ized Shwartzman phenomenon", because of the requirement that 2 separate injections be given with an intervening period of 24 hours. Black-Schaeffer(6) reported that the same renal lesion could be produced by repeated intravenous injections of meningococci in heavy doses. Apitz(7) reported that a single injection of meningococcal toxin occasionally produced bilateral cortical necrosis in pregnant rabbits. In normal, non-pregnant animals, single injections of meningococcal or *S. marcescens* toxin do not produce kidney lesions regardless of the dose employed or the length of time allowed to elapse following injection.

It is possible that the development of renal cortical necrosis during treatment with cortisone may be analogous to the change in the local skin reaction to meningococcal toxin which was noted earlier(1). In both instances, treatment with cortisone results in hemorrhage and necrosis when toxin is injected—locally when the latter is given intradermally, and in the kidneys when injected intravenously. The possible relation of these reactions to the Shwartzman phenomenon, in which changes in the susceptibility to tissue proteolysis or in the function of polymorphonuclear leucocytes have been postulated (8,9), is a subject for further investigation.

It should be noted that the doses of cortisone which were employed in these experiments were greatly in excess of those which have been used in the therapy of human disease. Until adequate information is available concerning the minimal effective amount of cortisone, no implications are warranted as to the possible effects of such therapy in humans. At this time the phenomenon is of interest because it provides a new experimental model for investigating both the action of cortisone and the mechanisms of tissue damage by gram-negative bacterial toxins.

Summary. 1. Bilateral cortical necrosis of the kidneys was observed in rabbits which were treated with large doses of cortisone and then given a single intravenous injection of meningococcal or *S. marcescens* (P-25) toxin. This lesion did not occur when animals were given injections of cortisone alone, or toxin alone. 2. A similar renal lesion occurred in cortisone-treated Syrian Hamsters following an intraperitoneal injection of P-25 toxin.

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Effect of Hypophysectomy on Electrolyte and Water Metabolism in the Dog.*† (18575)

D. P. EARLE, Jr., R. C. DE BODO, I. L. SCHWARTZ,‡ S. J. FARBER, M. KURTZ§ AND J. GREENBERG.

From the Departments of Pharmacology, Medicine and Physiology, New York University College of Medicine.

The adrenalectomized animal exhibits severe disturbances in electrolyte and water metabolism as well as in carbohydrate and protein metabolism. The hypophysectomized animal with marked adrenal cortical atrophy also has profound disturbances in organic metabolism. The purpose of the present in-

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‡ Dazian Foundation Fellow (1949-1950); Porter Fellow of the Am. Physiol. Soc., (1950-1951).

§ Dazian Foundation Fellow.

vestigation was to determine whether the hypophysectomized dogs concurrently exhibit disturbances in water and electrolyte metabolism. The response to loads of water and potassium and to sodium restriction was observed. Glomerular filtration rate and renal plasma flow were measured in an effort to evaluate the role played by alterations of these functions in the inorganic metabolism of hypophysectomized dogs.

Methods. Fifteen hypophysectomized female dogs were used in the various phases of this study. The operative technic,‖ aftercare, and diet were described previously(1,2). The response to insulin was determined in the post-absorptive state in each dog according to a previously described technic(2). This was taken as a measure of the impairment of carbohydrate and protein metabolism. Glomerular filtration rate, effective renal plasma flow, Tm_{PAH} and $Tm_{Glucose}$ were measured in lightly restrained, unanesthetized dogs in the post-absorptive state according to standard technics(3,4). Each renal function value in the subsequent tables represents the average of 3 or more consecutive periods. Water loads consisted of 40 ml per kg body weight, administered by stomach tube to well hydrated dogs. The per cent of this load excreted during the subsequent 3 hours was determined. Sodium restriction was achieved by the administration of a diet that furnished 1 to 2 mEq sodium daily ("Lonalac", prepared by Mead Johnson and Co.).¶ The dogs were maintained in metabolism cages on this diet for 3 weeks. Sodium output was measured in 24-hour urine collections while serum sodium concentrations were determined at intervals. The last serum sodium determination was made on the last day of salt restriction. Potassium chloride or thiosulfate was delivered intravenously at rates that varied between 0.31 and 0.98 mEq per minute for different experiments. After 1½ hours, four 15 minute urine collections were made. Arterial blood was obtained at the mid-point of each collection period. Potassium in the plasma and urine as well as glomerular filtration rate were measured in these studies. In order to facilitate tubular excretion of potassium(5) 3 of the 4 dogs studied were given 4 g potassium chloride twice daily by mouth for 3 to 5 days prior to the experimental day. Sodium and potassium concentrations were measured on an internal standard flame photometer.

To date, post-mortem examination of 5 of the animals used in this study has been completed. The operative area was studied by examination of serial sections of a block consisting of a portion of the sphenoid bone, the tissue occupying the region of the sella turcica and the hypothalamus. The adrenal glands were weighed after 24 hours of fixation in formalin and then multiple sections of each gland were prepared and examined(6).**

Results. Response to insulin. Six weeks or more postoperatively all the hypophysectomized dogs exhibited maximum sensitivity to the hypoglycemic action of insulin(2).

