

JOURNAL OF THE
American Geriatrics Society

Official Journal of the American Geriatrics Society

Volume XVIII

September 1970

Number 9

STRESS AND AGING*

HANS SELYE, M.D., Ph.D., D.Sc.

*Institut de Médecine et de Chirurgie expérimentales, Université de Montréal,
Montréal, Canada*

ABSTRACT: The experimental "aging" exemplified in the progeria-like syndrome (induced by dihydrotachysterol, DHT, in rats) is not the cause but the consequence of disturbed calcium metabolism. Certain anabolic steroids can prevent the loss of body weight (protein) and the abnormal tissue calcification. Moreover, steroid substances designated "catatoxic" have been found to play a role in adaptive reactions, particularly the maintenance of resistance to stress. Thus the anti-DHT effect of the steroids is not due to their antimineralcorticoid or anabolic action, but to their catatoxic (antitoxic) potency.

An experimental biochemical disease model—the "Electrolyte-Steroid-Cardiopathy with Necrosis" (ESCN)—was developed to demonstrate a typical pluricausal disease in which several factors operate conjointly to produce a lesion. Glucomineralocorticoids plus sodium salts were outstanding factors in the production of cardiac necrosis. This experimental necrosis could be prevented by KCl or MgCl₂. However, oral administration of KCl has many drawbacks for the prophylaxis or treatment of myocardial infarction; more convenient and lasting methods of providing potassium are needed. Certain catatoxic steroids also were found to be efficacious in preventing ESCN.

These data may eventually help in finding ways to combat spontaneous aging. Aging has no specific cause. Body hormones and numerous other factors play decisive roles.

In a strictly medical sense, stress is the rate of wear and tear to which a living being is exposed at any one moment. By contrast, aging appears to

* Presented at the 27th Annual Meeting of the American Geriatrics Society, New York, N. Y., April 3-4, 1970.

reflect the sum of all the stresses which have acted upon the body during a life-span.

Research on stress has made a great deal of progress since 1936 when we first noted that the human body, like that of animals, responds to various stress-producing or "stressor" agents in essentially the same manner (1).

An important part of this response is the secretion of certain defensive "stress hormones" such as ACTH and cortisone-like substances. By elucidating the mechanism of this stereotyped reaction to stress in general (the "General-Adaptation-Syndrome" or G.A.S.), we have learned a great deal not only about the way our body defends itself against stress, but also about the so-called "diseases of adaptation" which are largely due to derailments of the stress-defense mechanism (2, 3). Among the diseases in which stress plays a major role, are: peptic ulcers, hypertension, certain forms of arthritis and related inflammatory conditions, as well as acute cardiac accidents.

There appears to be some correlation not only between stress and aging but also between aging and a disturbance in calcium metabolism. In old people the bones tend to lose calcium while certain soft tissues (e.g., vessels, periarticular connective tissue, the crystalline lens) appear to develop a particular affinity for calcium as manifested by the formation of massive calcium hydroxylapatite depositions at these sites.

The assumption was made, however, that the calcium deposition must be secondary to some "dystrophic" tissue damage that characterizes aging. In the course of our work on calciphylaxis (4) we noted that, in young animals, the induction of certain types of disturbances in calcium metabolism may result in a variety of changes characteristic of aging such as normally occur in old individuals [e.g., kyphosis, loss of hair, wrinkling of the skin with histologic changes reminiscent of senile elastosis, loss of muscle protein, thymic lymphatic involution, atrophy of the sex organs, anomalies of the teeth (Fig. 1)]. This "progeria-like syndrome" was obtained, for example, in rats given dihydrotachysterol (DHT) daily per os (5).

On the other hand, it was shown that, under identical conditions, the development of the progeria-like syndrome could be totally prevented if the animals were previously given small doses of calciphylactic challengers [e.g., certain metallic salts or chelates (6) (Fig. 2)]. Apparently the challengers deviate the calcium from sites where (under the influence of DHT) it normally precipitates in large amounts, to sites consisting of minute foci of metal deposits from which the calcium hydroxylapatite crystals can be absorbed readily before they cause permanent damage.

These observations indicate at least that the experimental "aging" of the progeria-like syndrome is not the cause but the consequence of disturbed calcium metabolism and can be prevented by agents which counteract this alteration.

