The discovery of the therapeutic properties of certain steroids has recently given rise to interesting chemical and pharmacological problems. The remarkable antiphlogistic activities of halogenated derivatives of hydrocortisone, and the disappearance of secondary effects obtained by the Δ₁-diene derivatives of cortisone, have suggested the synthesis of a steroid which joins the two chemical characteristics (Hirschmann, Miller, Beyler, Sarett, and Tishler, 1955; Stafford, Barnes, Bowman, and Meinzinger, 1955; Fried, Florey, Sabo, Herz, Restivo, Borman, and Singer, 1955; Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, 1955).

Preliminary experiments have been carried out with the following derivative: Δ₁-dehydro-9α-fluoro hydrocortisone acetate, the structural formula of which is shown in Fig. 1.

Fig. 1.—Chemical structure of Δ₁-dehydro-9α-fluoro hydrocortisone acetate.

The first biological researches show that in the liver glycogen deposition test the new steroid is 25 to 50 times as potent as hydrocortisone acetate; in the reduction of sodium excretion in the adrenal-ectomized rat it is two to five times stronger than desoxycorticosterone acetate (DCA). In the clinical field the work of Thorn, Renold, Morse, Goldfien, and Reddy (1955) makes evident that, in one normal subject and in three patients suffering from Addison's disease, Δ₁-9α-fluoro hydrocortisone acetate has 50 and 20 times more effect than hydrocortisone on electrolyte and organic metabolism respectively.

**Methods**

The new steroid was tested in three subjects with rheumatoid arthritis, in one with chronic gout, and in two with Addison's disease. Daily 4- to 10-mg. doses were administered orally for 10 days in the rheumatic diseases and 0·5 to 1 mg. for 7 days in Addison's disease.

The therapeutic properties of Δ₁-dehydro-9α-fluoro hydrocortisone acetate (Δ₁-9α-FFa) were estimated qualitatively and quantitatively, with particular reference to the comparison of activity with cortisone acetate (Ea), prednisolone (Δ₁ F), and 9α-fluoro hydrocortisone acetate (9α-FFa).

The metabolic study was carried out according to the methods described in previous papers (Villa, Ballabio, and Sala, 1955; Sala, D'Amico, Pasargiklian, Amira, and Ballabio, 1955) using the tests set out in the Table.

**Table: Laboratory Tests**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Authors</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedimentation rate</td>
<td>Westergren</td>
<td>1924</td>
</tr>
<tr>
<td>Serum mucoproteins</td>
<td>Wintzler, Devor, Mehl, and Smyth</td>
<td>1948</td>
</tr>
<tr>
<td>Plasma and urinary Na and K (by flame photometry)</td>
<td>Mosher, Boyle, Bird, Jacobson, Batchelor, Iseri, and Myers</td>
<td>1949</td>
</tr>
<tr>
<td>Plasma chloride</td>
<td>Van Slyke and Hiller</td>
<td>1947</td>
</tr>
<tr>
<td>Urinary chloride</td>
<td>Harvey</td>
<td>1910</td>
</tr>
<tr>
<td>Serum carbon dioxide</td>
<td>Van Slyke and Cullen</td>
<td>1917</td>
</tr>
<tr>
<td>Plasma and urinary endogenous creatinine</td>
<td>Bonsnes and Taussky</td>
<td>1945</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Hagedorn and Jensen</td>
<td>1923</td>
</tr>
<tr>
<td>Blood pyruvic acid</td>
<td>Friedemann, Haugen, and Kmiecik</td>
<td>1945</td>
</tr>
<tr>
<td>Plasma cholesterol</td>
<td>Bloor</td>
<td>1916</td>
</tr>
</tbody>
</table>

**Results**

**Antirheumatic Activity.**—Three patients affected by rheumatoid arthritis showed marked subjective and objective improvement within the first 48 hrs
of treatment, with relief of pain and aching on motion, reduction of stiffness and swelling, and lessening of tenderness, the improvement in function being clearly evident. The subject suffering from gout showed a subjective and objective improvement; the local improvement was accompanied with a general one, with a corresponding euphoria.

Two cases presented sleeplessness and restlessness.

Relapses occurred on discontinuing treatment in all the cases observed up to the present.

A definite decrease was observed in the sedimentation rate and in serum mucoproteins.

\( \Delta^{1-9-\alpha}\)-fluoro hydrocortisone acetate possesses all the anti-inflammatory and antirheumatic properties of cortisone and prednisone.

Comparing it with other steroids, maintenance therapy produces similar effects with doses two or three times lower than those required with prednisolone and practically equivalent to those required with 9-\( \alpha \)-fluoro hydrocortisone acetate, so that its antirheumatic activity may be considered ten–fifteen times higher than that of cortisone acetate.

### Metabolic Activity

**Salt and Water Balance.**—A marked difference between the effects of prednisolone and \( \Delta^{1-9-\alpha}\)-dehydro-9-\( \alpha \)-fluoro hydrocortisone acetate was observed at doses clinically equivalent.

