tion of sodium varies along the intestinal tract, the amount of sodium fixed to the resin changes, the exchange occurring as soon as the surrounding electrolytes change. When the content of the ileum reaches the colon, the resin is suspended in a solution containing about 140 mEq of sodium per liter(11). In the colon, sodium moves more rapidly from the lumen to the blood than from the blood to the lumen which results in a net reabsorption of sodium from the colon(12). As the sodium ion leaves the lumen of the colon a new equilibrium is established between that sodium on the resin and that in the colon contents. It is the balance of these two attractions, the resin and the colon mucosa, which eventually determines the effectiveness of cation exchange resins in removing sodium in the stool.

Summary. The present data indicate that the action of DOCA is not limited to a control of the transfer of sodium from the lumen of the kidney tubule to the surrounding blood stream but also influences the transfer of sodium from the lumen of the intestine to the surrounding blood stream. DOCA, in addition, influences the transfer of sodium through the sweat and salivary glands by decreasing the sodium concentrations in their secretions(13,14). The evidence indicates that DOCA affects the transfer of sodium through various organs, among them the colon, in each instance limiting the escape of sodium from the body.

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Bilateral Cortical Necrosis of Kidneys in Cortisone-Treated Rabbits Following Injection of Bacterial Toxins.* (18574)

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Thomas and Mogabgab(1) reported that treatment with cortisone or ACTH produced a striking modification of the local skin reaction of rabbits to the intradermal injection of Shwartzman's meningococcal toxin. The treated animals did not develop the usual reaction of edema and erythema caused by toxin; instead, numerous petechial hemorrhages appeared throughout the skin site approximately 24 hours after the intradermal injection of toxin. The observations suggested that cortisone and ACTH, while inhibiting the local inflammatory response to toxin, might have brought about an increase in the vulnerability of the tissue to direct damage by bacterial toxin. Similar experiments, briefly described elsewhere(2), were undertaken to determine the effect of cortisone on the course of skin infection by living microorganisms, employing various strains of Group A hemolytic streptococci which were known to produce local inflammatory reactions, sometimes followed by abscess formation, in normal rabbits. When cortisone was administered for 2 or 3 days before and after an injection of

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these microorganisms, little or no local reaction occurred in the skin but the rabbits regularly developed extensive bacteremia and died within the next 4-12 days. Colony-like deposits of streptococci were observed in the interstitial tissue of the heart and kidney in some of these animals(3).

In the light of the observed increase in susceptibility to the systemic effects of living microorganisms which was brought about by cortisone, it became of interest to learn whether treatment with this substance would alter the reaction of internal organs to bacterial toxin. Accordingly, rabbits were treated with cortisone and then given an intravenous injection of toxin derived from meningococci or *Serratia marcescens*, with accompanying control animals receiving cortisone alone or toxin alone. The present paper is concerned with a description of the kidney lesions which developed in cortisone-treated rabbits after a single intravenous injection of bacterial toxin.

Materials and methods. Albino male and female rabbits weighing 1.5-2.0 kg were obtained from a single breeding stock for these experiments, and were maintained on a diet of Purina rabbit pellets. Cortisone, supplied through the generosity of Merck and Company was injected intramuscularly as a suspension in 1.0 cc sterile saline. In most experiments the rabbits were given cortisone in a daily single dosage of 25 mg for 4 days, and toxin was injected in the marginal ear vein on the third day. In some experiments, indicated below, the treatment period was shortened or the daily dosage of cortisone was decreased. Meningococcal "agar washings" toxin(4) filtered free of bacteria, was kindly supplied by Dr. Gregory Shwartzman, of the Mount Sinai Hospital, N. Y. This material was given intravenously in the marginal ear vein, in a dose of 2 cc of 1-10 dilution in saline. A partially purified "polysaccharide toxin" from *Serratia marcescens*, similar to that employed in experimental tumor therapy (5), was supplied by Dr. Murray Shear, of the National Institutes of Health, Bethesda, Maryland. The latter material, designated as "P-25 toxin", was given intravenously in an amount of 0.4 mg contained in 2 cc saline.

The rabbits were divided into 5 groups and subjected to treatment in the following manner: 1. Thirty-six rabbits were treated with 25 mg cortisone per day for 4 days, and injected intravenously with meningococcal toxin on the third day. 2. Thirty rabbits were given the same amount of meningococcal toxin intravenously, without cortisone treatment. 3. Thirty rabbits were treated with 25 mg cortisone daily for 4 days, and received no toxin. 4. Twelve rabbits were treated with 25 mg cortisone daily for 4 days, and received an intravenous injection of Shear's P-25 toxin (0.4 mg) on the third day. 5. Twelve rabbits received the same dosage of P-25 toxin as above, and were not treated with cortisone. In addition, smaller groups of rabbits were treated with cortisone in lower dosage or for shorter periods of time prior to the injection of bacterial toxin.

