TABLE II. Effect of UVR on Iron-Saturated and Iron-Unsaturated Plasma Siderophilin.

UVR time (sec)	Iron-saturated—100% TIBC, μg Fe/ml	% TIBC	C × 10² × sec⁻¹	Iron-free— 74.4% Iron-saturated—25.6% TIBC, μg Fe/ml	% TIBC	C × 10² × sec⁻¹
0	3.94	100		3.94	100	
25	2.99	75.9	1.10	2.93	74.5	1.18
50	2.61	66.3	.82	2.76	70	.71
100	2.16	54.8	.60	2.06	52.3	.65
150	1.82	46.2	.52	1.93	49.1	.47

rates, whose magnitude was correlated with the absorption coefficients of the irradiated siderophilin solutions, followed essentially first order kinetics. 3. The UV inactivation rates of iron-free and iron-saturated siderophilin were found to be the same.

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Effect of New Adrenal Steroids on Electrolyte and Water Excretion. (22173)

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Recent clinical work has indicated that the Δ^1-analogues of hydrocortisone and cortisone, namely prednisolone and prednisone, are in certain respects more potent than the parent compounds and differ from them qualitatively in that they cause little or no sodium and water retention at therapeutically effective doses(Bunim, *et al.,* 1, 2; Spies, *et al.,* 3; and others). Pechet and Bartter(4) found that in Addisonian patients prednisone would cause sodium loss whereas cortisone caused sodium retention. This action was correlated with a marked ability of the Δ^1-compounds to increase the glomerular filtration rate. In animal studies, Perlman and Tolksdorf(5) found the Δ^1-steroids more potent than their natural counterparts in causing liver glycogen deposition, eosinopenia and life-maintenance, but their effects on electrolyte excretion were unchanged. In tests designed particularly to measure sodium-retaining potency, Stafford, *et al.*(6) found prednisolone to have "very slight" activity.

It is well known that adrenal cortical hormones are necessary for the maintenance of a normal rate of water diuresis and that deficiencies in this respect are repaired effectively by hydrocortisone and cortisone, but weakly, if at all, by desoxycorticosterone. We considered it of interest to determine, therefore, the relative activity of hydrocortisone, desoxycorticosterone (DC), prednisone* and prednisolone in this test. Excretion of sodium and potassium was measured also in the water-loaded test animals. Under the experimental conditions used, hydrocortisone and cortisone are known to increase sodium and potassium as well as water excretion.

Methods. Fasted male rats weighing approximately 200 g were tested 18 hours after adrenalectomy. At the beginning of an ex-

* Prednisone (Meticorten) and prednisolone (Meticortelone) were generously supplied to us by Schering Corp.

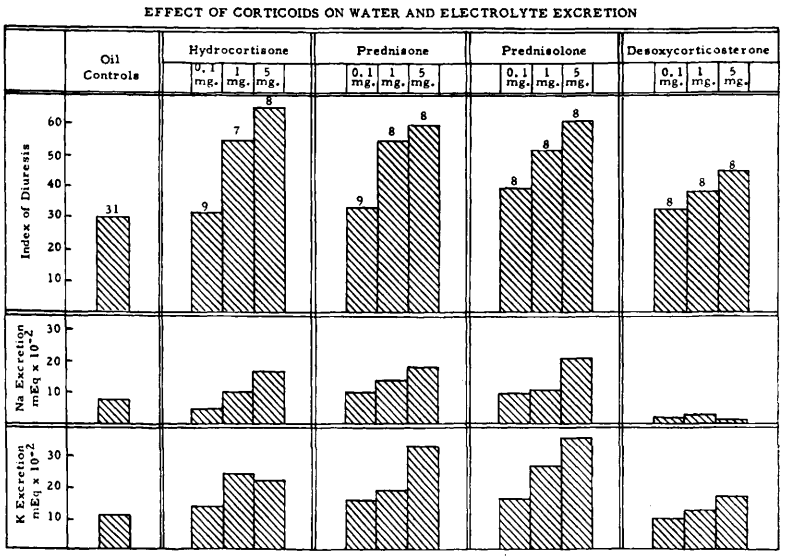

FIG. 1. Effect of various corticoids on water, sodium and potassium excretion over a 5-hr period in water-loaded adrenalectomized rats. Numbers above columns indicate number of animals on which mean values are based. "Index of Diuresis" represents in cm^2 the area under cumulative water excretion curves: increasing numbers represent increasing rates of water excretion.

periment, they were given 2 doses of distilled water (3 ml/100 cm^2 — ref. 7) an hour apart by stomach tube. The rate of water excretion was followed at half-hour intervals for 5 hours, starting from the first water load, and the total amounts of sodium and potassium excreted in that time were determined by flame photometry.