Loss of body weight, particularly loss of protein, is one of the most

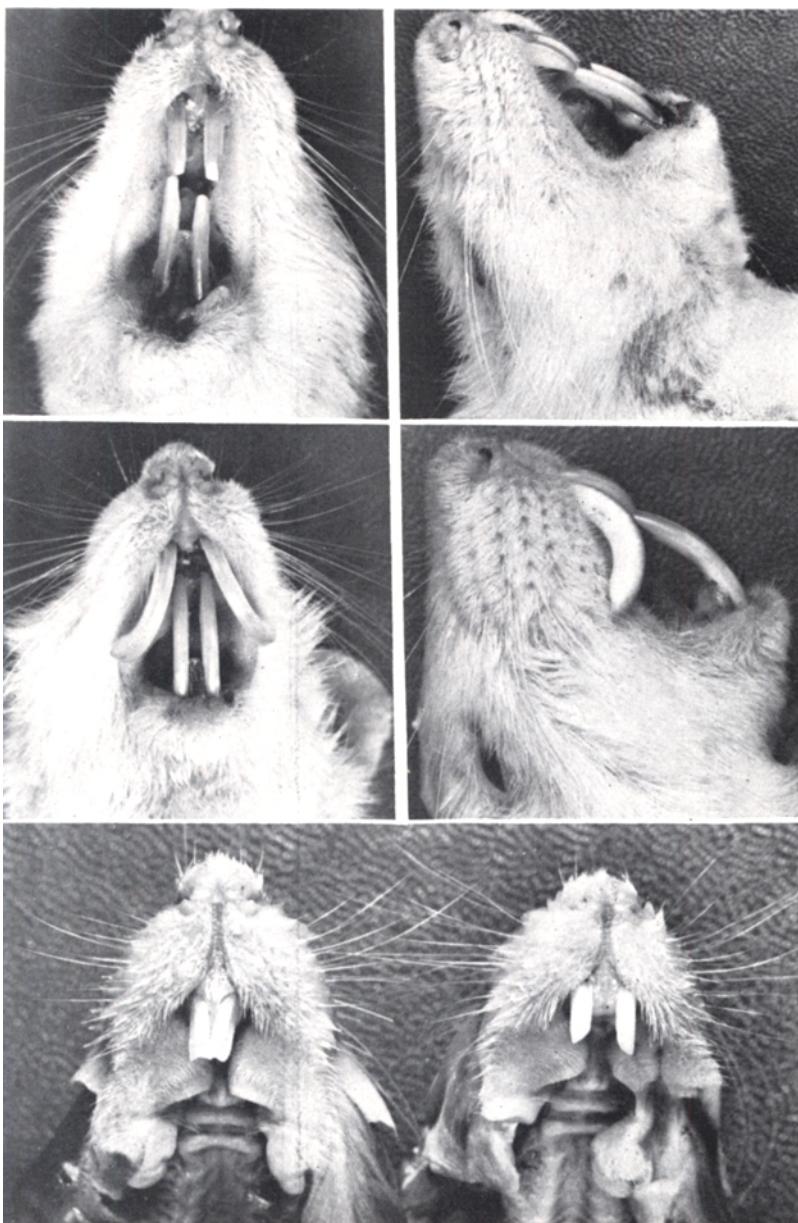


FIG. 1. *Inhibition by Fe-Dex of dental changes produced by DHT.*—*Top:* Rat treated with DHT alone. Frontal and lateral view of incisor teeth which have spread apart and are eroded owing to malocclusion. *Middle:* Similarly treated rat. Here, the upper incisors form tusk-like structures because they have spread apart so far that they can no longer be eroded by the lower pair during the process of mastication. *Bottom left:* Rat treated with DHT alone. The upper incisors have spread far apart and their tips are obliquely eroded owing to malocclusion. *Bottom right:* Concurrent treatment with Fe-Dex results in the maintenance of normal dental structure (5).

outstanding features of the experimental progeria-like syndrome. Hence, the question arose whether anabolic steroids (which would be expected to prevent the body-weight loss) would also protect against soft-tissue calcification. To explore this possibility, several experiments were performed in which the progeria-like syndrome was elicited in the usual manner by DHT, but certain groups of rats were simultaneously treated with testosterone, methyltestosterone, norbolethone, and other anabolic steroids. This work clearly showed that, irrespective of their virilizing effect, the anabolic