Anatomy. Examination of the serial sections of the "pituitary areas" of the 5 dogs

TABLE I. Effect of Hypophysectomy on Average Renal Functions of 5 Dogs.

Status	Glomerular filtration rate, ml/min.	Renal plasma flow, ml/min.	Filtration fraction, %
Control	68.1	250	27.2
Hypophysectomized	19.0	74	25.8

‖ We would like to thank Dr. A. C. Bratton, Jr., of Parke, Davis and Co. for the supply of Topical Thrombin which was most helpful in controlling hemorrhage during the operation.

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¶ A generous supply of Lonalac was obtained through the courtesy of Dr. Warren M. Cox and Mr. A. Bray from the Mead Johnson and Co.

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** All anatomical studies were done by Dr. Nathan Lane of the University Hospital, New York University-Bellevue Medical Center.

TABLE II. Effect of Hypophysectomy on Excretion of Water Load in the Dog.

No. of dogs	Status	% of water load excreted in 3 hr		Glomerular filtration rate (ml/min.)
		Avg	Range	
5	Control	101	85-113	66.3
	Hypophysectomized	28	11- 45	20.3
8	"	32	5- 47	18.5*

* Measured in 6 dogs only.

that have come to autopsy to date proved that each was completely hypophysectomized. The anatomical findings of these dogs (K-3, K-8, E-1, E-3, S-5) are reported in detail in a separate paper(6). Neither adenohypophyseal cells (pars distalis, pars tuberalis and pars intermedia) nor cells of the pars nervosa were found. The adrenal glands of all the dogs studied were markedly reduced in weight and showed atrophic changes of all the cortical layers, including the zona glomerulosa.

Renal functions. Several renal functions were measured in 5 dogs before and 6 to 14 weeks after hypophysectomy, at which time the animals showed maximum sensitivity to insulin. In confirmation of other workers (7) glomerular filtration rate and effective renal plasma flow were reduced to approximately one-third or one-fourth of normal (Table I). Filtration rate was also consistently reduced in 8 additional dogs used in the potassium and water load studies (Tables II and IV). Maximum ability of the tubules to excrete p-aminohippurate was measured in 2 dogs, and maximum ability to reabsorb glucose in one. These functions were also reduced to approximately one-third or less of normal following hypophysectomy. No consistent effect on filtration fraction occurred. Four dogs (K-3, E-1, E-3 and S-5) of this group were proven by histological study to be completely hypophysectomized.

Excretion of water load. Observations on the 3-hour urine excretion following the standard water load of 40 ml/kg were made in 5 dogs before and 6 to 11 weeks after hypophysectomy. Eight additional dogs were studied only after hypophysectomy (7 to 49 weeks post-operative). Multiple observations were made on the 13 dogs. The normal dog in water balance excretes approximately 100% of the standard water load within 3 hours(8). The ability of the hypophysectomized dog under identical conditions to excrete the water load was significantly reduced in each instance (Table II). The filtration rate was reduced at the time of observation in each of the 8 hypophysectomized animals in which this function was measured. The reduced excretion of the water load in the operated animals was most likely not due to decreased gastro-intestinal absorption of water since the stomach was empty 40 minutes after the administration of the water load and the animals never showed diarrhea. Three dogs (K-3, E-1 and E-3) proven by histological study to be completely hypophysectomized were part of the group subjected to water loads.

TABLE III. Effect of Severe Sodium Restriction for 3 Weeks on Serum Sodium Concentration in Six Hypophysectomized Dogs.

	No. of observations	Serum sodium concentration (mEq/liter)	
		Avg	Range
Control	12	141	136-147
During salt restriction	17	141	133-147
Last day of salt restriction	6	141	134-147

Sodium restriction. Six hypophysectomized dogs were maintained on a diet that furnished 1 to 2 mEq sodium daily for 3 weeks. Extremely low sodium concentrations were achieved in the urine, the average concentration for the 6 dogs being 0.3, 0.4, 0.5, 2, 4 and

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TABLE IV. Amount of Potassium Filtered by Glomeruli and Excreted in Urine During Infusion of Potassium in Hypophysectomized Dog.

Dog No.	Status	Potassium (microeq/min.) Infused	Filtered	Excreted	Glomerular filtration rate (ml/min.)	Range plasma potassium during infusion (mEq/liter)
S-1	Control	612	285	318*	51.9	5.0-5.9
	Hypophysectomized	368	96	168*	14.1	6.4-7.1
E-1	"	510	221	161	24.7	8.7-9.4
E-3	"	612	137	178*	17.2	7.8-8.4
E-5	"	306	389	386	43.1	8.8-9.3

* Tubular excretion of potassium is demonstrated in those instances where the urinary excretion of potassium exceeds the amount filtered.

