Experimental Production of an Anaphylactoid Purpura.* (29936)

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Parenteral administration of various histamine releasing mast-cell dischargers (*e.g.*, egg white, dextran, Compound 48/80, polymyxin) produces an acute, serous anaphylactoid inflammation, predominantly localized in the snout and paws of the rat(1,2). On the other hand, intravenous administration of various particulate, colloidal or readily precipitable materials, induces a thrombohemorrhagic phenomenon (THP) with multiple hemorrhages and microthromboses, especially in the kidneys, duodenum, heart and lung of the rat. The change most characteristic of this THP is the formation of hyaline thrombi within the renal glomerular capillaries such as are also typical of the generalized Schwartzman reaction. This syndrome is readily elicited, for example, by a single intravenous injection of a saturated agar solution. If, immediately after this treatment, epinephrine or norepinephrine are injected subcutaneously then, in addition to the systemic changes just mentioned, there develop, at the site of catecholamine administration, topical thrombohemorrhagic necrotizing lesions reminiscent of the local Shwartzman reaction(3).

In this communication we should like to show that, by combining an intravenous injection of agar with parenteral administration of various mast-cell dischargers, it is possible to produce an anaphylactoid purpura in the rat. Here, the thrombohemorrhagic lesions characteristic of agar treatment become localized in the anaphylactoid shock organs, especially the snout and paws.

Materials and methods. One hundred and eighty female rats of the Holtzman strain, with a mean initial body weight of 100 g (range 95-106 g) were divided into 9 equal groups and treated as indicated in Table I.

All the animals received 5 mg of *agar* (Agar U.S.P., Brickman & Co., Montreal, Canada) in 1 ml water into the jugular vein, under light ether anesthesia, on the first day. Immediately afterwards, the following agents were administered, to produce the classical anaphylactoid inflammation: *Compound 48/80* (Burroughs Wellcome & Co., Montreal, Canada), 300 μg in 0.2 ml water, subcutaneously. *Dextran* (Abbott Laboratories, North Chicago, Ill.), 0.5 ml of a 6% solution, intravenously. *Dextrin* (Testagar & Co. Inc., Detroit, Mich.), 0.5 ml of a 25% solution, intravenously. *Egg white,* 1 ml of a 50% aqueous solution (filtered once through two layers of Kleenex® tissue), intravenously. *Ferric dextran* (Imferon®, Benger Laboratories, Holmes Chapel, England), 1 ml equivalent to 10 mg of metallic iron, intravenously. *Pepsin extract* (Wilson Laboratories, Chicago, Ill.), 100 mg in 1 ml water, intravenously. *Polymyxin-B sulfate* (Pfizer Corp., Montreal, Canada), 1 mg in 0.2 ml water, subcutaneously. *Thorium dextrin* (Thorotrast®, Testagar & Co. Inc., Detroit, Mich.), 0.6 ml, intravenously.

The animals were maintained exclusively on Purina Laboratory Chow (Purina Co. of Canada) and tap water. The experiment was terminated after 24 hours and at autopsy the lesions were examined with a dissecting loupe and gauged in terms of an arbitrary scale of 0 = no lesion, 1 = just detectable, 2 = moderate, 3 = most severe lesions, as described elsewhere(4). The means of these readings, with the percentage mortality rate, are indicated in Table I. Specimens were fixed in Susa solution saturated with picric acid and stained with azure A, the PAS technique, and our "multipurpose polychrome stain," as described elsewhere(5).

Results. In the control rats treated with agar only, the lesions were those characteristic of the THP: hemorrhages and microthrombosis developed in various internal or-

