , Na-acetate, NaCl , NaClO_4 , NaHCO_3 , Na_2HPO_4 , 92
- ← Me-Cl-COL + NaH_2PO_4 , 93, 94, **Fig. 13**
- ← Me-Cl-COL + NaH_2PO_4 in mouse, rabbit, dog, rat and hamster, 91
- ← Me-Cl-COL + NaH_2PO_4 + KCl , 91, 94
- ← Me-Cl-COL + NaH_2PO_4 + MgCl_2 , 91
- ← Me-Cl-COL + NaHSO_4 , Na-lactate, NaNO_3 , Na_2SO_4 , $(\text{NH}_4)_2\text{HPO}_4$, NH_4HSO_4 , 92
- ← Medrol + NaClO_4 , NaH_2PO_4 , 92
- ← 6 α -methyl-21-desoxy-cortisol + NaClO_4 , NaH_2PO_4 , 92
- ← Mg-acetate, MgCl_2 , Mg(ClO_4)₂, $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$, MgSO_4 , Na-acetate, NaCl , NaClO_4 , Na_2HPO_4 , 96
- ← NaH_2PO_4 , 91, 96, **Fig. 12**
- ← NaH_2PO_4 + blood-letting, 115
- ← NaH_2PO_4 + KCl , MgCl_2 , 91
- ← NaHSO_4 , NaNO_3 , Na_2SO_4 , NH_4 -acetate, NH_4Cl ,

DHT—Continued

→ heart—Continued

NH₄ClO₄, NH₄H₂PO₄,
NH₄HSO₄, NH₄NO₃, 96

← pregnancy, 140

← restraint, starvation, trauma,
91

← triamcinolone + NaClO₄,
NaH₂PO₄, 92

→ mortality ← Ca-acetate, CaCl₂,
CaH₄(PO₄)₂, Ca(NO₃)₂,
K-acetate, KCl, KClO₄,
K₂HPO₄, KH₂PO₄, KHSO₄,
KNO₃, K₂SO₄, Mg-acetate,
MgCl₂, Mg(ClO₄)₂, MgH₄
(PO₄)₂, Mg(NO₃)₂, MgSO₄,
Na-acetate, NaCl, NaClO₄,
Na₂HPO₄, NaH₂PO₄, NaHSO₄,
NaNO₃, Na₂SO₄, NH₄-acetate,
NH₄Cl, NH₄ClO₄, NH₄H₂PO₄,
NH₄HSO₄, NH₄NO₃, 96

→ nephrocalcinosis ← Ca-acetate,
CaCl₂, CaH₄(PO₄)₂, Ca
(NO₃)₂, K-acetate, KCl,
KClO₄, K₂HPO₄, KH₂PO₄,
KHSO₄, KNO₃, K₂SO₄, Mg-
acetate, MgCl₂, Mg(ClO₄)₂,
MgH₄(PO₄)₂, Mg(NO₃)₂,
MgSO₄, Na-acetate, NaCl,
NaClO₄, Na₂HPO₄, NaH₂PO₄,
NaHSO₄, NaNO₃, Na₂SO₄,
NH₄-acetate, NH₄Cl,
NH₄ClO₄, NH₄H₂PO₄,
NH₄HSO₄, NH₄NO₃, 96

→ vessels ← pregnancy, 140

Diabetic acidosis → heart, 86

Dicumarol

→ heart ← vitamin-K, 104
← vitamin-K, vitamin-E, 99

8-(3-diethylaminopropylamino)-6-
methoxyquinoline; see Plasmocid

Diets → heart, 141

Diffuse endomyocardial sclerosis, 133

Diffuse myocarditis, 133

Digitalis

→ ECG ← K-deficiency, 101
→ heart, 6, 152
← DOC, 101
← K, 163
← K-deficiency, 101
← Pearce's virus III, 151
← thyroxin, 87
→ K in heart, 101
→ water in heart, 101
≤ corticoids, 100

Digitalis—Continued

≤ 9-F-COL, 100

in rat, cat, dog, man → heart, 100

Digitoxin

→ heart, 48, 147
→ heart ← Me-Cl-COL, 147

Diisopropylfluorophosphate

→ heart, 147
→ heart ← Me-Cl-COL, 147

Dinitrophenol

→ heart, 104, 147
→ heart ← Me-Cl-COL, 147

Diphtheria → heart, 124

Diphtherotoxin

→ glycogen in heart, 124
→ heart, 124, 147
→ heart ← Me-Cl-COL, 147
→ oxidase in heart, 124

Direct trauma → heart, 112

"Diseases of adaptation," 8, 54, 155

→ heart, 155

Diseases of the heart, spontaneous

≤ ESCN, 164

Diseases (spontaneous) → heart, 126

Diseases (various) → heart in animals,
137

DOC

→ blood pressure, 46
in fowl, 8, 55
← NaCl, 10, 60
→ ECG ← NaCl, 63
→ heart, 9, 54
← DHT + NaClO₄, NaH₂PO₄, 92
← digitalis, 101
← hypophysectomy + unine-
phrectomy + NaCl, 81
← KCl, 9
← KCl in bird, 10
← KCl in fowl, 60
← K-deficiency, 29, 62
← K-deficiency in man, 56
← local burns, 63
← Me-Cl-COL + K-acetate, 92
← NaCl, 9, 10, 55, 60
← NaCl, in bird, 9
← NaCl in fowl, 60
← NaCl + KCl, 62, 63
← NaCl + KCl in bird, 10
← NaCl + KCl in fowl, 60
← NaCl + NH₄Cl, 63
← NaH₂PO₄, 65, 69
← NaH₂PO₄ + restraint, 144
← NaH₂PO₄ + restraint in rat
and monkey, 117
← nephrectomy, 82, 113

DOC—Continued

- heart—Continued
 - ← stress, 56
 - ← uninephrectomy, 112
 - ← uninephrectomy + NaCl, 61
 - ← uninephrectomy + NaCl + CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, 61
 - in cat, dog, 56
 - in fowl, 8, 55
- K in muscles, 48
- kidney, 54
 - ← K, 8
 - ← KCl, 54
 - ← NaCl, 10
 - ← NaCl in fowl, 60
 - ← NaCl + anti-rat-kidney serum, 63
 - ← NaCl + anti-rat-kidney serum + KCl, 63
 - ← NaCl-deficiency + anti-rat-kidney serum, 63
 - ← NaCl + KCl, NH₄Cl, 63
 - ← NaH₂PO₄, 65
 - ← uninephrectomy + NaCl + CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, NH₄NO₃, (NH₄)₂SO₄, 61
 - in fowl, 8, 55
 - liver, mortality ← NaH₂PO₄, 69
 - Na in heart, 48
 - Na in muscles, 48
 - nephrocalcinosis ← NaH₂PO₄, 69
 - nephrosclerosis ← NaCl, 10, 50
 - nephrosis ← NaCl, 50
 - periarteritis ← NaCl, 60
 - periarteritis ← NaCl + KCl, 63
 - periarteritis nodosa ← NaCl, 10
- DOC *in vitro* → heart, 47
 - K in heart, 48
 - ← NaCl, 62
- toxicity: hypokalemia, 55, 56

ECG

- ← adrenaline, 84
- ← carbon monoxide, 103
- ← *Cor pulmonale*, 112
- ← digitalis + K-deficiency, 101
- ← DOC + NaCl, 63
- ← histamine, 107
- ← insulin, 86
- ← Me-Cl-COL + NaH₂PO₄, 45
- ← muscular exercise, 116
- ← Na-lactate, 131

ECG—Continued

- ← pulmonary emboli, 112
- ← "Shwartzman reaction", 126
- E. coli* endotoxin → heart, 125
- Eczema myocarditis, 133
- Eczema → Fiedler's myocarditis, 132
- Edema of coronaries, 128
- Edema of heart, 141
- Electrocautery → heart, 112
- Electrolyte preparations, list of, 15, 16
- Electrolytes**
 - heart, 17
 - (theory) → ESCN, 154
 - "desensitizing," 26
- Electron-microscopy of heart, 29
 - ← hypoxia, 116
 - ← triiodothyronine, 87
- Electroshock**
 - Ca in heart, 118
 - heart, 118, 151
 - K in heart, 118
- Embolization of coronaries → heart, 111
- Emotions → heart, 119
- "Endocardiocytotoxic serum," 125
- Endomyocardial fibrosis, 45, 133
- Endomyocardial necroses, 133, Fig. 17
- Enzymes**
 - Anitschkow-myocytes in heart, 104
 - heart, 104
 - muscles, 104
- Ephedrine → heart ← cardiac infarcts, depressor nerve severance, 85
- Epidemic typhus → heart, 125
- Epilepsy → Fiedler's myocarditis, heart, 136
- ESCH; see also Heart**
 - ⇒ ESCN, 10, 11, 60, 64
 - ⇒ rheumatic carditis, 10
 - definition, 10
- ESCN; see also Heart**
 - ← cardiac work (theory), 152
 - ← hypersensitivity (theory), 154
 - ← hypoxia (theory), 151
 - ← infections (theory), 153
 - ← metabolic toxins (theory), 154
 - ← stress, steroids, and electrolytes (theory), 154
 - ⇒ cardiac infarcts, 93, 157
 - ⇒ ESCH, 10, 11, 60, 64
 - ⇒ nephrocalcinosis, 50
 - ⇒ Shwartzman phenomenon, 110
 - ⇒ spontaneous heart diseases, 164

- ESCN—Continued**
- chronology in its production, 120, 121, 122
 - histologic characteristics, **Figs. 1, 2**
 - histology of, 43
 - history, 3
 - indispensability of Na in production of, 25
 - inhibition by chlorides, 32
 - in the rat, **Figs. 2, 3**
 - outlook for further research, 161
 - pathologic chemistry, 161
 - prevention by anion, 26
 - prevention by cation, 28
 - production by cation, 24
 - standardized experimental technique for study of, 19
 - theories, 26, 150
- Estradiol** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 66
- Estrone** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 66
- Ethanol**
- heart, 106
 - heart ← Me-Cl-COL + Na_2HPO_4 , 106
 - topical → heart, 112
- 17 α -ethyl- Δ^4 -androstene-3-one-11 β , 17 β -diol** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 77
- Ethylandrostendiol** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 76
- Ethylandrostenolone** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 76
- Ethyl laurate** → heart ← choline deficiency, 98
- Ethynortestosterone** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 76
- Ethyndiol** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 77
- Ethinylestosterone** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 77
- Exercise** → heart ← carbon monoxide, 103
- Exhaustion necroses of the myocardium**, 133
- Fatty acids** → heart, kidney ← choline deficiency, 98
- F-COL** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 64, 71
- 9-F-COL** ⇌ digitalis, 100
- 9-F-COL (in vitro)** → heart, 48
- Fear** → heart, 116
- Fibrinoid**, definition, 10
- Fibrosis of myocardium**, 14
- Ficin** → heart, 104
- Fiedler's myocarditis**, 5, 132, 133
- ← acromegaly, 59
 - ← adrenaline, 84
 - ← arsenic, 102
 - ← colloid goiter, 88
 - ← eczema, 132
 - ← epilepsy, 136
 - ← hypersensitivity, 126
 - ← infections, 132
 - ← myasthenia gravis, 137
 - ← toxins, uremia, 132
 - giant cells in heart, 132
 - ⇒ "aphthous fever," 139
 - ⇒ "puerperal myocarditis," 140
- Fluorine** → heart, 107
- 9-fluoro-11-hydroxyprogesterone** → heart, liver, mortality, nephrocalcinosis ← NaH_2PO_4 , 70
- Food** → heart, 141–143
- Fowl**, as test object for DOC over dosage, 55
- Friedreich's ataxia** → heart, 136
- Fuchsinophilia**
- histology, **Figs. 1, 6**
 - in cardiac infarcts of man, 129
 - in heart ← heart failure, 162
- Fuchsinophilic degeneration**, 13, 43, **Figs. 1, 6**
- (theory), 155
- Fuchsinophilic material**, histochemical demonstration, 43
- Gastric fistula** → heart, 113
- Gauley's cardiopathy**, 133
- Genetics** → heart ← Me-Cl-COL + NaH_2PO_4 , 141
- Giant cells in heart**
- ← Fiedler's myocarditis, 132
 - ← streptococci, 125
- Glucocorticoids** → cardiac infarcts in man, 57
- Glucose** → heart, nephrocalcinosis ← Me-Cl-COL + NaH_2PO_4 , 103
- Glycogen** in heart ← diphtheria toxin, 124
- "Granuloma-pouch," technique, 42, 90

Granulomatous myocarditis, 133
Group A streptococci → heart, 125
Gum acacia ← heart, 107
 ← Pearce's virus III, 107, 151

Heart; *see also* ESCH; ESCN; Myocardium
 ← acetoxypregneneolone + NaH₂PO₄, 72
 ← 17-acetoxy-progesterone + NaH₂PO₄, 69
 ← acetylcholine, 102
 ← ACTH + NaH₂PO₄, repeated pregnancies, 82
 ← adrenalectomy
 + Me-Cl-COL + NaH₂PO₄, 84
 + nephrectomy + parathyroid extract, 84
 + nephrectomy + parathyroid extract + corticoids, 84
 ← adrenaline, 6, 84, 147, 152
 + blood-letting, NaClO₄, Na₂HPO₄, Ha₂SO₄, 86
 + caffeine, sparteine, typhoid bacilli, 85
 ← "adrenaline sensitizer" + adrenaline, 85
 ← adrenosterone + NaH₂PO₄, 66
 ← allergy, 125
 ← anaphylaxis, 126
 ← anoxia, 115
 ← "aphthous fever" in cattle, 139
 (arrhythmias) ← ACTH in man, 59
 (arrhythmias) ← K, Mg, 163
 ← arsenic, arsphenamine, 102
 ← arsphenamine + Na₂HPO₄ + KCl, 102
 ← "Arthus phenomenon," 126
 ← azide, 103
 ← bacterial toxins, 123
 ← barium, 103
 ← barium + Pearce's virus III, 103
 ← blood-letting, 147, 151
 + plasmocid, 110
 ← 12α-bromo-11β-hydroxyprogesterone + NaH₂PO₄, 70
 ← bromoxoprogesterone + NaH₂PO₄, 70
 ← burns, 114
 ← carbon monoxide, 103, 152
 ← cardiac aglycones, 100
 ← cardiac glycosides, 100
 ← cardiac glycosides + K, 100
 ← cardiac work (theory), 152
 ← cardiovascular surgery, 111

Heart—Continued
 ← cerebral lesions, 136
 ← chelating agents, 165
 ← 4-chloro-adrenosterone, 4-chlorotestosterone + NaH₂PO₄, 67
 ← cholesterol, 103
 + muscular exercise, 117
 ← choline deficiency, 98
 ← choline deficiency + betaine, fatty acids, K, methionine, 98
 ← Cl-COL + NaH₂PO₄, 65, 71
 ← cold baths, 146
 ← constriction of renal arteries, 113
 ← coronary embolization, 111
 ← coronary occlusion, 57
 ← coronary vessel ligature + ACTH, cortisone, 57
 ← corticoids
 + stress, 12
 ≡ K, 47
 ≤ cardiac glycosides, 48
 ← cortisol
 + DHT + NaClO₄, NaH₂PO₄, 92
 + NaH₂PO₄, 69
 + NaH₂PO₄ + restraint, 144, **Fig. 5**
 ← Δ¹-cortisol + NaH₂PO₄, 72
 ← cortisone + NaH₂PO₄, 65, 70
 ← cortisone *in vitro*, 47
 ← Δ¹-cortisone + NaH₂PO₄, 72
 ← dehydro-iso-androsterone + NaH₂PO₄, 67
 ← depressor-nerve transection, 119
 + ephedrine, 85
 ← dermatitis, 102
 ← desoxycortisol + NaH₂PO₄, 69
 ← DHT
 + Ca-acetate, CaCl₂, CaH₄(PO₄)₂, Ca(NO₃)₂, K-acetate, KCl, KClO₄, KH₂PO₄, K₂HPO₄, KHSO₄, KNO₃, K₂SO₄, Mg-acetate, MgCl₂, Mg(ClO₄)₂, MgH₄(PO₄)₂, Mg(NO₃)₂, MgSO₄, Na-acetate, NaCl, NaClO₄, Na₂HPO₄, NaHSO₄, NaNO₃, Na₂SO₄, NH₄-acetate, NH₄Cl, NH₄ClO₄, NH₄H₂PO₄, NH₄HSO₄, NH₄NO₃, 96
 + cold, heat, restraint, starvation trauma, 91
 + Me-Cl-COL + NaH₂PO₄, 93, 94, **Fig. 13**
 + NaH₂PO₄, 91, 96, **Fig. 12**

Heart—Continued

- ← DHT—Continued
 - + NaH₂PO₄ + blood-letting, 115
 - + NaH₂PO₄ + KCl, MgCl₂, 91
 - + pregnancy, 140
- ← diabetic acidosis, 86
- ← dicumarol + vitamin-E, 99
- ← dicumarol + vitamin-K, 99, 104
- ← diets, 141
- ← digitalis in rat, cat, dog, man, 6, 100, 152
- ← digitalis + K, 163
- ← digitoxin, 48, 147
- ← diisopropylfluorophosphate, 147
- ← dinitrophenol, 104, 147
- ← diphtherotoxin, 124, 147
- ← direct trauma, 112
- ← diseases (spontaneous), 126
- ← diseases (various) in animals, 137
- ← "diseases of adaptation," 155
- ← DOC, 9, 54
 - in cat, dog, 56
 - in fowl, 8, 55
 - + DHT + NaClO₄, NaH₂PO₄, 92
 - + digitalis, 101
 - + digitalis *in vitro*, 47
 - + KCl, 9
 - + KCl in bird, fowl, 10, 60
 - + K-deficiency, 29, 62
 - + K-deficiency in man, 56
 - + local burns, 63
 - + NaCl, 9, 10, 55, 60
 - + NaCl in fowl, 9, 60
 - + NaCl + KCl, 62, 63
 - + NaCl + KCl in fowl, 10, 60
 - + NaCl + NH₄Cl, 63
 - + NaH₂PO₄, 65, 69
 - + NaH₂PO₄ + restraint, 144
 - + NaH₂PO₄ + restraint in rat and monkey, 117
 - + nephrectomy, 82, 113
 - + stress, 56
 - + uninephrectomy + NaCl, 61
 - + uninephrectomy + NaCl +
 - CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, 61
 - ← *E. coli* endotoxin, 125
 - ← electrocautery, 112
 - ← electrolytes, 17
 - ← electroshock, 118, 151
 - ← embolization of coronaries, 111
 - ← emotions, 119