4 mEq per liter. The dogs' general condition did not change during the period of salt restriction and body weight was maintained within narrow limits. In spite of the severe sodium restriction, serum sodium levels showed no significant trends (Table III). These observations were made 12 to 33 weeks after operation. Two dogs (E-1 and K-8) proven by histological study to be completely hypophysectomized were included in the group.

Potassium administration. Large doses of potassium were administered intravenously to 4 hypophysectomized dogs. One dog was studied before and after operation. All but dog E-1 received oral potassium for 3 to 4 days before observation. This dog received potassium chloride intravenously, the remainder potassium thiosulfate. The amounts of potassium infused, filtered by the glomeruli and excreted in the urine are summarized in Table IV. Excretion of potassium by the renal tubules is demonstrated whenever the amount of potassium in the urine exceeds the amount of potassium filtered. This phenomenon occurred in two of the hypophysectomized dogs that received potassium pre-treatment and the thiosulfate salt intravenously. The third dog treated in this fashion exhibited almost equal rates of potassium filtration and urinary excretion. Perhaps because of the reduced filtration rate in the operated animals, plasma potassium levels increased during the potassium infusions somewhat more in the hypophysectomized dogs than in normal animals given comparable amounts. Nevertheless, the retained ability of the renal tubules to excrete potassium appeared to be a factor in the protection of the hypophysectomized dog against excessive increases in plasma potassium concentration. Indeed, dog S-1 excreted in the urine almost the same proportion of administered potassium after hypophysectomy as she did before operation, while dog E-5, whose filtration rate was not reduced as much as the others excreted more potassium in the urine than was administered. Dogs E-1 and E-3 were proven by histological study to be completely hypophysectomized.

Discussion. To date post-mortem studies have been completed in 5 of the 15 dogs. All 5 were found to be completely hypophysectomized. Since the remaining dogs showed the same maximum sensitivity to insulin as the animals proven to be completely hypophysectomized, they too probably will prove to be "completely" or "nearly completely" devoid of adenohypophyseal cells(6). Thus the hypophysectomized dog that manifests severely disturbed carbohydrate and protein metabolism and considerable reduction in some renal functions, retains, despite atrophic changes of all layers of the adrenal cortex(6), the capacity to conserve sodium and excrete potassium in a manner comparable to the normal dog. However, the hypophysectomized dog does exhibit a pronounced impairment of the ability to excrete a water load. The reduced filtration rate may contribute to the impaired ability of the hypophysectomized dog to excrete a water load, and may perhaps assist the animal to withstand salt deprivation. In contrast, the adrenalectomized dog with approximately the same degree of impairment of filtration rate is unable to withstand salt restriction.

The available evidence does not permit a conclusion as to the nature of the hormonal

factors which enable the hypophysectomized animal to maintain adequate electrolyte metabolism. Perhaps the hypophysectomized dog, in spite of the lack of adrenocorticotrophic hormone, produces a sufficient amount of adrenocortical steroids to conserve sodium and excrete potassium but not enough to handle water properly. A further possibility would be that the adrenals of the hypophysectomized dog can produce a "salt regulating" but not a "water regulating" hormone. An alternative hypothesis might be that a complete lack of adrenocortical steroids in the hypophysectomized dog is counterbalanced by the absence of one or more pituitary hormones.

The effect of the anterior pituitary growth hormone upon water metabolism in the hypophysectomized dog is the subject of one of the papers of this series.

Summary. Study of hypophysectomized dogs that manifest (a) atrophic changes in all three cortical layers of the adrenals, (b) severe disturbances in carbohydrate and protein metabolism and (c) reduced renal functions (glomerular filtration rate, renal plasma flow and tubular transfer maxima) reveals that: (1) their ability to excrete an orally administered water load is impaired, (2) their ability to withstand sodium restriction is normal and (3) their renal tubules retain the ability to excrete potassium and the animals are able to handle potassium loads almost as well as the normals.

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Effect of Growth Hormone on Water Metabolism in Hypophysectomized Dogs.* (18576)

R. C. DE BODO, I. L. SCHWARTZ,† J. GREENBERG, M. KURTZ,‡ D. P. EARLE, JR., AND S. J. FARBER.

From the Departments of Pharmacology, Physiology, and Medicine, New York University College of Medicine.

During the course of a study of the effects of growth hormone on carbohydrate metabolism in hypophysectomized dogs(1-3) it was observed that the animals developed a severe polyuria. Since there was no glycosuria and the specific gravity of the urine was very low, the increased water exchange appeared comparable to that seen in experimentally induced diabetes insipidus. The polyuria disappeared after cessation of growth hormone administration. These observations suggested that the hypophysectomized dog's impaired ability to excrete a water load(4,5) might, at least in part, be due to lack of growth hormone.

The present investigation deals with the study of the effects of purified anterior pituitary growth hormone on the response to water load and the daily water exchange in hypophysectomized dogs. Glomerular filtration rate and renal plasma flow were concomitantly determined in an effort to evaluate the role of these functions in the alterations in water

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