Results. In the cortisone-treated rabbits which were given intravenous meningococcal or P-25 toxin (Groups 1 and 4), kidney lesions occurred within 24-72 hours which had the gross and microscopic characteristics of bilateral renal cortical necrosis. The incidence of these lesions is indicated in Table I, in

TABLE I. Bilateral Renal Cortical Necrosis in Cortisone-Treated Rabbits Following an Injection of Meningococcal or *S. marcescens* Toxin.

Group	Exp. procedure: Cortisone treatment	Exp. procedure: Bacterial toxin	No. of rabbits	No. with bilateral renal cortical necrosis
I	25 mg/day for 4 days	M.t.* 3rd day	36	19
II	0	M.t.	30	0
III	25 mg/day for 4 days	0	30	0
IV	25 mg/day for 4 days	P-25 t. 3rd day	12	10
V	0	P-25 t.	9	0

* Meningococcal toxin.

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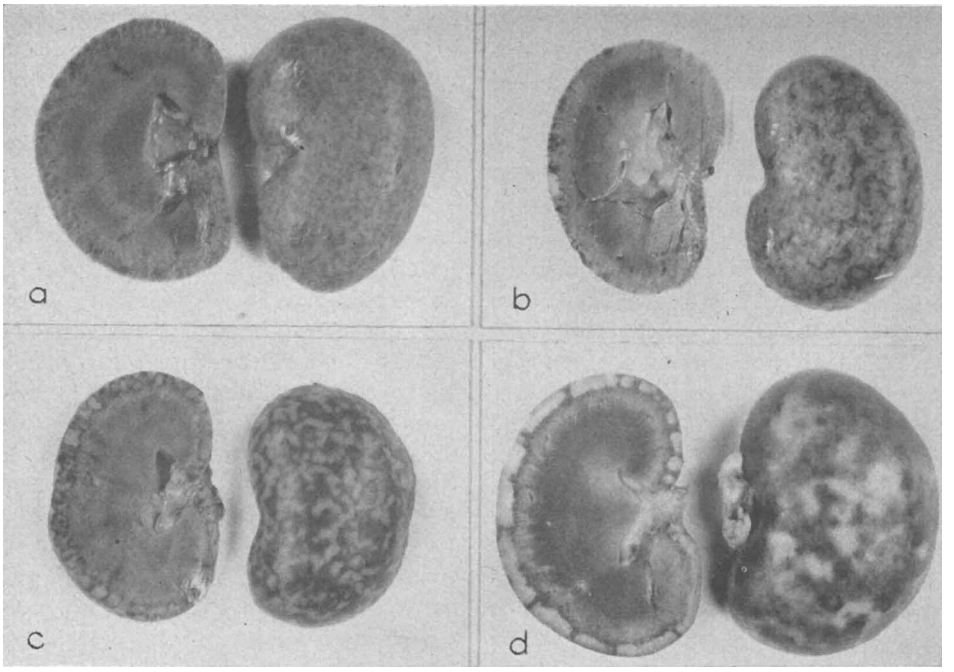

FIG. 1.
Gross appearance of kidneys of 4 cortisone-treated rabbits 48 hr after an intravenous inj. of meningococcal endotoxin.

which it will be seen that 19 of 36 cortisone-treated rabbits receiving meningococcal toxin, and 10 of 12 similar animals receiving P-25 toxin, exhibited bilateral cortical necrosis. In 30 control rabbits treated with cortisone alone, and in 42 receiving toxin alone, renal necrosis did not occur.

The gross appearance of the kidneys in the rabbits given both cortisone and toxin is illustrated in Fig. 1, in which photographs of the surface and cut edge of the kidneys of 4 representative animals are shown. Multiple deep red or purple areas of punctate hemorrhage, and white, pin-head sized areas of necrosis were observed throughout the renal cortices. In general, little or no involvement of the medulla was grossly discernible. Microscopically, the lesions were marked by severe tubular necrosis, interstitial hemorrhages, and many hyaline thromboses in the glomeruli. Fig. 2 illustrates the demarcation of necrosis and hemorrhage within the cortex (Fig. 2a), and the extent of tubular necrosis and hemorrhage (Fig. 2b). A more detailed account of the pathology in these animals will be given in a later communication. Variability was noted in the extent of hemorrhage and necrosis in different rabbits receiving the same doses of cortisone and toxin. The most severe lesions were observed in animals which died spontaneously within 24-72 hours after the injection of toxin. Animals which survived and seemed well at the end of the 3 day period showed less extensive cortical hemorrhage and necrosis, although the lesions were easily seen by gross inspection.

