Renal Effects of Long Term Administration of Triamcinolone Acetonide in Normal Dogs

G. W. Osbaldiston*

SUMMARY

Triamcinolone acetonide was administered in excessive dosage to dogs to study the renal mechanism responsible for polyuria which is a clinically undesirable side effect of long term glucocorticoid therapy.

Polyuria occurred coincident with a significant increase in urinary solute output. Although continuous administration of triamcinolone acetonide at 0.1 or 0.2 mg/lb/day caused a small but significant increase in creatinine output, the primary mechanism for the polyuria was increased solute excretion. Associated with the polyuria was pronounced hyperphagia and polydipsia. The cause of the hyperphagia was not established. The increase in electrolyte excretion caused by this synthetic steroid was probably compensated for by the hyperphagia. Because all the dogs showed muscle weakness and loss of body condition, it is likely that alteration in protein and amino acid metabolism was responsible for the hyperphagia.

RÉSUMÉ

On administra des doses excessives d'acétonure de triamcinolone à des chiens, afin d'étudier la pathogénèse de la polyurie, cliniquement observée après des traitements prolongés par les glucocorticoïdes.

La polyurie produite coincide avec une augmentation significative de l'émission de solutés urinaires. Bien que l'administration continue d'acétonure de triamcinolone à raison de 0.1 ou 0.2 Mg/livre/ jour ait entraîné une légère augmentation de l'élimination de créatinine, l'augmentation de l'excrétion des solutés demeura la principale cause de la polyurie. Une hypergphagie marquée et de la polydipsie accompagnait la polyurie.

On ne put établir la cause de l'hyperphagie, mais elle compensait probablement l'augmentation de l'élimination des électrolytes produite par ce stéroïde de synthèse. La faiblesse musculaire et la perte de forme physique, manifestées par tous les chiens, suggèrent que l'hyperphagie était probablement provoquée par une altération du métabolisme des protéines et des acides aminés.

INTRODUCTION

Triamcinolone acetonide[1] (9α-fluro-16α, 17α-isopropylidenedioxy[1]-hydrocortisone) is the most potent, systemically active, anti-inflammatory glucocorticoid in animals (10, 36). In veterinary medicine, it is not unusual to administer corticosteroids for long durations, particularly for the treatment of hypersensitive reactions of the skin. In such therapeutic regimens, a frequent complaint is that dogs develop polydipsia and polyuria. Generally no other untoward signs are observed. *Diabetes mellitus,* steroid diabetes, can be initiated by excess corticoid therapy (39), but the incidence in dogs is low.

The biological activity of corticosteroids is dependent on their chemical structure. For this reason, each steroid in common clinical use should be studied in relation to the animal species in which it is to be used. They increase glomerular filtration rate (GFR) and renal blood flow (RBF) independent of changes of sodium balance (16), and are also particularly effective kaluretic agents (2). Glucocorticoids in normal animals increase gluconeogenesis (21), produce a sustained rise in blood glucose concentration (25), and glucosuria (17).

*Department of Infectious Diseases, College of Veterinary Medicine, Kansas State University, Manhattan, Kansas 66502.

[1]Vetalog, E. R. Squibb and Sons, Inc., East Brunswick, New Jersey.

The mechanism for the polyuria in prolonged triamcinolone acetonide administration has not been explained. The present paper reports experience which investigated increased GFR, antagonism with antidiuretic hormone (ADH), and osmotic diuresis due to either glucosuria or to increased electrolyte excretion, as possible causes of this condition.

MATERIALS AND METHODS

Experiments were performed on 12 mongrel dogs weighing from 7.2-22.5 kilograms. During the 12 weeks of the experiment seven dogs were removed from the procedures due to respiratory and urinary tract infections or anesthetic death.

Dogs were kept in cages in a temperature controlled room, average temperature 20°C. They were fed a standard laboratory dog diet[2] to appetite given as two separate feeds; water was provided *ad libitum*. They were not exercised.

After a control period in which the experimental procedures were performed on each animal, triamcinolone acetonide was administered daily for nine weeks. Table I shows the dose of triamcinolone acetonide administered to the five surviving dogs. During the last five days of each three-week period of corticosteroid administration, the following studies were made on each dog: (a) two consecutive 24-hour urine collections with dogs in metabolism cages, (b) inulin and para-aminohippurate (PAH) clearance, (c) the renal response to an infusion of 0.005 mu/kg/min of ADH in 0.1 ml of saline, (d) tubular maximum reabsorptive capacity for glucose (Tm_G), and (e) fasting blood glucose and serum electrolyte determinations.