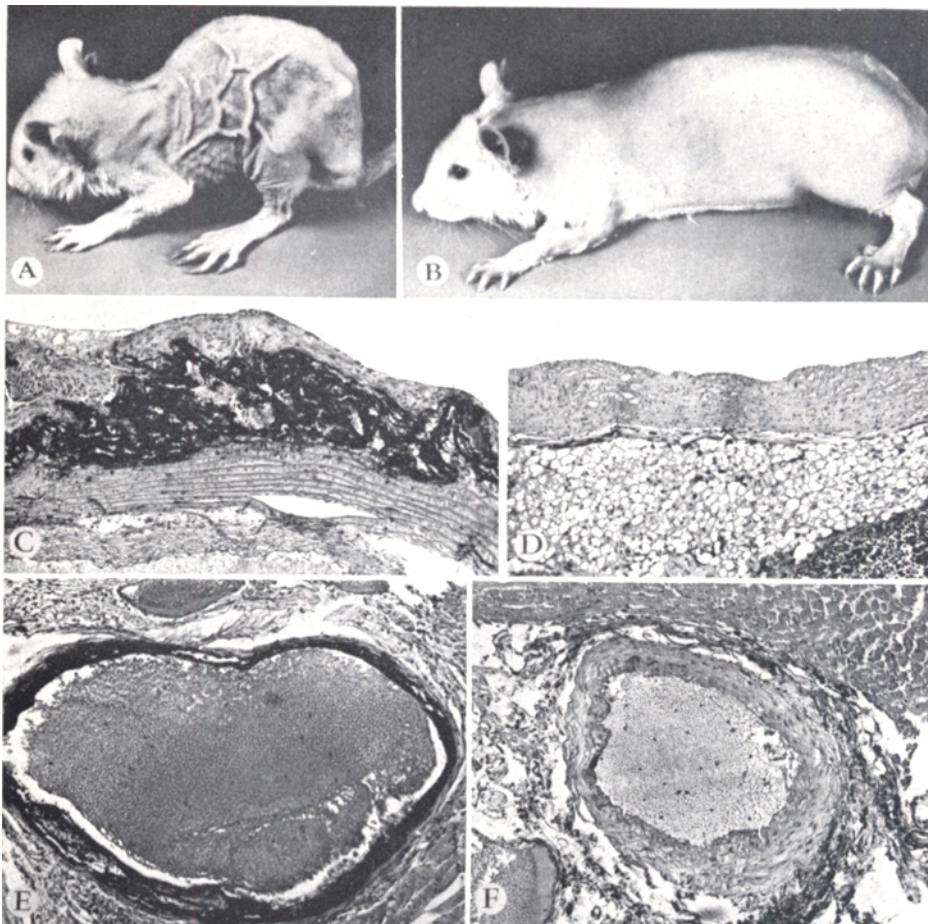


FIG. 2. *Prevention of DHT intoxication by Fe-Dex.*—*A:* General appearance of a rat treated with DHT alone. Marked kyphosis; pelvic bones and ribs visible through wrinkled, inelastic skin. *B:* Rat treated with DHT + Fe-Dex. Essentially normal appearance. (Both these rats were shaved for better visualization of body.) *C:* Aorta near arch, and *E:* Left circumflex coronary artery of rat treated with DHT alone shows intense calcinosis and distortion. *D* and *F:* Corresponding vessels of rat treated with DHT + Fe-Dex are essentially normal, but adventitia contains many iron-storing (here dark) phagocytes and mast cells. (All sections, von Kóssa $\times 84$.) (After Selye & Strebler; Courtesy of *Proc. Soc. Exper. Biol. & Med.* 110: 673, 1962.)

steroids which prevent body-weight loss in the DHT-treated rat also protect the animal against abnormal tissue calcification.

All these observations appear to show close connections between the degenerative tissue changes characteristic of aging on the one hand, and disturbances in calcium and protein metabolism on the other.

STEROID HORMONES AND RESISTANCE TO STRESS

It has long been recognized that steroid hormones participate in the regulation of growth, reproduction and general metabolism; yet, it is only in the course of the last three decades that we became aware of their participation in diverse nonspecific adaptive reactions and particularly in the maintenance of the body's resistance to stress.

