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# Hypertension, Increased Aldosterone Secretion and Low Plasma Renin Activity Relieved by Dexamethasone

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**A father and son are described with a condition characterized by benign hypertension, potassium deficiency, increased aldosterone secretion rate (ASR), raised plasma volume and suppressed plasma renin activity (PRA). There were intermittent elevations of urine 17-ketosteroids and 17-hydroxycorticoids (17-OHCS) but no increase in urine THS, normal circadian rhythm of plasma 17-OHCS, and normal urine 17-OHCS response to dexamethasone and intravenous ACTH. Plasma ACTH and corticosterone secretion were not elevated. Pregnanetriol excretion was normal but urine pregnanediol was increased. At operation on the father no adrenal tumour was found; the excised left adrenal weighed 7 g. and showed nodular cortical hyperplasia; juxtaglomerular cells showed only occasional granules. Following operation hypertension persisted and ASR was half the preoperative value. All abnormalities in father and son were relieved by dexamethasone (DM) 2 mg. daily. The condition recurred following cessation of DM but was relieved by a second course of treatment. No such response to DM was seen in a normal subject or in a patient with Conn's syndrome. For a number of reasons it is suggested that patients with hypertension, increased ASR and low PRA be given a trial of dexamethasone treatment before undergoing adrenal surgery.**

**Les auteurs ont observé un père et son fils, dont l'état était caractérisé par une forme bénigne d'hypertension, une insuffisance de potassium, une augmentation de la vitesse de sécrétion d'aldostérone (VSA), une augmentation du volume plasmatique et la suppression de l'activité de la rénine plasmatique (ARP). On a noté des augmentations intermittentes des 17-cétostéroïdes et des 17-hydroxycorticostéroïdes (17-OHCS) urinaires, mais pas d'augmentation du THS urinaire. Le rythme du 17-OHCS plasmatique et la réaction des 17-OHCS urinaires à la dexaméthasone et à l'ACTH étaient normaux. La concentration plasmatique d'ACTH et la sécrétion de corticostérone n'étaient pas augmentées. L'excrétion de prégnantriol était normale, mais la concentration urinaire de prégnandiol était augmentée. L'opération effectuée sur le père ne révéla aucune tumeur surrénale; la surrénale gauche excisée pesait 7 g. et montrait une hyperplasie nodulaire du cortex; les cellules juxtaglomérulaires ne contenaient que de rares granules. Après l'opération, l'hypertension a persisté et la valeur de la VSA n'était que la moitié de sa valeur pré-opératoire. Toutes les anomalies, tant chez le père que chez le fils, ont disparu sous l'influence d'une dose quotidienne de 2 mg de dexaméthasone (DM). Ces anomalies ont réapparu après suspension du traitement, mais ont disparu après une seconde cure. Un sujet normal et un autre qui présentait un syndrome de Conn n'ont pas réagi de cette façon à la dexaméthasone. Pour plusieurs raisons, on propose d'essayer la dexaméthasone chez les malades qui présentent de l'hypertension, une augmentation de la VSA et une diminution de l'ARP, avant de songer à précéder à une intervention surgicale sur les surrénales.**

IT IS generally recognized that hypertension with increased aldosterone secretion may occur in three conditions: renal artery stenosis,[1] severe to malignant hypertension,[2] and primary aldosteronism due to an adrenocortical tumour (Conn's syndrome).[3] Separation of the third from the first two conditions has been made possible by the finding that increased plasma volume[4] and suppressed plasma renin activity[5] are characteristic of Conn's syndrome.

The present report describes what we believe to be a new condition, one which mimics Conn's syndrome but, unlike that syndrome, is relieved by dexamethasone 2 mg./day. The condition occurred in a father and son and was characterized by benign hypertension, potassium depletion, increased aldosterone secretion, increased plasma volume and undetectable plasma renin activity. Additional findings were a modest increase in pregnanediol excretion and *intermittent* elevations of urine 17-ketosteroids and 17-hydroxycorticoids.

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## METHODS AND MATERIALS

Sodium and potassium were measured by flame photometry, magnesium with a Perkin-Elmer Model 303 atomic absorption spectrophotometer and chloride with a Cotlove chloridometer. The Astrup method was used to determine capillary blood pH and plasma bicarbonate. Urine pH was estimated with nitrazine paper. Blood and plasma volumes were measured by means of radioiodinated serum albumin;[6] the values are expressed as percentage deviations from predicted normal values calculated on the basis of height and weight.[7] Serum "true" creatinine was estimated by the method of Haugen and Blegen,[8] urine creatinine by the procedure of Lambert.[9] Endogenous creatinine clearances were corrected to a surface area of 1.73 sq.m. The normal range for creatinine clearance using the "true" creatinine technique has been established by Doolan, Alpen and Theil.[10] Plasma renin activity (PRA) determinations were performed in the laboratory of Dr. Jacques Genest; in all instances the blood was drawn between 11 a.m. and 12 noon after the patient had been upright for approximately four hours.[11]

Plasma 17-hydroxycorticoids (17-OHCS) were measured by the method of Peterson, Karrer and Guerra,[12] urinary 17-OHCS by the procedure of Reddy[13] and urine 17-ketosteroids (17-KS) by a modification of the technique of Drekter *et al.*[14] whereby the colour reaction was carried out according to Callow, Callow and Emmens.[15] The method of Henke, Dee and Jacobson[16] was used to estimate 3$\alpha$,17$\alpha$,21-trihydroxy-pregnan-20-one(THS). Corticosterone secretion rates were determined by a modification of the technique of Bledsoe *et al.*,[17] and the secretion rates of aldosterone and of 11$\beta$,18,21-trihydroxy-$\triangle^4$-pregnen-3,20-dione (18-hydroxycorticosterone, 18-OH-B) by the procedure of Ulick and Vetter.[18] For the secretion rates, urine was collected for 48 hours after intravenous injection of the tritiated hormone; all secretion rates are reported in terms of $\mu$g. per day. When the $H^3/C^{14}$ ratio in the urinary metabolite was greater than 20, the value is reported as less than the value calculated using a $H^3/C^{14}$ ratio of 20. Urine estrone, 17$\beta$-estradiol and estriol were measured by the method of Hobkirk and Nilson[19] (performed in Dr. R. Hobkirk's laboratory), urine total estrogens by a modification of the technique of Ittrich,[20] and urine pregnanediol and pregnanetriol by the procedure of Stern.[21] The latter three determinations were done in Dr. S. Solomon's laboratory. Plasma ACTH was measured in Dr. G. W. Liddle's laboratory.[22] Unless otherwise stated, all blood samples were drawn at 8 a.m. (before breakfast) and all urines were collected from 8 a.m. to 8 a.m.

In studies carried out in hospital the patients were maintained on constant diets and their posture and activity were controlled.[23] All blood pressures were taken with the patient supine. Outpatient blood pressures were taken at the same time of day. In-patient blood pressures were determined four times daily; the values shown in the figures are mean values. The heparin-like compound used was N-formyl chitosan polysulfuric acid (R01-8307, Hoffmann-LaRoche).[23] The preparation of ACTH for intramuscular injection was Duracton (Nordic Biochemicals Ltd., Montreal, P.Q.). The two-day intravenous ACTH test was performed according to Laidlaw *et al.*[24] The dexamethasone suppression test was carried out in the manner described by Liddle.[25] The angiotensin infusion test was performed as outlined by Kaplan and Silah.[26]

## CASE REPORTS

The father J.S., a 41-year-old pharmacist, was first told he had hypertension at age 19 at a pre-employment examination. At age 30, his blood pressure—the earliest reading known to us—was 170/100 mm. Hg. Subsequently, similar blood pressure readings were obtained on many occasions by insurance examiners. The hypertension was asymptomatic. In the summer of 1964, at age 41, he was given reserpine 0.2 mg. daily for two months without effect on the hypertension. Subsequently he received chlorthalidone 100 mg. daily. The drug was discontinued after a week because of the appearance of leg cramps and the finding of a serum potassium level of 2.0 mEq./l. He was admitted to the Toronto General Hospital on October 5, 1964.