The 24 hour urine samples were collected using toluene as a preservative. The volume was measured and an aliquot taken for analysis, pH was measured as soon as possible thereafter. Urine was stored at 4°C. Creatinine was measured by the method of Bonsnes and Taussky (6), using 10% trichloroacetic acid buffered to pH 2.15 as the protein precipitating agent. Sodium and potassium were determined using an atomic absorption spectrophotometer. Total solute was measured with a Fiske osmometer.

Inulin and PAH clearances were determined following a priming dose of 30 mg/kg inulin and 3 mg/kg PAH followed by a constant infusion of 5 mg of each respectively. The bladder was catheterized and urine was collected for six consecutive 20 minute periods. Inulin, in plasma and urine, was determined by the method of Roe *et al* (30); PAH was determined by the method of Bratton and Marshall (7).

For Tm_G determinations, urine was collected via a bladder catheter. Glucosuria was established by intravenous infusion of 20% glucose. Tm_G was determined during three 20 minute urine collection periods in which glucosuria occurred. In these experiments GFR was measured as creatinine clearance, plasma and urine creatinine being determined as above (6). Glucose was measured by a standard clinical laboratory procedure (38).

In most experiments, 30-60 minutes after the glucose infusion had ceased, an intravenous pitressin infusion was commenced. In five experiments, the pitressin response was studied the day after the Tm_G determinations. Urine was collected via a bladder catheter for two ten minute periods prior to and then every ten minutes during the 60 minute ADH infusion. A blood sample was withdrawn at the mid-point of each urine period. Creatinine concentration in plasma and urine were determined as before. The dogs generally were amenable to handling and most procedures were performed without anesthesia. In some experiments in which animals were fractious, phenobarbital anesthesia was used. Plasma creatinine, serum sodium and potassium and fasting blood glucose were determined on blood samples withdrawn when the dogs were in their three-day period in the metabolism cage.

[2]Purina Dog Chow, Ralston Purina Company, St. Louis, Missouri.

TABLE I. Dosage of Triamcinolone Acetonide (mg/kg) Administered to Normal Dogs

Dog	Body-weight (kg)	Control	1—21 Days	22—42 Days	44—63 Days
1	18	None	0.023	0.023	0.045
2	21	None	0.045	0.045	0.090
3	8	None	0.045	0.090	0.045
4	17	None	0.023	0.023	0.045
5	10	None	0.023	0.023	0.045

TABLE II. Effect of Triamcinolone Acetonide on Renal Hemodynamics of Healthy Dogs

Dog #1	Prior	Weeks of Continuous Steroid Treatment 3 weeks	6 weeks	9 weeks
(a) Inulin Clearance (ml/kg/min)				
1	2.61[a]	2.72	2.56	3.29
2	3.35	3.10	3.38	3.82
3	3.46	2.60	4.25	3.20
4	3.18	3.06	2.67	3.70
5	2.42	3.10	2.71	3.29
(b) PAH Clearance (ml/kg/min)				
1	12.5	11.2	14.6	12.3
2	12.3	13.4	13.0	11.7
3	12.2	9.8	12.6	11.8
4	10.6	11.2	10.1	11.9
5	10.6	10.7	10.3	10.5
(c) Filtration Fraction: C_{IN}/C_{PAH}				
1	0.23	0.24	0.19	0.27
2	0.27	0.23	0.26	0.33
3	0.28	0.27	0.34	0.27
4	0.30	0.27	0.26	0.31
5	0.24	0.29	0.26	0.31

[a]Values are the average of five or six, 20-minute clearance periods

TABLE III. Effect of Triamcinolone Acetonide On Tubular Reabsorptive Capacity of Glucose[a]

Dog	Prior	Weeks of Continuous Steroid Treatment 3 weeks	6 weeks	9 weeks
1	3.61[b]	4.08	3.52	6.62
2	4.42	5.52	6.06	4.31
3	8.42	6.67	9.42	7.67
4	4.49	5.32	5.34	4.01
5	4.00	6.10	5.75	5.64

[a]Tm_G mg/kg/min
[b]Values are the average of two or three, 20-minute collection periods

RESULTS

Table II shows inulin and PAH clearance, and filtration fractions at the various stages of the experiment. Over the nine week period triamcinolone acetonide administration did not cause any consistent alteration in renal hemodynamics.