Heart—Continued

- ← enzymes, 104
- ← ephedrine + cardiac infarcts, 85
- ← epidemic typhus, 125
- ← epilepsy, 136
- ← estradiol + NaH₂PO₄, 66
- ← estrone + NaH₂PO₄, 66
- ← ethanol, 106
- ← ethanol, topical, 112
- ← ethinylandrostenediol +
 - NaH₂PO₄, 77
- ← ethinyltestosterone + NaH₂PO₄, 77
- ← 17 α -ethyl- Δ^4 -androstene-3-one-11 β , 17 β -diol + NaH₂PO₄, 77
- ← ethylandrostenol + NaH₂PO₄, 76
- ← ethylandrostenolone +
 - NaH₂PO₄, 76
- ← ethyl laurate + choline deficiency, 98
- ← ethynortestosterone +
 - NaH₂PO₄, 76
- ← exercise + carbon monoxide, 103
- ← F-COL + NaH₂PO₄, 64, 71
- ← 9-F-COL *in vitro*, 48
- ← fear, 116
- ← ficin, 104
- ← fluorine, 107
- ← 9 α -fluoro-11 β -hydroxyprogesterone + NaH₂PO₄, 70
- ← food, 141–143
- ← Friedreich's ataxia, 136
- ← gastric fistula, 113
- ← group A streptococci, 125
- ← gum acacia, 107
 - + Pearce's virus III, 107
- ← hepatectomy (partial) +
 - Me-Cl-COL + Na₂HPO₄, Na₂SO₄, NaClO₄, 113
- ← histamine, 107, 152
- ← H₂O, 23
- ← hormones, 54
- ← hot baths, 146
- ← 16 α -hydroxy-9 α -fluorocortisol +
 - NaH₂PO₄, 71
- ← 11 β -hydroxy-methyltestosterone + NaH₂PO₄, 68
- ← hypersensitivity, 125
- ← hypersensitivity (theory), 154
- ← hyperthyroidism, 87
 - in man, 88
- ← hypokalemia in man, 87
- ← hypophysectomy + DOC +
 - uninephrectomy + NaCl, 81

Heart—Continued

- ← hypoxia, 115, 117
 - + cholesterol, 115
 - (theory), 151
- ← ileitis, 139, **Figs. 19, 20**
- ← infections, 123
 - in mice, 138
 - (spontaneous) in rabbits, 138
 - (theory), 153
- ← infectious mononucleosis, 125
- ← influenza, 125
- ← insulin, **86**
- ← iodine, 107
- ← K-deficiency, 7, 28
 - in man, 56
 - + digitalis, 101
 - + $MgCl_2$ + papain, 106
- ← KCl + K-deficiency, 31
- ← KCl + papain, 105
- ← 11-ketoprogesterone +
 - NaH_2PO_4 , 69
- ← lanatoside-C, 48
- ← lead, 108
- ← ligature of coronaries, **111**
- ← lightning, 118
- ← lipids, **108**
 - + choline deficiency, 98
- ← lung disease, **135**
- ← lycopodium intravenously, 112
- ← malononitrile, 109
- ← measles, 125
- ← Me-Cl-COL
 - + adrenaline, 147
 - + $Al_2(SO_4)_3$, 25
 - + arsphenamine + KCl, $MgCl_2$, 102
 - + blood-letting, 114, 147
 - + $CaH_4(PO_4)_2$, 25
 - + cold baths, 114, 146
 - + DHT + Ca-acetate,
 - $CaH_4(PO_4)_2$, K-acetate,
 - $KClO_4$, K_2HPO_4 , KH_2PO_4 ,
 - $KHSO_4$, $Mg(ClO_4)_2$,
 - $MgH_4(PO_4)_2$, $MgSO_4$, Na-acetate, $NaCl$, $NaClO_4$,
 - $NaHCO_3$, Na_2HPO_4 ,
 - NaH_2PO_4 , 92
 - + DHT + NaH_2PO_4 + $MgCl_2$, 91
 - + DHT + $NaHSO_4$, Na-lactate, $NaNO_3$, Na_2SO_4 , $(NH_4)_2HPO_4$, NH_4HSO_4 , 92

Heart—Continued

- ← Me-Cl-COL—Continued
 - + digitoxin, diisopropylfluorophosphate, dinitrophenol, diphtherotoxin, 147
 - + H_2O , 20
 - + hot baths, 114, 1
 - + K-deficiency, 31
 - + $KClO_4$, 25
 - + K_2HPO_4 , 25
 - + KH_2PO_4 , 24, 25
 - + $KHSO_4$, Li_3PO_4 ,
 - + $Mg(ClO_4)_2$, $MgSO_4$, $MnSO_4$,
 - + $MgCl_2$ + K-deficiency, 31
 - + muscular exercise, 146
 - + Na-arsenate, Na-arsenite, 147
 - + $NaClO_4$ + KCl, $KClO_4$
 - $MgCl_2$, $Mg(ClO_4)_2$, 35
 - + Na-citrate, 21
 - + $NaCl$, 18, 20
 - + $NaClO_4$, 20, 35, 40
 - + $NaCl$ + $NaClO_4$, 35
 - + Na_2CO_3 , 21
 - + Na-fluoroacetate, 107, 147
 - + $NaHCO_3$, 21
 - + Na_2HPO_4 , Na_2HPO_4 , 18, 20
 - + Na_2HPO_4 + $CaCl_2$, 33
 - + Na_2HPO_4 + ethanol, 106
 - + Na_2HPO_4 + KCl, 33, 37, 41
 - + Na_2HPO_4 + KCl + $MgCl_2$, 41
 - + Na_2HPO_4 + KCl + nerve transection, vagotomy, 120
 - + Na_2HPO_4 + $KClO_4$, KH_2PO_4 , $KHSO_4$, KNO_3 , $KOOC\cdot CH_3$, 37
 - + Na_2HPO_4 + lipids, 109
 - + Na_2HPO_4 + $MgCl_2$, 33, 37, 41
 - + Na_2HPO_4 + $MgCl_2$ + vagotomy, nerve transection, 120
 - + Na_2HPO_4 + $Mg(ClO_4)_2$,
 - $MgH_4(PO_4)_2$, $Mg(NO_3)_2$,
 - $Mg(OOC\cdot CH_3)_2$, $MgSO_4$, 37
 - + Na_2HPO_4 + $MnCl_2$, 33
 - + Na_2HPO_4 + Na-acetate, Na-citrate, 27
 - + Na_2HPO_4 + $NaCl$, 27, 33
 - + Na_2HPO_4 + $NaClO_4$, $NaHCO_3$, Na-lactate, $NaMnO_4$, $NaNO_3$, Na_2SO_4 , Na-urate, 27
 - + Na_2HPO_4 + NH_4Cl , $RbCl$, 33
 - + NaH_2PO_2 , NaH_2PO_3 , 18, 20
 - + NaH_2PO_4 , 17, 18, 20, 40, 73

Heart—Continued

- ← Me-Cl-COL—Continued
 - + NaH_2PO_4 , Figs. 1-4, 17, 18
 - + NaH_2PO_4 + adrenaline, 85, 144
 - + NaH_2PO_4 + age, 139
 - + NaH_2PO_4 + beans, 142
 - + NaH_2PO_4 + blood-letting, 114, 151
 - + NaH_2PO_4 + bone fractures, 144
 - + NaH_2PO_4 + casein, 142
 - + NaH_2PO_4 + cold baths, 114, 144
 - + NaH_2PO_4 + corn, 142
 - + NaH_2PO_4 + DHT in mouse, rabbit, dog, rat and hamster, 91
 - + NaH_2PO_4 + DHT + KCl, 91, 94
 - + NaH_2PO_4 + genetics, species, 141
 - + NaH_2PO_4 + glucose, 103
 - + NaH_2PO_4 + hypophysectomy, 82
 - + NaH_2PO_4 + hot baths, 114
 - + NaH_2PO_4 in monkey, Fig. 6
 - + NaH_2PO_4 + KH_2PO_4 , 39
 - + NaH_2PO_4 + kidney diet, lard, lentils, liver diet, meat, 142
 - + NaH_2PO_4 + NaClO_4 , NaHSO_4 , 40
 - + NaH_2PO_4 + NaHSO_4 + NaClO_4 , 40
 - + NaH_2PO_4 + nephrectomy, 113
 - + NaH_2PO_4 + nerve transection, 119, 144
 - + NaH_2PO_4 + noradrenaline, 86
 - + NaH_2PO_4 + papain, Fig. 11
 - + NaH_2PO_4 + papain + MgCl_2 , Fig. 11
 - + NaH_2PO_4 + parathyroidectomy, 89
 - + NaH_2PO_4 + peas, potatoes, 142
 - + NaH_2PO_4 + pregnancy, 140
 - + NaH_2PO_4 + Purina, 141
 - + NaH_2PO_4 + pylorus ligature, 113
 - + NaH_2PO_4 + restraint, 117
 - + NaH_2PO_4 + rice, 142
 - + NaH_2PO_4 + sex, 140
 - + NaH_2PO_4 + spinal-cord transection, 119

Heart—Continued

- ← Me-Cl-COL—Continued
 - + NaH_2PO_4 + spleen diet, starch, 142
 - + NaH_2PO_4 + trauma, 114, 144
 - + NaH_2PO_4 + uninephrectomy, 113
 - + NaH_2PO_4 + vagotomy, 119, 144
 - + NaH_2PO_4 + vasopressin, 84
 - + NaHSO_3 , 21
 - + NaHSO_4 , 20, 40
 - + NaHSO_4 + NaClO_4 , 40
 - + Na-iodoacetate, 147
 - + NaKHPO_4 , 39
 - + Na-lactate, NaMnO_4 , NaNO_3 , NaOH , $\text{NaOOC}\cdot\text{CH}_3$, 21
 - + $\text{Na}_4\text{P}_2\text{O}_6$, $\text{Na}_4\text{P}_2\text{O}_7$, 18, 20
 - + Na_3PO_4 , 20
 - + $(\text{NaPO}_3)_6$, 18, 20
 - + Na_2SO_3 , 21
 - + Na_2SO_4 , 21, 35
 - + Na_2SO_4 + KCl, KHSO_4 , MgCl_2 , MgSO_4 , NaCl , 35
 - + Na-urate, Na-tartrate, 21
 - + nerve transection, 119, 146
 - + nephrectomy, 82, 89
 - + $\text{NH}_4\text{H}_2\text{PO}_4$, $(\text{NH}_4)_2\text{HPO}_4$, NH_4HSO_4 , 25
 - + noradrenaline, 147
 - + papain, 105
 - + parathyroidectomy + nephrectomy, 89
 - + pentamethylenetetrazol, picrotoxin, *Pseudomonas aeruginosa*, 147
 - + RbClO_4 , RbHSO_4 , Rb_2SO_4 , 25
 - + restraint in rat and monkey, 117, 118, 146
 - + restraint + KCl, MgCl_2 (during restraint only), 122
 - + spinal-cord transection, 119, 146
 - + thyroidectomy + nephrectomy, 89
 - + trauma, 114, 144
 - + vagotomy, 119, 146
 - + vasopressin, 83, 147
 - ← 6-Me-COL + NaH_2PO_4 , 75
 - ← Medrol + DHT + NaClO_4 , NaH_2PO_4 , 92
 - ← Me-F-COL + NaH_2PO_4 , 64, 73
 - ← 6-Me-9F-COL + NaH_2PO_4 , 75
 - ← meningococcal endotoxin, 124, 125

Heart—Continued

- ← metabolic toxins (theory), 154
- ← 6 α -methyl-21-desoxycortisol + DHT + NaClO₄, NaH₂PO₄, 92
- ← 6 α -methyl-21-desoxycortisol, 6 α -methyl-11 β -hydroxyprogesterone, 6 α -methyl-11-keto-progesterone + NaH₂PO₄, 74
- ← 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol + NaH₂PO₄, 76
- ← 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-3, 20-dione-11 β , 17 β -diol-21-fluorine, 6 α -methyl- Δ^4 -pregnenene-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol + NaH₂PO₄, 75
- ← 2 α -methyl- Δ^4 -pregrene-3, 20-dione-9, 11 β -oxido-17 α , 21-diol-21-acetate + NaH₂PO₄, 73
- ← methylandrostanetriol + NaH₂PO₄, 67
- ← methylandrostenediol + NaH₂PO₄, 68
- ← methylcellulose (intravenously), 112
- ← methyltestosterone + NaH₂PO₄, 67
- ← Mg + cholesterol, 32
- ← MgCl₂ + K-deficiency, 30, 31
- ← MgCl₂ + papain, 105
- ← Mg-deficiency + KCl + papain, 106
- ← microbes, 123
- ← muscular exercise, 6, 116, 146, 151
- ← myasthenia gravis, 137
- ← Na-arsenate, Na-arsenite, 147
- ← Na-citrate, NaCl, 23
- ← Na-exchange rosins, 165
- ← Na-fluoroacetate, 107, 147
- ← Na-iodoacetate, 147
- ← Na ≈ K, 30
- ← Na-lactate, NaMnO₄, 23
- ← Na-monoiodoacetate, 108
- ← Na-selenite, 110
- ← Na-tartrate, Na-urate, 23
- ← NaCl
 - in bird, 9
 - + cold baths, 149
 - + K-deficiency, 31
 - + restraint, 149
- ← NaClO₄, 23
 - + cold baths, 149

Heart—Continued

- ← NaClO₄—Continued
 - + K-deficiency, 31
- ← Na₂CO₃, 23
- ← NaHCO₃, Na₂HPO₄, Na₃HPO₄, 23
- ← Na₂HPO₄
 - + arsphenamine + MgCl₂, 102
 - + cold baths, 149
 - + K-deficiency, 31
 - + papain, 105
 - + plasmocid, 110
- ← NaH₂PO₄, 23
- ← NaH₂PO₄, 23, 78
 - + Me-Cl-COL + neuromuscular exertion, restraint, 143
 - + plasmocid, 110
- ← NaHSO₃, NaHSO₄, 23
- ← NaI, 107
- ← NaNO₃, NaOH, NaOOC·CH₃, (NaPO₃)₆, Na₃PO₄, Na₄P₂O₇, 23
- ← Na₂SO₃, Na₂SO₄, 23
- ← Na₂SO₄ + cold baths, 149
- ← Na₂SO₄ + K-deficiency, 31
- ← nephrectomy, 113
 - + Me-Cl-COL, parathyroidectomy, 113
- ← nerve transection, 146
- ← nervous diseases, 136
- ← noradrenaline, 147
- ← noradrenaline + blood-letting, 86
- ← noradrenaline + plasmocid, 110
- ← orthostatic collapse, 117
- ← orthostatic hypotension, 151
- ← overeating, 141
- ← oxygen deficiency, 115
- ← pancreatitis, 136
- ← papain, 104, Fig. 11
- ← papain + blood-letting, K-deficiency, Mg-deficiency, noradrenaline, 106
- ← *Paracolobactrum coliforme*, 139
- ← parathyroidectomy + nephrectomy, 89
- ← parathyroid extract
 - + KCl, MgCl₂, 90
 - + NaH₂PO₄, 89
 - + NaH₂PO₄ + KCl, MgCl₂, 89
- ← parathyroid hormone, 89
- ← *Pasteurella pseudotuberculosis*, 139

Heart—Continued

- ← Pearce's virus III, 85
 - + barium chloride, adrenaline, vasopressin, gum acacia, 151
 - + cardiac puncture, 112
 - + chloroform, corn syrup, nicotinamide, digitalis, papaverine, saline, 151
- ← pentamethylenetetrazol, 109, 147
- ← peptone, 109
- ← pH, 18
- ← picrotoxin, 147
- ← plasmocid, 109
- ← plastic beads intravenously, 112
- ← poliomyelitis, 125
- ← progesterone *in vitro*, 47
- ← progesterone, pregnanediol + NaH₂PO₄, 68
- ← pregnenolone + NaH₂PO₄, 71
- ← propylidihydronortestosterone + NaH₂PO₄, 77
- ← *Pseudomonas aeruginosa*, 147
- ← psyche, 119
- ← pulmonary disease, 135
- ← pulmonary emboli, 112, 126
- ← pylorus ligature, 113
- ← regional ileitis, 139, Fig. 19, 20
- ← renal injury + lipids, 108
- ← renal lesions + lipids + pregnancy, 140
- ← restraint, 117, 146, 152
- ← restraint + papain, 106
- ← Rocky Mountain spotted fever, 125
- ← rutin + constriction of renal arteries, 113
- ← scrub typhus, 125
- ← selenium + vitamin-E, 110
- ← sensitizing electrolytes, 17
- ← "Schwartzman reaction," 126
- ← silver nitrate (topical), 112
- ← skin diseases, 136
- ← spinal-cord transection, 146
- ← spontaneous diseases, 126
- ← status thymicolumphanticus, 136
- ← stress, 143
- ← stress of battle, 128
- ← stress, history, 12
- ← stress, steroids, and electrolytes (theory), 154
- ← streptococcal proteinase, 105
- ← streptococci, 125
- ← streptolysin O, 124
- ← streptokinase, 104
- ← strophanthin-G, 48