The son, L.S., aged 16, had throbbing morning headaches for one year before the discovery of hypertension at age 13 at the time of appendectomy. On reserpine 0.2 mg. and chlorthalidone 50 mg. daily his blood pressure was maintained at about 135/90. These drugs were discontinued one month before his admission to the Toronto General Hospital on June 22, 1965.

Of the 11 siblings of the father of J.S. three are known to have died of a cerebrovascular accident, two in their 40's and one in his 60's. Two of J.S.'s first cousins are known to have hypertension. His wife and 3-year-old daughter have normal blood pressures. The families of J.S. and his wife are to be studied further.

On admission the father's blood pressure was 190/110, the son's 180/120. In both there were grade I changes (according to Keith-Wagener classification) in the optic fundi. The patients were of average height (father 69 in., son 67 in.) but slightly overweight (father 174 lb., son 163 lb.). Neither had signs of Cushing's syndrome. Fasting eosinophil count[27] was 150/c.mm. in the father and 128/c.mm. in the son. Fasting blood sugar, measured by the method of Hoffman[28] modified for the autoanalyser (normal range: 60-100 mg. %), was 86 mg. % in the father and 68 mg. % in the son. There was no evidence of hypothyroidism, acromegaly, coarctation of the aorta or lupus erythematosus. Vanillylmandelic acid (VMA) excretion[29] was normal in both patients, 5.2 mg./day in

the father, 4.0 mg. in the son (normal: less than 7.0 mg.). In both father and son examination of white blood cells revealed a normal male chromosome pattern, 46/XY.

The periods of study and the principal studies in each were as follows:

*Father:*

October 6-November 12, 1964, in hospital: R01-8307 given October 26-November 3.
January 1-9, 1965, in hospital: Recheck.
March 5-April 4, 1965, in hospital: Spironolactone (Aldactone A) given March 12-24.
April 3-7, 1965, outside hospital: Dexamethasone suppression test.
April 17-May 3, 1965, in hospital: Left adrenalectomy, April 19.
June 28-July 2, 1965, outside hospital: Plasma renin study on low sodium diet.
July 12-17, 1965, in hospital: Recheck.
July 18-October 12, 1965, outside hospital: Aldactone A given July 27-September 7; dexamethasone started September 27.
October 12-17, 1965, in hospital: On dexamethasone.
October 17, 1965-January 9, 1966, outside hospital: On dexamethasone until October 24.
January 10-February 2, 1966, in hospital: Dexamethasone restarted January 22.
February 2-April 18, 1966, outside hospital: On dexamethasone until March 9.
April 18-May 6, 1966, in hospital: ACTH intramuscularly April 27-May 3.
May 22-26, 1966, in hospital: ACTH intravenously May 24, 25.
May 26-August 11, 1966, outside hospital: Dexamethasone restarted June 23.
August 11-15, 1966, in hospital: Recheck on dexamethasone.

*Son:*

June 23-August 1, 1965, in hospital: Dexamethasone given July 3, 4; R01-8307 given July 13-23.
August 20-25, 1965, in hospital: Recheck.
August 25-December 24, 1965, outside hospital: On dexamethasone September 27-November 20.
December 24, 1965—January 17, 1966, in hospital: Dexamethasone restarted January 3.
January 17-April 11, 1966, outside hospital: On dexamethasone until February 19; cortisol started February 20.
April 11-15, 1966, in hospital: Recheck on cortisol.
April 15, 1966 to present, outside hospital: On cortisol until May 29; dexamethasone restarted May 30.

## RESULTS

### A. *Control Studies of Electrolyte and Renal Function*

The control values for electrolyte and renal function are shown in Table I. Unless otherwise stated, these values were obtained in both patients during the first hospital admission. The father showed hypernatremia. Both father and son had a hypokalemic alkalosis and a urinary pH which was somewhat higher than normal. The electrocardiogram (ECG) in both showed u waves and evidence of left ventricular hypertrophy. The blood volume measurements were made on January 19, 1966, for J.S. and December 31, 1965, for L.S. Blood volume in the father was 5900 ml., 115% of the predicted value;[7] in the son blood volume was 5500 ml., 112% of the predicted value. With increased blood volumes and a low normal venous hematocrit (uncorrected for trapped plasma) of 43% for the father and 40% for the son, it is clear that in both patients plasma volume was increased. Apart from specific gravity and pH, urinalysis was normal in both. Endogenous creatinine clearance and PSP excretion were also normal in both patients. Each showed a mild impairment of renal concentrating power, probably a reflection of potassium deficiency. Split renal function was normal in the son. In the father, with water diuresis, sodium concentration was equal on the two sides but there was a 45% lower volume and 55% lower creatinine clearance on the left; with urea diuresis, the volume difference remained but creatinine clearance became equal on the two sides and sodium concentration on the left was 50% of that on the right. The significance of these findings is not clear. On aortography the renal arteries were normal in both patients. Plasma renin activity was undetectable on several occasions in both father and son: on a constant normal sodium intake on three occasions in the father and on two occasions in the son. The second measurement in the son was done on the day following 11 days of R01-8307 administration. PRA was also undetectable on the fourth day of a low sodium intake (17 mEq./day)

TABLE I.—CONTROL VALUES FOR ELECTROLYTE AND RENAL MEASUREMENTS. ALL DETERMINATIONS WERE MADE DURING THE FIRST HOSPITAL ADMISSION EXCEPT FOR THE MEASUREMENTS OF BLOOD VOLUME AND CERTAIN OF THE ESTIMATES OF PLASMA RENIN ACTIVITY.

| *Determination* | *Father J.S.* | *Son L.S.* |
|---|---|---|
| Serum Na, mEq./l. | 145–148 | 142–145 |
| Serum K, mEq./l. | 2.5–3.1 | 3.2–3.8 |
| Serum Cl, mEq./l. | 100–102 | 102–107 |
| Serum Mg, mEq./l. (N 1.4–2.1) | 1.3–1.6 | 1.7 |
| Plasma bicarbonate, mEq./l. (N 23–28) | 34 | 30 |
| Blood pH (N 7.34–7.44) | 7.44 | 7.36 |
| Blood volume | +15% | +12% |
| Urine pH | 6.5 | 6.5 |
| Urine culture | Negative | Negative |
| Endogenous creatinine clearance, ml./min. (N 65–162) | 98 | 122 |
| Fishberg concentration test (maximum specific gravity) | 1021 | 1023 |
| PSP excretion | 29% in 15 min. 78% in 120 min. | 21% in 15 min. 78% in 120 min. |
| Split renal function | Abnormal | Normal |
| Aortogram | Normal | Normal |
| Plasma renin activity | Undetectable | Undetectable |

in both father and son. With the angiotensin infusion test in the father (April 12, 1965) a rise of 20 mm. Hg in blood pressure was achieved at a rate of 4 mμg./kg./min.; this value lies within the range for patients with essential hypertension or primary aldosteronism but below the range for patients with renovascular hypertension.[26]

On the third day of a 17 mEq. sodium diet urinary sodium fell to 17 mEq. for the father and 16 mEq. for the son; this finding would appear to exclude a renal sodium-losing state. The circadian rhythm of urine volume and sodium was reversed in both patients. On a four-day collection from the father, January 16-19, 1966, stool sodium was 2.7 mEq., and potassium 10 mEq./day, both normal values.

### B. *Steroid Studies*

The control values for steroid secretion and excretion are shown in Table II. Unless otherwise indicated the values were obtained in both patients during the first hospital admission.