Table III presents Tm_G (mg/kg/min) results for five dogs. Simultaneous GFR measurements were made. In some experiments, there was considerable splay in the individual data. In all but one dog (dog 3) Tm_G increased within 21 days of steroid treatment. The responses at 43 and 63 days were unrelated to the change at 21 days. The overall data showed no consistent effect on renal tubular capacity to reabsorb glucose.

TABLE IV. Blood Glucose and Serum Electrolyte Concentrations in Normal Dogs Prior to and at 21, 42 and 63 Days after Receiving Daily Injections of Triamcinolone Acetonide

Dog	Prior	21 days	42 days	63 days
(a) Fasting blood glucose concentrations (mg/100 ml)				
1	118	125	175	196
2	132	128	139	153
3	113	151	238	295
4	125	144	134	148
5	104	173	144	159
(b) Serum sodium concentrations (mEq/liter)				
1	146	146	—	136
2	138	141	144	138
3	133	131	137	138
4	144	—	144	152
5	150	—	146	148
(c) Serum potassium concentration (mEq/liter)				
1	3.6	3.9	4.2	—
2	3.3	—	3.2	3.5
3	3.5	4.0	4.0	4.1
4	3.4	3.7	4.8	3.9
5	2.7	3.5	3.5	3.4

Table IV shows the fasting blood glucose, and serum electrolyte concentrations. The initial response to continuous dosing with triamcinolone acetonide was a significant increase in blood glucose concentration ($P<0.05$). With dog 3, which was the smallest dog in the group, the dose of glucocorticoid was increased to 0.2 mg/lb/day after the third week. Following this change blood glucose concentration increased from 151 to 238 mg/100 ml. When the dose of triamcinolone acetonide was reduced after the sixth week, blood glucose concentration continued to rise. This dog, therefore, had probably developed steroid diabetes. In dogs 1, 2 and 4 the highest fasting blood glucose concentration corresponded with the period of maximum glucocorticoid administration. In dog 5, maximum blood glucose concentration did not occur at the highest steroid dose.

With continuous triamcinolone acetonide administration, serum potassium concentration increased in all animals. The change was not influenced by dose level of glucocorticoid. There was no consistent alteration in serum sodium concentration.

When ADH was infused at a rate of 0.005 mu/kg/min, urine volume decreased. A more sensitive indicator of the water conservation at low urine flows is the urine

to plasma (U/P) creatinine concentration ratio (22). Table V shows the average creatinine U/P ratio for two ten minute collection periods, 40-50 and 50-60 minutes after the start of the ADH infusion. In normal animals, creatinine U/P ratio is approximately 50. Except when daily urine volume was excessive, the creatinine U/P ratio before the ADH infusion varied from 40-70 in these experiments. The data in Table V suggests that all dogs were capable of normal renal concentration.

TABLE V. Effect of ADH on Renal Concentrating Ability of Normal Dogs Prior to and at 21, 42 and 63 Days After Receiving Daily Injections of Triamcinolone Acetonide (renal concentrating ability was measured as urine to plasma creatinine concentration ratio following continuous ADH infusion, 0.005 mu/kg/min, for 60 minutes)

Dog	Prior	21 Days	42 Days	63 Days
1	149[a]	100	153	62
2	102	57	113	169
3	80	76	74	58
4	130	80	61	102
5	137	103	79	56

[a]The values are the average of the 40-50 and 50-60 minute collection periods

Continuous daily metabolic studies were not made. Instead, dogs were placed in metablism cages for two or three days toward the end of each 21 day period of the continuous triamcinolone acetonide administration, and 24 hour urine collections were made for two consecutive days. Data for urine volume, pH, and excretory products are presented in Table VI.

The average daily urine volume was 2.5% of the body weight, range 1.7 to 3.6%, during the control period. Urine volume always increased when the daily dose of glucocorticoid was doubled, irrespective of the dosage given. Dogs 2 and 3, which were given 0.2 mg/day as their higher dose, increased their urine volume 229 and 542% respectively as compared with their output prior to corticosteroid administration. Dogs 1, 4 and 5 showed increases of 230, 328 and 301% respectively when given 0.1 mg/day of steroid as a maximum dose.

