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PRODUCTION OF HYPERTENSION AND HYALINOSIS BY DESOXOCORTISONE

BY

HANS SELYE, M.D., Ph.D., D.Sc., F.R.S.(C.)

*Professor and Director of the Institute of Experimental Medicine and Surgery,
Université de Montréal, Montreal, Canada*

[WITH SPECIAL PLATE]

A few years ago we observed that, in animals, overdosage with desoxycorticosterone reproduces the experimental equivalent of certain hypertensive, rheumatic, and allergic diseases of man—in particular, malignant nephrosclerosis, necrotizing arteritis similar to periarteritis nodosa, cardiac nodules resembling Aschoff bodies, joint lesions comparable to rheumatic or rheumatoid arthritis, as well as an intense and persistent rise in arterial blood pressure. All these changes were most readily observed in animals sensitized to these toxic actions of DCA-overdosage by unilateral nephrectomy and a high sodium intake. Essentially the same changes developed in similarly sensitized animals if we exposed them to a variety of noxious agents capable of producing a general-adaptation syndrome with the characteristic stimulation of the adrenal cortex. Since in man these diseases are often preceded by exposure to cold, infections, intoxications, or other damaging agents, we expressed the opinion "that the above-mentioned diseases are, at least partly, caused by an abnormal (probably excessive) adaptive response of the adrenal cortex and represent diseases of adaptation" (Selye and Pentz, 1943).

It has been noted, furthermore, that DCA causes arthritis more easily in adrenalectomized than in intact animals (Selye *et al.*, 1944; Pirozynski and Akert, 1949), and that a gluco-corticoid compound (corticosterone) increases, while a mineralo-corticoid substance (desoxycorticosterone) diminishes, resistance to traumatic shock (Selye, Dosne, Bassett, and Whittaker, 1940).

Subsequent investigations revealed that the arthritis (Selye, 1949a), the anaphylactoid reactions (Selye, 1949b), as well as the cardiovascular and hypertensive changes (Selye, *in press*), whose development is enhanced by desoxycorticosterone, can also be inhibited by cortisone. All these observations led us to formulate the working hypothesis that, as a result of exposure to stress (for example, that caused by emotional stimuli, infections, intoxications), the adrenal may, under certain circumstances, respond with a disproportionate over-production of either the gluco- or the mineralo-corticoids. The above-mentioned diseases of adaptation could perhaps be the result of an unbalanced excess of the latter type of steroid.

The most serious objection raised against this kind of reasoning was that desoxycorticosterone has not been definitely proved to be produced by the adrenal cortex. It has only once been isolated from suprarenal glands (Reichstein and von Euw, 1938), and some chemists expressed the

suspicion that this may have been an artifact (for literature, see Selye, "Stress"). Of course Hartmann's "sodium factor" and Kendall's "amorphous fraction" possess mineralo-corticoid potency, and these are indubitably natural adrenal steroids; but the latter compounds have not been available in the quantities required to examine whether they would actually produce lesions characteristic of the above-mentioned "diseases of adaptation."

Using certain impure anterior-pituitary preparations, we found that hypertension, periarteritis nodosa, cardiac nodules, nephrosclerosis (Selye, 1944), and arthritis (Selye, 1946, 1949a) are produced simultaneously with a pronounced adrenocortical enlargement. However, these extracts contained much foreign protein, and hence there still remained some doubt concerning the mechanism through which they produced these changes. In particular, the question has been raised whether both desoxycorticosterone and our impure extracts could not have acted merely by eliciting allergic responses if they are toxic substances foreign to the body.

In view of these uncertainties we felt that it would be of fundamental importance, for the interpretation of the "diseases of adaptation," to demonstrate that an unquestionably natural mineralo-corticoid can also produce them. This has now become possible, and in this communication we should like to report upon the results of our pertinent observations.

The mineralo-corticoid with which this work was performed is Reichstein's compound "S" or 11-desoxocortisone. It bears nearly the same relationship to cortisone as desoxycorticosterone to corticosterone. For the discussion of the problem under consideration it is unnecessary to devote much space to the chemistry of these steroids, but it will facilitate the understanding of our subject to list the structural formulae of the principal compounds to which reference has been made.

It will be noted that desoxycorticosterone and desoxocortisone differ from corticosterone and cortisone, respectively, only in that the former two steroids do not possess an oxygen on carbon atom 11. The presence of oxygen in this position is indispensable for the gluco-corticoid actions (Selye, 1943, Selye, Dosne, Bassett, and Whittaker, 1940). In corticosterone it is a hydroxylic (hence the prefix "desoxy-"), in cortisone a ketonic (hence "desoxo-"), oxygen that is removed.