Heart—Continued

- ← succinylsulfathiazole, 110
- ← sulfa drugs + vitamin-E, vitamin-K, 110
- ← sulfaguanidine, 110
- ← sulfur, 110
- ← syphilis, 125
- ← testosterone + NaH₂PO₄, 66
- ← thyroid hormone, 87
- ← thyroidectomy + NaI, 87
- ← thyroparathyroidectomy + Me-Cl-COL + NaH₂PO₄, 89
- ← thyroxin, 87
 - + cold, 88
 - + digitalis, 87
 - + lipids, noradrenaline, restraint, stressors, 88
- ← triamcinolone
 - + adrenaline, cold, 84
 - + DHT + NaClO₄, NaH₂PO₄, 92
 - + heat, 84
 - + NaH₂PO₄, 65, 73
 - + noradrenaline, 84
- ← trauma, 114, 147
- ← trypsin, 104
- ← undernutrition, 141
- ← uninephrectomy + DOC, 112
- ← uremia, 135
- ← vagotomy, 146
- ← vasopressin, 83, 147, 152
- ← vasopressin + age, 83
- ← vasopressin + Pearce's virus III, 83
- ← virus infections (various), 125
- ← vitamin-B₁ deficiency, 97
- ← vitamin-C deficiency, 99
- ← vitamin-D, 6, 90
- ← vitamin-D in monkey, 91
- ← vitamin-D + muscular exercise, 90
- ← vitamin-E deficiency, vitamin-K deficiency, 99
- disease in pig, silver fox, 97
- failure ← ACTH, 58, 59
- failure → fuchsinophilia in heart, 162
- "idiopathic enlargement," 137
- "lymphorrhages," 137
- "Mantelödem" of cardiac muscle fibers, 141
- spontaneous diseases ← ESCN, 164
- Heat → heart
 - ← DHT, 91
 - ← triamcinolone, 84
- Hemorrhage; see Blood-letting

- Hepatectomy (partial) → heart → Me-Cl-COL + Na₂HPO₄, Na₂SO₄, NaClO₄, 113
- Hepatic; *see* Liver
- Histamine
→ ECG, 107
→ heart, 107, 152
→ liver, 107
- Histiocytes in heart ← thyroid hormone, 87
- Histology of ESCN, 43
- History of ESCN, 3
- H₂O → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 20
- H₂O → heart, nephrocalcinosis, 23
- Hofmeister series, 4
- Hormones → heart, 54
- Hot baths
→ heart, 146
→ heart ← Me-Cl-COL, 114, 146
→ heart ← Me-Cl-COL + NaH₂PO₄, 114
- Hyaline definition, 10
- "Hydropic change" in cardiac infarcts, 129
- 16α-Hydroxy-9α-fluorocortisol → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 71
- 11β-hydroxy-methyltestosterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 68
- Hypercorticoidism → K, Na in aorta, 161
- Hypersensitivity
→ Fiedler's myocarditis, 126
→ heart, 125, 154
- Hypertension
→ K in aorta, 161
→ Na in aorta, 161
metacorticoid, 46
renal, 46
(theory) → ESCN, 154
- Hyperthyroidism, 87
← vitamin-B₁ deficiency, 97
→ heart in man, 88
- Hypokalemia
→ heart in man, 87
↔ toxicity of DOC, 55, 56
- Hypophysectomy
→ heart ← DOC + uninephrectomy + NaCl, 81
→ heart ← Me-Cl-COL + NaH₂PO₄, 82
- Hypoxia
→ electron microscopy of heart, 116
- Hypoxia—Continued
→ heart, 115, 117
→ heart ← cholesterol, 115
(theory) → ESCN, heart, 151
- Idiopathic, diffuse myocarditis fibrosis in young men, 133
- "Idiopathic enlargement" of the heart, 137
- Ileitis → heart, 139, **Figs. 19, 20**
- Inhibition of ESCN by chlorides, 32
- Infections
→ Fiedler's myocarditis, 132
→ heart, 123
→ heart in mice, 138
(spontaneous) → heart in rabbits, 138
(theory) → ESCN, heart, 153
- Infectious mononucleosis → heart, 125
- Inflammation in ESCN, 45
- Influenza → heart, 125
- Insulin → ECG, heart, 86
- Intestine, absorption of salts, 42
- Intramolecular antagonisms between Na and K, 38
- Iodine → heart, 107
- Isolated myocarditis, 133
- Isolated productive giant-cell myocarditis, 133
- K**
→ heart
(arrhythmias), 163
← cardiac glycosides, 100
← choline deficiency, 98
- K-acetate → aorta, heart, mortality, nephrocalcinosis ← DHT, 37, 96
- K-deficiency
→ blood pressure ← cortisone, renal hypertension, 46
→ ECG ← digitalis, 101
→ heart, 7, 28
→ heart ← digitalis, 101
→ heart ← DOC, 29, 62
→ heart ← DOC in man, 56
→ heart in man, 56
→ heart ← KCl, 31
→ heart ← Me-Cl-COL, 31
→ heart ← Me-Cl-COL + MgCl₂, 31
→ heart ← MgCl₂, 30, 31
→ heart ← MgCl₂ + papain, 106
→ heart, muscles ← Na₂HPO₄, Na₂SO₄, NaCl, NaClO₄, 31
→ heart ← papain, 106

- K in aorta ← hypercorticoidism, hypertension, 161
- K in blood
- ← cardiac glycosides, 100
 - ← cardiac infarct in man, 131
 - ← papain, 105
- K in heart
- ← angina in man, 131
 - ← cardiac infarcts, 111
 - ← cardiac infarcts in man, 49, 118, 131
 - ← choline deficiency, 98
 - ← coronary ligature, 111
 - ← coronary vessel ligature in dog, 49
 - ← digitalis, 101, 163
 - ← DOC, 48
 - ← DOC + NaCl, 62
 - ← electroshock, 118
 - ← Me-Cl-COL + NaH₂PO₄, 49
 - importance for contraction, 164
- K in muscles
- ← DOC, 48
- K in serum ← Me-Cl-COL + NaH₂PO₄, 49
- kidney ← DOC, 8
- K-metabolism ≈ cardiac glycosides, 163
- KCl
- aorta
 - ← DHT, 96
 - ← DHT + NaH₂PO₄, Fig. 15
 - arteriosclerosis
 - ← DHT + NaH₂PO₄, 91
 - ← Me-Cl-COL + NaH₂PO₄ + DHT, 94
 - heart
 - ← arsphenamine + Na₂HPO₄, 102
 - ← DHT, 96
 - ← DHT + NaH₂PO₄, 91
 - ← DOC, 9
 - ← DOC in bird, 10
 - ← DOC in fowl, 60
 - ← DOC + NaCl, 62, 63
 - ← DOC + NaCl in fowl, 60
 - ← DOC + uninephrectomy + NaCl, 61
 - ← K-deficiency, 31
 - ← Me-Cl-COL + arsphenamine, 102
 - ← Me-Cl-COL + NaClO₄, Na₂SO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 33, 37, 41

KCl—Continued

- heart—Continued
 - ← Me-Cl-COL + Na₂HPO₄ + MgCl₂, 41
 - ← Me-Cl-COL + Na₂HPO₄ + nerve transection, vagotomy, 120
 - ← Me-Cl-COL + NaH₂PO₄ + DHT, 91, 94
 - ← Mg-deficiency + papain, 106
 - ← papain, 105
 - ← parathyroid extract, 90
 - ← parathyroid extract + NaH₂PO₄, 89
 - liver
 - ← Me-Cl-COL + NaClO₄, Na₂SO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 33, 37–41
 - ← Me-Cl-COL + Na₂HPO₄ + MgCl₂, 41
 - ← papain, 105
 - kidney
 - ← DOC, 54
 - ← DOC + NaCl, 63
 - ← DOC + NaCl + anti-rat-kidney serum, 63
 - ← DOC + uninephrectomy + NaCl, 61
 - mortality
 - ← DHT, 96
 - ← Me-Cl-COL + NaClO₄, Na₂SO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 33, 37, 41
 - ← Me-Cl-COL + Na₂HPO₄ + MgCl₂, 41
 - nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL + NaClO₄, Na₂SO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 33, 37, 41
 - ← Me-Cl-COL + Na₂HPO₄ + MgCl₂, 41
 - periarteritis ← DOC + NaCl, 63
- KCl (during restraint only) → heart
- ← Me-Cl-COL + restraint, 122
- KCl, mechanism of action on heart, 163
- KClO₄
- aorta, heart ← DHT, 96
 - heart
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + DHT, 92

KClO₄-Continued

- heart—Continued
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaClO₄, 35
- liver
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaClO₄, 35
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaClO₄, 35
- nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaClO₄, 35

11-ketoprogesterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 69

K₂HPO₄

- aorta, heart ← DHT, 96
- heart ← Me-Cl-COL, 25
- heart ← Me-Cl-COL + DHT, 92
- liver ← Me-Cl-COL, 25
- mortality ← DHT, 96
- mortality ← Me-Cl-COL, 25
- nephrocalcinosis ← DHT, 96
- nephrocalcinosis ← Me-Cl-COL, 25

KH₂PO₄

- aorta, heart ← DHT, 96
- heart
 - ← Me-Cl-COL, 24, 25
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaH₂PO₄, 39
- liver
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaH₂PO₄, 39
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaH₂PO₄, 39
- nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + NaH₂PO₄, 39

KHSO₄

- aorta, heart ← DHT, 96

KHSO₄-Continued

- heart
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35
- liver
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35
- nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35

Kidney

- ← ACTH + NaH₂PO₄, 82
- ← choline deficiency + fatty acids, 98
- ← DOC, 54
 - in fowl, 8, 55
 - + K, 8
 - + KCl, 54
 - + NaCl, 10
 - + NaCl in fowl, 60
 - + NaCl + anti-rat-kidney serum, 63
 - + NaCl + anti-rat-kidney serum + KCl, 63
 - + NaCl-deficiency + anti-rat kidney serum, 63
 - + NaCl + KCl, NH₄Cl, 63
 - + NaH₂PO₄, 65
 - + uniphrectomy + NaCl + CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, NH₄NO₃, (NH₄)₂SO₄, 61
- (cortical necrosis) ← meningo-coccal endotoxin, 124
- diet → heart ← Me-Cl-COL + NaH₂PO₄, 142
- diet → nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142

KNO₃

- aorta, heart ← DHT, 96
- heart, liver ← Me-Cl-COL + Na₂HPO₄, 37
- mortality ← DHT, 96
- mortality ← Me-Cl-COL + Na₂HPO₄, 37

KNO₃—Continued

- nephrocalcinosis ← DHT, 96
- nephrocalcinosis ← Me-Cl-COL + Na₂HPO₄, 37

KOOC·CH₃ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL + Na₂HPO₄, 37

K₂SO₄ → aorta, heart, mortality, nephrocalcinosis ← DHT, 96

Lanatoside-C → heart, 48

Lard → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142

Lead → heart, 108

Lentils → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142

Ligature of coronaries → heart, 111

Lightning → heart, 118

Lipids

- heart, 108
- ← choline deficiency, 98
- ← Me-Cl-COL + Na₂HPO₄, 109
- ← renal injury, 108
- ← renal lesions + pregnancy, 140
- ← thyroxin, 88

in ESCN, 45

in heart ← choline deficiency, 98

Li₃PO₄ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25

Lipoproteins in blood ← cardiac infarcts, 49, 108

Lipoproteins in blood ← MgSO₄, 130

Liquid; *see* Na-polyanethol-sulfonate

Li₂SO₄ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25

Liver

- ← acetoxypregnенolone + NaH₂PO₄, 72
- ← 17-acetoxy-progesterone + NaH₂PO₄, 69
- ← adrenosterone + NaH₂PO₄, 66
- ← 12α bromo-11β-hydroxyprogesterone, bromoxoprogesterone + NaH₂PO₄, 70
- ← 4-chloro-adrenosterone, 4-chloro-testosterone + NaH₂PO₄, 67
- ← choline deficiency, 98
- ← Cl-COL + NaH₂PO₄, 71
- ← cortisol + NaH₂PO₄, 69
- ← Δ¹-cortisol + NaH₂PO₄, 72
- ← cortisone + NaH₂PO₄, 70
- ← Δ¹-cortisone + NaH₂PO₄, 72
- ← dehydro-iso-androsterone + NaH₂PO₄, 67

Liver—Continued

- ← desoxycortisol, DOC + NaH₂PO₄, 69
- ← estradiol, estrone + NaH₂PO₄, 66
- ← ethinylandrostenediol, ethinyl-testosterone + NaH₂PO₄, 77
- ← ethylandrostendiol + NaH₂PO₄, 76
- ← 17α-ethyl-Δ⁴-androstene-3-one-11β, 17β-diol + NaH₂PO₄, 77
- ← ethylandrostenolone, ethynor-testosterone + NaH₂PO₄, 76
- ← F-COL + NaH₂PO₄, 71
- ← 9α-fluoro-11β-hydroxyproges-terone + NaH₂PO₄, 70
- ← histamine, 107
- ← 16α-hydroxy-9β-fluorocortisol + NaH₂PO₄, 71
- ← 11β-hydroxy-methyltestosterone + NaH₂PO₄, 68
- ← 11-ketoprogestrone + NaH₂PO₄, 69
- ← Me-Cl-COL
 - + Al₂(SO₄)₃, CaH₄(PO₄)₂, 25
 - + H₂O, 20
 - + KClO₄, K₂HPO₄, KH₂PO₄, KHSO₄, Li₃PO₄, Li₂SO₄, Mg(ClO₄)₂, MgH₄(PO₄)₂, MgSO₄, MnSO₄, 25
 - + Na-citrate, 21
 - + NaCl, 20
 - + NaCl + NaClO₄, 35
 - + NaClO₄, 20, 35, 40, **Figs. 9, 10**
 - + NaClO₄ + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, 35
 - + Na₂CO₃, NaHCO₃, 21
 - + Na₂HPO₄, 20
 - + Na₂HPO₄, 20, 50
 - + Na₂HPO₄ + CaCl₂, 33
 - + Na₂HPO₄ + KCl, 33, 37, 41
 - + Na₂HPO₄ + KCl + MgCl₂, 41
 - + Na₂HPO₄ + KClO₄, KH₂PO₄, KHSO₄, KNO₃, KOOC·CH₃, 37
 - + Na₂HPO₄ + MgCl₂, 33, 37, 41
 - + Na₂HPO₄ + Mg(ClO₄)₂, MgH₄(PO₄)₂, Mg(NO₃)₂, Mg(OOC·CH₃), MgSO₄, 37
 - + Na₂HPO₄ + MnCl₂, 33
 - + Na₂HPO₄ + Na-acetate, Na-citrate, 27

Liver—Continued

- ← Me-Cl-COL—Continued
 - + Na₂HPO₄ + NaCl, 27, 33
 - + Na₂HPO₄ + NaClO₄, 27
 - + Na₂HPO₄ + NaHCO₃, Na-lactate, NaMnO₄, NaNO₃, Na₂SO₄, Na-urate, 27
 - + Na₂HPO₄ + NH₄Cl, 33
 - + Na₂HPO₄ + RbCl, 33
 - + NaH₂PO₂, NaH₂PO₃, 20
 - + NaH₂PO₄, 20, 40, 73
 - + NaH₂PO₄ + KH₂PO₄, 39
 - + NaH₂PO₄ + NaClO₄, NaHSO₄, NaHSO₄ + NaClO₄, 40
 - + NaHSO₃, 21
 - + NaHSO₄, 20, 40
 - + NaHSO₄ + NaClO₄, 40
 - + NaKHPO₄, 39
 - + Na-lactate, NaMnO₄, NaNO₃, NaOH, NaOOC·CH₃, 21
 - + Na₂PO₄, (NaPO₃)₆, Na₄P₂O₆, Na₄P₂O₇, 20
 - + Na₂SO₃, 21
 - + Na₂SO₄, 21, 35
 - + Na₂SO₄ + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - + Na-tartrate, Na-urate, 21
 - + NH₄H₂PO₄, (NH₄)₂HPO₄, NH₄HSO₄, RbClO₄, RbHSO₄, Rb₂SO₄, 25
 - + papain, 105
 - ← 6-Me-COL + NaH₂PO₄, 75
 - ← Me-F-COL + NaH₂PO₄, 73
 - ← 6-Me-9F-COL + NaH₂PO₄, 75
 - ← methylandrostanetriol + NaH₂PO₄, 67
 - ← methylandrostenediol + NaH₂PO₄, 68
 - ← 6 α -methyl-21-desoxycortisol, 6 α -methyl-11 β -hydroxyprogesterone, 6 α -methyl-11-ketoprogesterone + NaH₂PO₄, 74
 - ← 6 α -methyl- Δ^{14} -pregnadiene-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol + NaH₂PO₄, 76
 - ← 6 α -methyl- Δ^{14} -pregnadiene-3, 20-dione-11 β , 17 α -diol-21-fluorine, 6 α -methyl- Δ^4 -pregnene-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol + NaH₂PO₄, 75
 - ← 2 α -methyl- Δ^4 -pregnene-3, 20-dione-9, 11 β -oxido-17 α , 21-diol-21-acetate + NaH₂PO₄, 73

Liver—Continued

- ← methyltestosterone + NaH₂PO₄, 67
- ← Mg-deficiency, 31
- ← Na₂HPO₄ + papain, 105
- ← papain + KCl, MgCl₂, 105
- ← *Paracolobactrum coliforme*, *Pasteurella pseudotuberculosis*, 139
- ← pregnanedione + NaH₂PO₄, 68
- ← pregneneolone + NaH₂PO₄, 71
- ← progesterone + NaH₂PO₄, 68
- ← propyldihydronortestosterone + NaH₂PO₄, 77
- ← testosterone + NaH₂PO₄, 66
- ← triamcinolone + NaH₂PO₄, 73
- diet → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
- Local burns → heart ← DOC, 63
- Locke solution, 5
- Lung disease → heart, 135
- Lycopodium* intravenously → heart, 112
- "Lymphorrhages" in heart, 137
- "Lyotrope series," 4
- Magnesium; see Mg
- Malononitrile → heart, 109
- Manganese, see Mn
- "Mangelstoffwechselprodukte," 154
- "Mantelödem" of cardiac muscle fibers, 141
- Measles → heart, 125
- Meat → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
- 6-Me-COL → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 75
- Me-Cl-COL
 - arteriosclerosis
 - ← NaH₂PO₄ + DHT + KCl, MgCl₂, 94
 - blood pressure, 47
 - ← NaH₂PO₄, 47
 - brain edema ← NaClO₄, 51
 - Ca in heart, in serum ← NaH₂PO₄, 49
 - coronaries
 - ← NaH₂PO₄ + DHT, Figs. 13, 14
 - ← NaH₂PO₄ + DHT (pretreatment), 94
 - ECG ← NaH₂PO₄, 45
 - heart
 - ← arsphenamine + KCl, MgCl₂, 102