The data in Table VI shows that in these experiments triamcinolone acetonide affected the urine output of the smaller dogs (dogs 3 and 5) to a greater extent than

TABLE VI. Daily Urinary Excretion Products of Dogs Receiving Triamcinolone Acetonide[a]

	Weeks of Continuous Steroid Dosing			
	Prior	2 weeks	6 weeks	9 weeks
Dog #1				
Volume	17.2	19.0	15.9	39.6
pH	6.8	7.0	6.7	6.6
Total solute[b]	252.0	223.0	302.0	474.0
Sodium[c]	18.7	29.1	31.0	70.1
Potassium[c]	15.7	12.9	31.6	64.7
Creatinine[d]	18.1	17.2	15.5	20.1
Dog #2				
Volume	36.3	32.5	34.7	83.4
pH	6.4	6.5	6.6	6.4
Total solute	260.0	229.0	183.0	354.0
Sodium	31.4	28.1	22.0	53.4
Potassium	15.3	9.7	21.8	33.4
Creatinine	15.1	12.8	15.2	16.7
Dog #3				
Volume	21.6	44.9	117.0	28.6
pH	6.4	6.5	6.4	5.5
Total solute	226.0	306.0	600.0	285.0
Sodium	22.9	27.6	46.7	22.9
Potassium	15.1	23.0	34.2	22.9
Creatinine	18.9	15.4	27.2	14.6
Dog #4				
Volume	18.8	17.1	20.2	61.6
pH	6.9	6.8	6.8	6.0
Total solute	266.0	235.0	316.0	457.0
Sodium	12.2	12.7	13.3	62.0
Potassium	7.6	0.8	13.6	42.6
Creatinine	15.1	11.8	19.6	20.1
Dog #5				
Volume	31.2	41.6	58.6	93.9
pH	6.3	4.6	6.2	6.4
Total solute	224.0	305.0	416.0	624.0
Sodium	13.2	18.2	65.0	143.0
Potassium	20.6	17.9	38.8	70.7
Creatinine	15.3	17.3	24.8	20.6

[a]All values are the average of two days collection near the end of each three week period
[b]Total solute, mOs/kg/day
[c]Sodium, potassium, mEq/kg/day
[d]Creatinine, mg/kg/day

that of the larger dogs. Of those animals given 0.05 mg/day, dog 5 excreted 5.9% of its bodyweight as urine and dogs 1 and 4 excreted 1.6 and 2.0% respectively. When the steroid dosage was doubled urine output increased to 9.4% of the bodyweight for dog 5, 4.0% for dog 1 and 6.2% for dog 4. A similar pattern of results were found with dogs 2 and 3 which received 0.1 and 0.2 mg/lb/day.

Dog 3 received 0.2 mg/lb/day triamcinolone acetonide for 21 days after which it was reduced to 0.1 mg/lb/day (Table I). The reduction in steroid dosage was associated with a marked decrease in the daily

urine volume from 11.7% to 2.9% of the dog's bodyweight even though the fasting blood glucose concentration increased. The urinary effects due to glucocorticoid administration are therefore reversible.

Table VI shows that maximum daily urine volume (ml/kg/day) of each dog coincided with the largest total solute output (mOs/kg/day). Therefore, one contributing factor to the polyuria induced by glucocorticoid administration was the quantity of solute requiring excretion. With the exception of dog 2, urine sodium excretion was found to be increased when triamcinolone acetonide had been administered for approximately 18 days. Dog 2 received the higher initial dose level, and there was no increase in sodium excretion in this animal even after 42 days administration. Dog 2 also had the highest sodium output and urine volume prior to steroid administration, and in part, this may have masked some effect due to the steroid. At the higher glucocorticoid dosage for each dog, electrolyte excretion was not consistent, but after approximately 38 days of treatment potassium excretion had increased 188% over the control excretion.

However, comparison of the creatinine excretion at the highest steroid dose levels for each dog, with the corresponding control excretion, shows that triamcinolone acetonide was responsible for a significant increase ($P<0.05$) in daily creatinine excretion (mg/kg/day). An estimation of GFR can be obtained from the 24 hour creatinine determination. GFR derived in this way also showed an increase similar in magnitude to that of creatinine output.

Clinical observation of the experimental animals showed that chronic over-dosing with triamcinolone acetonide caused hyperphagia, muscle weakness, loss of bodyweight and polydipsia and polyuria. The combined effect of hyperphagia and polydipsia caused the feces to be moist (shapeless) and voluminous and at casual observation food appeared undigested as fecal material was the same color as the food nuggets. The extent of the hyperphagia was approximately a two- or threefold increase in the dogs food consumption. With the ravenous appetite, it was surprising that the experimental dogs lost their vigour and body condition. At the highest daily dose (0.2 ml/lb) the dogs were very weak and lethargic. Dog 3, in which the steroid dosage was reduced during the six to nine week period, showed marked improvement in body condition and activity after 14 days at the lower treatment level. This suggests that these effects, like that of the polyuria, are quickly reversible.