We were especially interested in determining whether desoxocortisone would produce the diseases of adaptation

of the "hyalinosis" type because it is so closely related to cortisone, which inhibits the progress of these same diseases both in clinical and in experimental medicine (for literature, see Selye, 1949a). Furthermore, cortisone has repeatedly been isolated—in comparatively large amounts—from normal adrenal tissue (Reichstein, 1938, Reichstein and von Euw, 1938, 1940).

Methods

The experimental animals used in this study were immature male piebald rats, with an initial body-weight of 40–60 g. All animals were castrated and unilaterally nephrectomized at the beginning of the experiment. Throughout the period of observation they were fed exclusively on "purina fox chow" (as supplied by the Ralston Purina Co., Montreal) and given 1% NaCl as a drinking-fluid instead of tap-water to drink.

Young animals were used, because our supply of desoxocortisone is very limited and we felt that the greatest effect could be expected from a given dose in small rats. Gonadectomy was performed, since this permitted us, simultaneously with the main investigation, to determine whether desoxocortisone has any testoid (or "androgenic") effects, as judged by the stimulation of the seminal vesicles, prostates, and penis. The unilateral nephrectomy and the administration of excess sodium served to "condition" the rats for the toxic actions of mineralo-corticoid overdosage.

Five rats received desoxocortisone as a saline suspension of desoxocortisone acetate microcrystals. The preparation was that distributed by Merck and Co., Rahway, N.J., in which suspending agents (to keep the microcrystals from settling) and 1.5% benzyl alcohol (as a preservative) are added. This suspension contains 25 mg. per millilitre, and 2.5 mg. was given daily subcutaneously to each animal.

For the statistical evaluation of the data the standard errors were calculated by the equation:

$$SEM = \sqrt{\frac{d^2}{n(n-1)}}$$

To calculate the organ-weight/body-surface ratio, the constant 9.1 was employed in the formula: $S = K \times W^{\frac{2}{3}}$, where S is the surface area in cm^2 , K is the constant, and W the body-weight in g. "P" was calculated according to Fisher's "t" table (1936).

The blood pressure was measured with the tail-cuff method, under very light ether anaesthesia, on the 22nd

day of treatment, and all animals were killed two days later. The organs were preserved in alcohol-formalin mixture and weighed immediately after fixation. For histological examination they were embedded in paraffin and stained with haematoxylin and eosin.

Experimental Observations

To facilitate the evaluation of our data the main findings have been summarized in the following Table, in which—wherever it appeared of interest—the standard errors, and the probability of the statistical significance of the deviation from the normal ("P"), have also been listed. In the case of the kidney, heart, and brain, the organ weights are expressed both in absolute terms and as a function of the body surface. Statistically significant deviations from the norm are indicated in bold type.

TABLE I.—Principal Changes Occasioned by Desoxocortisone Overdosage

Treatment	Controls	Desoxocortisone	"P"
Body weight { Initial	54 ± 2	54 ± 1	—
in g. Final	132 ± 5	123 ± 7	—
Blood pressure (mm. Hg.) ..	125 ± 5	156 ± 6	<0.01
Fluid intake (ml./day)	45 ± 2	59 ± 2	<0.01
Kidney { in mg.	871 ± 55	1,001 ± 64	>0.2
mg./100 cm. ² B.S. ..	374 ± 30	447 ± 17	>0.05
Nephrosclerosis ..	0	++	—
Heart { in mg.	530 ± 32	679 ± 15	<0.01
mg./100 cm. ² B.S. ..	233 ± 14	305 ± 10	<0.01
Myocarditis	0	++	—
Brain { in mg.	1,265 ± 47	1,450 ± 32	<0.01
mg./100 cm. ² B.S. ..	543 ± 34	653 ± 37	<0.1
Encephalopathy ..	0	++	—
Mesenteric periarteritis nodosa ..	0	++	—
Thymus (mg.)	400 ± 37	307 ± 85	>0.2
Iliac lymph nodes (mg.)	26 ± 3	39 ± 7	>0.2
Spleen (mg.)	998 ± 63	1,045 ± 439	—
Adrenal (mg.)	29 ± 2	30 ± 1	—

The body-weight of the experimental animals lagged only slightly behind that of the controls in spite of the widespread organ damage. This agrees with our previous observations, which revealed that only the gluco-corticoids cause sufficient tissue catabolism and inhibition of growth to depress the body-weight markedly. Nevertheless, probably the loss of weight was greater than the figures in our table would suggest, since the desoxocortisone-treated rats developed considerable tissue oedema, and this would mask their failure to grow.