Our most recent observations have shown that certain steroid hormones which are produced under the influence of stress (and also their derivatives) can induce the synthesis of defensive enzymes in the microsomes of the liver, thus raising resistance against a great variety of exogenous and endogenous toxic agents. Steroidal substances capable of eliciting this effect have been designated as "catatoxic" (from the Greek "kata" = down, against) since "antitoxic," which would also be appropriate, is already in current use for a class of specific antibodies (7).

Numerous observations revealed that various catatoxic steroids can prevent death in intact rats treated with normally fatal doses of diverse toxic agents such as nicotine, cinchophen, ethion, and several phosphothioate insecticides. However, here we shall discuss only the prevention of certain well-characterized functional or structural changes such as the calcification of soft tissues, the progeria-like syndrome, and myocardial necroses (8).

A considerable amount of work has been done on the prevention of soft-tissue calcification and the progeria-like syndrome by catatoxic steroids. Norbolethone, SC-7924, and fluoxymesterone proved to be the most active among 36 steroids examined for their ability to protect the rat against the symptoms of premature aging (catabolism, wrinkling of the skin, gonadal atrophy, kyphosis, calcifying arteriosclerosis, and skeletal and dental lesions similar to those seen in senility) which were elicited by prolonged treatment with dihydrotachysterol (DHT) or related compounds (9).

The generalized tissue calcinosis produced by a single high dose of DHT could be inhibited (in approximately decreasing order of activity) by pre-treatment with: SC-11927, norbolethone, oxandrolone, ethylestrenol, methyl-androstendiol (MAD), methyltestosterone, prednisone and spironolactone. A trace of inhibition was apparently also obtained by progesterone, prednisolone and triamcinolone, but with the latter two compounds the mortality was so high that the mildness of calcification may have been due to the premature death of the animals. Desoxycorticosterone had no protective action (10).

These findings suggested that the anti-DHT effect of the steroids is not

due to their antimineralcorticoid, anabolic or any other classic steroid hormone action, but to their catatoxic potency.

STRESS AND CARDIAC ACCIDENTS

Ever since the first description of the G.A.S., we were anxious to develop a conditioning technique in which stress would be the immediate cause of cardiac necrosis. An experimental model of this type seemed especially desirable since, in man, physical or mental exertion has long been suspected of provoking myocardial infarction. Acute cardiac accidents tend to occur with particular frequency in middle-aged and older persons, especially upon exposure to stress (11).

To examine the importance of the age factor in the production of various cardiac lesions, experiments were performed on 240 female rats, 4 weeks to 10 months of age (Figs. 3 and 4). It was found that papain, norepinephrine, vasopressin, dihydrotachysterol, and combined treatment with



FIG. 3. *The age factor in experimental cardiopathies.*—Cross-section through the whole heart of a 50-gram (left) and of a 300-gram (right) rat. Note complete absence of calcium deposition in the heart of the young animal, whereas the heart of the old rat is studded with calcified (here black) tissue lesions (von Kóssa $\times 11$). (After Selye & Bajusz; Courtesy of *J. Gerontol.* 14: 164, 1959).