DISCUSSION

Triamcinolone acetonide when administered continuously in the high dosage for nine weeks had very pronounced renal and metabolic effects. Polydipsia, polyuria, hyperphagia, muscle weakness and loss of bodyweight were the most prominent signs. Normal parenteral dosage of triamcinolone acetonide is 0.05 mg/lb bodyweight weekly or every second week. The daily dose of 0.05, 0.1 or 0.2 mg/lb bodyweight as used in these experiments was therefore greatly in excess of the normal therapy. This was deliberate as an attempt was made to exaggerate any untoward effects of this synthetic steroid.

The results suggest that it was not the absolute dosage of triamcinolone acetonide which determined urine response, but the increased dosage once the steroid was being administered, that is, the change from 0.05 to 0.1 or 0.1 to 0.2 mg/lb/day. Dogs 2 and 3 received 0.1 mg/lb bodyweight of steroid as their dose, whereas dogs 1, 4 and 5 were given 0.05 mg for 42 days before being treated with 0.1 mg/lb. Thus, all five dogs received 0.1 mg/lb bodyweight of triamcinolone acetonide for at least 21 days at some stage of the experiment. Examination of the data for those specific periods show each dog was given 0.1 mg/lb bodyweight glucocorticoid (irrespective of the prior glucocorticoid treatment) suggests that urine output was unrelated to dosage which determines the magnitude of the renal response. The data indicates that the initial glucocorticoid administration sensitized the kidney in some manner so that the increase in dose rate, whether it was from 0.05 to 0.1 or 0.1 to 0.2 mg/lb/day produced the intense polyuria. It is not possible to predict from the results of this experiment what the long-term effects of constant dosage may be. The clinical problem is polyuria developing some time after the constant dosage therapy begins. Documented cases discussing this effect have not been found in the literature. Several authors have discussed overdosage (1, 26, 39) of various steroid analogues.

Triamcinolone acetonide is the most po-

tent anti-inflammatory systemic glucocorticoid in animals (5) whereas, in man, it is most effective by topical application and seldom administered by other routes. There are no published reports of renal effects of triamcinolone acetonide in dogs (37). In chemical terms, it is closely related to its parent compound triamcinolone which has been extensively studied. This has been shown to have increased toxicity as compared with prednisolone and methylprednisolone (14) when each was administered at a rate of 5 mg/kg. At necropsy, triamcinolone treated dogs showed gastrointestinal hemorrhage, reduction in bone marrow activity, liver damage and marked loss of muscle mass. Triamcinolone, however, has less effect on plasma electrolytes, nonprotein nitrogen and glucose concentrations (15, 31), but promotes increased sodium excretion and water loss (9).

The signs of hyperadrenalcorticism in dogs are bilateral alopecia and edema. In cases of prolonged duration extensive hair loss, muscular weakness, trembling, polyuria and thirst are observed (4). In this syndrome, there is an excess of cortisol-like steroids caused by pituitary or adrenal hypersecretion. The clinical verification of cortisol hypersecretion usually involves the estimation of plasma or urine 17 hydroxycorticosteroids (33). Their increased activity may not be exclusively dependent on increased adrenocorticosteroid output since Eik-Nes and Samuels (12) have suggested the changes in cortisol metabolism in dogs may reflect decreased adrenal arterial blood flow and reduced hepatic inactivation; thus, increased plasma 17 hydroxycorticosteroid levels can result from decreased, normal or increased adrenocorticosteroid output and a normal or decreased rate of metabolism of adrenocorticosteroid depending on the circumstances. Because of the physiological, microscopic, and electron microscopic similarities of the dog adrenal gland to that of man (18) results of studies on humans are probably indicative of expected changes in the dog. Large doses of cortisol initially cause decreased sodium and water excretion and increased potassium excretion in normal humans, but with prolonged administration, urine flow and sodium excretion increase (35). When desoxycorticosterone (DCA) is regularly administered to animals, sodium and water excretion are decreased initially, but within a few weeks, polyuria and polydipsia are observed (29). This "escape" from the sodium retaining effects of these naturally occurring hormones, and the supervening polyuria is typical of that found with some synthetic steroids.