The blood pressure was measured and found to be significantly above normal on several occasions. This was also the case two days before necropsy, as shown by the figures listed in the table. It will be noted that our method measures the mean blood pressure and that in several of our animals this value was well over 160 mm. Hg. In normal rats the mean resting blood pressure measured under similar conditions does not rise over 135 mm. Hg.

In order to obtain data concerning the water turnover it is more accurate to measure the intake than the output in experiments on the rat. The figures given in the table represent averages of such measurements taken during the last twelve days of the experiment. It will be noted that, although desoxocortisone significantly raised the fluid intake, this increase was much less pronounced than that which we have previously observed in rats in which a similar degree of organ damage was produced by desoxycorticosterone (Selye, in the press). Nevertheless it may be concluded that desoxocortisone also possesses a diuretic effect.

The weight of the kidneys was not significantly raised by desoxocortisone, when expressed either in absolute terms or as a function of body surface. On the other hand, histologically, all the treated animals showed marked nephrosclerosis, with hyalinization of many glomerular loops and

FIG. 1.—Kidney of a normal rat under low magnification.

FIG. 2.—Kidney of a desoxocortisone-treated rat under low magnification: enlargement and hyalinization of some glomeruli; irregularity of tubules, some dilated and containing casts, others collapsed.

FIG. 3.—High magnification of a glomerulus from the kidney shown in Fig. 1.

FIG. 4.—High magnification of a glomerulus from the kidney shown in Fig. 2: hyalinization of several glomerular loops and dilatation of surrounding tubules.

FIG. 5.—Arteriole in the myocardium of a normal control rat.

FIG. 6.—Arteriole in myocardium of a desoxocortisone-treated rat: although the lumen of this vessel is approximately the same size as that in Fig. 5, there is a heavy dark layer of hyalin material underneath the intima, and the outer walls are greatly thickened by a granuloma.

FIG. 7.—Section through a mesenteric artery of a desoxocortisone-treated rat: irregular hyalin deposits underneath dark line which corresponds to intima; endothelium is loosened and in some places intima is in direct contact with circulating blood; outer coats of this artery completely lost their normal structure because of proliferating granuloma tissue.

FIG. 8.—Periarteritis nodosa in a pancreatic vessel, with normal pancreatic acini on the left; similar changes were seen throughout pancreatic arterial tree; oedema and connective-tissue proliferation were evident even at a distance from vessels between the pancreatic acini.

FIG. 9.—Periarteritis nodosa and connective-tissue proliferation in submucosa of upper small intestine in a desoxocortisone-treated rat: note greatly dilated lymph vessel just underneath muscular coat.

FIG. 10.—Periarteritis nodosa and granulomatous proliferation of connective tissue in submucosa of stomach in a desoxocortisone-treated rat.

FIG. 11.—Intense oedema of stroma with marked dilatation of lymphatic vessels in glottis region of a desoxocortisone-treated rat.

afferent glomerular arterioles. Hyalin casts and great dilatation or collapse of tubules were also commonly observed (see Figs. 1 to 4, Special Plate).

The heart showed marked hypertrophy in the treated animals. This proved to be significant even in absolute terms, but the probability of the significance was even greater when expressed as a function of body surface. This enlargement was presumably the consequence of hypertension. It was accompanied by manifest signs of periarteritis nodosa of the cardiac vessels (see Figs. 5 and 6) and numerous islets of hyalinization underneath the endocardium. Many of these islets contained polynuclear giant cells similar to those seen in Aschoff's nodules.

The weight of the brain was likewise very significantly increased. This was quite obvious even at naked-eye inspection. As a result of brain oedema and increased accumulation of cerebrospinal fluid the still rather soft cranium of these young growing rats became distended and more rounded than that of the controls. At the same time the brain surface was extremely pale and moist owing to oedema. In all but one of these animals there also developed a characteristic encephalopathy, which we had previously noted in desoxycorticosterone-treated animals. It will be recalled that this is characterized by hyalinizing arteritis of the smaller brain vessels, often accompanied by small haemorrhages or the formation of foci of liquefaction necrosis. At the same time there is intense glial proliferation. The general histological characteristics of this lesion are highly reminiscent of those seen in man suffering from hypertensive encephalopathy, periarteritis nodosa of the brain, allergic encephalitis, the so-called "brain rheumatism," and other collagen diseases.