Me-Cl-COL—Continued

- heart—Continued
 - ← adrenalectomy + NaH_2PO_4 , 24
 - ← adrenaline, 147
 - ← $\text{Al}_2(\text{SO}_4)_3$, 25
 - ← blood-letting, 114, 147
 - ← $\text{CaH}_4(\text{PO}_4)_2$, 25
 - ← cold baths, 114, 146
 - ← DHT + Ca-acetate, $\text{CaH}_4(\text{PO}_4)_2$, 92
 - ← DHT + K-acetate, KClO_4 , K_2HPO_4 , KH_2PO_4 , KHSO_4 , $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, MgSO_4 , Na-acetate, NaCl , NaClO_4 , NaHCO_3 , Na_2HPO_4 , 92
 - ← DHT + NaH_2PO_4 , 92, Fig. 13
 - ← DHT + NaH_2PO_4 + MgCl_2 , 91
 - ← DHT + NaHSO_4 , Na-lactate, NaNO_3 , Na_2SO_4 , $(\text{NH}_4)_2\text{HPO}_4$, NH_4HSO_4 , 92
 - ← DHT (pretreatment) + NaH_2PO_4 , 93, 94
 - ← digitoxin, diisopropylfluorophosphate, dinitrophenol, diphtherotoxin, 147
 - ← hepatectomy (partial) + Na_2HPO_4 , Na_2SO_4 , NaClO_4 , 113
 - ← H_2O , 20
 - ← hot baths, 114, 146
 - ← KClO_4 , 25
 - ← K-deficiency, 31
 - ← K_2HPO_4 , 25
 - ← KH_2PO_4 , 24, 25
 - ← KHSO_4 , Li_2PO_4 , Li_2SO_4 , 25
 - ← MgCl_2 + K-deficiency, 31
 - ← $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, MgSO_4 , MnSO_4 , 25
 - ← muscular exercise, 146
 - ← Na-arsenate, 147
 - ← Na-citrate, 21
 - ← Na-fluoroacetate, 107, 147
 - ← NaCl , 18, 20
 - ← NaClO_4 , 20, 35, 40
 - ← NaClO_4 + KCl , KClO_4 , MgCl_2 , $\text{Mg}(\text{ClO}_4)_2$, NaCl , 35
 - ← Na_2CO_3 , 21
 - ← NaHCO_3 , 21
 - ← Na_2HPO_3 , Na_2HPO_4 , 18, 20
 - ← Na_2HPO_4 + CaCl_2 , 33
 - ← Na_2HPO_4 + ethanol, 106
 - ← Na_2HPO_4 + KCl , 33, 37, 41
 - ← Na_2HPO_4 + $\text{KCl} + \text{MgCl}_2$, 41

Me-Cl-COL—Continued

- heart—Continued
 - ← Na_2HPO_4 + KCl + nerve transection, vagotomy, 120
 - ← Na_2HPO_4 + KClO_4 , KH_2PO_4 , KHSO_4 , KNO_3 , $\text{KOOC}\cdot\text{CH}_3$, 37
 - ← Na_2HPO_4 + lipids, 109
 - ← Na_2HPO_4 + MgCl_2 , 33, 37, 41
 - ← Na_2HPO_4 + MgCl_2 + vagotomy, nerve transection, 120
 - ← Na_2HPO_4 + $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$, $\text{Mg}(\text{OOC}\cdot\text{CH}_3)_2$, MgSO_4 , 37
 - ← Na_2HPO_4 + MnCl_2 , 33
 - ← Na_2HPO_4 + Na-acetate, Na-citrate, 27
 - ← Na_2HPO_4 + NaCl , 27, 33
 - ← Na_2HPO_4 + NaClO_4 , NaHCO_3 , Na-lactate, NaMnO_4 , NaNO_3 , Na_2SO_4 , Na-urate, 27
 - ← Na_2HPO_4 + NH_4Cl , RbCl , 33
 - ← NaH_2PO_3 , 18, 20
 - ← NaH_2PO_4 , 17, 18, 20, 40, 73, Figs. 1-4, 17, 18
 - ← NaH_2PO_4 in monkey, Fig. 6
 - ← NaH_2PO_4 + adrenaline, 85, 144
 - ← NaH_2PO_4 + age, 139
 - ← NaH_2PO_4 + beans, 142
 - ← NaH_2PO_4 + blood-letting, 114, 151
 - ← NaH_2PO_4 + bone fractures, 144
 - ← NaH_2PO_4 + casein, 142
 - ← NaH_2PO_4 + cold baths, 114, 144
 - ← NaH_2PO_4 + corn, 142
 - ← NaH_2PO_4 + DHT in mouse, rabbit, dog, rat and hamster, 91
 - ← NaH_2PO_4 + DHT + KCl , 91, 94
 - ← NaH_2PO_4 + genetics, species, 141
 - ← NaH_2PO_4 + glucose, 103
 - ← NaH_2PO_4 + hot baths, 114
 - ← NaH_2PO_4 + hypophysectomy, 82
 - ← NaH_2PO_4 + KH_2PO_4 , 39
 - ← NaH_2PO_4 + kidney-diet, lard, lentils, liver-diet, meat, 142

Me-Cl-COL—Continued

- heart—Continued
 - ← $\text{NaH}_2\text{PO}_4 + \text{NaClO}_4$, NaHSO_4 , 40
 - ← $\text{NaH}_2\text{PO}_4 + \text{NaClO}_4 + \text{NaHSO}_4$, 40
 - ← $\text{NaH}_2\text{PO}_4 + \text{nephrectomy}$, 113
 - ← $\text{NaH}_2\text{PO}_4 + \text{nerve transection}$, 119, 144
 - ← $\text{NaH}_2\text{PO}_4 + \text{neuromuscular exertion}$, 143
 - ← $\text{NaH}_2\text{PO}_4 + \text{noradrenaline}$, 86
 - ← $\text{NaH}_2\text{PO}_4 + \text{papain}$, Fig. 11
 - ← $\text{NaH}_2\text{PO}_4 + \text{papain} + \text{MgCl}_2$, Fig. 11
 - ← $\text{NaH}_2\text{PO}_4 + \text{parathyroidectomy}$, 89
 - ← $\text{NaH}_2\text{PO}_4 + \text{peas, potatoes}$, 142
 - ← $\text{NaH}_2\text{PO}_4 + \text{pregnancy}$, 140
 - ← $\text{NaH}_2\text{PO}_4 + \text{pylorus ligature}$, 113
 - ← $\text{NaH}_2\text{PO}_4 + \text{restraint}$, 117, 143
 - ← $\text{NaH}_2\text{PO}_4 + \text{rice}$, 142
 - ← $\text{NaH}_2\text{PO}_4 + \text{sex}$, 140
 - ← $\text{NaH}_2\text{PO}_4 + \text{spinal-cord transection}$, 119
 - ← $\text{NaH}_2\text{PO}_4 + \text{spleen diet}$, starch, 142
 - ← $\text{NaH}_2\text{PO}_4 + \text{trauma}$, 114, 144
 - ← $\text{NaH}_2\text{PO}_4 + \text{uninephrectomy}$, 113
 - ← $\text{NaH}_2\text{PO}_4 + \text{vagotomy}$, 119, 144
 - ← $\text{NaH}_2\text{PO}_4 + \text{vasopressin}$, 84
 - ← NaHSO_4 , 21
 - ← NaHSO_4 , 20, 40
 - ← $\text{NaHSO}_4 + \text{NaClO}_4$, 40
 - ← Na-iodoacetate , 147
 - ← NaKHPO_4 , 39
 - ← Na-lactate , NaMnO_4 , NaNO_2 , NaOH , NaOOC-CH_3 , 21
 - ← Na_3PO_4 , 20
 - ← $(\text{NaPO}_4)_2$, $\text{Na}_4\text{P}_2\text{O}_7$, $\text{Na}_4\text{P}_2\text{O}_7$, 18, 20
 - ← Na_2SO_4 , 21
 - ← Na_2SO_4 , 21, 35
 - ← $\text{Na}_2\text{SO}_4 + \text{KCl}$, KHSO_4 , MgCl_2 , MgSO_4 , NaCl , 35
 - ← Na-tartrate , Na-urate , 21
 - ← nephrectomy , 82, 89, 113
 - ← nerve transection , 119, 148
 - ← $\text{NH}_4\text{H}_2\text{PO}_4$, NH_4HSO_4 , 25
 - ← noradrenaline , 147
 - ← papain , 105

Me-Cl-COL—Continued

- heart—Continued
 - ← $\text{parathyroidectomy} + \text{nephrectomy}$, 89
 - ← $\text{pentamethylenetetrazol}$, picrotoxin, *Pseudomonas aeruginosa*, 147
 - ← RbClO_4 , RbHSO_4 , Rb_2SO_4 , 25
 - ← restraint , 117, 146
 - ← $\text{restraint in rat and monkey}$, 118
 - ← $\text{restraint} + \text{KCl}$, MgCl_2 (during restraint only), 122
 - ← $\text{spinal-cord transection}$, 119, 146
 - ← $\text{thyroidectomy} + \text{nephrectomy}$, 89
 - ← $\text{thyroparathyroidectomy} + \text{NaH}_2\text{PO}_4$, 89
 - ← trauma , 114, 147
 - ← vagotomy , 119, 146
 - ← vasopressin , 83, 147
- K in heart, in muscles, in serum
 - ← NaH_2PO_4 , 49
- liver
 - ← $\text{Al}_2(\text{SO}_4)_3$, $\text{CaH}_4(\text{PO}_4)_2$, 25
 - ← H_2O , 20
 - ← KClO_4 , K_2HPO_4 , KH_2PO_4 , KHSO_4 , Li_2PO_4 , Li_2SO_4 , $\text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, MgSO_4 , MnSO_4 , 25
 - ← Na-citrate , 21
 - ← NaCl , 20
 - ← NaClO_4 , 20, 35, 40, Figs. 9, 10
 - ← $\text{NaClO}_4 + \text{KCl}$, KClO_4 , MgCl_2 , $\text{Mg}(\text{ClO}_4)_2$, NaCl , 35
 - ← Na_2CO_3 , NaHCO_3 , 21
 - ← Na_2HPO_4 , 20
 - ← Na_2HPO_4 , 20, 50
 - ← $\text{Na}_2\text{HPO}_4 + \text{CaCl}_2$, 33
 - ← $\text{Na}_2\text{HPO}_4 + \text{KCl}$, 33, 41
 - ← $\text{Na}_2\text{HPO}_4 + \text{KCl} + \text{MgCl}_2$, 41
 - ← $\text{Na}_2\text{HPO}_4 + \text{KClO}_4$, KH_2PO_4 , KHSO_4 , KNO_3 , KOOC-CH_3 , 37
 - ← $\text{Na}_2\text{HPO}_4 + \text{MgCl}_2$, 33, 37, 41
 - ← $\text{Na}_2\text{HPO}_4 + \text{Mg}(\text{ClO}_4)_2$, $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$, $\text{Mg}(\text{OOC-CH}_3)$, MgSO_4 , 37
 - ← $\text{Na}_2\text{HPO}_4 + \text{MnCl}_2$, 33
 - ← $\text{Na}_2\text{HPO}_4 + \text{Na-acetate}$, Na-citrate , 27
 - ← $\text{Na}_2\text{HPO}_4 + \text{NaCl}$, 27, 33

Me-Cl-COL—Continued

→ liver—Continued

- ← $\text{Na}_2\text{HPO}_4 + \text{NaClO}_4, \text{NaHCO}_3$,
 $\text{Na-lactate}, \text{NaMnO}_4,$
 $\text{NaNO}_2, \text{Na}_2\text{SO}_4, \text{Na-urate},$
 27
- ← $\text{Na}_2\text{HPO}_4 + \text{NH}_4\text{Cl}, \text{RbCl}$, 33
- ← $\text{NaH}_2\text{PO}_2, \text{NaH}_2\text{PO}_4$, 20
- ← NaH_2PO_4 , 20, 40, 73
- ← $\text{NaH}_2\text{PO}_4 + \text{KH}_2\text{PO}_4$, 39
- ← $\text{NaH}_2\text{PO}_4 + \text{NaClO}, \text{NaHSO}_4$,
 40
- ← $\text{NaH}_2\text{PO}_4 + \text{NaHSO}_4 +$
 NaClO_4 , 40
- ← NaHSO_4 , 21
- ← NaHSO_4 , 20, 40
- ← $\text{NaHSO}_4 + \text{NaClO}_4$, 40
- ← NaKHPO_4 , 39
- ← $\text{Na-lactate}, \text{NaMnO}_4, \text{NaNO}_2,$
 $\text{NaOOC-CH}_3, \text{NaOH}$, 21
- ← $(\text{NaPO}_4)_2, \text{NaPO}_4, \text{Na}_2\text{P}_2\text{O}_7,$
 $\text{Na}_4\text{P}_2\text{O}_7$, 20
- ← $\text{Na}_2\text{SO}_4, \text{Na}_2\text{SO}_4$, 21
- ← Na_2SO_4 , 35
- ← $\text{Na}_2\text{SO}_4 + \text{KCl}, \text{KHSO}_4,$
 $\text{MgCl}_2, \text{MgSO}_4, \text{NaCl}$, 35
- ← $\text{Na-tartrate}, \text{Na-urate}$, 21
- ← $\text{NH}_4\text{H}_2\text{PO}_4, (\text{NH}_4)_2\text{HPO}_4,$
 NH_4HSO_4 , 25
- ← papain, 105
- ← $\text{RbClO}_4, \text{RbHSO}_4, \text{Rb}_2\text{SO}_4$, 25
- Mg in heart ← NaH_2PO_4 , 49
- mortality
- ← $\text{Al}_2(\text{SO}_4)_3, \text{CaH}_4(\text{PO}_4)_2$, 25
- ← H_2O , 20
- ← $\text{KCIO}_4, \text{K}_2\text{HPO}_4, \text{KH}_2\text{PO}_4,$
 $\text{KHSO}_4, \text{Li}_2\text{PO}_4, \text{Li}_2\text{SO}_4$, 25
- ← Na-citrate , 21
- ← NaCl , 20
- ← NaClO_4 , 20, 35, 40
- ← $\text{NaClO}_4 + \text{KCl}, \text{KClO}_4,$
 $\text{MgCl}_2, \text{Mg}(\text{ClO}_4)_2, \text{NaCl}$,
 35
- ← $\text{Na}_2\text{CO}_3, \text{NaHCO}_3$, 21
- ← $\text{Na}_2\text{HPO}_4, \text{Na}_2\text{HPO}_4$, 20
- ← $\text{Na}_2\text{HPO}_4 + \text{CaCl}_2$, 33
- ← $\text{Na}_2\text{HPO}_4 + \text{KCl}$, 33, 37, 41
- ← $\text{Na}_2\text{HPO}_4 + \text{KCl} + \text{MgCl}_2$, 41
- ← $\text{Na}_2\text{HPO}_4 + \text{KClO}_4, \text{KH}_2\text{PO}_4,$
 $\text{KHSO}_4, \text{KNO}_3, \text{KOOC-CH}_3$, 37
- ← $\text{Na}_2\text{HPO}_4 + \text{MgCl}_2$, 33, 37,
 41
- ← $\text{Na}_2\text{HPO}_4 + \text{Mg}(\text{ClO}_4)_2,$
 $\text{MgH}_4(\text{PO}_4)_2, \text{Mg}(\text{NO}_3)_2$

Me-Cl-COL—Continued

→ mortality—Continued

- ← $\text{Mg}(\text{OOC-CH}_3)_2, \text{MgSO}_4$,
 37
- ← $\text{Na}_2\text{HPO}_4 + \text{MnCl}_2$, 33
- ← $\text{Na}_2\text{HPO}_4 + \text{Na-acetate}, \text{Na-}$
 citrate, 27
- ← $\text{Na}_2\text{HPO}_4 + \text{NaCl}$, 27, 33
- ← $\text{Na}_2\text{HPO}_4 + \text{NaClO}_4, \text{NaHCO}_3$,
 $\text{Na-lactate}, \text{NaMnO}_4,$
 $\text{NaNO}_2, \text{Na}_2\text{SO}_4, \text{Na-urate},$
 27
- ← $\text{Na}_2\text{HPO}_4 + \text{NH}_4\text{Cl}, \text{RbCl}$, 33
- ← $\text{NaH}_2\text{PO}_2, \text{NaH}_2\text{PO}_4$, 20
- ← NaH_2PO_4 , 20, 40, 73
- ← $\text{NaH}_2\text{PO}_4 + \text{KH}_2\text{PO}_4$, 39
- ← $\text{NaH}_2\text{PO}_4 + \text{NaClO}_4, \text{NaHSO}_4$,
 40
- ← $\text{NaH}_2\text{PO}_4 + \text{NaHSO}_4 +$
 NaClO_4 , 40
- ← NaHSO_4 , 21
- ← NaHSO_4 , 20, 40
- ← $\text{NaHSO}_4 + \text{NaClO}_4$, 40
- ← NaKHPO_4 , 39
- ← $\text{Na-lactate}, \text{NaMnO}_4, \text{NaNO}_2,$
 $\text{NaOH}, \text{NaOOC-CH}_3$, 21
- ← $(\text{NaPO}_4)_2, \text{Na}_2\text{PO}_4, \text{Na}_4\text{P}_2\text{O}_7,$
 $\text{Na}_4\text{P}_2\text{O}_7$, 20
- ← Na_2SO_4 , 21
- ← Na_2SO_4 , 21, 35
- ← $\text{Na}_2\text{SO}_4 + \text{KCl}, \text{KHSO}_4,$
 $\text{MgCl}_2, \text{MgSO}_4, \text{NaCl}$, 35
- ← $\text{Na-tartrate}, \text{Na-urate}$, 21
- ← $\text{NH}_4\text{H}_2\text{PO}_4, (\text{NH}_4)_2\text{HPO}_4,$
 $\text{NH}_4\text{HSO}_4, \text{Mg}(\text{ClO}_4)_2,$
 $\text{MgH}_4(\text{PO}_4)_2, \text{MgSO}_4,$
 $\text{MnSO}_4, \text{RbClO}_4, \text{RbHSO}_4,$
 Rb_2SO_4 , 25
- muscles ← NaClO_4 , 51
- Na in heart, in muscles, in
 serum ← NaH_2PO_4 , 49
- nephrocalcinosis
- ← $\text{Al}_2(\text{SO}_4)_3, \text{CaH}_4(\text{PO}_4)_2$, 25
- ← H_2O , 20
- ← $\text{KCIO}_4, \text{K}_2\text{HPO}_4, \text{KH}_2\text{PO}_4,$
 $\text{KHSO}_4, \text{Li}_2\text{PO}_4, \text{Li}_2\text{SO}_4,$
 $\text{Mg}(\text{ClO}_4)_2, \text{MgH}_4(\text{PO}_4)_2,$
 $\text{MgSO}_4, \text{MnSO}_4$, 25
- ← Na-citrate , 21
- ← NaCl , 20
- ← NaClO_4 , 20, 35, 40
- ← $\text{NaClO}_4 + \text{KCl}, \text{KClO}_4,$
 $\text{MgCl}_2, \text{Mg}(\text{ClO}_4)_2, \text{NaCl}$,
 35
- ← $\text{Na}_2\text{CO}_3, \text{NaHCO}_3$, 21