During the sodium "escape" phase, with prolonged administration of deoxycorticosterone acetate (DCA) the persistent polyuria and polydipsia was unresponsive to vasopressin (29). This resistance to the effect of ADH has been shown to be independent of potassium or sodium intake (13, 23). In adrenal insufficiency, the ability to excrete a water load is diminished, and this is restored by the administration of cortisone (34), but not by mineralocorticoids such as DCA or aldosterone (16). It has been shown that there is increased ADH activity in urine following adrenalectomy (24). That release, turnover or renal response to ADH are not responsible for the water diuresis in adrenal insufficiency has recently been established (19). Cortisone restores the response to water loading primarily by its action on the renal tubules by promoting solute free water for excretion (20) and possibly by inhibiting release of ADH (11).

One explanation for the polyuria with prolonged administration of triamcinolone acetonide was therefore a possible antagonism with ADH. In these experiments, pitressin was infused at the rate of 0.005 mu/kg/min which in the normal dog provides a concentration in the plasma in the normal physiological range. It has been shown that a single injection of 0.08 mu/kg intravenously of pituitary posterior lobe extract produces full inhibition of water diuresis (27), and that the release of 0.2 to 0.3 mu/kg/hr of ADH from the pituitary is sufficient to maintain a low rate of urine flow (22). Thus, 0.005 mu/kg/min of pitressin is neither insufficient nor excessive. All dogs were capable of producing a creatinine U/P ratio greater than 50, and thus, there was no evidence that triamcinolone acetonide antagonized the action of ADH. Further evidence that polyuria was not simply a water diuresis is that the osmolarity was always hypertonic.

Triamcinolone acetonide influences glucose metabolism, but had no effect on Tm_G. It was most unlikely that an effect on Tm_G would have occurred. Tm_G is not affected by glucose concentration in the glomerular filtrate; its rate of transport is dependent on the quantity of carrier available in the proximal tubule cells (28).

Polyuria was primarily the result of in-

creased solute load requiring excretion. It was reversible, and responded quickly when the daily dose of steroid was reduced. In these experiments, the renal effects were measured at 21 day intervals, and because of this it is only possible to speculate on the mechanisms responsible for the polyuria and hyperphagia. It is unlikely that the renal electrolyte, especially potassium, loss was the mechanism responsible because in hypokalemia, urine is not concentrated. Although the animals were weak and lethargic, serum potassium concentration remained normal. As no balance studies were performed, or muscle or red blood cell electrolyte concentration determined, the potassium status of these dogs is not known. Because of the hyperphagia, daily potassium intake would have been high and possibly therefore the animals were not in an abnormally low potassium status.

The polyuria was probably secondary to the hyperphagia. The stimulation for the hyperphagia was not determined. Corticosteroids have a marked effect on amino acid and nitrogen metabolism; they increase protein catabolism and decrease the rate of protein synthesis (8), increase uptake of amino acids by hepatic cells (4), increase urinary amino acid excretion (3), and increase urinary nitrogen excretion (25). Neither aminoaciduria or the increased urine nitrogen excretion would be responsible for the polyuria. Excessive renal loss of amino acids may be responsible in part for the hyperphagia.

Hyperphagia and the clinically undesirable changes were only observed when the administered dose was sharply increased. Although the dogs received an excessive therapeutic dose initially, at either level of dosage, they did not show polyuria or hyperphagia. Why altering the dosage triggered such a marked response cannot be answered from the present experiments. This observation is not in keeping with the clinical problem in which polyuria is reported to have occurred with dogs maintained on a constant dosage. The dogs in this study were fed to appetite as judged by an experienced dog handler, and the increased appetite may not have been satisfied. This in turn may have masked the increased urine flow rate. The pronounced hyperphagia and loss of body condition are not the usual clinical observations and it is to be emphasized that they were only produced at excessively high therapeutic dosage.

