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CAN THE ADMINISTRATION OF DESOXY-
CORTICOSTERONE ACETATE GIVE RISE TO
NEPHROSCLEROSIS?*"

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Desoxycorticosterone acetate (DCA), the synthetic
adrenocortical compound, is extensively used because of its
ability to replace the adrenocortical hormones in adrenal ins-
sufficiencies of various kinds. The considerable rise of the
blood pressure and the effect on the sodium-potassium balance
of the organism caused by its administration in, for example,
Addison’s disease, encouraged attempts to induce an experi-
mental rise of the blood pressure by means of large doses of
the preparation. Many investigators have reported that a con-
siderable rise of the blood pressure has been obtained both
in experimental animals and in man with large doses of DCA
given together with saline (Engel et al. 1942, Ferrebee et al.
1939, Grollman et al. 1940, Perera et al. 1944, Roth et al. 1943,
Soffer et al. 1940, Swingle et al. 1941, Thorn, Howard et al.
1939, Thorn, Dorrance & Day, 1942). It is remarkable that

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both in animals and in man already suffering from hypertension a greater sensitivity to DCA than in normal subjects was found (Kuhlmann et al. 1939, Perera & Blood, 1947, Rodbard & Freed, 1942). Results do not, however, appear to be uniform and experiments have also been reported in which it was not possible to induce a rise of the blood pressure with DCA alone or combined with saline (Braun-Menendez et al. 1946, Knowlton et al. 1946, Raab, 1942). Perera & Blood (1947), with a daily dose of 10 mg. of DCA, obtained a rise of the blood pressure in subjects with hypertension, but succeeded in inducing it in normal individuals only after lengthy treatment.

Some workers consider that they have found changes in the adrenals in cases of essential hypertension in man (Aubertin & Ambard, 1904, Schur & Wiesel, 1907, Philpot, 1909, Oppenheimer & Fishberg, 1924, Allen, 1929, Goldzieher, 1931, v. Locadou, 1935, Rinehart et al. 1941). This fact, together with the hypertensive effect of large doses of DCA, has given rise to the assumption that the adrenals play a definite role in the development of this disease.

In order to throw further light on this question, Selye (1939—46) and his coworkers (Dontigny et al. 1946, Hall & Selye, 1945, Hall et al. 1946, Masson & Beland, 1943) have studied the effect of large doses of DCA in combination with saline on various experimental animals, chiefly rats. They found histological changes in the kidneys, involving the tubules, the interstitial tissue, the glomeruli, and the vessels. The effect of DCA and saline appeared to be increased very considerably if one kidney was removed before the start of the experiments, when the changes in the glomeruli and the vessels became particularly marked. The abovementioned investigators are of the opinion that these renal changes are similar to those found in subjects suffering from essential hypertension and that the administration of DCA can cause nephrosclerosis. They also consider that renal lesions of the same kind can be caused by physical strain of long duration or lengthy exposure to low temperatures. Under such conditions
there is also an enlargement of the adrenals, this is taken to indicate that the effect on the kidneys takes place through the adrenals. *Selye et al.* have summarized the results of their experiments as follows: A number of extrinsic factors (cold, strain, psychic irritation, etc.) cause a reaction in the body which presumably consists *inter alia* in an increase in the hormone production of the adrenal cortex (alarm reaction) which, on repeated and lengthy irritation, gives rise to changes in the vessels, particularly in the kidneys, similar to those found in essential hypertension.

Closer study of the illustrations of these investigators and their descriptions of the histological changes in the kidneys nevertheless raise doubts concerning their statement that a true nephrosclerosis has been produced. In mild cases the tubular lesions consist of a dilatation of the convoluted tubules with an increase in the size of the epithelial cells. Mitoses can at times be seen. There is also an increase in the weight of the kidneys. Sometimes protein casts are also seen in the tubules. The glomeruli may be somewhat enlarged but are usually unchanged. In more severe cases there is inflammatory oedema with many round cells around the renal pelvis, and in the interstitial connective tissue of the kidney. There is also atrophy of the tubular cells. Finally, in the most severe cases new connective tissue is formed in the stroma of the kidney; the glomeruli shrink and are hyalinized. Large scars may thus arise on the surface of the shrunken kidney.

The lesions are thus chiefly localized to the tubules and the interstitial tissue, whereas the glomeruli and the vessels only undergo changes in the most severe cases (very large doses of DCA). This is not in agreement with the conditions found in nephrosclerosis in which the lesions in the arterioles predominate even in the very early stages, whereas the lesions in the glomeruli and the interstitial tissue are not found until the disease (hypertension) has been present for some time. (In the experiments of *Selye et al.* the period of treatment did not as a rule exceed two months). Furthermore, it appears that renal lesions of the same type as those described by these
authors can be brought about in other ways. Knowlton et al. (1946) thus obtained only tubular lesions with DCA and saline, whereas they found lesions in the glomeruli and the interstitial tissue after the administration of serum containing antibodies against the renal substance given either alone or in combination with DCA.

Selge and his co-workers also describe damage to the cardiac muscles and the joints reminiscent of those found in acute rheumatic fever, as well as arterial lesions which they interpret as periarteritis nodosa caused by the administration of DCA in combination with saline, in unilateraly nephrectomised animals. Under the same conditions, cold and strain also produce similar changes.

