

Effect of Cortisone on Serum Calcium, Magnesium and Phosphate Levels in Nephrectomized Dogs. (20958)

ARTHUR GROLLMAN.

From the Department of Experimental Medicine, Southwestern Medical School, University of Texas, Dallas.

During the course of studies on the electrolyte exchange between the tissues and extracellular fluid after nephrectomy, it was noted that the survival of nephrectomized dogs was shortened by the injection of cortisone (5 mg per kilo of body weight daily) and that such animals showed the cardiotoxic and other effects of hypercalcemia(1). This was confirmed by analyses of the blood which revealed marked increases in the calcium of the serum to toxic levels.

Methods. Mongrel dogs were nephrectomized in two stages with an interval of at least two weeks between the operations. Following nephrectomy the animals were maintained on an electrolyte-free, fat and carbohydrate diet with an amount of water (25 ml/kg of body weight) to compensate for the insensible perspiration. By this procedure the survival period of the animals in good condition is prolonged for periods of 4 to 7 days without vomiting. Serum calcium was determined by Clark and Collip's modification of the Kramer-Tisdall method(2); magnesium by Hawk, Oser and Summerson's modification of Denis' method(3) and inorganic phosphate by the method of Fiske and SubbaRow(4). The Coleman Universal Spectrophotometer was used for all colorimetric comparisons.

The *results* of typical experiments are reproduced in Table I. The values for the serum calcium, inorganic phosphate and magnesium of five dogs on the day following nephrectomy are compared with the values noted 3 or 4 days later during which time they received injections of 50 or 100 mg of cortisone intramuscularly, daily.

Discussion. It is well known that cortisone induces a negative calcium balance which is reflected in the osteoporosis observed in patients suffering from Cushing's disease. However, the level of the serum calcium in the presence of normal renal function, remains unaffected by the administration of cortisone,

TABLE I. Effect of Cortisone on Serum Calcium, Inorganic Phosphorus and Magnesium Levels of the Nephrectomized Dog. All values are expressed as mg/100 ml of serum.

	Calcium	Phosphate	Magnesium
Control	10.8	7.6	2.0
After 100 mg cortisone for 3 days	14.9	13.6	2.8
24 hr later	11.5	16.8	3.5
Control	11.0	6.0	1.9
After 50 mg cortisone for 4 days	15.9	14.7	3.1
24 hr later	12.0	16.0	3.0
Control	8.8	9.9	2.0
After 50 mg cortisone for 3 days	13.7	13.5	2.3
Control	10.3	8.4	2.1
After 50 mg cortisone for 3 days	13.3	13.6	2.5
Control	10.8	6.8	1.8
After 50 mg cortisone for 4 days	15.4	15.2	3.0

the calcium mobilized from the blood being excreted in the urine and to a large extent into the gut(5,6). In the presence of normal renal function there may actually be a tendency towards hypocalcemia in the presence of hypoparathyroidism(6). In the nephrectomized dog, on the other hand, where renal excretion is impossible and where excretion through the gut may perhaps also be decreased, the mobilized calcium increases and may reach toxic levels as shown in Table I. Studies on nephrectomized dogs not receiving cortisone reveal a slight rise in serum calcium on the day following nephrectomy with a slight progressive decline thereafter.

The present findings are not without practical interest since they indicate the need for taking precautions in the use of cortisone (and presumably of ACTH) in the face of renal insufficiency to avoid the toxic effects of hypercalcemia.

Summary. The injection of cortisone in the nephrectomized dog increases the serum calcium to toxic levels despite the concomitant

rise in serum inorganic phosphate and magnesium. On cessation of therapy the serum calcium level declines again to normal levels.

1. Grollman, A., *Pharmacology and Therapeutics*, 2nd ed., Lea & Febiger, Philadelphia, 1954.
2. Clark, E. P., and Collip, J. B., *J. Biol. Chem.*, 1925, v63, 461.
3. Hawk, P. B., Oser, B. L., and Sommerson, W. N., *Practical Physiological Chemistry*, 12th ed.,

The Blakiston Co., Philadelphia, 1947.

4. Fiske, C. H., and SubbaRow, Y., *J. Biol. Chem.*, 1925, v66, 375.
5. Soffer, L. J., Gabrilove, J. L., and Jailer, J. W., *J. Clin. Endocrinol.*, 1950, v10, 594.
6. Moehlig, R. C., and Steinbach, A. L., *J. Am. Med. Assn.*, 1954, v154, 42.

Received January 19, 1954. P.S.E.B.M., 1954, v85.

Changes in Patterns of Secretion of Corticosteroids in Rabbits after Prolonged Treatment with ACTH.* (20959)

E. H. KASS, O. HECHTER, I. A. MACCHI, AND T. W. MOU.
(Introduced by M. Finland.)

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, the Department of Medicine, Harvard Medical School and the Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

The nature of the adrenocortical secretion in diverse species has now been evaluated *in vivo* and *in vitro*. It was first shown that the isolated bovine gland, perfused with ACTH, synthesizes a mixture of corticosteroids, the major components of which are 17-hydroxycorticosterone (hydrocortisone) and corticosterone(1). Subsequent examination of the steroids present in adrenal vein blood has revealed that either hydrocortisone or corticosterone (or a mixture of both) is uniformly present in highest concentration in all species studied(2). The relative amounts of hydrocortisone and corticosterone, however, vary widely among species. It has been reported that the adrenal glands of sheep and monkeys secrete primarily hydrocortisone, those of rabbits and rats produce predominantly corticosterone, while cows, ferrets, cats and dogs secrete mixtures of both(2,3). Recent studies indicate that human adrenal vein blood contains primarily hydrocortisone, although lesser amounts of corticosterone have been detected(4). These differences between species have been reported by Bush(2,3) to be constant and unaltered by ACTH; the inference has been drawn that the species

differences may be fixed genetically.

The view that the nature of the steroids released in response to ACTH is fixed in unalterable fashion seemed at variance with certain observations on the comparative effects of ACTH and corticosteroids on lymphoid tissues of the rabbit. Thus, ACTH, cortisone and hydrocortisone induced significant changes in the weight and concentrations of ribonucleic acid in lymph nodes. Corticosterone, on the other hand, the presumed product of adrenal secretion in rabbits, had no significant effect at the same dosage levels as the other 2 steroids(5,6). The response of the rabbits to ACTH was not explicable on the assumption that rabbits secrete corticosterone exclusively. Inasmuch as the effects of ACTH on lymph nodes were observed after relatively prolonged administration, the possibility was considered that prolonging the treatment with ACTH might alter the pattern of secretion of corticosteroids in this species. Accordingly, experiments were undertaken to test this view. The results to be reported demonstrate that the prolonged administration of ACTH to the rabbit leads to an alteration in the pattern of secretion of corticosteroids so that hydrocortisone becomes the predominant steroid component of adrenal vein blood.

Methods. White male rabbits weighing between 2.5 and 3.5 kg, with no apparent dis-

* Aided by grants from the U. S. Public Health Service and the Research and Development Division, Office of the Surgeon General, Department of the Army.