In all rabbits given cortisone in a dosage of 25 mg daily for 3 or more days, whether or not toxin was also administered, gross abnormality of the liver was observed. This organ was larger than normal and extremely friable; microscopically the hepatic cells showed marked enlargement and cytoplasmic vacuolization. In some of the rabbits treated with cortisone alone, the kidneys were somewhat larger and paler than normal and showed, on microscopic examination, generalized dilation of the tubules throughout the cortex. No tubular necrosis or hemorrhages were seen in microscopic sections of these kidneys.

In the group of control rabbits given menin-

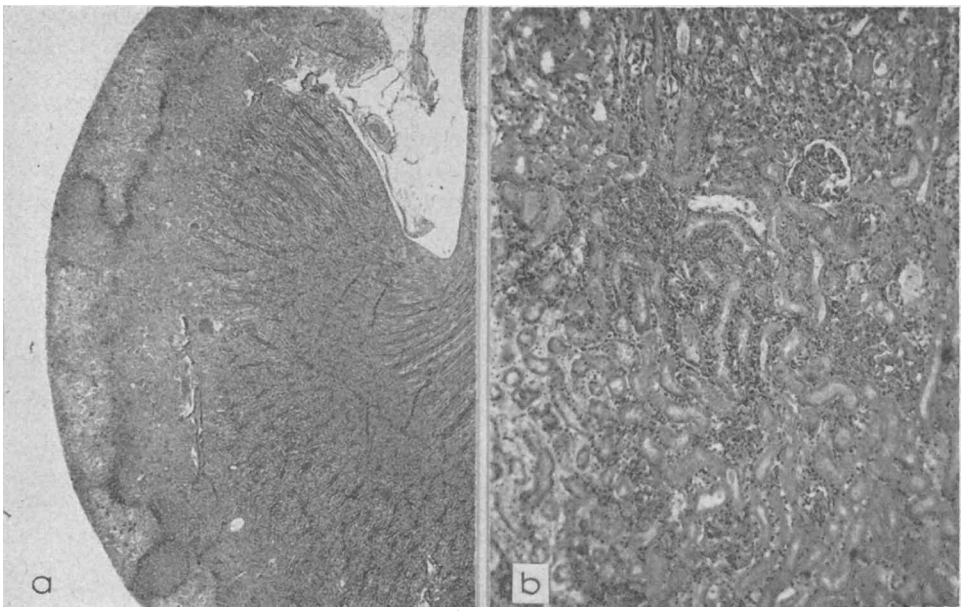

FIG. 2.
Microscopic appearance of kidney of a cortisone-treated rabbit 48 hr after an intravenous inj. of meningococcal endotoxin.

gococcal or P-25 toxin alone, some animals appeared sick and ruffled for several hours after injection and a few (less than 10%) died within 4-12 hours with no demonstrable tissue lesions. The remainder of the group survived without apparent ill effect and, when sacrificed 3 days later, exhibited no gross or microscopic abnormalities in the kidney, liver or other organs.

The minimal effective dose of cortisone for the production of renal necrosis in combination with toxin has not yet been accurately determined. In preliminary experiments, the lesions occurred in 2 of 6 rabbits which received 5 mg of cortisone daily for 4 days prior to the injection of P-25 toxin. In 6 animals the effect of shortening the period of pretreatment with cortisone was studied. These animals received 25 mg of cortisone for 3 days, and P-25 toxin intravenously on the second day; 5 of the 6 rabbits developed bilateral cortical necrosis of the kidneys within 24-72 hours after toxin. When cortisone was limited to a single injection of 25 mg on the day of injection of toxin, or 24 hours later, no renal lesions were observed.

Cultures of the blood and kidney tissue of 12 rabbits with renal necrosis were made, and all were negative. No instances of a similar kidney lesion were demonstrable in rabbits subjected to other, unrelated experimental procedures, including more than 50 animals which died following treatment with cortisone and experimental infection with hemolytic streptococci(2,3).

Similar hemorrhagic necrosis of the renal cortex was produced in 7 of 8 cortisone-treated Syrian hamsters, following intraperitoneal injection of Shear's P-25 toxin. These animals were treated for 4 days with 10 mg cortisone daily, and 0.2 mg of toxin was injected on the third day. Hamsters given cortisone alone, or toxin alone, showed no kidney lesions. A more detailed report of the experimental disease in hamsters will be included in a later communication.

Discussion. It is known that bilateral cortical necrosis of the kidneys may occasionally be produced in rabbits when an intravenous injection of gram-negative bacterial toxin is followed, after 24 hours, by another intravenous injection of similar material(4). The development of this lesion has been regarded as the characteristic feature of the "general-

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)

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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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