

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE GENERALIZED SHWARTZMAN REACTION*

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(Received for publication, June 8, 1961)

Recently we reported that the accelerated generalized Shwartzman reaction, which is produced by giving the thorotrast-pretreated rabbit a small dose of endotoxin several hours afterward, can also be produced by substituting for the endotoxin an additional small dose of thorotrast, a non-absorbable antibiotic given by gavage, or a brief exposure to hemorrhagic shock (1). We also observed the reaction without giving anything afterward when the dose of thorotrast was large enough to kill. But the reaction did not occur in any of the foregoing experiments in rabbits whose intestines were free or nearly free of coliform bacteria. From these observations and a subsequent one showing that endotoxins enter the circulation from the gut (2), we concluded that endotoxin derived from the intra-intestinal coliform flora are necessary to elicit the accelerated generalized Shwartzman reaction. At the same time it was also observed that dibenamine not only prevented the accelerated generalized Shwartzman reaction, but also prevented the death which frequently occurred in these animals. This led to the further inference that endotoxins will not produce necrosis of the renal cortex without the participation of the catechol amines. In what follows we report experiments devised to test this inference.

Materials and Methods

Under nembutal anesthesia, the left kidney of healthy adult albino rabbits was exposed through a lumbar retroperitoneal incision, and its vascular pedicle dissected free of its bed. The nerve supply, which consists of two nerves, one on the renal artery, and a larger one between the artery and the vein, together with numerous fine perivascular branches, was excised.

4 to 21 days later, two intravenous injections of *Escherichia coli* endotoxin (Difco) were given 18 hours apart to evoke the generalized Shwartzman reaction. The first dose, which varied from 0.15 to 0.22 mg/kg, was 1 MSD/100 (*i.e.*, the maximum dose that will not kill a previously uninjected rabbit). The second dose was half as much, *i.e.*, 0.08 to 0.11 mg/kg. If the rabbits did not die within 48 hours after the second dose, they were killed by exsanguini-

* Aided by a grant from the National Institutes of Health, Bethesda, and by a contract with the Office of the Surgeon General, United States Army.

nation. The kidneys of all the animals were examined in the gross and by microscopy of formalin-fixed paraffin sections. These were stained variously with hematoxylin and eosin, the Verhoeff-Van Gieson stain, periodic acid-Schiff reagent, phosphotungstic acid hematoxylin, aldehyde fuchsin, or Gomori's trichrome stain.

RESULTS

Table I lists the data from a series of seven rabbits which showed the gross or microscopic evidence of the generalized Shwartzman reaction. Additional rabbits which died too early to develop the reaction, or survived the second injection of endotoxin with no sign of the reaction, are omitted. In all seven rabbits the reaction was outspoken in the non-denervated (right) kidney

TABLE I
Effect of Denervation of Renal Pedicle on Occurrence of Generalized Shwartzman Reaction

Exp. No.	Interval after unilateral renal denervation	Survival after second dose of toxin	Generalized Shwartzman reaction	
			Normal (right) kidney	Denervated (left) kidney
	<i>days</i>	<i>hrs.</i>		
1	6	7	+	+
2	6	12	+	-
3	4	18	+++	-
4	5	25	+++	-
5	21	33	+++	+
6	13	48*	+++	-
7	5	48*	+++	+

* Killed for study.

(Figs. 1 *A*, and 2), but in four of these there was no gross or microscopic evidence of the Shwartzman reaction in the denervated (left) kidney (Figs. 1 *B* and 3). The reaction was present but much less severe in the remaining three left kidneys.

Two of the seven rabbits died within 12 hours after the second injection of endotoxin. Microscopy of the right kidney showed the earliest signs of the generalized Shwartzman reaction, *i.e.*, severe congestion in the cortex and sub-cortex, with focal hemorrhages, fibrin thrombi in some of the glomerular tufts, capillaries and arterioles, but without necrosis, inflammation or damage to the tubules (Fig. 4). In the other five there was extensive confluent patchy necrosis of the cortex with necrotic glomeruli and arterioles, many of which contained fibrin thrombi (Fig. 2). In all of these there was one constant pathologic change which we have not seen described. This was hemorrhage within the wall of the arterioles and interlobular arteries without obvious disruption of the elastic lamina (Fig. 4).

DISCUSSION

The mechanism of action of endotoxin is obscure. The French school long ago implicated the central nervous system by showing (*a*) that typhoid toxin injected into the third ventricle of the brain produced the morphologic evidence of typhoid fever; (*b*) that if endotoxin is applied to a splanchnic nerve the intestinal lesions characteristic of endotoxin poisoning are produced; and (*c*) that endotoxin applied directly to the nervous system is more damaging than when given by other routes (3, 4). More recently, Penner and Bernheim (5) showed in dogs that the dose of endotoxin required to produce the systemic manifestations of endotoxin poisoning when injected directly into the third ventricle of the brain is very much smaller than the dose required when it is given intravenously.