TABLE II.—CONTROL VALUES FOR STEROID SECRETION AND EXCRETION. WHEN DETERMINATIONS WERE NOT DONE DURING THE FIRST HOSPITAL ADMISSION THE DATES ON WHICH THEY WERE PERFORMED ARE INDICATED WITHIN THE PARENTHESES. "EXC." MEANS EXCRETION.

| *Determination* | *Father J.S.* | *Son L.S.* |
|---|---|---|
| 17-KS exc., mg./day (N 8-20) | 17.4-29.2 | 16.4-29.3 |
| 17-OHCS exc., mg./day (N 1-10) | 7.8-13.3 | 4.8-9.2 |
| THS, mg./day (N < 2) | 0 (April 1 and Dec. 11/65) | 0.3 (Dec. 11/65) |
| Plasma 17-OHCS, μg.% (N, 8-10 a.m., 6-25) | 16.7 | 12.2 (Dec. 26/65) |
| Corticosterone SR, mg./day (N 1.5-4)* | 2.5 (Jan. 15-16/66) | 3.4 (Dec 27-28/65) |
| | 2.4 (Jan. 17-18/66) | 3.7 (Dec. 29-30/65) |
| Aldosterone SR, μg./day (N 70-210) | 700 | 400 |
| 18-OH-B SR, μg./day (N 145-460) | 2560 | — |
| Pregnanediol, mg./day (N 0.4-1.4) | 2.9 (Jan. 14/66) | 2.7 (Jan. 1/66) |
| Pregnanetriol, mg./day (N 0.7-2.5) | 1.2 (Jan. 14/66) | 1.7 (Jan. 1/66) |
| Total estrogens, μg./day (N 18-35) | 78 (Jan. 14/66) | 64 (Jan. 1/66) |
| Estrone, μg./day (N 0.8-7.1) | 7.5 (Jan. 19/66) | 7.1 (Dec. 12/65) |
| 17β-estradiol, μg./day (N 0.4-1.7) | 2.2 (Jan. 19/66) | 1.7 (Dec. 12/65) |
| Estriol, μg./day (N 1.5-10.4) | 3.4 (Jan. 19/66) | 2.3 (Dec. 12/65) |

*The normal range given for corticosterone SR is that of Peterson[30] who used the same urinary metabolite, 3α, 11β, 21-trihydroxy-5α-pregnan-20-one (allo THB), as do the authors.

### 1. *17-Ketosteroids and Glucocorticoids*

Over the long period of study in both patients changes occurred in the control excretion of 17-KS and 17-OHCS. In contrast, apart from a change in J.S. following operation, control aldosterone secretion remained elevated and relatively constant. As illustrated in Fig. 1, the father, when first seen in October 1964, had an intermittently elevated 17-KS and 17-OHCS excretion and increased aldosterone secretion. Three and six months following left adrenalectomy, his aldosterone secretion rate was still elevated but only one-half the preoperative value. Urine 17-KS remained high three months after surgery but were normal six months later, while urine 17-OHCS were only occasionally elevated after adrenalectomy. The son, when first seen in June 1965, was found to have a high aldosterone secretion and intermittently elevated 17-KS and 17-OHCS excretion. Subsequently aldosterone secretion and urine 17-OHCS changed little but urine 17-KS fell to normal. The reasons, apart from operation on the father, for the changes in 17-KS and 17-OHCS excretion are not clear. Both patients were given R01-8307 and dexamethasone during their studies and the father received Aldactone A as well (see list of studies at end of case report).

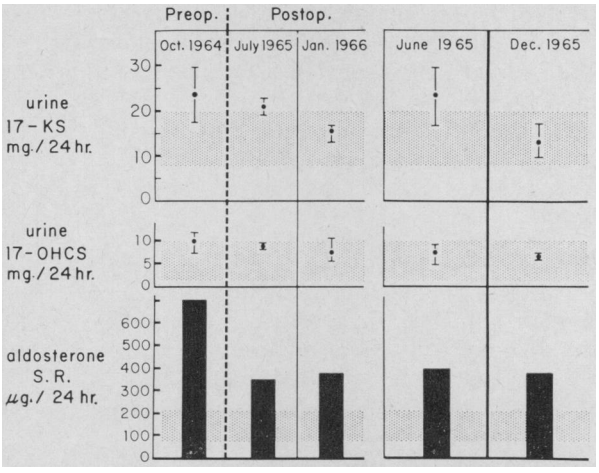


Fig. 1.—Change in secretion or excretion of certain steroids over period of study in J.S. (left) and L.S. (right). The mean and range are shown for 17-KS and 17-OHCS. The number of values involved for 17-KS and 17-OHCS were 16, 5 and 11 respectively for the three periods in the father and 3 and 10 for the two periods in the son. The shaded areas indicate normal ranges.

No increase in THS excretion was found by the colorimetric technique.[16] Furthermore, no THS was detected in either patient when urine extracts were chromatographed on paper in Dr. S. Solomon's laboratory. Corticosterone secretion was normal in both patients. All of these determinations were made when urine 17-KS and 17-OHCS were within normal limits. In the father, at a time when 17-KS and 17-OHCS excretion was normal but aldosterone secretion was increased, plasma drawn at 6:30 a.m. contained 0.2 milliunits per cent of ACTH, a normal value.[22]

In both patients there was a normal circadian rhythm of plasma 17-OHCS (Fig. 2). Before the small-dose dexamethasone test[25] in both subjects, the urine 17-OHCS were increased; they suppressed normally on dexamethasone (Fig. 3). A two-day intravenous ACTH test carried out in the father at a time when urine 17-KS and 17-OHCS were normal showed a normal urine 17-OHCS response[24]

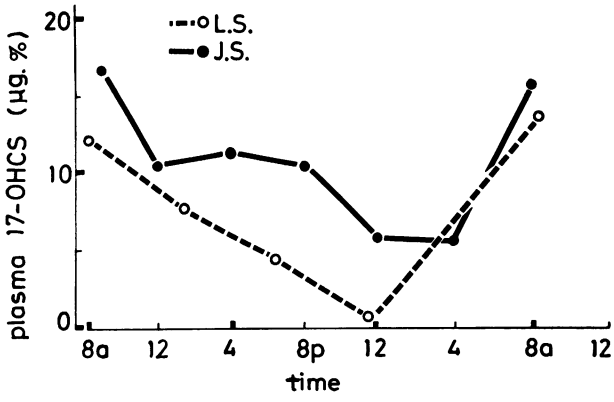


Fig. 2.—Circadian rhythm of plasma 17-OHCS in J.S. (determinations done on October 20, 1964) and L.S. (determinations done on December 26, 1965).

(Fig. 4). In this test corticosterone secretion rose from 2.5-15 mg./day in response to ACTH.

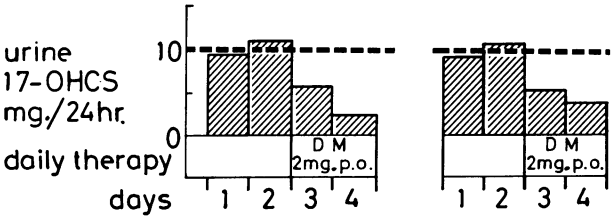


Fig. 3.—Small-dose dexamethasone test in J.S. (left) and L.S. (right). The interrupted horizontal line indicates the upper limit of the normal range of urine 17-OHCS.

## 2. *Mineralocorticoids*

As already stated, control aldosterone secretion was consistently elevated in both patients. 18-OH-B secretion, measured only in the father, was 2560 µg./day, a high value.