In fact prednisolone (or prednisone) increases urine volume and sodium excretion without greatly affecting potassium loss; serum electrolytes not being consistently modified. On the contrary \( \Delta^{1-9-\alpha}\)-dehydro-9-\( \alpha \)-fluoro hydrocortisone acetate causes initial decrease of urine volume, strong sodium retention, and potassium loss*; successively, after 3 to 4 days of treatment, a diuresis occurs with sodium and chloride loss up to values higher than the basal ones (Fig. 2).

It is worth mention that a similar pattern in the sodium balance was observed in the same cases, treated with equivalent doses of 9-\( \alpha \)-fluoro hydrocortisone acetate.

In the serum a sharp fall in potassium to 2·5 to 2 mEq/l., and a slight increase in sodium concentration, was observed; haematocrit values (per cent. cells) are constantly decreased, as an expression of hemodilution (Fig. 3).

The marked activity of \( \Delta^{1-9-\alpha}\)-dehydro-9-\( \alpha \)-fluoro hydrocortisone acetate on water and electrolyte metabolism causes an increase in body weight, blood pressure, and heart size, to a decrease of heart rate, and alterations in the electrocardiogram (lengthening of QT-space, displacing of ST-segment, depression of T-wave).

In adrenal insufficiency, daily doses of 0·5 to 1 mg. \( \Delta^{1-9-\alpha}\)-dehydro-9-\( \alpha \)-fluoro hydrocortisone acetate are able to normalize electrolyte metabolism or even to cause sodium retention and potassium loss.

In these preliminary experiments we have not

---

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>( \Delta^{1-9-\alpha}) FF ( \alpha ) (40 mg/daily)</th>
<th>( \Delta^{1-9-\alpha}) FF ( \alpha ) (6-8 mg/daily)</th>
<th>( 9-\alpha) FF ( \alpha ) (8-10 mg/daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematocrit Cells (%)</strong></td>
<td>47</td>
<td>48</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td><strong>Plasma K (mEq/l.)</strong></td>
<td>5</td>
<td>5·3</td>
<td>2·8</td>
<td>1·9</td>
</tr>
<tr>
<td><strong>Plasma Cl (mEq/l.)</strong></td>
<td>110</td>
<td>110</td>
<td>104</td>
<td>98</td>
</tr>
<tr>
<td><strong>Plasma Na (mEq/l.)</strong></td>
<td>146</td>
<td>145</td>
<td>158</td>
<td>154</td>
</tr>
<tr>
<td><strong>Body Weight (kg)</strong></td>
<td>46·7</td>
<td>45·4</td>
<td>48·7</td>
<td>46·1</td>
</tr>
<tr>
<td><strong>Urine K (mEq/24 hr)</strong></td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Urine Cl 250 (mEq/24 hr)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Urine Na 250 (mEq/24 hr)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Urine Volume (ml/24 hr)</strong></td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

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Fig. 2.—Metabolic balance in a woman aged 43 with rheumatoid arthritis treated with various steroids.
EFFECTS OF Δ¹-DEHYDRO-9-ALPHA-FLUORO HYDROCORTISONE ACETATE

<table>
<thead>
<tr>
<th>PLASMA VALUES</th>
<th>BEFORE TREATMENT</th>
<th>ΔE or ΔF</th>
<th>9αFF a</th>
<th>Δ9αFF a</th>
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</thead>
<tbody>
<tr>
<td>HAEMATOCRIT 45</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CELLS (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na (mEq/l.)</td>
<td>150</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl (mEq/l.)</td>
<td>110</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K (mEq/l.)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- R.A. and GOUT
- ADDISON'S DISEASE

The treatment, a presented acetate is acetate sone mg. administered the new Al-dehydro-9-o-fluoro concerned, pneumatic four pyruvic acid fasting with the urine increasing Addison's disease, a these cases not did (100-200 y). doses chlorides remain almost steroid, administered of the obtained electrolytes in three patients with rheumatoid arthritis, one with gout, and two with Addison's disease.

gone below a daily 500 γ dose, but the intensity of the obtained effect suggests the use of reduced doses (100-200 γ).

In plasma a loss of potassium and a moderate increase in sodium and CO₂ may occur, while the chlorides remain almost unchanged (Fig. 3).

A fall in the ratio Na/K (from 0·41 to 0·24) in the non-stimulated saliva was noticed in one case after a 3-days treatment with 500 γ of the new steroid, administered daily.

As far as the diuretic activity of corticoids is concerned, Δ¹-dehydro-9-α-fluoro hydrocortisone acetate is even more efficient than prednisolone when increasing the urine output after a water load in Addison's disease, at doses 10-20 times smaller.

Carbohydrate Metabolism.—In three out of the four rheumatic patients treated up to date, who presented a normal glucose tolerance test before the treatment, Δ¹-dehydro-9-α-fluoro hydrocortisone acetate did not modify glucose tolerance and did not cause glycosuria.

It is to be noticed that a decrease in glucose tolerance had previously been caused in two out of these cases by treatment with prednisolone (30-40 mg. administered daily).