Vrubel (6) observed that sympathetic denervation of an extremity reduced the intensity of the local Schwartzman reaction in that area. Our study indicates that denervation of the kidney prevents the generalized Schwartzman reaction, which is a specific effect of endotoxin on this organ. The denervation of the renal pedicle was total, but we infer that the sympathetic fibers provided the protection, for work in progress shows that subdiaphragmatic bilateral vagotomy without denervation of the renal pedicle does not prevent the generalized Schwartzman reaction. Because dibenamine also protects (2), one may assume further that the sympathectomy protects by eliminating the local production of the catecholamines. If this is correct, it follows that the endotoxin cannot act directly to produce the necrosis, but requires the presence of the catechol amines.(7)

SUMMARY AND CONCLUSION

Unilateral denervation of the renal pedicle was performed in a series of rabbits. 5 to 21 days later two intravenous injections of *E. coli* endotoxin were given 18 hours apart. In seven rabbits the generalized Schwartzman reaction developed in the non-denervated kidney. Four of the seven denervated kidneys did not show the reaction, and in the remaining three only a mild reaction was present. From these and previous observations we conclude that an intact sympathetic nervous system as well as endotoxin from the intestine, are necessary for the production of the generalized Schwartzman reaction.

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EXPLANATION OF PLATES

PLATE 55

FIG. 1 A. Cut surface of the right kidney, showing cortical necrosis. (Experiment 6, Table I.)

FIG. 1 B. Cut surface of the denervated (left) kidney of the same rabbit, showing no gross pathology. (Experiment 6, Table I.)

FIG. 2. Non-denervated right kidney of Experiment 6 showing diffuse focal necrosis of the cortex. Hematoxylin and eosin stain. $\times 30$.

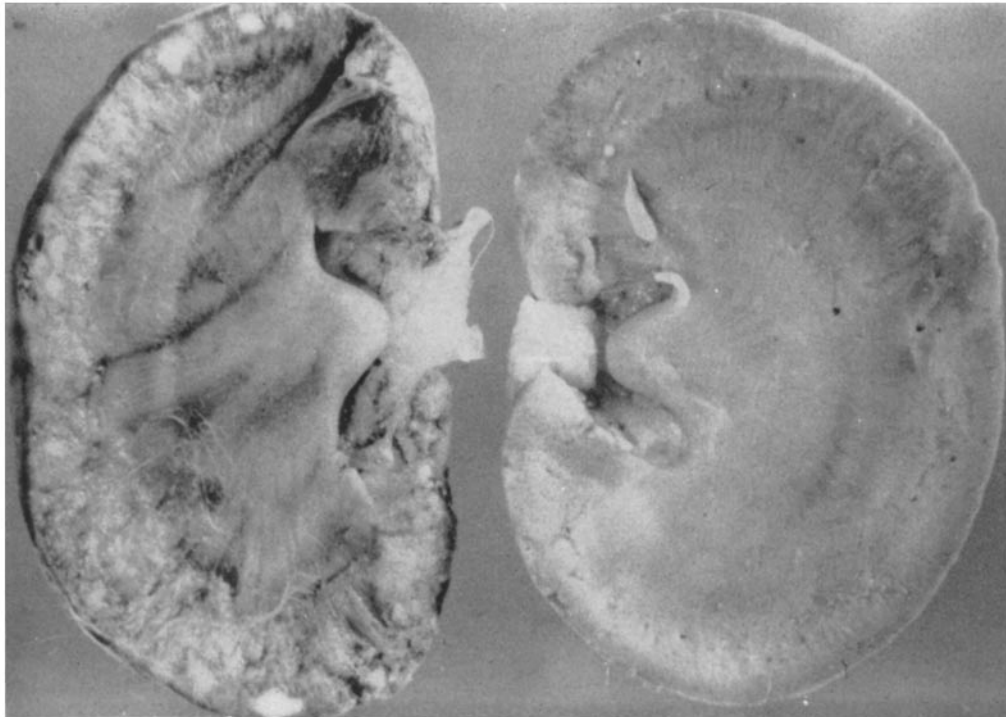
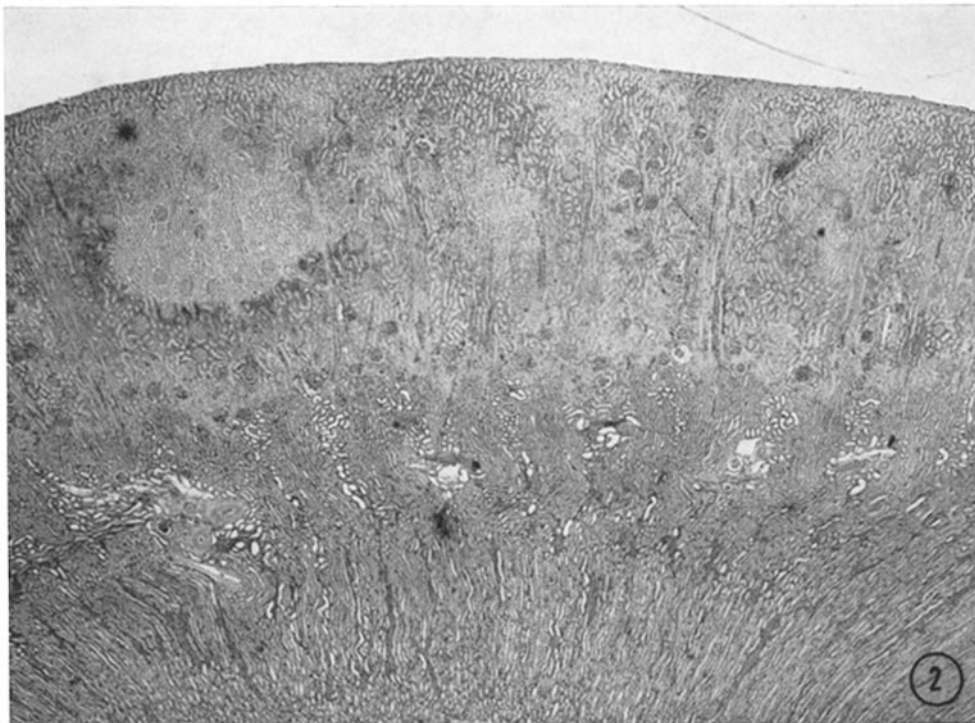