To express the effect of treatment on water excretion as one figure, the method of Krieger and Kilvington(8), as used by Ham and Landis(9), was employed: for each rat the rate of cumulative water excretion, expressed as per cent total load given, was plotted for the 5-hour period. The scale of the graph was such that 1 cm on the ordinate equaled 10% excretion of the total water load and 1 cm on the abscissa equaled 30 minutes time. The area under each curve was measured with a planimeter and the region encompassed in sq. cm designated the *Index of Diuresis*. Steroids were administered in oil, either in solution (small doses) or partial suspension (large doses) in amounts of 0.1 mg to 5 mg/rat. One-half of the total dose was injected subcutaneously at the time of adrenalectomy and one-half 30 minutes before the first water load. Control rats received sesame oil.

The significance of possible differences between the different treatments was tested primarily by analyses of variance (Snedecor, 10).† Since the nature of the results is in most respects self-evident from the graphs, statistical details are not included here.

Results. 1. *Water Excretion.* All of the steroids tested enhanced the sluggish rate of diuresis which characterizes adrenal insufficient animals and man (Fig. 1). In this respect no clearly significant differences were observed between the action of hydrocortisone, prednisone and prednisolone at any dose level. All 4 of the compounds tested gave dose-response curves with essentially parallel slopes. The response to DC, however, was definitely weaker ($P = <.01$) than any of the other compounds. None of the steroids was clearly effective at 100 μg dose levels.

2. *Potassium Excretion.* All 4 compounds increased potassium excretion (Fig. 1). Again DC was the weakest of the 4 and consistently active only at 5 mg doses.

3. *Sodium Excretion.* The only qualitative difference observed between the 4 compounds

† The authors are indebted to Mr. James Webster for statistical analysis of these data.

was that DC caused sodium retention and the other 3 steroids enhanced sodium excretion (Fig. 1). The 3 natriuretic compounds were equi-potent.

Discussion. It has been repeatedly demonstrated that the action of adrenal cortical steroids on water and electrolyte excretion can be altered or reversed depending upon a number of variables, some of which are undefined. For instance, hydrocortisone may cause either sodium retention or sodium diuresis when used in different rat tests specifically designed to detect and measure sodium-retaining activity. In other words, the response to the steroid is determined in part by intrinsic properties of the steroid itself, but equally or more so by the physiological environment with which it is provided. The present results and those of Perlman and Tolksdorf(5) suggest that those alterations in sodium-retaining properties of certain steroids resulting from the presence of a 1-2 double bond do not alter their ability to enhance sodium excretion under conditions where such activity might be expected.‡

From all of the work now available it is apparent that the Δ^1-steroids are, relative to their parent compounds, weaker in certain respects (*e.g.*, sodium retention in clinical use), stronger in several properties (anti-inflammatory effects, etc.) and of unchanged potency in others (water diuresis, etc.).

Summary. The effects of prednisone, prednisolone, hydrocortisone and desoxycorticosterone on excretion of water, sodium, and potassium, were compared in water-loaded adrenalectomized rats. All steroids stimulated water diuresis and potassium excretion. Hydrocortisone, prednisone and prednisolone were equi-potent; desoxycorticosterone was weaker. Hydrocortisone, prednisone and prednisolone stimulated sodium excretion at all doses having any effect and were again approximately equi-potent. Desoxycorticosterone had the opposite effect and caused sodium retention. The relative inability of the Δ^1-steroids to cause sodium retention under conditions of clinical use is, therefore, not associated with any comparable inability to cause natriuresis under appropriate circumstances.

‡ In addition, the authors have found (unpublished) that hydrocortisone, prednisone and prednisolone have about equal potency in antagonizing the antidiuretic effect and enhancing the natriuretic effect of exogenous vasopressin.

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