In one patient, a woman aged 43, 8-mg. doses of the new steroid daily for 10 days caused diabetes with fasting blood glucose of 160 mg. per cent., pyruvic acid of 2·45 mg. per cent., daily glycosuria of 15-20 g., and a decrease in glucose tolerance (Fig. 4). It must be noted that this patient showed a slight decrease in carbohydrate tolerance before treatment.

![Figure 4](http://ard.bmj.com/)

Comment

Practical considerations prevented us from studying a large series of patients, but our results allow us to define the clinical and metabolic activity of Δ¹-dehydro-9-α-fluoro hydrocortisone acetate.

From the clinical point of view this steroid shows a strong antirheumatic action when administered in...
ANNALS OF THE RHEUMATIC DISEASES

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doses remarkably inferior to those needed with
cortisone and prednisone or prednisolone. According
to our experiments, the new steroid is two to
times more active than prednisone and 10 to
25 times more active than cortisone acetate.
However, the introduction of a double bond in
C₁–C₉ is not able to avoid the strong mineral-
corticoid activity of 9-α-fluoro hydrocortisone
acetate, so that the high activity against electrolyte
metabolism prevents the practical use of Δ₁⁻9-α-
fluoro hydrocortisone acetate, at least in rheumatic
diseases.

Sodium retention, although temporary and
reversible, may be dangerous in the presence of
abnormal cardiocirculatory conditions.

The constant and lasting decrease of plasma
potassium causes a depletion in intracellular
potassium and may cause serious functional changes
in the nervous and circulatory systems, as demon-
strated by the electrocardiogram.

On the other hand, the high mineralcorticoid
activity of Δ₁⁻dehydro-9-α-fluoro hydrocortisone
suggests that it should be used in Addison’s
disease to normalize the metabolism; efficient doses of this
new steroid in Addison’s disease seem about the
same size with aldosterone.

Δ₁⁻9-α-fluoro hydrocortisone acetate appeared
to have a diabetogenic effect, but the small number of
patients treated prevents us from establishing the
importance of this side-effect as compared with
cortisone, prednisone, and prednisolone.

Summary

(1) The clinical and metabolic effects of Δ₁-
dehydro-9-α-fluoro hydrocortisone acetate were
determined in four patients affected by rheumatic
diseases, and in two patients with adrenal
insufficiency.

(2) In rheumatic disease the compound is two to
three times more potent than prednisone, and 10–25
times more active than cortisone acetate. In
Addison’s disease daily doses of 0.5 to 1 mg. are
able to reduce most of the metabolic alterations to
normal.

(3) The marked effect on electrolyte metabolism
(sodium retention and potassium loss) prevents the
practical use of this drug in rheumatic diseases;
but it may be usefully employed to treat adrenal
insufficiency.

The authors wish to thank Merck and Co., Rahway,
N.J., for the Δ₁⁻dehydro-9-α-fluoro hydrocortisone
acetate, the 9-α-fluoro hydrocortisone acetate, and the
prednisolone used in this study.

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Effets cliniques et métaboliques de l’acétate de
Δ₁⁻dehydro-9-α-fluoro hydrocortisone

Résumé

(1) Les effets cliniques et métaboliques de l’acétate de
Δ₁⁻dehydro-9-α-fluoro-hydrocortisone furent déterminés
chez quatre sujets atteints de maladie rhumatismale et
chez deux sujets atteints d’insuffisance suprarrenal.

(2) Pour les cas de rhumatisme, le produit est deux ou
trois fois plus puissant que la prednisone et 10 à 25 fois
plus actif que l’acétate de cortison.
Dans la maladie d’Addison des doses quotidiennes de 0,5 à 1 mg.
sont capables de ramener la plupart des altérations métaboliques
da la normale.

(3) L’effet marqué sur le métabolisme electrolyte
(retention du sodium et perte du potassium) empêche
l’utilisation pratique de ce médicament dans les maladies
rhumatismales, mais il peut être utilement employé
pour traiter l’insuffisance surrenale.

Efectos clínicos y metabólicos del acetato de
Δ₁⁻dehydro-9-α-fluoro hidrocortisona

Sumario

(1) Se determinaron los efectos clínicos y metabólicos
del acetato de Δ₁⁻dehydro-9-α-fluoro hidrocortisona
en cuatro enfermos afectos de enfermedades reumáticas
y en dos con insuficiencia suprarrenal.

(2) En la enfermedad reumática este compuesto es
dos o tres veces más poderoso que prednisone y 10 a 25
tiempas más activo que el acetato de cortisona. En
la enfermedad de Addison dosis diarias de 0,5 a 1 mg.
pueden normalizar la mayoría de las alteraciones metabólicas.

(3) El efecto marcado sobre el metabolismo electro-
lítico (retención de sodio y perdida de potasio) previene
el uso práctico de este medicamento en las enfermedades
reumáticas; se puede, sin embargo, emplearse útilmente
para tratar insuficiencia suprarrenal.
Clinical and Metabolic Effects of Δ¹-Dehydro-9-Alpha-Fluoro Hydrocortisone Acetate
L. Villa, G. Sala and C. B. Ballabio

doi: 10.1136/ard.15.3.237

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