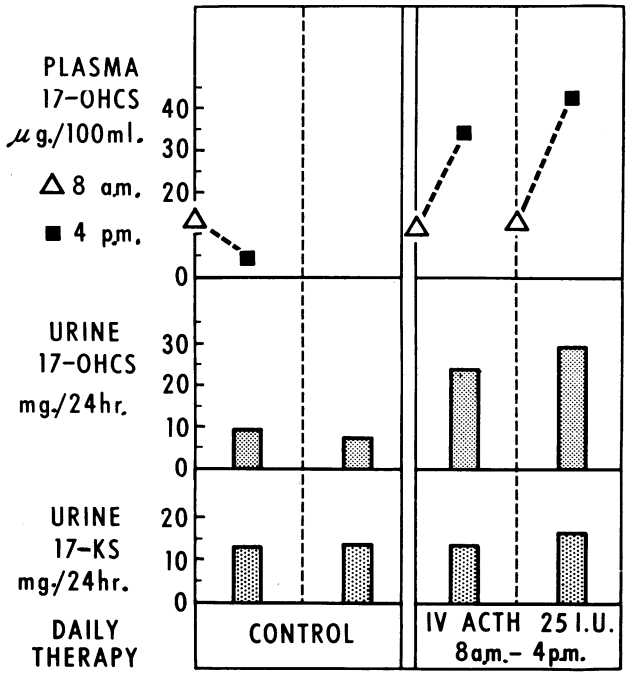


Fig. 4.—Two-day intravenous ACTH test in J.S.

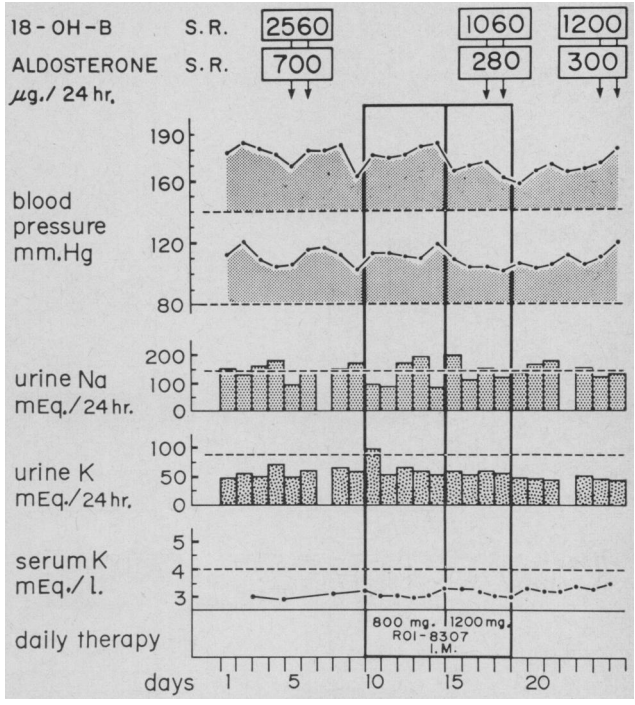


Fig. 5.—Influence of R01-8307 in J.S. The horizontal lines on the urine sodium and potassium sections indicate determined intakes. The vacant areas on these sections indicate days on which the urine was incompletely collected.

The influence of R01-8307 in J.S. and L.S. is shown in Figs. 5 and 6. This compound is known to produce a marked fall in the aldosterone secretion rate (ASR).[23] Aldosterone secretion fell in both father and son but only in the son did it fall to within the normal range. Blood pressure did not

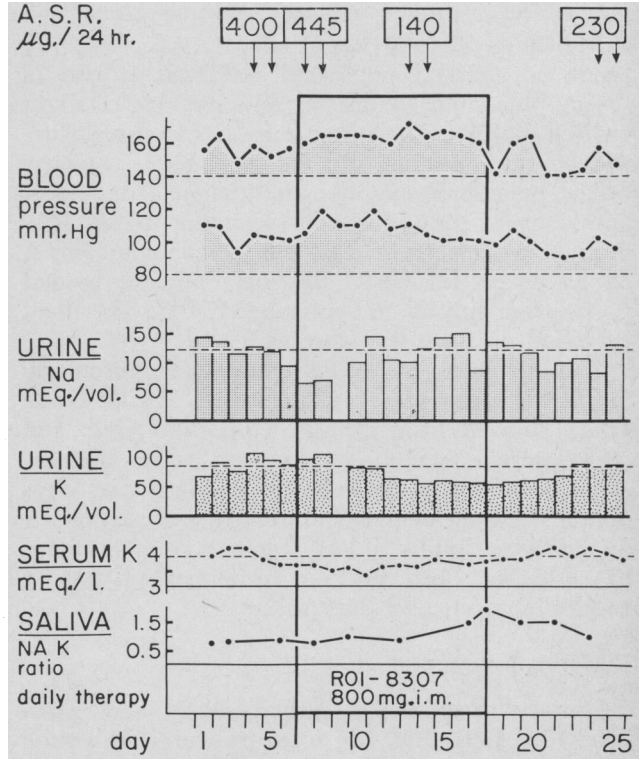


Fig. 6.—Effect of R01-8307 in L.S.

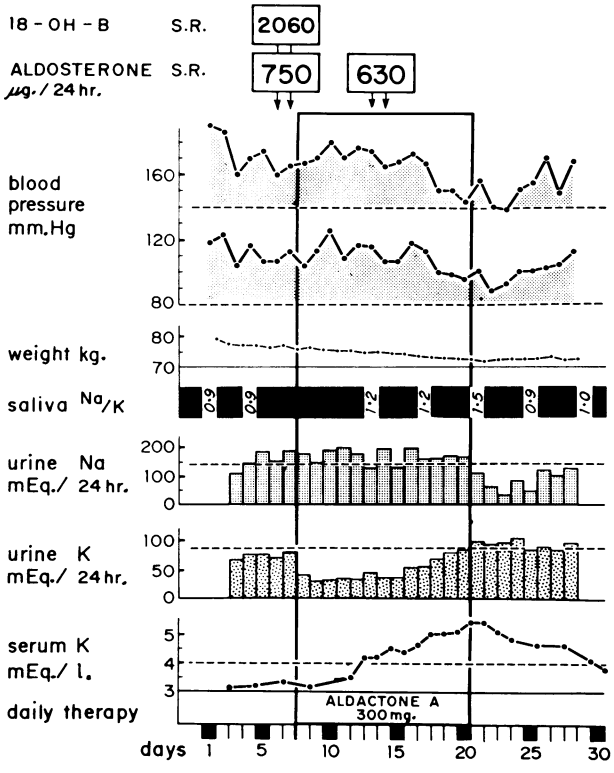


Fig. 7.—Influence of aldactone A in J.S.

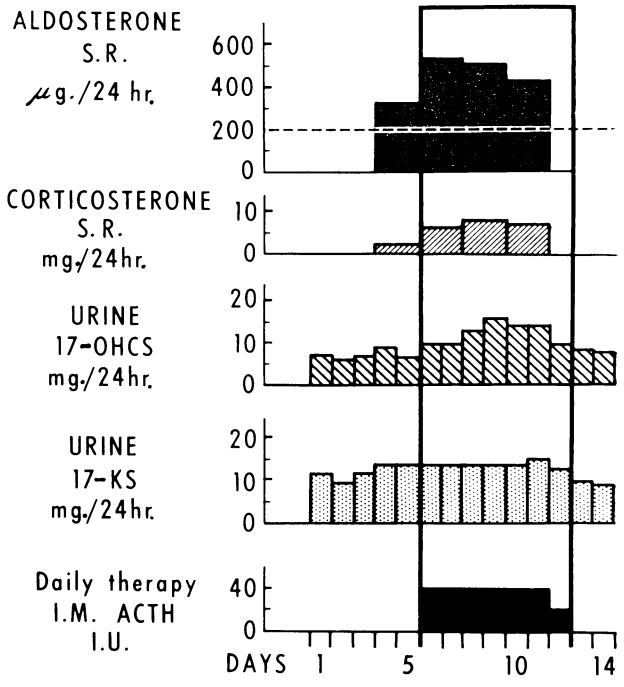


Fig. 8.—Effect of ACTH given intravenously for seven days in J.S. For the first six days 20 I.U. was given at 8 a.m. and again at 10:30 p.m.; on the seventh day only the morning dose was given.

change in the father but may have declined slightly in the son. Urinary sodium did not appear to have been affected in either except for an initial sodium retention in the son. There was an initial potassium diuresis but the fall in urine potassium and rise in serum potassium were delayed. This delay in potassium retention with R01-8307 was not seen in one patient with proved primary aldosteronism.[23]

Aldactone A, 300 mg. daily, in J.S. (Fig. 7) produced marked potassium retention, a rise in serum potassium to normal and possibly a slight sodium diuresis. There was a fall in blood pressure. Aldosterone secretion did not increase in response to the potassium retention, indicating a degree of autonomy of the aldosterone-secreting tissue. Subsequent to this study J.S. was given aldactone A on an outpatient basis, 100 mg. daily in divided doses, from July 27 to September 7, 1965. No effect on blood pressure was observed.