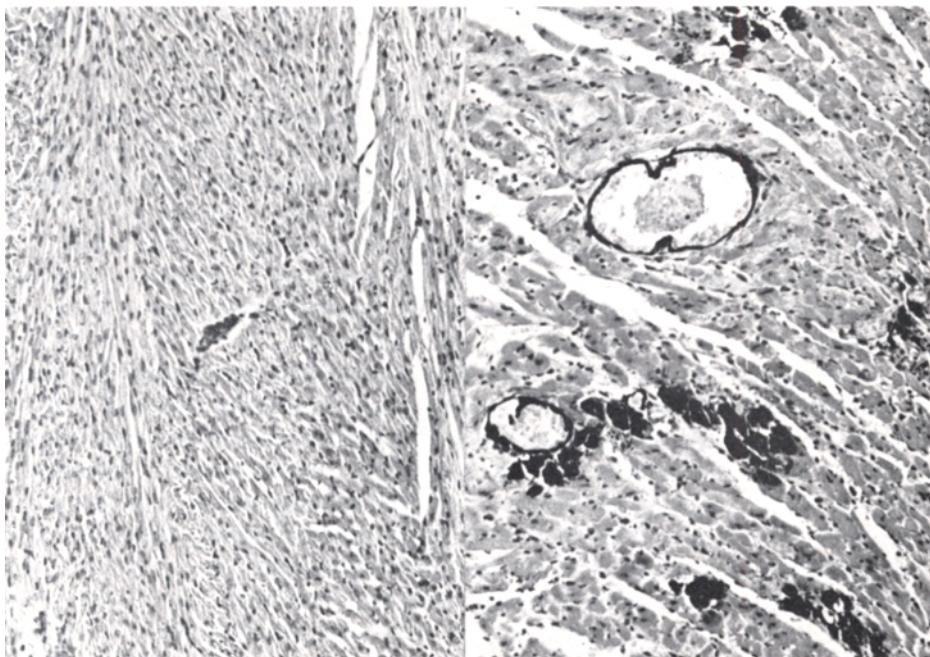


FIG. 4. *The age factor in experimental cardiopathies.*—Higher magnification of comparable regions from the hearts of the rats shown in Figure 3. There is no detectable change in the myocardium of the young rat (left), whereas in the older animal (right) there is intense calcification in the myocardial fibers as well as in the walls of the coronaries (von Kóssa $\times 120$). (After Selye & Bajusz; Courtesy of *J. Gerontol.* 14: 164, 1959.)

2α -methyl- 9α -chlorocortisol (Me-Cl-COL) + Na_2HPO_4 induce much more pronounced cardiac lesions in old than in young rats, when the dose of these substances is adjusted to body weight. On the other hand, under the same circumstances, plasmocid is about equally effective in producing cardiac lesions in young and in old animals. Two highly stressful procedures which did not depend upon the injection of exogenous drugs or hormones (forced restraint and motor denervation of all four extremities) produced only mild and inconstant cardiac lesions irrespective of the age of the experimental animals (12).

In 1958, we succeeded in producing an experimental model of the acute stress-induced cardiac accident. By pretreating animals with certain adrenal hormones and sodium salts, no obvious cardiovascular damage is induced. However, if such animals are subsequently exposed to stress (forced muscular exercise, cold baths, nervous tension, or physical trauma), acute signs of cardiac insufficiency regularly develop and the animals eventually die with structural changes in the heart, similar to those seen in man after coronary thrombosis.

Two monographs were devoted to the description of experiments showing

that, depending upon controllable conditioning factors, stress and various "stress hormones" (ACTH, corticoids, catecholamines) can either produce or prevent cardiovascular diseases in a predictable manner (13, 14). We have also described elsewhere in greater detail how topical stress—such as is caused by the direct application of pressure or chemical agents to a vessel—even can determine the localization of lesions, and how their histologic structure (hyalinization, necrosis, calcification, thrombosis) can be varied at will by appropriate conditioning (4, 15). Here, I shall limit myself to the principal cardiovascular lesions produced by exposure to stress or by the stress hormones which regulate the body's response during the G.A.S.

In our experimental animals, these cardiac lesions were associated with a severe drop in myocardial potassium and an increase in sodium (16), but obstructive coronary lesions were not observed. Hence, the large necrotic areas were called "infarctoid." Through this term, we wanted not only to indicate their similarity to true cardiac infarcts but also to emphasize (by the suffix "-oid" = like) that they are not necessarily identical with typical myocardial infarcts as they occur in man. Still, on the basis of statistical data available at the time, we suggested that the considerable number of clinical myocardial infarcts in which no recent occlusive coronary thrombi could be found might be due to a biochemical mechanism similar to that operative in the "Electrolyte-Steroid-Cardiopathy with Necrosis" (ESCN), as our experimental disease model came to be called (13).