REFERENCES

1. **ANDERSON, D. C.** Corticosteroid overdosage in dogs. N.Z. vet. J. **16**: 18-19. 1968.
2. **BARTTER, F. C.** and **P. FOURMAN.** The different effects of aldosterone-like steroids and hydrocortisone-like steroids on urinary excretion of potassium and acid. Metabolism **11**: 6-20. 1962.
3. **BERGENSTAL, D. K., R. L. LANDAN, J. KIRSNER** and **K. LUGIBIHL.** Effects of ACTH and related hormones on amino acid metabolism. Proc. Second Clinical ACTH Conference. J. R. Mote (ed). Vol. 1. p. 250. Philadelphia: Blakiston. 1951.
4. **BLOOM, F.** The endocrine glands. **In** "Canine Medicine." H. P. Hoskin, J. V. Lacroix and K. Mayer (eds). p. 377. Santa Barbara, California: American Veterinary Publications. 1969.
5. **BOLAND, E. W.** Anti-rheumatic potency of chemically modified adrenocortical steroids. Am. J. Med. **31**: 581-590. 1961.
6. **BONSNESS, R. W.** and **H. H. TAUSSKY.** Colormetric determination of creatinine by the Jaffe Reaction. J. biol. Chem. **158**: 581-591. 1945.
7. **BRATTON, A. C.** and **E. K. MARSHALL.** A new coupling component for sulfanilimide determination. J. biol. Chem. **128**: 537-550. 1939.
8. **CANNON, P. R., L. E. FRAZIER** and **R. H. HUGHES.** The influence of cortisone upon protein metabolism. Archs Path. **61**: 271-279. 1956.
9. **CRIEP, L. H.** Triamcinolone in the treatment of allergic conditions. J. Allergy **30**: 50-60. 1959.
10. **DEMOS, C. H., V. A. PLACE** and **J. M. RUEGSEGGER.** Structure function relationships of 16x-hydroxylated steroids and the acetonide analogues. p. 759. Advance Abstracts of Short Communications. First International Congress of Endocrinology. Copenhagen. 1960.
11. **DINGMAN, J. F.** and **R. H. DESPOINTES.** Adrenal steroid inhibition of vasopressin release from the neurohypophysis of normal subjects and patients with Addison's Disease. J. clin. Invest. **39**: 1851-1863. 1960.
12. **EIK-NES, K. B.** and **L. T. SAMUELS.** Metabolism of cortisol in normal and stressed dogs. Endocrinology **63**: 82-88. 1958.
13. **FERREBEE, J. W., D. PARKER, W. H. CARNES, M. K. GERITY, D. W. AITCHLEY** and **R. F. LOEB.** Certain effects of desoxycorticosterone. The development of "diabetes insipidus" and the replacement of muscle potassium by sodium in normal dogs. Am. J. Physiol. **135**: 230-237. 1941.
14. **FIELDER, F. C. E., E. J. HOFF** and **C. B. THOMAS.** Study on the subacute toxicity of prednisolone. methylprednisolone, and triamcinolone in dogs. Toxic. appl. Pharmac. **1**: 305-314. 1959.
15. **FREYBERG, R. H., C. A. BERNSTEN** and **L. HELLMAN.** Further experience with triamcinolone in treatment of patients with rheumatic arthritis. Arthritis Rheum. **1**: 215-229. 1958.
16. **GARROD, O., S. A. DAVIES** and **G. CAHILL.** The action of cortisone and desoxycortisone acetate on glomerular filtration rate and sodium water exchange in the adrenalectomized dog. J. clin. Invest. **34**: 761-776. 1955.
17. **INGLE, D. J.** Production of glucosuria in normal rat by means of 17 hydroxy 11 dehydrocorticosterone. Endocrinology **29**: 649-652. 1941.
18. **KANINSKY, N., S. LUSE** and **P. HABTROFT.** Ultrastructure of the adrenal cortex of the dog treated with D.D.D. J. natn. Cancer Inst. **29**: 127-134. 1962.
19. **KLEEMAN, C. R., J. W. CZACAKES** and **R. CUTLER.** Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. IV. Antidiuretic hormone in primary and secondary adrenal insufficiency. J. clin. Invest. **44**: 1641-1648. 1964.
20. **KLEEMAN, C. R., M. H. MAXWELL** and **R. E. ROCKNEY.** Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. I. Role of altered glomerular filtration rate and solute excretion. J. clin. Invest. **37**: 1799-1808. 1958.
21. **KOEPF, C. F., H. W. HORN, C. L. GEMMILL** and **C. W. THORN.** Effect of adrenal cortical hormone on the synthesis of carbohydrate in liver slices. Am. J. Physiol. **196**: 175-186. 1959.
22. **LAUSON, H. D.** The problems of estimating rate of secretion of ADH in man. Am. J. Med. **11**: 135-156. 1951.
23. **LEVINSKY, N., D. G. DAVIDSON** and **R. W. BERLINER.** Changes in urine concentration during prolonged administration of vasopressin and water. Am. J. Physiol. **196**: 451-456. 1956.
24. **LLOYD, C. W.** and **J. W. LOBOTSKY.** Serum antidiuretic substances and urinary corticosteroid in the human. J. clin. Endocr. Metab. **10**: 318-329. 1950.