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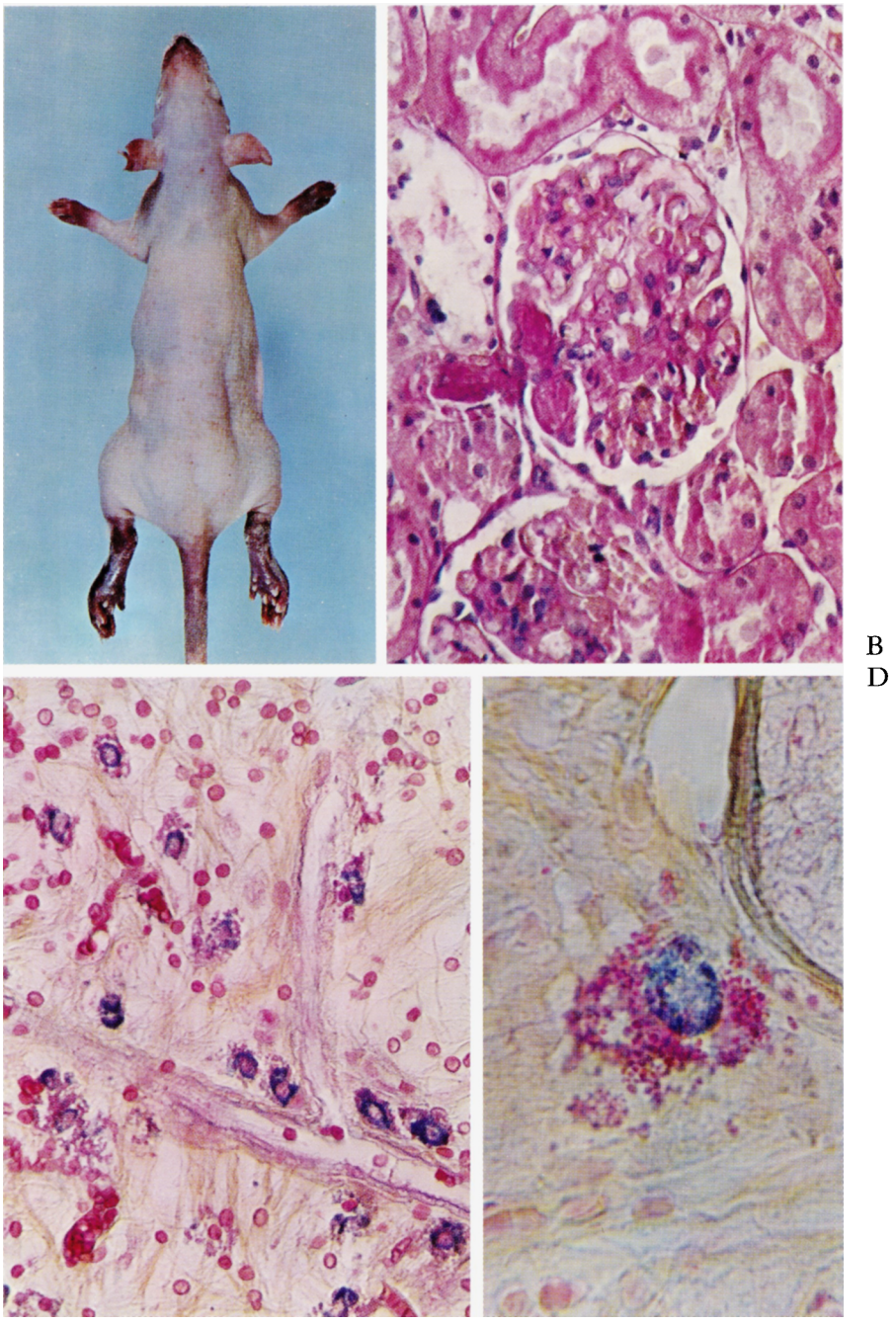

FIG. 1. *Anaphylactoid purpura produced by agar + dextrin.* *A:* Hemorrhagic lesions in the anaphylactoid shock organs (snout, ears, paws, root of tail). *B:* Glomerulus with thrombus in afferent arteriole and adjacent glomerular capillaries (PAS, X 460). *C:* Erythrocytes and partially discharged mast cells in connective tissue of paw (multipurpose polychrome, X 460). *D:* A single mast cell from preceding preparation, clearly indicating purplish-blue intracytoplasmic and red discharged mast-cell granules (multipurpose polychrome, X 1,000).

TABLE I. Anaphylactoid Purpura Elicited by Agar Plus Various Mast-Cell Dischargers.