The ESCN is a typical "pluricausal disease" (17) in that it is caused not by a single pathogen but by a "pathogenic situation" in which several factors must act conjointly to elicit a lesion. The most characteristic among these evocative agents is the steroid component, usually a hormone possessing both gluco- and mineralocorticoid potency (e.g., fluorocortisol, chlorocortisol, methylfluorocortisol, methylchlorocortisol or mixtures of pure glucocorticoids and mineralocorticoids), but other steroid derivatives such as vitamin-D compounds, dihydrotachysterol and digitalis aglycones are likewise effective. The electrolytes most powerful in eliciting cardiac necroses, when given in conjunction with such steroids, are sodium salts (e.g., Na_2HPO_4 , NaH_2PO_4 , Na_2SO_4 , NaClO_4). Calcium salts and phosphates of cations other than sodium tend to produce myocardial calcification when administered in combination with appropriate steroids (particularly those of the vitamin-D group), and in this case the ensuing necroses appear to be secondary (4, 14).

After pretreatment with glucomineralocorticoids, even mere exposure to stress (e.g., trauma, restraint) or to injections of catecholamines (epinephrine, norepinephrine) suffices to produce infarctoid myocardial necroses in the rat. It is doubtful whether here we can speak of an ESCN, since no electrolytes are given. However, the large infarctoid necroses so produced are certainly related to the ESCN in that: 1) the ease with which they are

produced is proportional to the sodium intake, and 2) potassium and potassium-sparing agents offer protection against these lesions.

The production of an ESCN by glucomineralocorticoids plus sodium salts is greatly facilitated by concurrent exposure to stressors or oral administration of lipids. In this respect, both triglycerides of animal or vegetable origin and a great variety of pure fatty acids have been found to be active (14).

It is difficult to see why, in the induction of these pluricausal cardiopathies, stress can be replaced by dietary lipids. Yet, this finding is of interest in connection with the well-known increase in the serum level of free fatty acid during stress and the curious relationship that exists between hyperlipemia and the predisposition to cardiovascular disease in man.

The ESCN is currently used for many studies concerning pharmacologic agents which might protect the aging heart against necrotizing pathogens.

Metabolic infarctoid necroses without occlusive vascular lesions have been produced by various combinations of steroids, electrolytes, stress and lipids (13, 14). However, for the routine screening of potentially antinecrotic agents, we usually employ those variants that are produced by glucomineralocorticoids (e.g., methylchlorocortisol, fluorocortisol) in combination with Na_2HPO_4 , stressors, or lipids. These models of metabolic myocardial necroses have been selected because, unlike those elicited by cardiotoxic drugs (e.g., plasmocid, papain), they depend upon factors likely to play a role also in the cardiac diseases of man.

The ESCN is associated with a sharp drop in myocardial and serum potassium (16). Furthermore, this type of experimental cardiac necrosis can be prevented by the oral administration of KCl or MgCl_2 (13). Hence industry has made available a large number of potassium and magnesium preparations, among them several organic salts, recommended for the prophylaxis of myocardial infarction and even for treatment during the post-infarction period. However, oral treatment with KCl is not ideal for clinical use; the salt is unpleasant to take, and it may cause gastrointestinal irritation or even jejunal ulcers; besides, its effect is of short duration. After a single oral dose of KCl, the concentration of blood potassium rises sharply, often to dangerous levels, but soon returns to normal. Thus, this medication does not lend itself well to the prophylaxis of cardiac necroses which may occur unpredictably at any time and therefore require prolonged preventive therapy. In our animal experiments, KCl was highly effective, but only because we could predict the onset of myocardial necrosis within hours and, hence, had to provide the necessary potassium only during a very limited period.

It seemed reasonable, therefore, to look for more convenient and more lasting ways to provide the myocardium with the necessary amount of potassium. Again using our experimental models of infarctoid cardiac necroses, we found that spironolactone (Aldactone) is likewise highly effica-

cious against the corticoid-dependent type of the ESCN; its beneficial action was at first ascribed to the well-known antimineralcorticoid property of this steroid (18). However, the compound also proved to be very efficacious in abolishing the digitoxin-dependent variant of the ESCN [(19) (Fig. 5)]. This effect could not be readily explained by an antimineralcorticoid action, although it might have depended upon alterations in electrolyte metabolism which are known to influence the toxicity of cardiac glycosides. The protection offered by spironolactone and other catatoxic steroids against a great variety of quite unrelated intoxications apparently was not due to any of the classic steroid hormone actions, but to their catatoxic potency. It was found in subsequent experiments that several types of infarctoid myocardial necroses could also be prevented by catatoxic steroids and that, therefore, this hitherto unsuspected mechanism may be just as important as changes in electrolyte metabolism or specific antimineralcorticoid effects in determining predisposition for this type of myocardial damage.