Myocardial lesions of this kind have also been found in patients with Addison's disease treated with DCA, who died of cardiac insufficiency. They have also been demonstrated in experimental animals given a diet with a low potassium content. It therefore appears very probable that these lesions are caused by an insufficiency of potassium in the blood (Currens & White, 1944, Darrow & Miller, 1942, Godolf & McBryde, 1944) and that they are not identical with the myocardial lesions found in acute rheumatic fever. Periarteritis nodosa and acute rheumatic fever are generally considered to be allergic diseases in which the organic lesions are caused by an antigen-antibody reaction. The presence of similar vascular lesions in connexion with DCA treatment appears to us to indicate that the abovementioned workers have probably induced an allergy to DCA in their experimental animals, and that the lesions are thus not brought about by a specific effect of the substance administered.

We therefore consider it justifiable to discuss these questions briefly and to give an account of similar experiments made by us, particularly since a review of the work of Selge et al. has recently appeared in Nordisk Medicin (37, 89, 1948) in which the final conclusions of these investigators have, to large extent, been accepted.
EXPERIMENTS

1. (Bergstrand).

Ten male albino rats, weighing approximately 200 gm. were given daily subcutaneous injections of DCA in solution in oil (»Doca«, Pharmacia). The daily doses were 4, 2, 1, 0.5 and 0.25 mg. respectively. At the same time they also received 2—5 mg. subcutaneously, of physiological saline solution daily. Unilateral nephrectomy was not performed and they were given tap water to drink. The blood pressure was taken daily, using the method described by Williams, Harrison & Grollman (1939). One of the animals that was given 4 mg. of »Doca« daily, showed a slow rise of the systolic blood pressure from a mean of 120 mm. Hg before the experiment, to approximately 140 mm. Hg after 14 days. The blood pressure remained at this level until the end of the experiments (two months). Otherwise no changes in the blood pressure were observed in the experimental animals.

Histological examination of the kidneys revealed no changes in the glomeruli or in the vessels. There was no appreciable dilatation of the tubules. The epithelial cells of the convoluted tubules were usually large with much protoplasm. They contained large agglomerations of a structureless substance which stained deeply with acids. Here and there lysis of the nuclei and disintegration of the epithelial cells were seen. No casts of any kind were observed in the lumen of the tubules. The lesions corresponded in appearance to the degenerative phenomena with hyaline granules occasionally observed in the tubular cells. They could also be seen, although to a considerably lesser extent, in untreated control animals. There were no inflammatory changes in the interstitial connective tissue.

2. (Bechgaard).

Unilateral nephrectomy was performed on 15 albino rats, weighing approximately 200 gm. One pellet containing 20 mg. of DCA (»Percorten«, Ciba) was implanted subcutaneously in 10 of the animals. Five rats were kept as controls. Alle the ani-
mais were given 0.9 per cent saline solution to drink during the entire period of the experiment (4 months). One animal in the experimental group and one of the controls died shortly after the start of the experiments. Using the same method as in the first experimental series, recordings of the blood pressure showed a mean rise of 18 mm. Hg in the systolic pressure. Microscopic examination (performed by H. Gormsen) of the kidneys revealed dilatation of the tubules without epithelial damage in four of the experimental animals and in one control. No damage to the glomeruli or to the vascular system could be seen. In one case, however, small infiltrations of lymphocytes were observed surrounding a few slightly shrunken ischaemic glomeruli.

During the course of the experiments the mean increase in body weight was 50 gm. for the controls and 26 gm. for the experimental animals. Finally the post mortem examination revealed insignificant remains of unabsorbed pellets.

DISCUSSION

It is thus seen that we were unable to induce any definite or constant rise of the systolic blood pressure by means of the administration of DCA together with saline. In those cases in which unilateral nephrectomy was performed there was a slight rise in the systolic pressure. In the kidneys, a dilatation of the tubules was found in a few cases and in others, degenerative changes in the epithelium of the convoluted tubules could be observed. On the other hand, we were unable to demonstrate any damage to the glomeruli or to the vascular system.

We used somewhat smaller quantities of DCA than those usually administered by Selye et al. These writers have, nevertheless, described renal lesions, which they interpreted as nephrosclerosis, even with doses as small as those used in our experiments. Swingle et al. (1941) also state that the maximum effect of DCA on dogs was produced with doses not exceeding 0.5 mg. per day.

Our experiments were only performed on a small scale and
not under the best conditions. Nevertheless, we are of the opinion that, without further investigation of this problem, the statement that »large doses of DCA (possibly with the simultaneous administration of saline and unilateral nephrectomy) can give rise to nephrosclerosis« must be regarded with scepticism.

By this statement we do not mean that DCA has no effect whatever on the kidneys. In agreement with other workers we have found changes in the renal tubules in some of our experimental animals. Nevertheless we consider it doubtful whether these changes can be entirely attributed to a specific effect of DCA. Similar change have been found after the administration not only of other hormones of similar chemical structure but also of substances of completely different constitution (Longcope, 1913).

SUMMARY

Ten albino rats were treated daily for two months with subcutaneous injections of 4.0—0.25 mg. of desoxycorticosterone acetate in oil (Pharmacia) together with 2—5 ml. of saline. No definite rise of the blood pressure was observed after two months. Slight degeneration of the tubular cells of the kidney was found in some cases. No changes in the renal vascular system were observed.

Ten unilaterally nephrectomized albino rats were treated with subcutaneous implantation of pellets containing 20 mg. of desoxycorticosterone acetate (Ciba). They were given saline instead of drinking water. In the course of four months, only a slight rise of the blood pressure occurred.

Slight dilatation of the tubules or degenerative changes in the tubular epithelium was observed in some cases, but there were no changes in the vascular system or in the glomeruli.

It is concluded that under these conditions desoxycorticosterone acetate may have a slight effect on the blood pressure, but that this is neither constant nor marked. Furthermore, the damage caused to the kidney is not of the same type as that found in malignant hypertension (nephrosclerosis) in man.
REFERENCES