Me-Cl-COL—Continued

- nephrocalcinosis—Continued
 - ← Na₂HPO₄, Na₂HPO₄, 20
 - ← Na₂HPO₄ + CaCl₂, 33
 - ← Na₂HPO₄ + NaCl, 27, 33
 - ← Na₂HPO₄ + KCl, 33, 37, 41
 - ← Na₂HPO₄ + HCl + MgCl₂, 41
 - ← Na₂HPO₄ + KClO₄, KH₂PO₄, KHSO₄, KNO₃, KOOC·CH₃, 37
 - ← Na₂HPO₄ + MgCl₂, 33, 37, 41
 - ← Na₂HPO₄ + Mg(ClO₄)₂, MgH₄(PO₄)₂, Mg(NO₃)₂, Mg(OOC·CH₃)₂, MgSO₄, 37
 - ← Na₂HPO₄ + MnCl₂, 33
 - ← Na₂HPO₄ + Na-acetate, Na-citrate, NaClO₄, NaHCO₃, Na-lactate, NaMnO₄, NaNO₃, Na₂SO₄, Na-urate, 27
 - ← Na₂HPO₄ + NH₄Cl, RbCl, 33
 - ← NaH₂PO₂, NaH₂PO₃, 20
 - ← NaH₂PO₄, 20, 40, 73, Fig. 7
 - ← NaH₂PO₄ + age, 140
 - ← NaH₂PO₄ + beans, casein, corn, 142
 - ← NaH₂PO₄ + glucose, 103
 - ← NaH₂PO₄ + KH₂PO₄, 39
 - ← NaH₂PO₄ + kidney-diet, lard, lentils, liver-diet, meat, 142
 - ← NaH₂PO₄ + NaClO₄, NaHSO₄, 40
 - ← NaH₂PO₄ + NaHSO₄ + NaClO₄, 40
 - ← NaH₂PO₄ + peas, potatoes, 142
 - ← NaH₂PO₄ + pregnancy, 140
 - ← NaH₂PO₄ + rice, spleen-diet, starch, 142
 - ← NaHSO₃, 21
 - ← NaHSO₄, 20, 40
 - ← NaHSO₄ + NaClO₄, 40
 - ← NaKHPO₄, 39
 - ← Na-lactate, NaMnO₄, NaNO₃, NaOH, NaOOC·CH₃, 21
 - ← (NaPO₃)_n, Na₃PO₄, Na₄P₂O₇, Na₄P₂O₇, 20
 - ← Na₂SO₃, 21
 - ← Na₂SO₄, 21, 35
 - ← Na₂SO₄ + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - ← Na-tartrate, Na-urate, 21
 - ← NH₄H₂PO₄, (NH₄)₂HPO₄, NH₄HSO₄, 25

Me-Cl-COL—Continued

- ← phosphates, 18
- ← RbClO₄, RbHSO₄, Rb₂SO₄, 25
- PO₄ in heart, in muscles, in serum ← NaH₂PO₄, 49
- subendocardial necroses ← NaH₂PO₄, Fig. 17
- subepicardial necrosis ← NaH₂PO₄, Fig. 18
- Medrol → heart ← DHT + NaClO₄, NaH₂PO₄, 92
- Me-F-COL**
 - heart ← NaH₂PO₄, 64
 - heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 73
- 6-Me-9F-COL → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 75
- Meningococcal endotoxin → coronaries, cortical necrosis, heart, kidney, 124
- Meningococcal toxin → heart, 125
- Metabolic toxins (theory) → ESCN, heart, 154
- Metacorticoid hypertension, 46
- Methionine → heart ← choline deficiency, 98
- Methylandrostanetriol
 - heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 67
- Methylandrostenediol
 - heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 68
- Methylcellulose intravenously → heart, 112
- 6α-methyl-21-desoxycortisol → heart ← DHT + NaClO₄, NaH₂PO₄, 92
- 6α-methyl-21-desoxycortisol → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 74
- 6α-methyl-11β-hydroxyprogesterone
 - heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 74
- 6α-methyl-11-ketoprogesterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 74
- 6α-methyl-Δ^{1,4}-pregnadiene-3,20-dione-9α, 21-difluoro-11β, 17α-diol → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 76
- 6α-methyl-Δ^{1,4}-pregnadiene-3,20-dione-11β, 17α-diol-21-fluorine → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 75

- 6 α -methyl- Δ^4 -pregnene-3,20-dione-9 α ,
 21-difluoro-11 β , 17 α -diol → heart,
 liver, mortality, nephrocalcinosis
 ← NaH₂PO₄, 75
- 2 α -methyl- Δ^4 -pregnene-3,20-dione-9,
 11 β -oxido-17 α , 21-diol-21-acetate
 → heart, liver, mortality, nephro-
 calcinosis ← NaH₂PO₄, 73
- Methyltestosterone → heart, liver, mor-
 tality, nephrocalcinosis ←
 NaH₂PO₄, 67
- Mg → cardiac infarcts in man, 130
 → heart (arrhythmias), 163
 → heart ← cholesterol, 32
- Mg-acetate → aorta, heart, mortality,
 nephrocalcinosis ← DHT, 96
- Mg-deficiency
 → aorta, atheromatosis ← chole-
 sterol, 32
 → blood vessels, 31
 → heart ← KCl + papain, 106
 → heart ← papain, 106
 → liver, 31
 → mitochondria in heart, 88
 → nephrocalcinosis, 31
- Mg in blood
 ≈ cardiac infarcts in man, 130
 ≈ cholesterol in blood, 130
- Mg in heart
 ← Me-Cl-COL + NaH₂PO₄,
 49
 importance for contraction, 164
- Mg-metabolism ← thyroxin, 88
- Mg-theobromine-oleate → arterio-
 sclerosis, 32
- MgCl₂
 → aorta ← DHT, 96
 → aorta ← DHT + NaH₂PO₄, Fig.
 15
 → arteriosclerosis ← DHT +
 NaH₂PO₄, 91
 → arteriosclerosis ← Me-Cl-COL
 + NaH₂PO₄ + DHT, 94
 → heart
 ← DHT, 96
 ← DHT + NaH₂PO₄, 91
 ← DOC + uninephrectomy +
 NaCl, 61
 ← K-deficiency, 30, 31
 ← K-deficiency + papain, 106
 ← Me-Cl-COL + arsphenamine,
 102
 ← Me-Cl-COL + DHT +
 NaH₂PO₄, 91
 ← Me-Cl-COL + K-deficiency,
 31

MgCl₂-Continued

- heart—Continued
 ← Me-Cl-COL + NaClO₄, 35
 ← Me-Cl-COL + Na₂HPO₄, 33,
 37, 41
 ← Me-Cl-COL + Na₂HPO₄ +
 KCl, 41
 ← Me-Cl-COL + NaH₂PO₄ +
 papain, Fig. 11
 ← Me-Cl-COL + Na₂HPO₄ +
 vagotomy, nerve transec-
 tion, 120
 ← Me-Cl-COL + Na₂SO₄, 35
 ← Me-Cl-COL + restraint,
 122
 ← Na₂HPO₄ + arsphenamine,
 102
 ← papain, 105
 ← parathyroid extract, 90
 ← parathyroid extract +
 NaH₂PO₄, 89
 mechanism of action, 163
 → kidney ← DOC + uninephrec-
 tomy + NaCl, 61
 → liver
 ← Me-Cl-COL + NaClO₄, 35
 ← Me-Cl-COL + Na₂HPO₄, 33,
 37, 41
 ← Me-Cl-COL + Na₂HPO₄ +
 KCl, 41
 ← Me-Cl-COL + Na₂SO₄, 35
 ← papain, 105
 → mortality
 ← DHT, 96
 ← Me-Cl-COL + NaClO₄, 35
 ← Me-Cl-COL + Na₂HPO₄, 33,
 37, 41
 ← Me-Cl-COL + Na₂HPO₄ +
 KCl, 41
 ← Me-Cl-COL + Na₂SO₄, 35
 → nephrocalcinosis
 ← DHT, 96
 ← Me-Cl-COL + NaClO₄, 35
 ← Me-Cl COL + Na₂HPO₄, 33,
 37, 41
 ← Me-Cl-COL + Na₂HPO₄ +
 KCl, 41
 ← Me-Cl-COL + Na₂SO₄, 35
Mg(ClO₄)₂
 → aorta, heart ← DHT, 96
 → heart
 ← Me-Cl-COL, 25
 ← Me-Cl-COL + DHT, 92
 ← Me-Cl-COL + NaClO₄, 35
 ← Me-Cl-COL + Na₂HPO₄,
 37

$Mg(ClO_4)_2$ —Continued

- liver
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 37
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 37
- nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 37

 $MgH_4(PO_4)_2$

- aorta, heart ← DHT, 96
- heart
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + Na₂HPO₄, 37
- liver
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
- nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37

 $Mg(NO_3)_2$

- aorta, heart ← DHT, 96
- heart, liver ← Me-Cl-COL +
 - Na₂HPO₄, 37
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL + Na₂HPO₄, 37
- nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL + Na₂HPO₄, 37

 $Mg(OOC\cdot CH_3)_2$; see Mg-acetate $MgSO_4$

- aorta ← DHT, 96
- blood-coagulation, 130
- heart
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35
- lipoproteins in blood, 130
- liver
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37

 $MgSO_4$ —Continued

- liver—Continued
 - ← Me-Cl-COL + Na₂SO₄, 35
 - mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35
 - nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + Na₂HPO₄, 37
 - ← Me-Cl-COL + Na₂SO₄, 35
- Microbes → heart, 123
- Mitochondria in heart, 29
 - ← Mg-deficiency, thyroxin, 88
- $MnCl_2$ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL +
 - Na₂HPO₄, 33
- $MnSO_4$ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25
- Mortality
 - ← acetoxypregnenolone +
 - NaH₂PO₄, 72
 - ← 17-acetoxy-progesterone +
 - NaH₂PO₄, 69
 - ← adrenalectomy + cardiac glycosides, 100
 - ← adrenosterone + NaH₂PO₄, 66
 - ← 12 α -bromo-11 β -hydroxyprogesterone, bromoxoprogesterone + NaH₂PO₄, 70
 - ← 4-chloro-adrenosterone, 4-chlorotestosterone + NaH₂PO₄, 67
 - ← Cl-COL + NaH₂PO₄, 71
 - ← cortisol + NaH₂PO₄, 69
 - ← Δ^1 -cortisol + NaH₂PO₄, 72
 - ← cortisone + NaH₂PO₄, 70
 - ← Δ^1 -cortisone + NaH₂PO₄, 72
 - ← dehydro-iso-androsterone + NaH₂PO₄, 67
 - ← desoxycortisol + NaH₂PO₄, 69
 - ← DHT + Ca-acetate, CaCl₂,
 - CaH₄(PO₄)₂, Ca(NO₃)₂, K-acetate, KCl, KClO₄, K₂HPO₄, KH₂PO₄, KHSO₄, KNO₃, K₂SO₄, Mg-acetate, MgCl₂, Mg(ClO₄)₂, Mg(NO₃)₂, MgH₄(PO₄)₂, MgSO₄, Na-acetate, NaCl, NaClO₄, NaNO₃, Na₂HPO₄, NaH₂PO₄, NaHSO₄, Na₂SO₄, NH₄-acetate, NH₄Cl, NH₄ClO₄, NH₄H₂PO₄, NH₄HSO₄, NH₄NO₃, 96

Mortality—Continued

- ← DOC + NaH₂PO₄, 69
- ← estradiol, estrone + NaH₂PO₄, 66
- ← ethynodiol, ethynodiol, ethynodiol + NaH₂PO₄, 77
- ← ethynodiol, ethynodiol, ethynodiol + NaH₂PO₄, 76
- ← 17α-ethyl-Δ⁴-androstene-3-one-11β, 17β-diol + NaH₂PO₄, 77
- ← ethynodiol + NaH₂PO₄, 76
- ← F-COL + NaH₂PO₄, 71
- ← 9α-fluoro-11β-hydroxyprogesterone + NaH₂PO₄, 70
- ← 16α-hydroxy-9α-fluorocortisol + NaH₂PO₄, 71
- ← 11β-hydroxy-methyltestosterone + NaH₂PO₄, 68
- ← 11-ketoprogestrone + NaH₂PO₄, 69
- ← Me-Cl-COL
 - + Al₂(SO₄)₃, CaH₄(PO₄)₂, 25
 - + H₂O, 20
 - + KClO₄, K₂HPO₄, KH₂PO₄, KHSO₄, Li₂PO₄, Li₂SO₄, Mg(ClO₄)₂, MgH₄(PO₄)₂, MgSO₄, MnSO₄, 25
 - + Na-citrate, 21
 - + NaCl, 20
 - + NaClO₄, 20, 35, 40
 - + NaClO₄ + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, NaCl, 35
 - + Na₂CO₃, NaHCO₃, 21
 - + Na₂HPO₄, Na₂HPO₄, 20
 - + Na₂HPO₄ + CaCl₂, 33
 - + Na₂HPO₄ + KCl, 33, 37, 41
 - + Na₂HPO₄ + KCl + MgCl₂, 41
 - + Na₂HPO₄ + KClO₄, KH₂PO₄, KHSO₄, KNO₃, KOOC-CH₃, 37
 - + Na₂HPO₄ + MgCl₂, 33, 37, 41
 - + Na₂HPO₄ + Mg(ClO₄)₂, MgH₄(PO₄)₂, Mg(NO₃)₂, Mg(OOC-CH₃)₂, MgSO₄, 37
 - + Na₂HPO₄ + MnCl₂, 33
 - + Na₂HPO₄ + Na-acetate, Na-citrate, 27
 - + Na₂HPO₄ + NaCl, 27, 33
 - + Na₂HPO₄ + NaClO₄, NaHCO₃, Na-lactate, NaMnO₄, NaNO₃, Na₂SO₄, Na-urate, 27
 - + Na₂HPO₄ + NH₄Cl, RbCl, 33

Mortality—Continued

- ← Me-Cl-COL—Continued
 - + NaH₂PO₄, NaH₂PO₃, 20
 - + NaH₂PO₄, 20, 40, 73
 - + NaH₂PO₄ + KH₂PO₄, 39
 - + NaH₂PO₄ + NaClO₄, NaHSO₄, 40
 - + NaH₂PO₄ + NaClO₄ + NaHSO₄, 40
 - + NaHSO₃, 21
 - + NaHSO₄, 20, 40
 - + NaHSO₄ + NaClO₄, 40
 - + NaKHPO₄, 39
 - + Na-lactate, NaMnO₄, NaNO₃, NaOH, 21
 - + NaOOC-CH₃, 21
 - + Na₂PO₄, (NaPO₃)₆, Na₄P₂O₇, Na₂P₂O₇, 20
 - + Na₂SO₃, 21
 - + Na₂SO₄, 21, 35
 - + Na₂SO₄ + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - + Na-tartrate, Na-urate, 21
 - + NH₄H₂PO₄, (NH₄)₂HPO₄, NH₄HSO₄, RbClO₄, RbHSO₄, Rb₂SO₄, 25
- ← 6-Me-COL + NaH₂PO₄, 75
- ← Me-F-COL + NaH₂PO₄, 73
- ← 6-Me-9F-COL + NaH₂PO₄, 75
- ← methylandrostanetriol + NaH₂PO₄, 67
- ← methylandrostenediol + NaH₂PO₄, 68
- ← 6α-methyl-21-desoxycortisol, 6α-methyl-11β-hydroxyprogesterone, 6α-methyl-11-ketoprogesterone + NaH₂PO₄, 74
- ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-11β, 17α-diol-21-fluorine, 6α-methyl-Δ⁴-pregnen-3, 20-dione-9α, 21-difluoro-11β, 17α-diol + NaH₂PO₄, 75
- ← 2α-methyl-Δ⁴-pregnene-3, 20-dione-9, 11β-oxido-17α, 21-diol-21-acetate + NaH₂PO₄, 73
- ← methyltestosterone + NaH₂PO₄, 67
- ← pregnanedione + NaH₂PO₄, 68
- ← pregnenolone + NaH₂PO₄, 71
- ← progesterone + NaH₂PO₄, 68
- ← propyldihydronortestosterone + NaH₂PO₄, 77
- ← testosterone + NaH₂PO₄, 66