The mesenteric arteries of all our animals were affected by a diffuse and intense hyalinizing panarteritis such as is seen in very acute types of periarteritis nodosa in man. Throughout the mesentery the arteries were hardened and thickened as judged by examination on the necropsy table. Histologically, the most prominent changes were the deposition of homogeneous, hyalin, eosinophilic masses between the endothelium and the lamina intima. At many places the endothelium became loosened and thrombi had formed. In other locations the hyalin material appeared to infiltrate into the outer coats of the vessels. At the same time there was marked proliferation of a granulomatous tissue which led to the complete disorganization of the normal arterial-wall structure (see Fig. 7). In some instances these granulomas were studded with eosinophil leucocytes, but this latter change was not constant.

Essentially similar vascular changes were noted in the pancreas (see Fig. 8), the small intestine (see Fig. 9), the stomach (see Fig. 10), as well as throughout the skeletal musculature, etc. Everywhere intense connective-tissue proliferation accompanied the arteritis. In view of the frequent occurrence of gastro-intestinal connective-tissue proliferation in various collagen diseases (e.g., scleroderma) it is interesting to note that desoxocortisone, a natural adrenal steroid, can produce such changes under suitable experimental conditions.

Presumably as a consequence of the water and salt retaining effect of this mineralo-corticoid, oedema and marked dilatation of the lymph vessels are also very prominent in most organs. A particularly pronounced oedema occurred in the trachea, especially in the glottis region. The stroma of the tracheal mucosa was greatly swollen and the lymphatic spaces were conspicuously engorged (see Fig. 11). Since corticoids are known to be discharged in conditions of acute stress, such lesions may perhaps play

a part in certain hitherto unexplained instances of acute oedema of the trachea and glottis.

Unlike the gluco-corticoids (for example, cortisone), desoxocortisone does not cause any significant involution of the lymphatic organs. Indeed the figures given in the table clearly indicate that the thymus underwent only an insignificant involution, while the iliac lymph nodes and spleen of the desoxocortisone-treated rats were actually (though not significantly) larger than those of the untreated controls. This agrees well with our previous observations, which revealed that, under comparable experimental conditions, desoxycorticosterone, unlike cortisone, causes no marked involution of the thymus and lymphatic organs (Selye, 1949a). The apparent enlargement of the lymph nodes is primarily due to a dilatation of the lymphatic sinusoids, as shown by our histological studies.

Neither the weight nor the histological structure of the adrenals showed any significant deviation from the normal after desoxocortisone treatment. It had previously been noted that, unlike cortisone, desoxycorticosterone causes only slight adrenal cortical involution, and it is a rather consistent characteristic of gluco-corticoids that they inhibit ACTH production by the pituitary, and hence cause "compensatory adrenocortical atrophy," more readily than the mineralo-corticoids. It is difficult to explain, however, why in the present series there was not even the slightest involution of the adrenal cortex. Perhaps the ability of desoxocortisone to inhibit ACTH production, by virtue of its specific pharmacological properties, is so slight that it was greatly overcompensated by the fact that it caused widespread organ damage; the resulting development of a general-adaptation syndrome would naturally tend to increase ACTH production.

The seminal vesicles of the desoxocortisone-treated (castrate) rats weighed 8.5 mg. (± 0.5) as compared with 5.6 mg. (± 0.7) in the controls. This slight enlargement was not accompanied by any histological signs of testoid activity and is probably merely the result of tissue oedema. It may therefore be concluded that desoxocortisone is not a virilizing compound; in this respect it again resembles desoxycorticosterone.

It is somewhat difficult to assess the relative toxicity of desoxocortisone in comparison with that of desoxycorticosterone, since we have not yet had occasion to examine the actions of the latter when administered in the form of such fine microcrystals (less than 10μ). It may be said, however, that under no conditions has it been possible up to now to obtain such widespread hyalinosis with desoxycorticosterone within 24 days. Furthermore, such intense and widespread periarteritis nodosa as that which developed in the present experimental series has not yet been produced under any conditions with other steroid hormones. It may therefore be concluded that desoxocortisone is highly active in producing hypertension and the histological lesions of hyalinosis which are so characteristic of certain hypertensive, rheumatic, and allergic diseases of man.

Summary and Conclusions

Desoxocortisone (Reichstein's compound "S"), a steroid normally occurring in the adrenal cortex, proved to be highly active in raising the blood pressure and water turnover. It also caused widespread and intense periarteritis nodosa, acute nephrosclerosis, and granulomatous nodules in the heart, accompanied by organ changes similar to those which occur in certain so-called "collagen diseases" of man.