In the rat, spironolactone inhibits the normally fatal extensive necroses

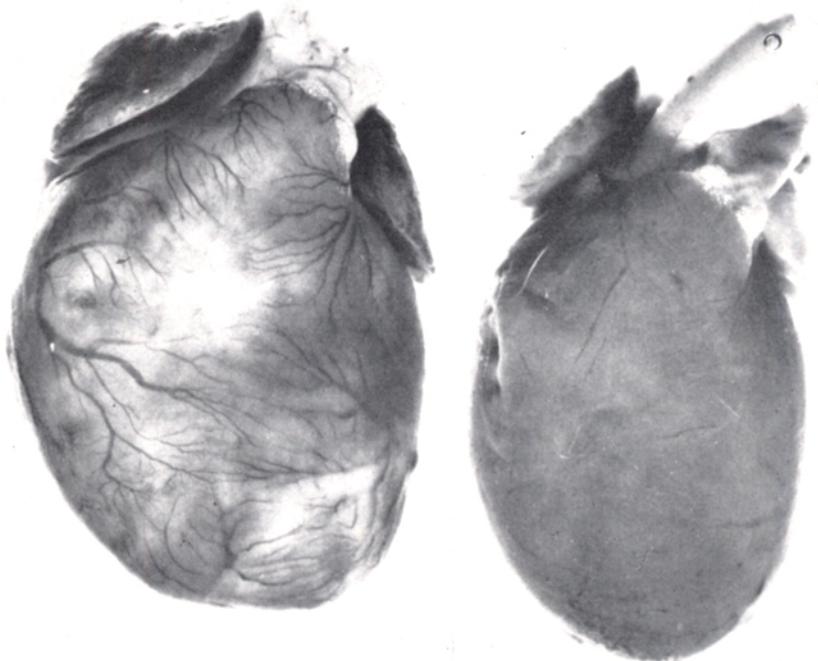


FIG. 5. *The digitalis cardiopathy and its prevention by compound SC-11927.—Left:* Macroscopic appearance of the extensive myocardial necroses (light areas) induced by combined treatment with digitoxin + Na_2HPO_4 + corn oil. *Right:* Similarly treated rat in which the cardiac lesions were completely prevented by SC-11927. (After Selye; Courtesy of *J. Molec. Cell. Cardiol.* 1: 91, 1970).

of the cardiac muscle produced by certain corticoids given in combination with bisodium phosphate, excess fat intake or exposure to stress (18). However, the electrolyte-steroid-cardiopathy with necrosis (ESCN) produced by fluorocortisol or digitoxin in combination with $\text{Na}_2\text{HPO}_4 +$ corn oil can also be prevented by such typical catatotoxic steroids as spironolactone, ethylestrenol, norbolethone and SC-11927. In this respect, oxandrolone, desoxycorticosterone, progesterone, prednisolone and triamcinolone had little or no protective value. The ESCN produced by fluorocortisol + $\text{Na}_2\text{HPO}_4 +$ restraint, or fluorocortisol + $\text{NaClO}_4 +$ corn oil proved to be much more resistant to prophylaxis; it was markedly diminished in intensity only by SC-11927 and spironolactone (18, 19). Presumably, in these experiments the protective action of the catatotoxic steroids may be ascribed to their ability to inactivate fluorocortisol and related mineralogluocorticoids which play an indispensable part in the production of this type of myocardial injury.

Thus it may be concluded from these and previous investigations that, in general, steroids exhibiting a typical catatoxic effect against one damaging agent are likely to be effective also against other substrates amenable to this type of inactivation.

It remains to be seen to what extent such animal experiments will help us to combat spontaneous aging, but there can be no doubt that really significant progress concerning the problems of the aged will not come by merely supplying the aged with food, shelter and social games, but through basic research into the fundamental phenomenon of senescence.

COMMENT

It has always been assumed as self-evident that aging has a specific cause and that, consequently, we might discover what this is and perhaps find ways to block it. There is no justification for such an assumption. Apparently no one has ever suggested that maturation, the process of growing up, has any one specific cause. Undoubtedly, the hormones regulating growth and sexual development, as well as numerous dietary, nervous and other factors, play decisive roles here. Yet, we have no reason to suspect that a unified theory of "the growing-up process" could be formulated or that in this respect the clock could be turned back by some panacea which would interfere with all the relevant biologic reactions.