The influence of ACTH given intramuscularly to J.S. for seven days is illustrated in Fig. 8. Urine 17-KS showed little change. Urine 17-OHCS and corticosterone secretion increased to a plateau. Aldosterone secretion rose on the first two days of ACTH, then declined gradually and slightly. A qualitatively similar aldosterone excretion response to ACTH has been observed in normal subjects by Liddle, Duncan and Bartter.[31]

### 3. *Other Steroids*

Urinary pregnanediol, pregnanetriol and estrogens (Table II; Fig. 13) were measured at a time when aldosterone secretion was increased but 17-KS and 17-OHCS excretion was normal. Urine pregnanetriol was normal in both father and son. Each showed a modest increase in pregnanediol excretion. Total estrogens, measured by the relatively non-specific Ittrich technique,[20] were also increased in both patients. When a method for specific estrogens[18] was used, both father and son were found to have a high normal to slightly elevated estrone and 17$\beta$-estradiol, but normal estriol, excretion.

## C. TREATMENT

### 1. *Surgery*

Initially, despite the intermittent elevation in urine 17-KS and 17-OHCS, it was thought that both father and son might have Conn's syndrome. On April 19, 1965, the father underwent adrenal exploration. No adrenal tumour was found. The left adrenal, which appeared larger than the right, was removed. It weighed 7 g. Multiple (at least 10) nodules, 0.1-0.4 cm. in diameter, were seen on gross examination. On microscopic examination these nodules were mainly in the zona fasciculata and were composed of clear cells. Biopsy of the right kidney revealed only occasional granules in the juxtaglomerular cells. There were scattered foci of atrophied tubules and partially or completely hyalinized glomeruli and arterioles. Some of the small arteries showed intimal hyalinization.

Following operation the hypertension persisted. Serum potassium rose to a maximum of 4.3 mEq./l. but by four weeks after adrenalectomy it had returned to the previous low levels. Two weeks postoperatively while J.S. was on his constant normal

intake (140 mEq. sodium and 90 mEq. potassium) aldosterone secretion was 290, and 18-OH-B secretion 1260, μg./day, approximately half the preoperative values.

2. *Dexamethasone*

(a) *J.S. and L.S.*—In the autumn of 1965 reexamination of the dexamethasone suppression test in the son showed that a rise in serum potassium had occurred. It was decided to give both father and son dexamethasone.

Fig. 9 shows an outpatient study conducted on the father in which blood pressure, serum sodium and serum potassium were measured during three control periods and two periods of dexamethasone administration, 0.5 mg. four times daily by mouth. The early part of the second dexamethasone study, indicated in the figure by the interrupted lines, was an in-patient study and will be discussed later. In both treatment periods blood pressure fell to normal. Serum sodium also fell. Serum potassium levels rose to within the normal range. Following discontinuance of dexamethasone on both occasions all three measurements returned to, or nearly to, control values.

A third course of dexamethasone, 2 mg./day, was begun on June 23, 1966, on an outpatient basis. Again blood pressure and serum sodium fell and serum potassium rose. When last seen as an outpatient on September 11, 1966 (81st day of dexamethasone), J.S. showed the following: blood pressure 140/90, serum sodium 137 mEq./l. and serum potassium 4.7 mEq./l. In hospital on the

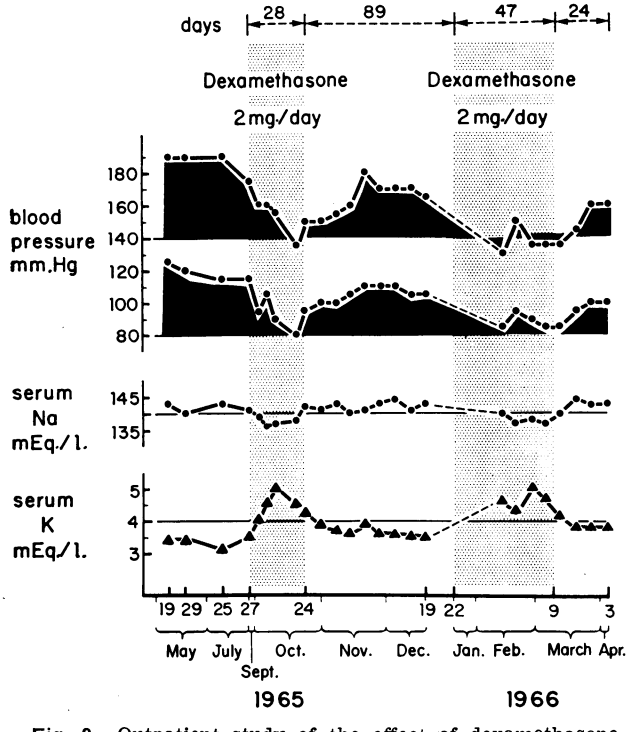


Fig. 9.—Outpatient study of the effect of dexamethasone on blood pressure, serum sodium and potassium in J.S. During the period indicated by the interrupted lines the patient was in hospital (Figs. 11 and 13).

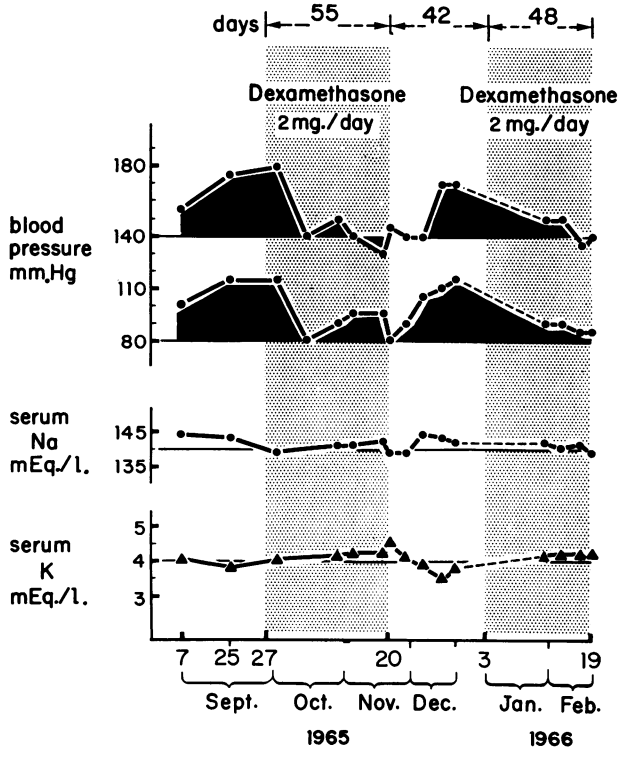


Fig. 10.—Outpatient study of the effect of dexamethasone on blood pressure, serum sodium and potassium in L.S. During the period indicated by the interrupted lines the patient was in hospital (Figs. 12 and 13).

52nd day of the third course of dexamethasone, J.S. had a plasma renin activity (PRA) (constant diet containing 140 mEq. sodium and 90 mEq. potassium daily) of 540 ng. angiotensin liberated per 100 ml. plasma/3 hr. incubation.* It will be recalled that under similar conditions before dexamethasone PRA was undetectable.

