# DESOXY-CORTICOSTERONE ACETATE IN ADDISON'S DISEASE WITH PRESENTATION OF A TYPICAL CASE

By Ed. J. Ryan, M.D. and E. Perry McCullagh, M.D.

Recent major advances in the management of adrenal cortical insufficiency include the use of cortical extracts[1,2,3], the use of added sodium chloride[4] and a low potassium diet[5]. Patients have been maintained in a reasonable degree of comfort with moderate activity for a number of years on such a program. The expense of the naturally derived cortical extract has been a matter of some concern, however.

Desoxy-corticosterone acetate*, produced by Steiger and Reichstein[6] and announced in 1937, is one of several synthetic adrenal cortical hormones, and is apparently identical with Kendall's substance B[7]. Reichstein and von Euw[8] have more recently demonstrated its presence in beef adrenals. Reports on its clinical application have been published by a number of investigators, including Levy-Simpson[9,10], Cleghorn et al[11], Thorn, Howard and Emerson[12], Wilkinson, Himsworth and Jones[10], Ferrebee, et al[13]. Chemically, it is closely related to progesterone[14].

We have treated six cases of Addison's disease with desoxy-corticosterone acetate for periods of six months to ten months. Dosage during various intervals of therapy has varied from 5 mgm. to as much as 20 mgm. daily. Added sodium chloride, 3 to 16 gm. per day as enteric-coated tablets, has been maintained in all cases, except during brief periods of observation. Potassium intake at first was limited in each case, but more recently severe dietary restrictions have been discontinued. Cortical extract in the form of eschatin** was given in four cases prior to initiating desoxy-corticosterone therapy.

Definite benefit was noted clinically in all cases. In two, complete symptomatic control resulted. In another two, the symptoms were materially lessened, but not completely alleviated, particularly the gastro-intestinal manifestations. In the remaining two, results were only moderately good, quite possibly a consequence of less consistent or inadequate treatment. At least 10 mgm. per day, in conjunction with other measures, was necessary before distinct initial improvement was obvious.

Blood pressure rise accompanied the use of desoxy-corticosterone in all six cases, and reached hypertensive levels in five. This has been observed particularly when 10 mgm. per day or more has been con-

*Desoxy-corticosterone acetate (Cortate) used in the treatment of these cases was supplied through the courtesy of Dr. I. Schwenk, Dr. Max Gilbert and the Schering Corporation.

**Eschatin is adrenal cortical extract produced by Parke, Davis and Co., and obtained for these studies through the courtesy of Dr. E. A. Sharpe.

tinued over a period of weeks or months, especially in conjunction with large doses of sodium chloride. The amount of clinical improvement has not paralleled the degree of hypertension. The mechanism by which the rise is brought about is not entirely clear.

Gain in body weight has likewise occurred as a result of desoxy-corticosterone therapy. In general, it may be said that the patients with the greatest weight gain showed the most striking degree of improvement.

Hemoconcentration has been corrected by the use of desoxy-corticosterone, although the amount of hemodilution has not necessarily been indicative of the degree of clinical response. The negative sodium and chloride balance of Addison's disease has likewise been converted to normal by the drug[15].

Low plasma sodium and chloride levels have tended to rise, and elevated plasma potassium has fallen with the administration of desoxy-corticosterone. These changes have not always been consistent with the clinical condition of the patient.

No alteration has been observed in temperature, pulse, pigmentation or glucose tolerance.

One case was treated by subcutaneous implantation of 400 mgm. of desoxy-corticosterone. According to Thorn[16], this should have permitted the absorption of about 2 mgm. of the substance daily. At the end of three weeks, during which time the sodium chloride intake was limited to 8 gm., and later to 3 gm. daily, she was extremely weak and drowsy, and no appreciable degree of clinical improvement could be detected. The addition of eschatin, 7.5 cc. twice a day, resulted in increased strength and almost complete abolition of muscular aching and gastro-intestinal symptoms.

Levy-Simpson and Himsworth[10] have suggested on clinical grounds that desoxy-corticosterone may not represent complete replacement therapy, an observation corroborated by our studies. In two cases, rather marked degrees of hypertension were maintained for several months without complete alleviation of symptoms. In one case, the drug was withdrawn for a month, at the end of which time the patient appeared on the verge of crisis, although the blood pressure, which had been low before treatment was begun, was still within the upper range of normal. Hemodilution has resulted without corresponding clinical improvement. In one instance, desoxy-corticosterone caused marked chloride retention without clinical changes, while the addition of eschatin did not affect the chloride balance but did produce marked clinical benefit.

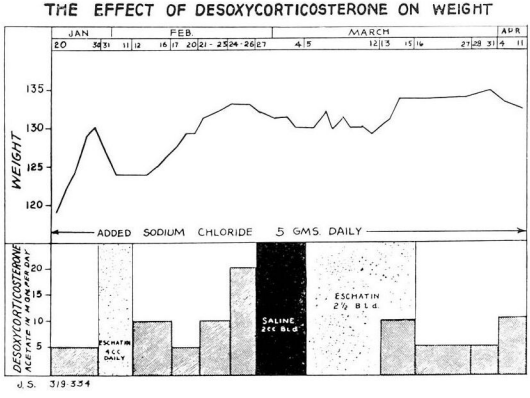
Evidences of overdosage include the hypertension previously mentioned, and edema, which has been observed in two cases. One of these patients gained 14 pounds in six days, after receiving 175 mgm. of desoxy-corticosterone with added sodium chloride in nineteen days' time.