In a period of basic research which has produced so many miracles from penicillin to interplanetary travel, optimism is understandable; far be it from me to discourage the exercise of unlimited imagination. What I have said is not intended to dissuade creative minds from continuing their search for an all-embracing theory which might lead to the prophylaxis or even the cure of the aging process itself. My purpose was only to point out that, at present, we have no objective basis for suspecting that such endeavors could be fruitful, whereas we do have many reliable techniques

(and good reasons to assume that even better ones could be developed) for the study of individual morbid lesions which decrease life expectancy.

Acknowledgments

This work was supported by the USPHS, Child Welfare (Grant HDO 2612 03) and also was undertaken as a special project of the Council for Tobacco Research, U.S.A., and the Canadian Tobacco Industry.

REFERENCES

1. SELYE, H.: A syndrome produced by diverse noxious agents, *Nature* (London) 138: 32, 1936.
2. SELYE, H.: Stress (1950) and Annual Reports on Stress (in collaboration with G. Heuser and A. Horava), Vols. I-V. Montreal, Acta Inc., Med. Publ., 1951-55/56.
3. SELYE, H.: The Story of the Adaptation Syndrome. Montreal, Acta Inc., Med. Publ., 1952.
4. SELYE, H.: Calciphylaxis. Chicago, University of Chicago Press, 1962.
5. SELYE, H.; STREBEL, R., AND MIKULAJ, L.: A progeria-like syndrome produced by dihydrotachysterol and its prevention by methyltestosterone and ferric dextran, *J. Am. Geriatrics Soc.* 11: 1, 1963.
6. SELYE, H., AND STREBEL, R.: Prevention by calciphylaxis of the progeria-like syndrome induced by chronic dihydrotachysterol overdosage, *Proc. Soc. Exper. Biol. & Med.* 110: 673, 1962.
7. SELYE, H.: Catatoxic steroids, *Canad. M. A. J.* 101: 51, 1969.
8. SELYE, H.: Adaptive steroids: retrospect and prospect, *Persp. Biol. & Med.* Spring issue, p. 1, 1970.
9. SELYE, H.; TUCHWEBER, B., AND JACQMIN, M. L.: Protection by various anabolic steroids against dihydrotachysterol-induced calcinosis and catabolism, *Acta endocrinol.* (Kbh.) 49: 589, 1965.
10. SELYE, H.; YEGHIAYAN, E., AND MANDEVILLE, R.: Protection by catatoxic steroids against dihydrotachysterol intoxication. *J. Atheroscler. Res.* 11: 321, 1970.
11. SELYE, H.: Experimental Cardiovascular Diseases. Berlin-Heidelberg-New York; Springer Verlag, 1970.
12. SELYE, H., AND BAJUSZ, E.: The age factor in the production of various experimental cardiopathies, *J. Gerontol.* 14: 164, 1959.
13. SELYE, H.: The Chemical Prevention of Cardiac Necroses. New York, Ronald Press Co., 1958.
14. SELYE, H.: The Pluricausal Cardiopathies. Springfield, Ill., Charles C Thomas, Publisher, 1961.
15. SELYE, H.: Thrombohemorrhagic Phenomena. Springfield, Ill., Charles C Thomas, Publisher, 1966.
16. PRIORESCHI, P.: Role of potassium in the pathogenesis of the "electrolyte-steroid-cardiopathy with necrosis," *Circulation Res.* 10: 782, 1962.
17. SELYE, H.: Pluricausal diseases, *Exper. Med. & Surg.* 24: 191, 1966.
18. SELYE, H.: Protection by a steroid-spirolactone against certain types of cardiac necroses, *Proc. Soc. Exper. Biol. & Med.* 104: 212, 1960.
19. SELYE, H.; KRAJNY, M., AND SAVOIE, L.: Digitoxin poisoning: prevention by spironolactone, *Science* 164: 842, 1969.
20. SELYE, H.: Prevention of various forms of metabolic myocardial necrosis by catatoxic steroids, *J. Molec. Cell. Cardiol.* 1: 91, 1970.