Fig. 10 illustrates a similar outpatient study in the son. Dexamethasone periods of 55 and 48 days' duration are depicted. The early part of the second dexamethasone study, indicated by the interrupted lines, was an in-patient study and will be discussed later. As in the father, on both occasions dexamethasone produced a fall in blood pressure and a rise in serum potassium. Little change in serum sodium occurred. Outside hospital on the 47th day of the first dexamethasone period, on the fourth day of a low sodium (17 mEq.) intake, L.S. showed a PRA of 306 ng. angiotensin/100 ml. plasma/3 hr. incubation. It will be recalled that under similar conditions before administration of dexamethasone PRA was undetectable.

On February 20, 1966, the day following conclusion of the outpatient study, dexamethasone was replaced by cortisol, 50 mg. by mouth daily in divided doses. By March 12, his blood pressure

*In the method of Boucher *et al.*[11] PRA is expressed as nanograms (ng.) of angiotensin/litre of plasma/minute of incubation. The units used here are those of Conn *et al.*[32] who, while employing the Boucher technique, have established normal ranges for particular states of diet and posture. For 180 mEq. sodium diet and upright posture the normal range has a mean of 262 ± 49 (1 S.D.); for 10 mEq. sodium diet (fourth day) and upright posture the normal range has a mean of 1288 ± 113 (1 S.D.).

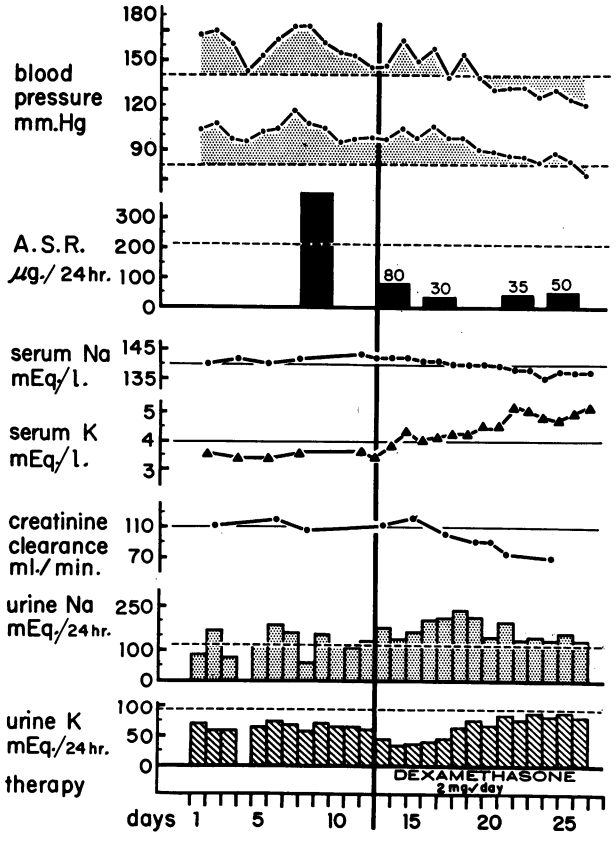


Fig. 11.—In-patient study of the effects of dexamethasone in J.S. ASR means aldosterone secretion rate. The interrupted horizontal line on the ASR section represents the upper limit of the normal range.

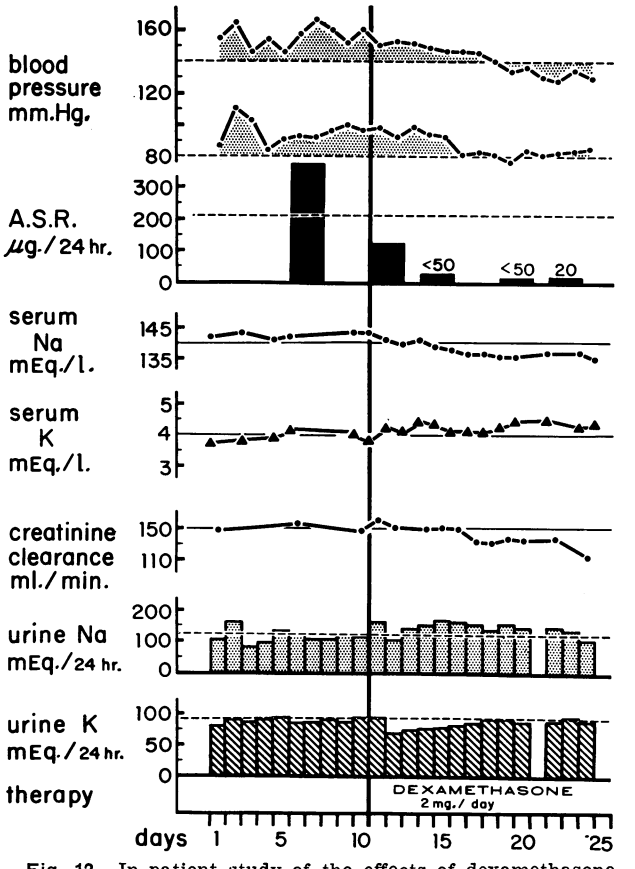


Fig. 12.—In-patient study of the effects of dexamethasone in L.S.

had risen from a mean of 140/85 to 160/100 and serum potassium had fallen from a mean of 4.2 to 3.8 mEq./l. These values showed little change until L.S. was admitted to hospital on April 11. In hospital on cortisol the mean value for blood pressure was 135/80 and for serum potassium 4.0 mEq./l. (*N.B.* In both patients blood pressure was consistently lower in hospital than outside.) Aldosterone secretion rate on a diet containing 120 mEq. of sodium and 94 mEq. of potassium, was less than 35 μg./day. Following discharge from hospital on April 15, L.S. continued on cortisol, 50 mg. daily until May 17, then 70 mg. daily until May 29. On this regimen serum potassium ranged between 3.8 and 4.2 mEq./l. and blood pressure gradually rose to a level of 180/115.

Cortisol was replaced by dexamethasone, 2 mg. daily, on May 30, 1966. Blood pressure gradually fell to a level of 150/90, and serum potassium gradually rose to a value of 4.5 mEq./l., on June 24. When last seen as an outpatient on September 11, 1966 (105th day of dexamethasone), L.S. showed the following: blood pressure 145/90, serum sodium 141 mEq./l. and serum potassium 4.3 mEq./l.

As previously stated, the early part of the second dexamethasone study in both patients was carried out in hospital on constant diet and controlled activity. The results of these studies are shown in Figs. 11-13 and Table III. Fig. 11 illustrates the effects of the first 14 days of treatment in the father. Blood pressure returned to normal, aldosterone secretion fell to very low levels, serum sodium also fell, serum potassium rose, creatinine clearance fell, urine sodium increased and, for the first six days at least, urine potassium decreased. Almost identical findings were obtained in the son (Fig. 12). Fig. 13 shows the effect of dexamethasone on the excretion or secretion of certain steroids in the previous two studies. It can be seen that in each instance the steroid excretion or secretion fell on dexamethasone. Other findings in these studies are shown in Table III.