- Mortality—Continued**
- ← triamcinolone + NaH₂PO₄, 73
- Muscles**
- ← enzymes, 104
 - ← Me-Cl-COL + NaClO₄, 51
 - ← myasthenia gravis, 137
 - ← NaCl, NaClO₄, Na₂HPO₄, Na₂SO₄ + K-deficiency, 31
 - ← vitamin-B₁ deficiency, 97
 - fuchsinophilia of, 44
- Muscular exercise**
- ECG, 116
 - heart, 6, 116, 146, 151
 - ← cholesterol, 117
 - ← Me-Cl-COL, 146
 - ← vitamin-D, 90
- Myasthenia gravis** → heart, Fiedler's myocarditis, muscle, 137
- Myocardial fibrosis**, 14
- Myocarditis; see also Heart**
- chronic, 14
 - definition, 153
 - (spontaneous) in rabbits, rats, 138
- Myocarditis perniciosa**, 133
- Myocardium; see Heart**
- Myolytic cardiopathy of the newborn**, 133
- Na ⇌ K → heart**, 30
- Na-acetate**
- aorta, heart ← DHT, 96
 - heart, 23
 - ← Me-Cl-COL + DHT, 92
 - liver, mortality ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - mortality, nephrocalcinosis ← DHT, 96
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- Na-arsenate**
- heart, 147
 - ← Me-Cl-COL, 147
- Na-citrate**
- heart, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - liver ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- Na-citrate—Continued**
- mortality ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- Na-exchange rosins** → heart, 165
- Na-fluoroacetate**
- heart, 107, 147
 - ← Me-Cl-COL, 107, 147
- Na in aorta** ← hypercorticoidism, hypertension, 161
- Na in heart**
- ← DOC, 48
 - ← Me-Cl-COL + NaH₂PO₄, 49
- Na in muscles**
- ← DOC, 48
 - ← Me-Cl-COL + NaH₂PO₄, 49
- Na in serum** ← Me-Cl-COL + NaH₂PO₄, 49
- Na indispensability for production of ESN**, 25
- Na-iodoacetate**
- heart, 147
 - ← Me-Cl-COL, 147
- Na-lactate**
- ECG, 131
 - heart, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - liver
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - mortality
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- Na-metabolism** ← stress, 149
- Na-monooiodoacetate** → heart, 108
- Na-selenite** → heart, 110
- Na-tartrate**
- heart, 23
 - liver, mortality ← Me-Cl-COL, 21
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
- Na-urate**
- heart, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27

Na-urate—Continued

- liver
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- mortality
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27

NaCl

- aorta ← DHT, 96
- blood pressure ← DOC, 10, 60
- ECG ← DOC, 63
- heart, 23
 - ← cold baths, 149
 - ← DHT, 96
 - ← DOC, 9, 10, 55, 60
 - ← DOC in bird, 9
 - ← DOC in fowl, 60
 - ← DOC + KCl, 62, 63
 - ← DOC + KCl in bird, 10
 - ← DOC + KCl in fowl, 60
 - ← DOC + NH₄Cl, 63
 - ← DOC + uninephrectomy, 61
 - ← DOC + uninephrectomy +
 - CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, 61
 - ← hypophysectomy + DOC + uninephrectomy, 81
 - ← K-deficiency, 31
 - ← Me-Cl-COL, 18, 20
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - ← Me-Cl-COL + Na₂HPO₄, 33
 - ← Me-Cl-COL + Na₂SO₄, 35
 - ← restraint, 149

NaCl-deficiency → kidney ← DOC + anti-rat-kidney serum, 63

NaCl in bird, 9

- K in heart ← DOC, 62
- kidney
 - ← DOC, 10
 - ← DOC in fowl, 60
 - ← DOC + anti-rat-kidney serum, 63
 - ← DOC + anti-rat-kidney serum + KCl, 63
 - ← DOC + KCl, NH₄Cl, 63
 - ← DOC + uninephrectomy +
 - CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, NH₄NO₃, (NH₄)₂SO₄, 61

NaCl in bird—Continued

- liver
 - ← Me-Cl-COL, 20
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27, 33
 - ← Me-Cl-COL + Na₂SO₄, 35
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 20
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27, 33
 - ← Me-Cl-COL + Na₂SO₄, 35
- muscles ← K-deficiency, 31
- nephrocalcinosis, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 20
 - ← Me-Cl-COL + NaClO₄, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27, 33
 - ← Me-Cl-COL + Na₂SO₄, 35
- nephrosclerosis ← DOC, 10, 50
- nephrosis ← DOC, 50
- periarteritis ← DOC, 60
- periarteritis ← DOC + KCl, 63
- periarteritis nodosa ← DOC, 10

NaClO₄

- aorta ← DHT, 96
- brain edema ← Me-Cl-COL, 51
- heart, 23
 - ← adrenaline, 36
 - ← cold baths, 149
 - ← cortisol + DHT, 92
 - ← DHT, 96
 - ← DOC + DHT, 92
 - ← heptectomy (partial) +
 - Me-Cl-COL, 113
 - ← K-deficiency, 31
 - ← Me-Cl-COL, 20, 35, 40
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - ← Me-Cl-COL + NaH₂PO₄, NaHSO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaHSO₄, 40
 - ← Medrol, 6α methyl-21-desoxy-cortisol, triamcinolone + DHT, 92

NaClO₄—Continued

- liver
 - ← Me-Cl-COL, 20, 35, 40, Figs. 9, 10
 - ← Me-Cl-COL + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - ← Me-Cl-COL + NaH₂PO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaHSO₄, 40
 - ← Me-Cl-COL + NaHSO₄, 40
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 20, 35, 40
 - ← Me-Cl-COL + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - ← Me-Cl-COL + NaH₂PO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaHSO₄, 40
 - ← Me-Cl-COL + NaHSO₄, 40
- muscles
 - ← K-deficiency, 31
 - ← Me-Cl-COL, 51
- nephrocalcinosis, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 20, 35, 40
 - ← Me-Cl-COL + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - ← Me-Cl-COL + NaH₂PO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaHSO₄, 40
 - ← Me-Cl-COL + NaHSO₄, 40

Na₂CO₃

- heart, 23
- heart, liver, mortality ← Me-Cl-COL, 21
- nephrocalcinosis, 23
- nephrocalcinosis ← Me-Cl-COL, 21

NaHCO₃

- heart, 23
 - ← DOC + uninephrectomy + NaCl, 61
- ← Me-Cl-COL, 21
- ← Me-Cl-COL + DHT, 92
- ← Me-Cl-COL + Na₂HPO₄, 27
- kidney ← DOC + uninephrectomy + NaCl, 61
- liver
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27

NaHCO₃—Continued

- mortality
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- Na₂HPO₄
 - heart, 23
 - ← Me-Cl-COL, 18, 20
 - liver, mortality ← Me-Cl-COL, 20
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 20
- Na₂HPO₄
 - aorta ← DHT, 96
 - heart, 23
 - ← adrenaline, 86
 - ← arsphenamine + KCl, MgCl₂, 102
 - ← cold baths, 149
 - ← DHT, 96
 - ← estrone, 66
 - ← hepatectomy (partial) + Me-Cl-COL, 113
 - ← K-deficiency, 31
 - ← Me-Cl-COL, 18, 20
 - ← Me-Cl-COL + CaCl₂, 33
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + ethanol, 106
 - ← Me-Cl-COL + KCl, 33, 37, 41
 - ← Me-Cl-COL + KCl + MgCl₂, 41
 - ← Me-Cl-COL + KCl + nerve transection, vagotomy, 120
 - ← Me-Cl-COL + KClO₄, KH₂PO₄, KHSO₄, KNO₃, HOOC·CH₃, 37
 - ← Me-Cl-COL + lipids, 109
 - ← Me-Cl-COL + MgCl₂, 33, 37, 41
 - ← Me-Cl-COL + MgCl₂ + vagotomy, nerve transection, 120
 - ← Me-Cl-COL + Mg(ClO₄)₂, MgH₂(PO₄)₂, Mg(NO₃)₂, Mg(OOC·CH₃)₂, MgSO₄, 37
 - ← Me-Cl-COL + MnCl₂, 33
 - ← Me-Cl-COL + Na-acetate, Na-citrate, NaCl, 27
 - ← Me-Cl-COL + NaCl, 33
 - ← Me-Cl-COL + NaClO₄, NaMnO₄, 27
 - ← Me-Cl-COL + NH₄Cl, 33

Na_2HPO_4 —Continued

- heart—Continued
- ← Me-Cl-COL + NaHCO_3 ,
Na-lactate, NaNO_3 , Na_2SO_4 ,
Na-urate, 27
- ← Me-Cl-COL + RbCl , 33
- ← papain, 105
- ← plasmocid, 110
- liver
- ← Me-Cl-COL, 20, 50
- ← Me-Cl-COL + CaCl_2 , 33
- ← Me-Cl-COL + KCl , 33, 41
- ← Me-Cl-COL + $\text{KCl} + \text{MgCl}_2$,
41
- ← Me-Cl-COL + KClO_4 ,
 KH_2PO_4 , KHSO_4 , KNO_3 ,
 $\text{KOOC}\cdot\text{CH}_3$, 37
- ← Me-Cl-COL + MgCl_2 , 33, 37,
41
- ← Me-Cl-COL + $\text{Mg}(\text{ClO}_4)_2$,
 $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$,
 $\text{Mg}(\text{OOC}\cdot\text{CH}_3)$, MgSO_4 ,
37
- ← Me-Cl-COL + MnCl_2 , 33
- ← Me-Cl-COL + Na-acetate,
Na-citrate, 27
- ← Me-Cl-COL + NaCl , 27, 33
- ← Me-Cl-COL + NaClO_4 , 27
- ← Me-Cl-COL + NaHCO_3 ,
Na-lactate, NaMnO_4 ,
 NaNO_3 , Na_2SO_4 , Na-urate,
27
- ← Me-Cl-COL + NH_4Cl , RbCl ,
33
- ← papain, 105
- mortality
- ← DHT, 96
- ← Me-Cl-COL, 20
- ← Me-Cl-COL + CaCl_2 , KCl , 33
- ← Me-Cl-COL + KCl , 37, 41
- ← Me-Cl-COL + $\text{KCl} + \text{MgCl}_2$,
41
- ← Me-Cl-COL + KClO_4 ,
 KH_2PO_4 , KHSO_4 , KNO_3 ,
 $\text{KOOC}\cdot\text{CH}_3$, 37
- ← Me-Cl-COL + MgCl_2 , 33, 37,
41
- ← Me-Cl-COL + $\text{Mg}(\text{ClO}_4)_2$,
 $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$,
 $\text{Mg}(\text{OOC}\cdot\text{CH}_3)_2$, MgSO_4 ,
37
- ← Me-Cl-COL + MnCl_2 , 33
- ← Me-Cl-COL + Na-acetate,
Na-citrate, 27
- ← Me-Cl-COL + NaCl , 27,
33
- ← Me-Cl-COL + NaClO_4 ,
 NaHCO_3 , Na-lactate,
 NaMnO_4 , NaNO_3 , Na_2SO_4 ,
Na-urate, 27
- ← Me-Cl-COL + NH_4Cl , RbCl ,
33

 Na_2HPO_4 —Continued

- mortality—Continued
 - ← Me-Cl-COL + NaClO_4 , 27
 - ← Me-Cl-COL + NaHCO_3 , Na-
lactate, NaMnO_4 , NaNO_3 ,
 Na_2SO_4 , Na-urate, 27
 - ← Me-Cl-COL + NH_4Cl , RbCl ,
33
 - muscles ← K-deficiency, 31
 - nephrocalcinosis, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 20
 - ← Me-Cl-COL + CaCl_2 , 33
 - ← Me-Cl-COL + KCl , 33, 37,
41
 - ← Me-Cl-COL + $\text{KCl} + \text{MgCl}_2$,
41
 - ← Me-Cl-COL + KClO_4 ,
 KH_2PO_4 , KHSO_4 , KNO_3 ,
 $\text{KOOC}\cdot\text{CH}_3$, 37
 - ← Me-Cl-COL + MgCl_2 , 33, 37,
41
 - ← Me-Cl-COL + $\text{Mg}(\text{ClO}_4)_2$,
 $\text{MgH}_4(\text{PO}_4)_2$, $\text{Mg}(\text{NO}_3)_2$,
 $\text{Mg}(\text{OOC}\cdot\text{CH}_3)_2$, MgSO_4 ,
37
 - ← Me-Cl-COL + MnCl_2 , 33
 - ← Me-Cl-COL + Na-acetate,
Na-citrate, 27
 - ← Me-Cl-COL + NaCl , 27,
33
 - ← Me-Cl-COL + NaClO_4 ,
 NaHCO_3 , Na-lactate,
 NaMnO_4 , NaNO_3 , Na_2SO_4 ,
Na-urate, 27
 - ← Me-Cl-COL + NH_4Cl , RbCl ,
33
- NaH_2PO_4
- heart, 23
 - ← Me-Cl-COL, 18, 20
 - liver, mortality ← Me-Cl-COL,
20
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 20
- NaH_2PO_3
- heart, 23
 - ← Me-Cl-COL, 18, 20
 - liver, mortality ← Me-Cl-COL,
20
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 20
- NaH_2PO_4
- aorta
 - ← DHT, 96
 - DHT + KCl , MgCl_2 , Fig. 15

NaH₂PO₄—Continued

- arteriosclerosis
 - ← DHT + KCl, MgCl₂, 91
 - ← Me-Cl-COL + DHT + KCl, MgCl₂, 94
- blood pressure ← Me-Cl-COL, 47
- Ca in heart, Ca in serum ← Me-Cl-COL, 49
- coronaries
 - ← DHT, **Fig. 16**
 - ← Me-Cl-COL + DHT, **Figs. 13, 14**
- coronary arteries ← Me-Cl-COL + DHT pretreatment, 94
- ECG ← Me-Cl-COL, **45**
- heart, 23, 78
 - ← acetoxy pregneneolone, 72
 - ← 17-acetoxy-progesterone, 69
 - ← ACTH, 82
 - ← adrenalectomy + Me-Cl-COL, 84
 - ← adrenosterone, 66
 - ← 12α-bromo-11β-hydroxyprogesterone, bromoxoprogesterone, 70
 - ← 4-chloro-adrenosterone, 4-chloro-testosterone, 67
 - ← Cl-COL, 64, 71
 - ← cortisol, 69
 - ← cortisol + DHT, 92
 - ← cortisol + restraint, 144, **Fig. 5**
 - ← Δ¹-cortisol, 72
 - ← cortisone, 65, 70
 - ← Δ¹-cortisone, 72
 - ← dehydro-iso-androsterone, 67
 - ← desoxycortisol, 69
 - ← DHT, 91, 96, **Fig. 12**
 - ← DHT + blood-letting, 115
 - ← DHT + KCl, 91
 - ← DHT + Me-Cl-COL, **Fig. 13**
 - ← DHT pretreatment + Me-Cl-COL, 93, 94
 - ← DHT + MgCl₂, 91
 - ← DOC, 65, 69
 - ← DOC + DHT, 92
 - ← DOC + restraint, 144
 - ← DOC + restraint in rat and monkey, 117
 - ← estradiol, 66
 - ← ethynodiol, ethynodiol, ethynodiol, ethynodiol, 77
 - ← ethylandrostenediol, 76

NaH₂PO₄—Continued

- heart—Continued
 - ← 17α-ethyl-Δ⁴-androstene-3-one-11β, 17β-diol, 77
 - ← ethylandrostenolone, ethyl-nortestosterone, 76
 - ← F-COL, 64, 71
 - ← 9α-fluoro-11β-hydroxyprogesterone, 70
 - ← 16α-hydroxy-9α-fluorocortisol, 71
 - ← 11β-hydroxy-methyltestosterone, 68
 - ← 11-ketoprogesterone, 69
 - ← Me-Cl-COL, 17, 18, 20, 40, 73, Figs. 1-4, 17, 18
 - ← Me-Cl-COL in monkey, **Fig. 6**
 - ← Me-Cl-COL + adrenaline, 85, 144
 - ← Me-Cl-COL + age, 139
 - ← Me-Cl-COL + beans, 142
 - ← Me-Cl-COL + blood-letting, 114, 151
 - ← Me-Cl-COL + bone fractures, 144
 - ← Me-Cl-COL + casein, 142
 - ← Me-Cl-COL + cold baths, 114, 144
 - ← Me-Cl-COL + corn, 142
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + DHT in mouse, rabbit, dog, rat and hamster, 91
 - ← Me-Cl-COL + DHT + KCl, 91, 94
 - ← Me-Cl-COL + DHT + MgCl₂, 91
 - ← Me-Cl-COL + genetics, species, 141
 - ← Me-Cl-COL + glucose, 103
 - ← Me-Cl-COL + hot baths, 114
 - ← Me-Cl-COL + hypophysectomy, 82
 - ← Me-Cl-COL + KH₂PO₄, 39
 - ← Me-Cl-COL + kidney diet, lard, lentils, liver diet, meat, 142
 - ← Me-Cl-COL + trauma, 144
 - ← Me-Cl-COL + uninephrectomy, 113
 - ← Me-Cl-COL + vagotomy, 119, 144
 - ← Me-Cl-COL + vasopressin, 84
 - ← 6-Me-COL, 75
 - ← Medrol + DHT, 92

NaH₂PO₄—Continued

- heart—Continued
 - ← Me-F-COL, 64, 73
 - ← 6-Me-9F-COL, 75
 - ← methylandrostanetriol, 67
 - ← 6α-methyl-21-desoxycortisol, 74
 - ← 6α-methyl-21-desoxycortisol + DHT, 92
 - ← 6α-methyl-11β-hydroxyprogesterone, 74
 - ← 6α-methyl-11-ketoprogesterone, 74
 - ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-9α, 21-difluoro-11β, 17α-diol, 76
 - ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-11β, 17α-diol-21-fluorine, 75
 - ← 6α-methyl-Δ⁴-pregnen-3, 20-dione-9α, 21-difluoro-11β, 17α-diol, 74
 - ← 2α-methyl-Δ⁴-pregnen-3, 20-dione-9, 11β-oxido-17α, 21-diol-21-acetate, 73
 - ← methyltestosterone, 67
 - ← parathyroid extract, 89
 - ← parathyroid extract + KCl, MgCl₂, 89
 - ← plasmocid, 110
 - ← pregnanedione, 68
 - ← Me-Cl-COL + kidney-diet, lard, lentils, liver-diet, meat, 142
 - ← Me-Cl-COL + peas, potatoes, 142
 - ← Me-Cl-COL + pregnancy, 140
 - ← Me-Cl-COL + pylorus ligation, 113
 - ← Me-Cl-COL + restraint, 117, 143
 - ← Me-Cl-COL + rice, 142
 - ← Me-Cl-COL + sex, 140
 - ← Me-Cl-COL + spinal-cord transection, 119
 - ← Me-Cl-COL + spleen diet, starch, 142
 - ← Me-Cl-COL + trauma (systemic), 114
 - ← methylandrostenediol, 68
 - ← Me-Cl-COL + NaClO₄, NaHSO₄, 40
 - ← Me-Cl-COL + nephrectomy, 113