Another patient developed hydrops of each knee after receiving repeated injections of desoxy-corticosterone at the same site in each thigh a few inches above the knee.

The following case* is presented as illustrative of several of the features described.

*The patient was a 38 year old man with symptoms highly suggestive of Addison's disease. Definite hyperpigmentation of the buccal mucosa was present. The sodium and chloride excretion test*[18] *was typical of adrenal cortical deficiency. Injections of desoxy-corticosterone acetate, 5 mgm. per day, were begun on January 20, 1939. A low potassium diet and 5 gm. of added sodium chloride daily were used concurrently. Adrenal cortical extract in the form of eschatin was given in dosage of 5 cc. and 4 cc. daily for periods as shown on the charts.*

*On this program, he gained 11 pounds in 11 days, and subsequent determinations of weight have varied with the dose of desoxy-corticosterone (chart 1).*

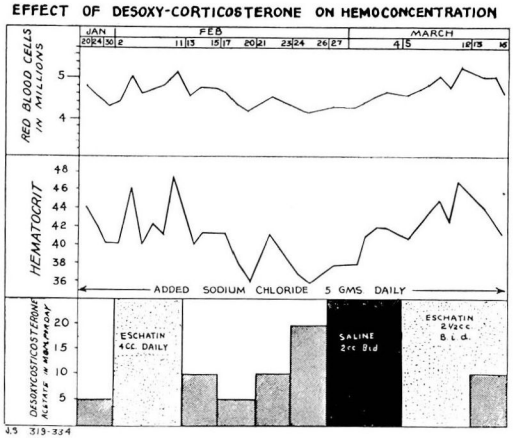



*A similar parallel has been noted between hemodilution and desoxy-corticosterone dosage, as contrasted to the relative hemoconcentration when eschatin or saline alone were given (chart 2).*

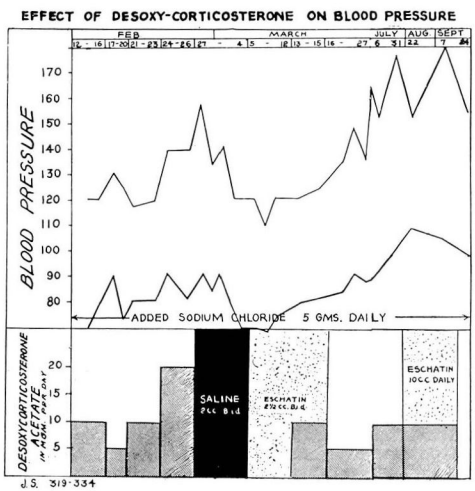
*The dose of desoxy-corticosterone varied somewhat during his entire course of treatment. Five to ten mgm. per day were given from March 12 to May 5, up to which time improvement had been very meager. During the subsequent period, the diet was gradually liberalized, eschatin was not given, and the added sodium chloride was maintained at 5 gm. per day. For three weeks in May, doses of 15 mgm. to 20 mgm. daily were given. During this period, he showed definite improvement in strength, nervous stability and general sense of well-being. This degree of improvement continued on doses of 10 mgm. per day.*

*Arterial tension rose, varying with the dosage to some extent, but has been in hypertensive range on practically all occasions since June (chart*

*This is the same as Case 3, previously reported[17].




*3). It is of interest that he has not been entirely symptom-free in spite of this.*




*There was some trend of plasma sodium and chloride to higher levels during desoxy-corticosterone therapy. Plasma potassium levels are extremely variable (table I).*

TABLE I.

| | *Sept. 4* | *Jan 7* | *Jan. 24* | *Feb. 22* | *March 3* | *May 18* | *Aug. 18* | *Aug. 24* |
|---|---|---|---|---|---|---|---|---|
| Sodium | 350 | 357 | 363 | 365 | 344 | 423 | 362 | 368 |
| Potassium | 18.9 | 22.9 | 16.9 | 16.7 | 19.2 | 19.7 | 15.5 | 18.7 |
| Chloride | 495 | 511 | 528 | . . . | . . . | 561 | . . . | . . . |

*The addition to his program of eschatin, in doses of 10 cc. per day for fifteen days was accompanied by the disappearance of practically all re-*

*maining symptoms. Withdrawal of eschatin for a month, during which time the same dose of desoxy-corticosterone was continued, resulted in a recurrence of the muscular aching, mild fatigue and abdominal distress. Subsequently, the addition of eschatin again in the same dose for twenty-five days brought distinct clinical improvement.*

From our observations we conclude that desoxy-corticosterone acetate is a valuable agent for the control of the symptoms of Addison's disease. It has a particularly powerful effect upon sodium, chloride and water balance. Overdosage effects may include arterial hypertension and massive edema of severe degree. For reasons mentioned, we believe it does not represent complete replacement therapy and should not be depended upon as the sole agent in therapy when symptoms are incompletely controlled by it or in the presence of crises.

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