(b) *Other Subjects.*—For comparison dexamethasone was given to three other patients. The

TABLE III.—VALUES BEFORE AND DURING DEXAMETHASONE DURING IN-PATIENT STUDY OF J.S. AND L.S. (SEE ALSO FIGS. 11 - 13). MEASUREMENTS ON DEXAMETHASONE WERE MADE ON THE SIXTH TO 14TH DAYS OF TREATMENT.

| *Determination* | *Father J.S.* | | *Son L.S.* | |
|---|---|---|---|---|
| | *Control* | *on DM* | *Control* | *On DM* |
| Plasma bicarbonate (mEq./l.) | 29 | 26 | 26 | 25 |
| Blood volume (ml.) | 5900 | 5500 | 5500 | 5400 |
| Urine pH | 6.5 | 6.0 | 6.5 | 6.0 |
| ECG | u waves | no u waves | u waves | no u waves |
| Plasma 17-OHCS (μg. %) | 10.0 | 5.7 | 12.2 | undetectable |
| Corticosterone SR (mg./per day) | 2.4 | 0.47 | 3.4 | 0.36 |

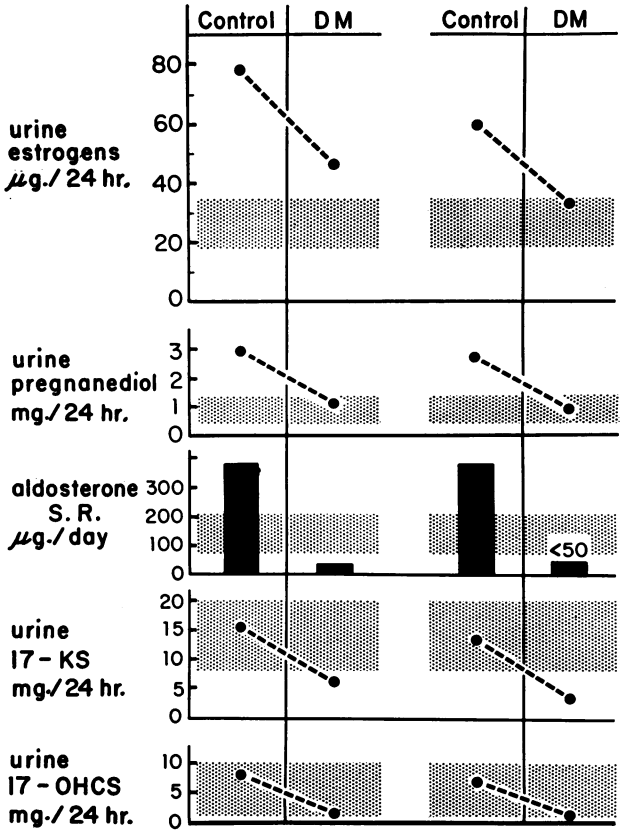


Fig. 13.—Influence of dexamethasone on certain steroids during the in-patient study of J.S. (left) and L.S. (right). The steroid values on dexamethasone were obtained during the period from the ninth to the 14th days of treatment. "Estrogens" refers to total estrogens as measured by the Ittrich technique.[20]

first was I.H., a 40-year-old woman with typical Conn's syndrome. Fig. 14 shows the right adrenal gland bearing the cortical adenoma removed at operation. Fig. 15 illustrates the study on I.H. Three periods are shown: the control period, eight days of dexamethasone 2 mg./day, and a two-week postoperative period. During the control and dexamethasone periods and from the seventh day after operation the patient was on a hospital 17 mEq. sodium diet supplemented by 103 mEq. of sodium chloride by mouth daily. Following adrenalectomy, blood pressure and serum potassium became normal, serum sodium and creatinine clearance fell and aldosterone secretion was less than 30 µg./day.

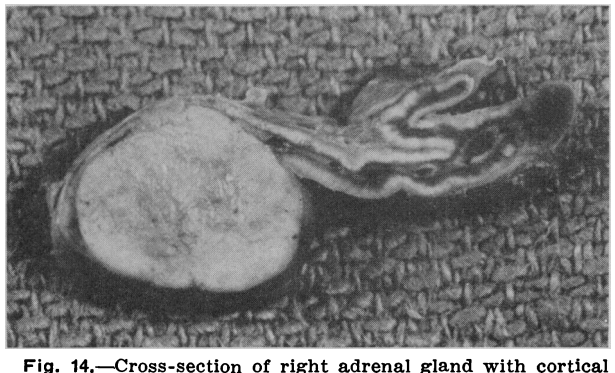

Fig. 14.—Cross-section of right adrenal gland with cortical adenoma removed at operation in patient I.H.

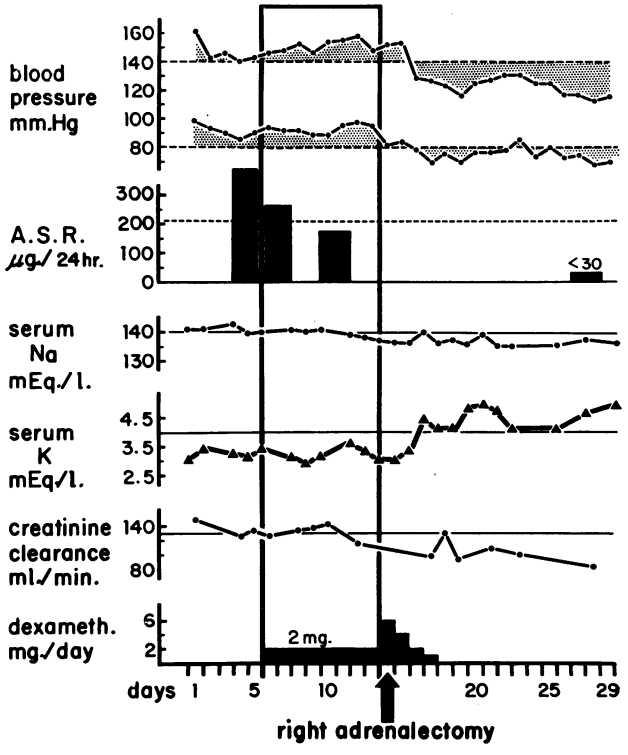


Fig. 15.—Influence of dexamethasone, 2 mg./day, and later, removal of an adrenocortical adenoma, in patient I.H.

During the eight-day dexamethasone period which immediately preceded operation, no alteration in blood pressure, serum sodium, serum potassium or creatinine clearance occurred. Only the aldosterone secretion rate changed. It did not, however, fall to the very low levels seen in J.S. and L.S. It is to be recalled that J.S. and L.S. were normotensive and normokalemic by the eighth day of dexamethasone. Slaton and Biglieri (personal communication) found no consistent change in aldosterone excretion when dexamethasone, 3 mg. daily for four days, was given to five patients with Conn's syndrome.

The second patient given dexamethasone for comparison with J.S. and L.S. was a normal male research physician, aged 33 years (Fig. 16). During the period of study he was maintained on a constant diet and continued his regular medical duties. On dexamethasone, 2 mg./day, aldosterone secretion remained within the normal range. No significant change was seen in serum sodium, serum potassium, creatinine clearance or urine sodium. Early in the treatment period potassium retention occurred.

The third patient given dexamethasone, a 50-year-old woman, M.McC., was considered to have severe essential hypertension. There were grade III changes in the optic fundi. Mild hypokalemia was present. Control aldosterone secretion rates were 160, 310 (above normal) and 140 µg./day. Renal arteriography and creatinine clearance were normal and PRA was not low,[32] 990 ng. (9th day of 18 mEq. sodium diet). During the period of study

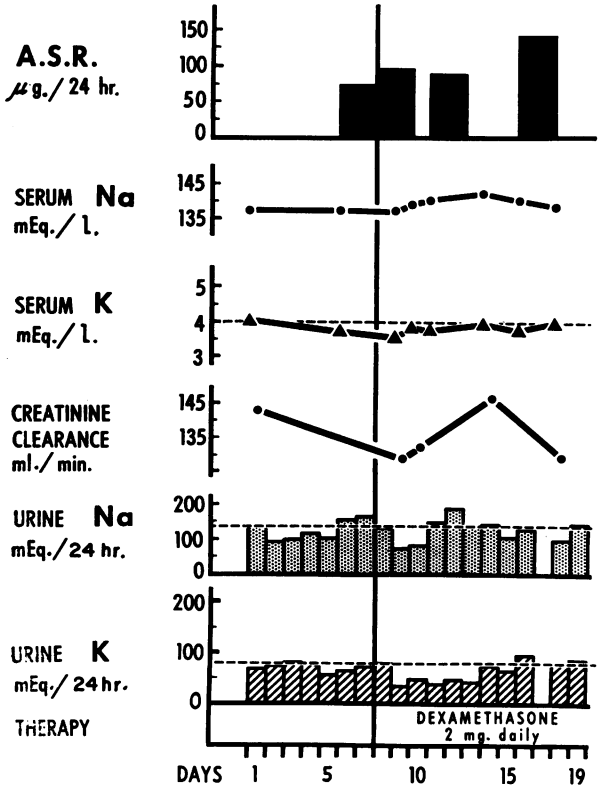


Fig. 16.—Effects of dexamethasone in a normal male subject.