NaH₂PO₄—Continued

- heart—Continued
 - ← Me-Cl-COL + neuromuscular exertion, 143
 - ← Me-Cl-COL + nerve, nerve transection, 119, 144
 - ← Me-Cl-COL + noradrenaline, 86
 - ← Me-Cl-COL + papain, Fig. 11
 - ← Me-Cl-COL + papain + MgCl₂, Fig. 11
 - ← Me-Cl-COL + parathyroidectomy, 89
 - ← pregnenolone, 71
 - ← progesterone, 68
 - ← propyldihydronortestosterone, 77
 - ← testosterone, 66
 - ← thyroparathyroidectomy + Me-Cl-COL, 89
 - ← triamcinolone, 65, 73
 - ← triamcinolone + DHT, 92
 - K in heart, muscles, serum ← Me-Cl-COL, 49
 - kidney ← ACTH, 82
 - ← DOC, 65
 - liver
 - ← acetoxy pregnenolone, 72
 - ← 17-acetoxy-progesterone, 69
 - ← adrenosterone, 66
 - ← 12α-bromo-11β-hydroxyprogesterone, bromoxoprogesterone, 70
 - ← 4-chloro-adrenosterone, 4-chlorotestosterone, 67
 - ← Cl-COL, 71
 - ← cortisol, 69
 - ← Δ¹-cortisol, 72
 - ← cortisone, 70
 - ← Δ¹-cortisone, 72
 - ← dehydro-iso-androsterone, 67
 - ← desoxycortisol, DOC, 69
 - ← estradiol, estrone, 66
 - ← ethinyl androstenediol, ethinyltestosterone, 77
 - ← ethylandrostenediol, 76
 - ← 17α-ethyl-Δ⁴-androstene-3-one-11β, 17β-diol, 77
 - ← ethylandrostenolone, ethynortestosterone, 76
 - ← F-COL, 71
 - ← 9α-fluoro-11β-hydroxyprogesterone, 70

NaH_2PO_4 —Continued

- liver—Continued
 - ← 16 α -hydroxy-9 α -fluorocortisol, 71
 - ← 11 β -hydroxy-methyltestosterone, 68
 - ← 11-ketoprogesterone, 69
 - ← Me-Cl-COL, 20, 40, 73
 - ← Me-Cl-COL + KH₂PO₄, 39
 - ← Me-Cl-COL + NaClO₄, NaHSO₄, 40
 - ← 6-Me-COL, 75
 - ← Me-F-COL, 73
 - ← 6-Me-9F-COL, 75
 - ← methylandrostanetriol, 67
 - ← methylandrostenediol, 68
 - ← 6 α -methyl-21-desoxycortisol, 6 α -methyl-11 β -hydroxyprogesterone, 6 α -methyl-11-ketoprogesterone, 74
 - ← 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-3, 20-dione-11 β , 17 α -diol-21-fluorine, 6 α -methyl- Δ^4 -pregnen-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol, 75
 - ← 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol, 76
 - ← 2 α -methyl- Δ^4 -pregnene-3, 20-dione-9, 11 β -oxido-17 α , 21-diol-21-acetate, 73
 - ← methyltestosterone, 67
 - ← pregnanedione, 68
 - ← pregneneolone, 71
 - ← progesterone, 68
 - ← propyldihydronortestosterone, 77
 - ← testosterone, 66
 - ← triamcinolone, 73
 - Mg in heart ← Me-Cl-COL, 49
 - mortality
 - ← acetoxy pregneneolone, 72
 - ← 17-acetoxy-progesterone, 69
 - ← adrenosterone, 66
 - ← 12 α -bromo-11 β -hydroxyprogesterone, bromoxoprogesterone, 70
 - ← 4-chloro-adrenosterone, 4-chlorotestosterone, 67
 - ← Cl-COL, 71
 - ← cortisol, 69
 - ← Δ^1 -cortisol, 72
 - ← cortisone, 70
 - ← Δ^1 -cortisone, 72
 - ← dehydro-iso-androsterone, 67

 NaH_2PO_4 —Continued

- mortality—Continued
 - ← desoxycortisol, 69
 - ← DHT, 96
 - ← DOC, 69
 - ← estradiol, estrone, 66
 - ← ethinylandrostenediol, ethinyl-testosterone, 77
 - ← ethylandrostendiol, 76
 - ← 17 α -ethyl- Δ^4 -androstene-3-one-11 β , 17 β -diol, 77
 - ← ethylandrostenolone, ethyl-nortestosterone, 76
 - ← F-COL, 71
 - ← 9 α -fluoro-11 β -hydroxyprogesterone, 70
 - ← 16 α -hydroxy-9 β -fluorocortisol, 71
 - ← 11 α -hydroxy-methyltestosterone, 68
 - ← 11-ketoprogesterone, 69
 - ← Me-Cl-COL, 20, 40, 73
 - ← Me-Cl-COL + KH₂PO₄, 39
 - ← Me-Cl-COL + NaClO₄, NaHSO₄, 40
 - ← Me-Cl-COL + NaHSO₄ + NaClO₄, 40
 - ← 6-Me-COL, 75
 - ← Me-F-COL, 73
 - ← 6-Me-9F-COL, 75
 - ← methylandrostanetriol, 67
 - ← methylandrostenediol, 68
 - ← 6 α -methyl-21-desoxycortisol, 6 α -methyl-11 β -hydroxyprogesterone, 6 α -methyl-11-ketoprogesterone, 74
 - ← 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol, 76
 - ← 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-3, 20-dione-11 β , 17 α -diol-21-fluorine, 6 α -methyl- Δ^4 -pregnen-3, 20-dione-9 α , 21-difluoro-11 β , 17 α -diol, 75
 - ← 2 α -methyl- Δ^4 -pregnene-3, 20-dione-9, 11 β -oxido-17 α , 21-diol-21-acetate, 73
 - ← methyltestosterone, 67
 - ← pregnanedione, 68
 - ← pregneneolone, 71
 - ← progesterone, 68
 - ← propyldihydronortestosterone, 77
 - ← testosterone, 66
 - ← triamcinolone, 73

NaH₂PO₄—Continued

- Na in heart, muscles, serum ← Me-Cl-COL, 49
- nephrocalcinosis, 23
 - ← acetoxy pregneneolone, 72
 - ← 17-acetoxyprogesterone, 69
 - ← adrenosterone, 66
 - ← 12α-bromo-11β-hydroxyprogesterone, bromoxoprogesterone, 70
 - ← 4-chloro-adrenosterone, 4-chloro-testosterone, 6
 - ← Cl-COL, 71
 - ← cortisol, 69
 - ← Δ¹-cortisol, 72
 - ← cortisone, 70
 - ← Δ¹-cortisone, 72
 - ← dehydro-iso-androsterone, 67
 - ← desoxycortisol, 69
 - ← DHT, 96
 - ← DOC, 69
 - ← estradiol, estrone, 66
 - ← ethinyl androstenediol, 17α-ethyl-Δ⁴-androstene-3-one-11β, 17β-diol, 77
 - ← ethylandrostendiol, ethylandrostenolone, ethynortestosterone, 76
 - ← ethinyltestosterone, 77
 - ← F-COL, 71
 - ← 9α-fluoro-11β-hydroxyprogesterone, 70
 - ← 16α-hydroxy-9α-fluorocortisol, 71
 - ← 11β-hydroxy-methyltestosterone, 68
 - ← 11-ketoprogesterone, 69
 - ← Me-Cl-COL, 20, 40, 73, **Fig. 7**
 - ← Me-Cl-COL + age, 140
 - ← Me-Cl-COL + beans, 142
 - + Me-Cl-COL + casein, corn, 142
 - ← Me-Cl-COL + glucose, 103
 - ← Me-Cl-COL + KH₂PO₄, 39
 - ← Me-Cl-COL + NaClO₄, NaHSO₄, 40
 - ← Me-Cl-COL + NaHSO₄ + NaClO₄, 40
 - ← Me-Cl-COL + peas, potatoes, 142
 - ← Me-Cl-COL + pregnancy, 140
 - ← Me-Cl-COL + rice, spleen-diet, starch, 142
 - ← 6-Me-COL, 75
 - ← Me-F-COL, 73

NaH₂PO₄—Continued

- ← 6-Me-9F-COL, 75
- ← methylandrostanetriol, 67
- ← methylandrostenediol, 68
- ← 6α-methyl-21-desoxycortisol, 6α-methyl-11β-hydroxyprogesterone, 6α-methyl-11-ketoprogesterone, 74
- ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-9α, 21-difluoro-11β, 17α-diol, 76
- ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-11β, 17α-diol-21-fluorine, 75
- ← 6α-methyl-Δ⁴-pregnene-3, 20-dione-9α, 21-difluoro-11β, 17α-diol, 75
- ← 2α-methyl-Δ⁴-pregnene-3, 20-dione-9, 11β-oxido-17α, 21-diol-21-acetate, 73
- ← methyltestosterone, 67
- ← pregnanedione, 68
- ← pregneneolone, 71
- ← progesterone, 68
- ← propyldihydronortestosterone, 77
- ← testosterone, 66
- ← triamcinolone, 73
- PO₄ in heart, muscles, serum ← Me-Cl-COL, 49
- subendocardial necroses ← cortisol + restraint, **Fig. 8**
- subendocardial necroses + Me-Cl-COL, **Fig. 17**
- subepicardial necrosis ← Me-Cl-COL, **Fig. 18**

NaHSO₄

- heart, 23
- liver, mortality
 - ← Me-Cl-COL, 21
- nephrocalcinosis, 23

NaHSO₄

- aorta ← DHT, 96
- heart, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 20, 40
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + NaClO₄, NaH₂PO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaClO₄, 40
- liver
 - ← Me-Cl-COL, 20, 40
 - ← Me-Cl-COL + NaClO₄, NaH₂PO₄, 40

- NaHSO₄.—Continued**
- mortality
 - ← DHT, 93
 - ← Me-Cl-COL, 20, 40
 - ← Me-Cl-COL + NaClO₄, NaH₂PO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaClO₄, 40
 - nephrocalcinosis, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 20, 40
 - ← Me-Cl-COL + NaClO₄, NaH₂PO₄, 40
 - ← Me-Cl-COL + NaH₂PO₄ + NaClO₄, 40
- NaI**
- heart, 107
 - ← thyroidectomy, 87
- NaKHPO₄** → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 39
- NaMnO₄**
- heart, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - liver
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - mortality
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- NaNO₃**
- aorta ← DHT, 96
 - heart, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - liver
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - nephrocalcinosis, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 21
 - ← Me-Cl-COL + Na₂HPO₄, 27
- NaOH**
- heart, 23
- liver, mortality ← Me-Cl-COL, 21
- nephrocalcinosis, 23
- ← Me-Cl-COL, 21
- NaOOC·CH₃; see Na-acetate**
- (NaPO₃)_n
- heart, 23
 - ← Me-Cl-COL, 18, 20
 - liver, mortality ← Me-Cl-COL, 20
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 20
- Na₃PO₄**
- heart, 23
 - liver, mortality ← Me-Cl-COL, 20
 - nephrocalcinosis, 20, 23
- Na₄P₂O₇**
- heart, 23
 - ← Me-Cl-COL, 18, 20
 - liver, mortality ← Me-Cl-COL, 20
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 20
- Na₄P₂O₇**
- heart, 23
 - ← Me-Cl-COL, 18, 20
 - liver, mortality ← Me-Cl-COL, 20
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 20
- Na₂SO₃**
- heart, 23
 - liver, mortality ← Me-Cl-COL, 21
 - nephrocalcinosis, 23
 - ← Me-Cl-COL, 21
- Na₂SO₄**
- aorta ← DHT, 96
 - heart, 23
 - ← adrenaline, 86
 - ← cold baths, 149
 - ← DHT, 96
 - ← DOC + uninephrectomy + NaCl, 61
 - ← hepatectomy (partial) + Me-Cl-COL, 113
 - ← K-deficiency, 31
 - ← Me-Cl-COL, 21, 35
 - ← Me-Cl-COL + DHT, 92
 - ← Me-Cl-COL + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
 - kidney ← DOC + uninephrectomy + NaCl, 61

Na₂SO₄—Continued

- liver
 - ← Me-Cl-COL, 21, 35
 - ← Me-Cl-COL + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
- mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 21, 35
 - ← Me-Cl-COL + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27
- muscles ← K-deficiency, 31
- nephrocalcinosis, 23
 - ← DHT, 96
 - ← Me-Cl-COL, 21, 35
 - ← Me-Cl-COL + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - ← Me-Cl-COL + Na₂HPO₄, 27

Necrotizing myocarditis ⇌ cardiac infarcts, 157

Nephrectomy

- heart, 113
- ← adrenalectomy + parathyroid extract, 84
- ← adrenalectomy + parathyroid extract + corticoids, 84
- ← DOC, 82, 113
- ← Me-Cl-COL, 82, 89, 113
- ← Me-Cl-COL + NaH₂PO₄, 113
- ← Me-Cl-COL + parathyroidectomy, thyroidectomy, 89
- ← parathyroidectomy, 89, 113

Nephrocalcinosis

- ← acetoxy pregneneolone + NaH₂PO₄, 72
- ← 17-acetoxyprogesterone + NaH₂PO₄, 69
- ← adrenosterone + NaH₂PO₄, 66
- ← 12α-bromo-11β-hydroxyprogesterone, bromoxoprogesterone + NaH₂PO₄, 70
- ← 4-chloro-adrenosterone, 4-chlorotestosterone + NaH₂PO₄, 67
- ← Cl-COL + NaH₂PO₄, 71
- ← cortisol + NaH₂PO₄, 69
- ← Δ¹-cortisol + NaH₂PO₄, 72
- ← cortisone + NaH₂PO₄, 70
- ← Δ¹-cortisone + NaH₂PO₄, 72
- ← dehydro-iso-androsterone + NaH₂PO₄, 67
- ← desoxycortisol + NaH₂PO₄, 69
- ← DHT + Ca-acetate, CaCl₂, CaH₄(PO₄)₂, Ca(NO₃)₂, K-acetate, KCl, KClO₄, K₂HPO₄,

Nephrocalcinosis—Continued

- KH₂PO₄, KHSO₄, KNO₃, K₂SO₄, Mg-acetate, MgCl₂, Mg(ClO₄)₂, MgH₄(PO₄)₂, Mg(NO₃)₂, MgSO₄, Na-acetate, NaCl, NaClO₄, Na₂HPO₄, NaHSO₄, NaNO₃, Na₂SO₄, NH₄-acetate, NH₄Cl, NH₄ClO₄, NH₄H₂PO₄, NH₄HSO₄, NH₄NO₃, 96
- ← DOC + NaH₂PO₄, 69
- ← estradiol, estrone + NaH₂PO₄, 66
- ← ethinyl androstenediol, ethinyltestosterone, 17α-ethyl-Δ⁴-androstene-3-one-11β, 17β-diol + NaH₂PO₄, 77
- ← ethylandrostendiol, ethylandrostenolone, ethynortestosterone + NaH₂PO₄, 76
- ← F-COL + NaH₂PO₄, 71
- ← 9α-fluoro-11β-hydroxyprogesterone + NaH₂PO₄, 70
- ← H₂O, 23
- ← 16α-hydroxy-9β-fluorocortisol + NaH₂PO₄, 71
- ← 11α-hydroxy-methyltestosterone + NaH₂PO₄, 68
- ← 11-ketoprogestrone + NaH₂PO₄, 69
- ← Me-Cl-COL
 - + Al₂(SO₄)₃, CaH₄(PO₄)₂, 25
 - + H₂O, 20
 - + KClO₄, K₂HPO₄, KH₂PO₄, KHSO₄, Li₂PO₄, Li₂SO₄, Mg(ClO₄)₂, MgH₄(PO₄)₂, MgSO₄, MnSO₄, 25
 - + Na-citrate, 21
 - + NaCl, 20
 - + NaClO₄, 20, 35, 40
 - + NaClO₄ + KCl, KClO₄, MgCl₂, Mg(ClO₄)₂, NaCl, 35
 - + Na₂CO₃, NaHCO₃, 21
 - + Na₂HPO₄, Na₂HPO₄, 20
 - + Na₂HPO₄ + CaCl₂, 33
 - + Na₂HPO₄ + KCl, 33, 37, 41
 - + Na₂HPO₄ + KCl + MgCl₂, 41
 - + Na₂HPO₄ + KClO₄, KH₂PO₄, KHSO₄, KNO₃, KOOC·CH₃, 37
 - + Na₂HPO₄ + MgCl₂, 33, 37, 41
 - + Na₂HPO₄ + Mg(ClO₄)₂, MgH₄(PO₄)₂, Mg(NO₃)₂, Mg(OOC·CH₃)₂, MgSO₄, 37