FIG. 1A

FIG. 1B

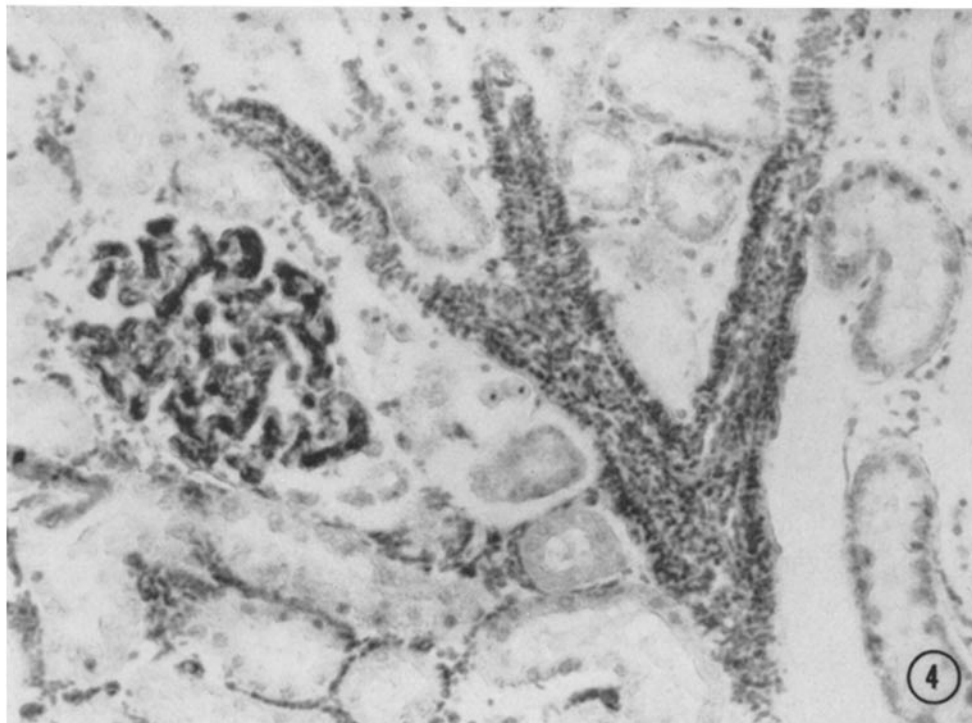


(Palmerio *et al.*: Generalized Shwartzman reaction)

PLATE 56

FIG. 3. Cortex of the denervated left kidney of Experiment 6 showing normal histology. Hematoxylin and eosin stain. $\times 8$.

FIG. 4. Cortex of the non-denervated (right) kidney of rabbit (Experiment 2) showing hemorrhage into the wall of a branching interlobular artery and fibrinoid thrombi in a glomerulus. Phosphotungstic acid hematoxylin stain. $\times 200$.



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