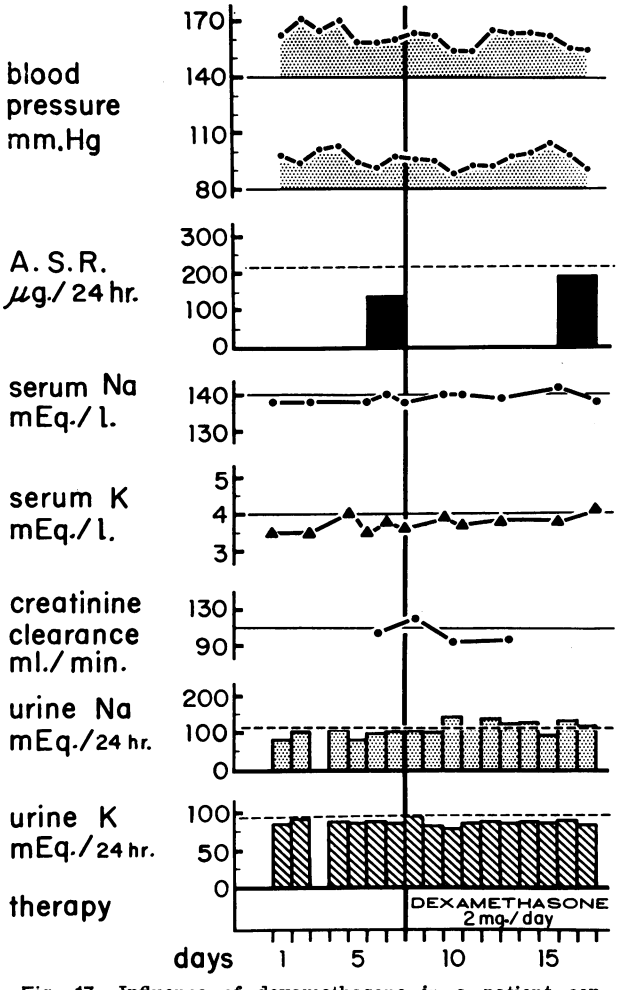


Fig. 17.—Influence of dexamethasone in a patient considered to have severe essential hypertension.

(Fig. 17) the patient was maintained on constant diet and controlled activity. On dexamethasone no significant alteration was seen in blood pressure, aldosterone secretion, serum sodium, serum potassium or urinary potassium. Perhaps a slight sodium diuresis occurred.

## DISCUSSION

A father and son have been described with benign hypertension and potassium depletion; intermittent elevations of 17-KS and 17-OHCS excretion; no increase in THS excretion; normal urine 17-OHCS response to dexamethasone; normal circadian rhythm of plasma 17-OHCS; increased pregnanediol, possibly increased estrogen, but normal pregnanetriol excretion; increased aldosterone, but normal corticosterone secretion; raised plasma volume and suppressed plasma renin activity. In the father plasma ACTH was normal, 18-OH-B secretion was high, and the urine 17-OHCS response to intravenous ACTH was normal; these measurements were not made in the son. In both patients all of the abnormalities disappeared on dexamethasone 2 mg./day. In the father a marked improvement in blood pressure and electrolytes also occurred on very large doses of aldactone A. It should be stressed that the corticosterone, pregnanetriol, plasma ACTH and intravenous ACTH studies were done at a time when aldosterone secretion and pregnanediol excretion were increased but urine 17-KS and 17-OHCS were normal. At present it is not certain whether cortisol secretion paralleled 17-OHCS excretion. Cortisol secretion rate measurements have not been completed, but it seems unlikely from the urine 17-OHCS, before and during intravenous ACTH, that a deficiency of cortisol production was present.

Because of the difference in response of blood pressure, electrolytes and aldosterone secretion between J.S. and L.S. on the one hand and patient I.H. (Fig. 15) on the other, it seems improbable that the father and son have Conn's syndrome. It seems unlikely that they have congenital adrenal hyperplasia due to 11$\beta$-hydroxylase deficiency or to a compensated deficiency of 21-hydroxylase or 17$\alpha$-hydroxylase. The first type[33] of enzyme deficiency is characterized by elevated THS excretion. In the second type,[34] while there may be increased aldosterone secretion, urine pregnanetriol is elevated and there are no clinical or biochemical manifestations of mineralocorticoid excess. In the third type,[35] even in a compensated form, one would expect an elevated corticosterone, and depressed aldosterone, secretion.

It may be that some of the cases for whom Conn and Conn[36] have used the term "congenital aldosteronism" have a condition similar to that described in the present report. One of the patients

cited by Conn is of particular interest.[37] He was 9 years old and had severe but not malignant hypertension, potassium depletion, increased aldosterone excretion, increased urine 17-OHCS (19.2 and 25.6 mg./day) and possibly increased urine 17-KS (8.0 mg./day) but normal THS excretion. He was not obese and there were no signs of Cushing's syndrome. There was no measurement of plasma renin activity and a renal arteriogram was not done. A total adrenalectomy was performed and nodular cortical hyperplasia was found. Postoperatively, on 15 mg. of cortisone and 0.1 mg. of 9α-fluorocortisol, blood pressure was normal and all other abnormalities had disappeared.

It must be said that we have little knowledge of the etiology of the condition in J.S. and L.S. It is possible that the hypertension and potassium depletion were due to increased aldosterone secretion. Conceivably there was a primary disturbance of cortical hormone synthesis of a type not yet recognized. Alternatively there may have been an abnormality, either within or outside the adrenal, in the regulation of aldosterone secretion. We considered, for example, that there might have been an altered response of aldosterone to normal levels of ACTH. The evidence on this point is conflicting. The dramatic decrease in aldosterone secretion on dexamethasone favours such a disturbance, while the decline in aldosterone with continued intramuscular ACTH is probably against it. Other possibilities are an alteration in regulation of aldosterone by potassium changes, and a disturbance in the renin-angiotensin-aldosterone feedback mechanism. In respect of the latter possibility it would be interesting to determine the ease of suppression of aldosterone by high sodium intake, desoxycorticosterone or plasma volume expansion. Finally the increased aldosterone secretion in J.S. and L.S. may indicate the presence of increased amounts of an unknown aldosterone-stimulating factor.

The reason for the beneficial effects of dexamethasone in J.S. and L.S. is equally obscure. It seems likely that this represents an action common to glucocorticoids because the effects of cortisol in L.S., in hospital at least, were similar to those of dexamethasone.

How may one distinguish the condition described in the present report from primary aldosteronism due to an adrenocortical tumour? It has been emphasized[36] that patients with Conn's syndrome have normal urine 17-KS and 17-OHCS. There were many occasions, however, when J.S. and L.S. also had normal urine 17-KS and 17-OHCS. Moreover, R. E. Peterson (personal communication) has studied a 10-year-old boy with a dexamethasone-remediable condition (hypertension, increased aldosterone secretion, low PRA) similar to that of J.S. and L.S. except that urine 17-KS and 17-OHCS were normal. On the other hand, a patient with Conn's syndrome and simple obesity might have increased urine 17-OHCS.[38] Increased 18-OH-B secretion is not a differentiating point because it may occur in Conn's syndrome.[39] Finally, J.S. and L.S. showed increased pregnanediol excretion. To our knowledge, however, values for pregnanediol excretion in male patients with Conn's syndrome have not been reported. Because of the foregoing considerations it would seem reasonable, in a patient with hypertension, increased aldosterone secretion and suppressed PRA, to institute a trial of dexamethasone before undertaking adrenal exploration. It must be conceded, however, that should such a patient have increased urine 17-OHCS and no obesity it is unlikely that he has Conn's syndrome.

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