25. **LONG, C. H. H., B. KATZIN** and **E. G. FRY.** Adrenal cortex and carbohydrate metabolism. Endocrinology **26**: 309-344. 1940.
26. **MUNDON, J. D.** and **B. E. BELSHAW.** Current Veterinary Therapy — Small Animal Practice. W. R. Kirk (ed). p. 317. Philadelphia: Saunders. 1966-67.
27. **O'CONNOR, W. J.** and **E. B. VERNEY.** The effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress. Q.J. exp. Physiol. **33**: 77-90. 1945.
28. **PITTS, R. F.** Physiology of the Kidney and Body Fluids. p. 74. Chicago: Year Book Medical Publishers. 1968.
29. **RAGAN, C. J., W. FERREBEE, P. PHYFE, D. W. ATCHLEY** and **R. F. LOEB.** A syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate. Am. J. Physiol. **131**: 73-78. 1940.
30. **ROE, J. H., J. H. EPSTEIN** and **N. P. GOLDSTEIN.** Photocolorimetric method for the determination of inulin in plasma and urine. J. biol. Chem. **178**: 839-845. 1949.
31. **SEGAL, M. S.** and **J. DIVENCI.** Triamcinolone therapy in bronchial asthma and other steroid responsive diseases. Bull. Tufts New Engl. Med. Center **4**: 71-79. 1958.
32. **SHANNON, J. A.** The control of water excretion. I. The effect of variations in the state of hydration on water excretion in the dog with diabetes insipidus. J. exp. Med. **76**: 387-399. 1942.
33. **SIEGEL. E. T.** Assessment of pituitary-adrenal gland function in the dog. Am. J. vet. Res. **29**: 173-180. 1968.
34. **SLESSOR, A.** Studies concerning the mechanism of water retention in Addison's disease and in hypopituitarism. J. clin. Endocr. Metab. **11**: 700-723. 1951.
35. **SPRAGUE, R. G., M. H. POWERS, H. L. MASON, A. ALBERT, D. R. MATHEISON, P. S. HENCH, E. C. KENDALL, C. H. SLOCUMB** and **H. F. POLLEY.** Observations on the physiological effects on cortisone and ACTH in man. Archs intern. Med. **85**: 199-258. 1950.
36. **STEELMAN, S. L.** and **R. HIRSCHMANN.** Synthetic analogues of the adrenal cortical steroids. In "The Adrenal Cortex." A. B. Eisenstein (ed). p. 371. Boston: Little Borwn and Co. 1967.
37. **SYMONDS, E. R.** Personal communication. 1969.
38. **VARLEY, H.** Practical Clinical Biochemistry. p. 89. New York: Interscience Books. 1967.
39. **WALKER, D.** Diabetes mellitus following steroid therapy in a dog. Vet. Rec. **74**: 1543-1545. 1962.
40. **WEBER, G., S. K. SRIVASTAVA** and **R. SINGHAL.** Role of enzymes in homeostasis. VII. Early effects of cortisteroid hormones on hepatic gluconeogenic enzymes, ribonucleic acid metaabolism, and amino acid level. J. biol. Chem. **240**: 750-756. 1965.

Book Review

ANIMAL GROWTH AND NUTRITION. *Edited by E. S. E. Hafez and I. A. Dyer. Published by Lea & Febiger and Macmillan of Canada, Toronto. 1969. 402 pages, 113 illustrations and 26 plates. Price $16.50.*

This book is the work of 25 different authors. It is divided into four sections and contains 20 chapters most of which are written by different authors. Each chapter is followed by a selected list of references. The first section discusses prenatal growth and fetal nutrition, the second discusses postnatal growth and development and factors which influence growth such as genetics and environment. The third section deals with body composition and the fourth discusses nutritional requirements for growth. The editors have moulded the writings of the various authors into a unit with logical sequence that is easy and pleasant to read.

In their preface, the editors state that they have attempted "to combine the pertinent physiochemical concepts of growth and the nutritional requirements controlling it into one volume for students of general biology, nutrition, physiology, and veterinary medicine". This they have succeeded in doing well. The book can be recommended as well to veterinarians even though, for many, much of the contents may not be new material. It will help maintain a conscious awareness of all the known biological phenomena that influence life and growth and of the interrelationship of disease, nutrition, environment, and genetics. — *W. T. Nagge.*