The data are interpreted as further evidence supporting the view that naturally occurring corticoids may be involved in the

pathogenesis of those "diseases of adaptation" which respond favourably to therapy with gluco-corticoids or ACTH.

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PROGRESS OF GASTRIC SURGERY IN THE LAST HALF-CENTURY*

BY

Sir JAMES WALTON, K.C.V.O., M.S., F.R.C.S.

I chose this subject for my address because I have had the rather unusual experience of having operated upon nearly 4,000 gastric lesions and because I have lived through practically the whole period of the growth of this surgical specialty. It was indeed an astonishment to me to find, when looking up the history for the first edition of my book, that the first gastro-enterostomy performed by Wolfer, the first excision of gastric ulcer by Rydygier, the first successful gastrectomy by Billroth, as well as the first cholecyst-enterostomy by von Winwarer were all carried out in the year of my birth, and I felt that I had indeed been born under the upper abdominal star. Since 1900, when I first started as a medical student, I have seen great changes in the selection of cases for operation, in the methods of performing the operation, and in the choice of operation for the individual lesion.

I have been singularly fortunate in that I have worked under many of the pioneers of gastric surgery, as a dresser under Sir Frederick Eve, who was one of the earliest to perform many gastro-enterostomies. In his day, so serious an operation was this considered that he had all his hospital patients nursed in a separate room with day and night special nurses, and they were kept on rectal feeds with nothing whatever by mouth for two weeks. Later I served under Mr. Roxburghe, the ophthalmic surgeon, who performed the first partial gastrectomy in this country; and for a short time was house-surgeon to that brilliant young surgeon Mr. Harold Barnard, who even in his short life did so much to advance abdominal surgery. I was then appointed house-surgeon to Mr. Mansell-Moullin, who in his day was regarded as one of the greatest gastric surgeons in this country and who

obtained very successful results, although he operated without gloves and while wearing three rings. Later I became registrar under those great abdominal surgeons Sir Hugh Rigby and Mr. James Sherren. To the latter especially I owe the greater part of my training, for not only was I his registrar at hospital but for several years was his private assistant, and after his retirement inherited from him the greater part of the upper abdominal surgery at the London Hospital.

Changes in Custom

During my student days it was the custom to treat all cases of peptic ulcer medically and to call in the aid of the surgeon only in the case of some complication. It was my old chief, Dr. J. F. Smith, who introduced the powder which later became so popular as MacLean's powder, although, unfortunately for him, he did not advertise it. Many physicians even claimed that pyloric obstruction could be cured by repeated gastric lavage, a belief that died very hard, so that in my early days as a surgeon I had to treat many cases of carcinomatous obstruction which had become completely inoperable while undergoing prolonged courses of lavage, and with other surgeons had a great fight to establish the dictum that all cases of pyloric obstruction should be treated surgically, for the obstruction might be carcinomatous, and in any case was mechanical in nature and must be treated mechanically.

Even up to several years later many surgeons stated that they had never seen the characteristic pathological picture of duodenal ulcer which Lord Moynihan had described so graphically, and they denied its existence. Great controversy raged then, and has done so up to times within the memory of you all, whether severe haematemesis should be treated with complete rest, with a restricted diet, with a high protein diet, or by immediate operation. In the same period many if not most physicians were opposed to the surgical treatment of carcinoma of the stomach, for they believed that a cure could never be obtained and that it only subjected the patient to much discomfort in the remaining short period of his life.

About 1910 opinion had entirely changed and had reached the other extreme, the tendency being to advise operation as soon as a peptic ulcer was diagnosed, no attempt being made by the physician to carry out medical treatment or indeed to make a detailed investigation. In fact, at that period nearly all such cases were admitted to hospital direct to the surgeon and the full investigation was performed by him, so that the greater part of our modern knowledge of the symptomatology and means of diagnosis of peptic ulceration and carcinoma of the stomach is due to the surgeons. It is very regrettable that the modern student is being taught to pay so little attention to a carefully taken clinical history, which at that time was shown to be the most valuable method of investigation. There is no doubt, however, that in treatment the pendulum had swung much too far, and many cases that were unsuitable for surgery or that could have been cured medically were subjected to an operation, which in most cases was a gastro-enterostomy.

As a result a reaction set in, and, following the writings of MacLean, of Izod Bennett, and more especially of Sir Arthur Hurst, surgical treatment in the mid-1920's fell into a certain amount of disrepute. The last-named physician claimed that all cases of peptic ulcer could be cured with adequate medical treatment and that if not so cured the treatment was inadequate; nevertheless he

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