Nephrocalcinosis—Continued

- ← Me-Cl-COL—Continued
 - + Na₂HPO₄ + MnCl₂, 33
 - + Na₂HPO₄ + Na-acetate, Na-citrate, 27
 - + Na₂HPO₄ + NaCl, 27, 33
 - + Na₂HPO₄ + NaClO₄, NaHCO₃, Na-lactate, NaMnO₄, NaNO₃, Na₂SO₄, Na-urate, 27
 - + Na₂HPO₄ + NH₄Cl, RbCl, 33
 - + NaH₂PO₂, NaH₂PO₃, 20
 - + NaH₂PO₄, 20, 40, 73, Fig. 7
 - + NaH₂PO₄ + beans, casein, corn, 142
 - + NaH₂PO₄ + glucose, 103
 - + NaH₂PO₄ + KH₂PO₄, 39
 - + NaH₂PO₄ + kidney diet, lard, lentils, liver diet, meat, 142
 - + NaH₂PO₄ + NaClO₄, NaHSO₄, 40
 - + NaH₂PO₄ + NaHSO₄ + NaClO₄, 40
 - + NaH₂PO₄ + peas, potatoes, 142
 - + NaH₂PO₄ + pregnancy, 140
 - + NaH₂PO₄ + rice, spleen diet, starch, 142
 - + NaHSO₃, 21
 - + NaHSO₄, 20, 40
 - + NaHSO₄ + NaClO₄, 40
 - + NaKHPO₄, 39
 - + Na-lactate, NaMnO₄, NaNO₃, NaOH, NaOOC·CH₃, 21
 - + (NaPO₃)₆, Na₃PO₄, Na₄P₂O₇, 20
 - + Na₂SO₃, 21
 - + Na₂SO₄, 21, 35
 - + Na₂SO₄ + KCl, KHSO₄, MgCl₂, MgSO₄, NaCl, 35
 - + Na-tartrate, Na-urate, 21
 - + (NH₄)₂HPO₄, NH₄H₂PO₄, NH₄HSO₄, 25
 - + phosphates, 18
 - + RbClO₄, RbHSO₄, Rb₂SO₄, 25
 - ← 6-Me-COL + NaH₂PO₄, 75
 - ← Me-F-COL + NaH₂PO₄, 73
 - ← 6-Me-9F-COL + NaH₂PO₄, 75
 - ← 6α-methyl-21-desoxycortisol, 6α-methyl-11β-hydroxyprogesterone, 6α-methyl-11-keto-progesterone + NaH₂PO₄, 74
 - ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-9α, 21-difluoro-11β, 17α-diol + NaH₂PO₄, 76

Nephrocalcinosis—Continued

- ← 6α-methyl-Δ^{1,4}-pregnadiene-3, 20-dione-11β, 17α-diol-21-fluorine, 2α-methyl-Δ⁴-pregnene-3, 20-dione-9, 11β-oxido-17α, 21-diol-21-acetate + NaH₂PO₄, 75
- ← 2α-methyl-Δ⁴-pregnene-3, 20-dione-9, 11β-oxido-17α, 21-diol-21-acetate + NaH₂PO₄, 73
- ← methylandrostanetriol + NaH₂PO₄, 67
- ← methylandrostenediol + NaH₂PO₄, 68
- ← methyltestosterone + NaH₂PO₄, 67
- ← Mg-deficiency, 31
- ← Na-citrate, NaCl, NaClO₄, Na₂CO₃, NaHCO₃, Na₂HPO₃, NaH₂PO₂, NaH₂PO₃, NaH₂PO₄, 23
- ← Na-tartrate, Na-urate, 23
- ← NaH₂PO₄ + Me-Cl-COL + age, 140
- ← NaHSO₃, NaHSO₄, Na-lactate, NaMnO₄, NaNO₃, NaOH, NaOOC·CH₃, Na₃PO₄, Na₄P₂O₆, Na₄P₂O₇, (NaPO₃)₆, Na₂SO₃, Na₂SO₄, 23
- ← pregnenolone + NaH₂PO₄, 71
- ← progesterone, pregnanedione + NaH₂PO₄, 68
- ← propyldihydronortestosterone + NaH₂PO₄, 77
- ← testosterone + NaH₂PO₄, 66
- ← triamcinolone + NaH₂PO₄, 73
- ⇒ ESCN, 50
- Nephrosclerosis ← DOC + NaCl, 10, 50
- Nerve transection
 - heart, 146
 - ← Me-Cl-COL, 119, 146
 - ← Me-Cl-COL + NaH₂PO₄, 119, 144
 - ← Me-Cl-COL + Na₂HPO₄ + KCl, MgCl₂, 120
- Nervous diseases → heart, 136
- Neuromuscular exertion → heart ← NaH₂PO₄ + Me-Cl-COL, 143
- NH₄-acetate → aorta, heart, mortality, nephrocalcinosis ← DHT, 96
- NH₄Cl → aorta, heart ← DHT, 96
 - heart
 - ← DOC + NaCl, 63

- NH₄Cl—Continued**
- heart—Continued
 - ← DOC + uninephrectomy + NaCl, 61
 - ← Me-Cl-COL + Na₂HPO₄, 33
 - kidney
 - ← DOC + NaCl, 63
 - ← DOC + uninephrectomy + NaCl, 61
 - liver ← Me-Cl-COL + Na₂HPO₄, 33
 - mortality
 - ← DHT, 96
 - ← Me-Cl-COL + Na₂HPO₄, 33
 - nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL + Na₂HPO₄, 33
- NH₄ClO₄**
- aorta, heart, mortality, nephrocalcinosis ← DHT, 96
 - heart
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + DHT, 92
 - liver, mortality, nephrocalcinosis
 - ← Me-Cl-COL, 25
- NH₄H₂PO₄**
- aorta, heart ← DHT, 96
 - heart, liver ← Me-Cl-COL, 25
 - mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
- NH₄HSO₄**
- aorta, heart ← DHT, 96
 - heart
 - ← Me-Cl-COL, 25
 - ← Me-Cl-COL + DHT, 92
 - liver ← Me-Cl-COL, 25
 - mortality
 - ← DHT, 96
 - ← Me-Cl-COL, 25
 - nephrocalcinosis
 - ← DHT, 96
 - ← Me-Cl-COL, 25
- NH₄NO₃**
- aorta, heart ← DHT, 96
 - kidney ← DOC + uninephrectomy + NaCl, 61
 - mortality, nephrocalcinosis ← DHT, 96
- (NH₄)₂SO₄ → kidney ← DOC + uninephrectomy + NaCl, 61
- Nicotinamide → heart ← Pearce's virus III, 151
- Noradrenaline**
- heart, 147
 - ← blood-letting, 86
 - ← Me-Cl-COL, 147
 - ← Me-Cl-COL + NaH₂PO₄, 86
 - ← papain, 106
 - ← plasmocid, 110
 - ← thyroxin, 88
 - ← triamcinolone, 84
- Orthostatic collapse → heart, 117
- Orthostatic hypotension → heart, 151
- Overeating → heart, 141
- Oxalacetate in heart, 163
- Oxidase in heart ← diphtheria toxin, 124
- Oxygen deficiency → heart, 115
- Pancreatitis → heart, 136
- Papain**
- heart, 104, **Fig. 11**
 - ← blood-letting, 106
 - ← KCl, 105
 - ← K-deficiency, 106
 - ← K-deficiency + MgCl₂, 106
 - ← Me-Cl-COL, 105
 - ← Me-Cl-COL + NaH₂PO₄, **Fig. 11**
 - ← Me-Cl-COL + NaH₂PO₄ + MgCl₂, **Fig. 11**
 - ← MgCl₂, 105
 - ← Mg-deficiency, 106
 - ← Mg-deficiency + KCl, 106
 - ← Na₂HPO₄, 105
 - ← noradrenaline, 106
 - ← restraint, 106
 - K in blood, 105
 - liver ← KCl, Me-Cl-COL, MgCl₂, Na₂HPO₄, 105
- Papaverine → heart ← Pearce's virus III, 151
- Paracolobactrum coliforme** → heart, liver, 139
- Parathyroidectomy**
- heart ← Me-Cl-COL + NaH₂PO₄, nephrectomy, 89
 - ← nephrectomy, 89, 113
- Parathyroid extract**
- heart
 - ← adrenalectomy + nephrectomy, 84
 - ← adrenalectomy + nephrectomy + corticoids, 84

- Parathyroid extract—Continued
heart—Continued
 ← KCl, MgCl₂, 90
 ← NaH₂PO₄, 89
 ← NaH₂PO₄ + KCl, MgCl₂, 89
- Pasteurella pseudotuberculosis* → heart, liver, 139
- Pathogenic constellations (theory), 156
- Pathologic chemistry of cardiac failure, ESCN, 161
- Pearce's virus III
 → heart, 85
 ← barium, 103
 ← barium chloride, adrenaline, vasopressin, gum acacia, 151
 ← cardiac puncture, 112
 ← chloroform, corn syrup, nicotinamide, digitalis, papaverine, saline, 151
 ← gum acacia, 107
 ← vasopressin, 83
- Peas → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
- Pentamethylenetetrazol
 → heart, 147, 109
 ← Me-Cl-COL, 147
- Peptone → heart, 109
- Periarthritis
 ← DOC + NaCl, 10, 60
 ← DOC + NaCl + KCl, 63
- pH → heart, 18
- Phagocytes in heart ← thyroid hormone, 87
- Phosphates → nephrocalcinosis ← Me-Cl-COL, 18
- "Physiologically balanced" salt solutions, 4
- Picrotoxin
 → heart, 147
 ← Me-Cl-COL, 147
- Pig, heart disease in, 97
- Plasmocid
 → heart, 109
 ← blood-letting, 110
 ← Na₂HPO₄, NaH₂PO₄, 110
 ← noradrenaline, 110
- Plastic beads intravenously → heart, 112
- PO₄ in heart, muscles, serum ← Me-Cl-COL + NaH₂PO₄, 49
- Poliomyelitis → heart, 125
- Potassium; see K
- Potatoes → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
- Pregnancy
 → heart ← DHT, 140
 ← Me-Cl-COL + NaH₂PO₄, 140
 ← renal lesions + lipids, 140
 → nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 140
 → vessels ← DHT, 140
- Pregnanedione → heart, liver, mortality, nephrosclerosis ← NaH₂PO₄, 68
- Pregneneolone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 71
- Progesterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 68
- Progesterone (*in vitro*) → heart, 47
- Propyldihydronortestosterone → heart, liver, mortality, nephrocalcinosis ← NaH₂PO₄, 77
- Pseudomonas aeruginosa* → heart ← Me-Cl-COL, 147
- Psyche → heart, 119
- "Puerperal myocarditis," 140
- Pulmonary disease → heart, 135
- Pulmonary emboli → ECG, heart, 112, 126
- Pylorus ligature → heart, 113
 ← Me-Cl-COL + NaH₂PO₄, 113
- Quadriplegia induced by nerve transections; see Nerve transection
- Quantitative relationships between sensitizing and desensitizing salts, 39
- RbCl → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL + Na₂HPO₄, 33
- RbClO₄ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25
- RbHSO₄ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25
- Rb₂SO₄ → heart, liver, mortality, nephrocalcinosis ← Me-Cl-COL, 25
- Regional ileitis, 139, Figs. 19, 20
- Renal arteries (constriction)
 → heart, 113
 ← rutin, 113
- Renal hypertension, 46
 → blood pressure + K-deficiency, 46

- Renal injury → heart ← lipids, 108
 Renal lesions → heart ← lipids + pregnancy, 140
 Repeated pregnancies → heart ← ACTH, 82
 Restraint
 → heart, 117, 146, 152
 ← cortisol + NaH₂PO₄, 144, Fig. 5
 ← DHT, 91
 ← DOC + NaH₂PO₄, 144
 ← DOC + NaH₂PO₄ in rat and monkey, 117
 ← Me-Cl-COL, 117, 146
 ← Me-Cl-COL in rat and monkey, 118
 ← Me-Cl-COL + KCl, MgCl₂ (during restraint only), 122
 ← Me-Cl-COL + NaH₂PO₄, 117
 ← NaCl, 149
 ← NaH₂PO₄ + Me-Cl-COL, 143
 ← papain, 106
 ← thyroxin, 88
 → subendocardial necroses ← cortisol + NaH₂PO₄, Fig. 8
 Rheumatic carditis ← ACTH, 58
 Rheumatic carditis ⇌ ESCH, 10
 Rice → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
 Ringer solution, 5
 Rocky Mountain spotted fever → heart, 125
 Rubidium; *see* Rb
 Rutin → heart ← constriction of renal arteries, 113

 Saline → heart ← Pearce's virus III, 151
 Salt solutions, "physiologically balanced," 4
 Scrub typhus → heart, 125
 Selenium → heart ← vitamin-E, 110
 Sensitizing electrolytes → heart, 17
 Sex → heart ← Me-Cl-COL + NaH₂PO₄, 140
 "Shwartzman reaction" → ECG, heart, 126
 Silver fox, heart disease in, 97
 Silver nitrate, topical → heart, 112
 Site of interaction between sensitizing and desensitizing electrolytes, 42
 Skin diseases → heart, 136
 Sodium; *see* Na
 Sparteine → heart ← adrenaline, 85

 Species → heart ← Me-Cl-COL + NaH₂PO₄, 141
 Spinal-cord transection
 → heart, 146
 ← Me-Cl-COL, 119, 146
 ← Me-Cl-COL + NaH₂PO₄, 119
 Spleen diet → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
 Spontaneous diseases → heart, 126
 "Spotty myolysis," 123, 133
 "Staircase phenomenon of Bowditch," 47
 Standardized experimental technique for study of ESCN, 19
 Starch → heart, nephrocalcinosis ← Me-Cl-COL + NaH₂PO₄, 142
 Starvation → heart ← DHT, 91
 Status thymicolumphanticus → heart, 136
 Steroid alkylamines, 100
 Steroids (theory) → ESCN, heart 154
 Streptococci → Ca in heart, giant cells in heart, heart, 125
 Streptococcal proteinase → heart, 105
 Streptokinase → heart, 104
 Streptolysin O → heart, 124
 Stress
 (theory) → ESCN, 154
 (theory) → heart, 154
 (of battle) → heart, 128
 → heart, 143
 ← corticoids, 12
 ← DOC, 56
 history, 12
 → Na-metabolism, 149
 Stressors → heart ← thyroxin, 88
 Strophanthin-G → heart, 48
 Subacute primary myocarditis, 133
 Subendocardial infarcts in man, 127
 Subendocardial necroses, 133, Fig. 5
 ← cortisol + NaH₂PO₄ + restraint, Fig. 8
 ← Me-Cl-COL + NaH₂PO₄, Fig. 17
 Subepicardial necrosis ← Me-Cl-COL + NaH₂PO₄, Fig. 18
 Succinylsulfathiazole → heart, 110
 Sulfa drugs → heart ← vitamin-E, vitamin-K, 110
 Sulfaguanidine → heart, 110
 Sulfur → heart, 110
 Syphilis → heart, 125

 Technique for demonstration of fuchsinophilic material, 43

- Testosterone → heart, liver, mortality
 ← NaH_2PO_4 , 66
- Theory of cardiac necroses, 150
- Theory of ESCN production, 26
- Thiamine; *see* Vitamin-B₁
- Thrombosis ← corticoids, 57
- Thyroid hormone → histiocytes in heart, 87
- Thyroidectomy
 → heart
 ← Me-Cl-COL + nephrectomy, 89
 ← NaI, 87
- Thyroparathyroidectomy → heart ← Me-Cl-COL + NaH_2PO_4 , 89
- Thyroxin
 → heart, 87
 ← cold, 88
 ← digitalis, 87
 ← lipids, noradrenaline, restraint, stressors, 88
- Thyroxin → Mg-metabolism, mitochondria in heart, 88
- Time relations; *see* Chronology
- Tocopherol; *see* Vitamin-E
- Toxic cardiac necrosis, 5
- Toxic myocardial necroses, 134
- Toxic myocarditis, 133
- Toxins → Fiedler's myocarditis, 132
- Transaminase in heart, 163
- Trauma
 → heart, 114, 147
 ← DHT, 91
 ← Me-Cl-COL, 114, 147
 ← Me-Cl-COL + NaH_2PO_4 , 114, 144
- Triamcinolone
 → heart
 ← adrenaline, cold, 84
 ← DHT + NaClO_4 , NaH_2PO_4 , 92
 ← heat, 84
 ← NaH_2PO_4 , 65, 73
 ← noradrenaline, 84
 → liver, mortality, nephrocalcinosis
 ← NaH_2PO_4 , 73
- Triiodothyronine → electron-microscopy of heart, 87
- Trypsin → heart, 104
- Typhoid bacilli → heart ← adrenaline, 85
- Tyrode solution, 5
- Uninephrectomy
 → heart
 ← DOC, 112
 ← DOC + NaCl, 61
- ← DOC + NaCl + CaCl_2 , KCl,
 MgCl_2 , NaHCO_3 , Na_2SO_4 ,
 NH₄Cl, 61
- ← hypophsectomy + DOC + NaCl, 81
- ← Me-Cl-COL + NaH_2PO_4 , 113
- kidney ← DQC + NaCl + CaCl₂, KCl, MgCl₂, NaHCO₃, Na₂SO₄, NH₄Cl, NH₄NO₃, (NH₄)₂SO₄, 61
- Undernutrition → heart, 141
- Uremia → heart, 135
 → Fiedler's myocarditis, 132
- Uremic cardiopathy, 133
- Vagotomy
 → heart, 146
 ← Me-Cl-COL, 119, 146
 ← Me-Cl-COL + NaH_2PO_4 , 119, 144
 ← Me-Cl-COL + Na_2HPO_4 + KCl, MgCl₂, 120
- Vasocostriction; *see* Blood vessels
- Vasodilatation; *see* Blood vessels
- Vasopressin
 → heart, 83, 147, 152
 ← age, 83
 ← Me-Cl-COL, 83, 147
 ← Me-Cl-COL + NaH_2PO_4 , 84
 ← Pearce's virus III, 83, 151
- Vessels ← DHT + pregnancy, 140
- Virus infections (various) → heart, 125
- Vitamin-B₁ deficiency
 → heart, 97
 → hypokalemia, 97
 in silver fox, etc., 97
- Vitamin-C deficiency → heart, 99
- Vitamin-D
 → heart, 6, 90
 in monkey, 91
 ← muscular exercise, 90
- Vitamin-E; *see also* Tocopherol
 → heart ← dicumarol, 99
 → heart ← selenium, sulfa drugs, 110
 deficiency → heart, 99
- Vitamin-K
 → heart ← dicumarol, 99, 104
 → heart ← sulfa drugs, 110
 deficiency → heart, 99
- Water in heart ← digitalis, 101

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