THE CHEMICAL PREVENTION OF Cardiac Necroses

HANS SELYE – M.D., Ph.D., D.Sc.

PROFESSOR AND DIRECTOR OF THE INSTITUTE OF
EXPERIMENTAL MEDICINE AND SURGERY
UNIVERSITY OF MONTREAL,
CANADA

THE RONALD PRESS COMPANY • NEW YORK

The Chemical Prevention of Cardiac Necroses

HANS SELYE, M.D., PH.D., D.SC.

PROFESSOR AND DIRECTOR OF THE
INSTITUTE OF EXPERIMENTAL MEDICINE AND SURGERY
UNIVERSITY OF MONTREAL
MONTREAL, CANADA

Library of Congress Catalog Card Number: 58–12955

PRINTED IN THE UNITED STATES OF AMERICA

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,

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.

The author welcomes this opportunity to express his gratitude to Mrs. Bridget Sacra, who helped with the editing of the rough draft and supervised the proofreading and checking of the references, assisted by Miss Rosalind Murray, Mrs. Thérèse Peternell, Miss S. Groulx, Miss D. Manseau, Miss C. de Tillieux, Miss G. Emond, Miss D. Doucet, Miss A. Niedre, and Mrs. V. Tomsons. All photographs were prepared by Mr. K. Nielsen, and the drawings by Miss M. Langlois.

HANS SELYE

Montreal, Canada
October, 1958

Contents

Tables

The Chemical Prevention of Cardiac Necroses

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 atheromatosis), 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.

I

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 stepwise, 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 *p*H, 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: $SO_4 < Cl < Br < NO_3 < SCN < I$, and the cations, thus: $Li < Na < Cs < Rb < K$. 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-