Group	Mast-cell discharger*	Lesions (scale: 0-3)						Mortality (%)
		Snout	Paws	Heart	Kidney	Lungs	Duodenum	
1	None	0	0	.3	1.7	1.3	1.1	50
2	Cpd. 48/80	0	.3	.2	.9	.2	.2	40
3	Dextran	.8	1.9	.1	1.2	.7	.2	15
4	Dextrin	.9	1.6	.3	1.2	.8	.3	30
5	Egg white	1.2	1.8	.3	2.3	1.4	.2	60
6	Ferric dextran	.9	2.0	.1	.9	.8	.1	5
7	Pepsin extract	1.2	2.5	.4	2.4	1.4	.5	60
8	Polymyxin	.5	.8	.7	1.5	.8	.6	55
9	Thorium dextrin	1.6	2.4	.5	2.3	1.6	.3	65

* In addition, all rats received *agar*, intravenously, as described in the text.

gans, particularly the heart, kidneys, lung and duodenum. In the kidney, which was most consistently and markedly affected, the characteristic changes consisted of thromboses in the glomerular capillaries, hyperemia and hemorrhages in the medulla, and sometimes renal cortical necrosis. Presumably, these lesions were mainly responsible for the mortality which ran roughly parallel in the various groups with the intensity of the renal damage. Furthermore, frequently foci of hemorrhagic necrosis (reminiscent of those seen in eclampsia) occurred in the liver. However, changes in the anaphylactoid shock organs (snout, paws) were not observed in any of the rats given agar alone.

In addition to these changes, all groups given agar plus the various mast-cell dischargers exhibited more or less pronounced hemorrhages in the snout and paws (Table I). Similar lesions occurred occasionally at the root of the tail, but these were not sufficiently constant to deserve tabulation. The semiquantitative assessment of the lesions in terms of a scale of 0-3 does not permit far-reaching conclusions concerning the relative effectiveness of the various mast-cell dischargers; yet, it was evident that among the compounds tested, Compound 48/80 and polymyxin were least effective in producing thrombohemorrhagic lesions in the anaphylactoid shock organs, while all other mast-cell dischargers proved to be highly potent in this respect. The impure pepsin extract was especially efficacious but since its action could not be duplicated by pure pepsin preparations, the anaphylactoid potency of the preparation is presumably due to some unidentified impurity.

Histologic investigation of the anaphylactoid shock organs showed that here, as in the internal organs, the predominant lesions consisted of diffuse hemorrhages accompanied by thromboses in the smallest venules. However, in addition, the mast cells showed intense granule discharge in the anaphylactoid shock organs. On sections stained with azure A, the discharged granules were difficult to see because they lost their metachromasia and took only a weak, orthochromatic stain. On the other hand, the "multipurpose polychrome" procedure revealed that the granules still within the cytoplasm of partially depleted mast cells stain dark violet (as do the granules of normal mast cells), while the discharged granules form a halo around each mast cell and assume a bright red color, similar to that of erythrocytes (Fig. 1). Although the degree of the lesions varied, their histologic character was the same, irrespective of the mast-cell discharger used.

Discussion. It is evident from these experiments that a type of anaphylactoid purpura develops in rats if they are simultaneously given an intravenous injection of an agent capable of eliciting the THP (here, agar) and a mast-cell discharger that normally causes only serous inflammation in the anaphylactoid shock organs. Apparently here, the mast-cell discharger merely localizes in the anaphylactoid shock organs the agar-induced general tendency for the formation of thrombohemorrhagic lesions. As judged by its morphologic characteristics, the resulting syndrome resembles the Shwartzman reaction as well as certain thrombohemorrhagic forms of purpura.

Summary. Experiments on rats indicate

that the parenteral administration of various mast-cell dischargers following an intravenous injection of agar induces a type of anaphylactoid purpura. This syndrome is characterized by thrombohemorrhagic lesions in the anaphylactoid shock organs, especially the snout, paws and sometimes the root of the tail.

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Systemic and Coronary Hemodynamic Effects of Pseudoephedrine.* (29937)

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Pseudoephedrine (Sudafed®) has been promoted as a nasal and tracheo-bronchial decongestant because it has been found to have less effect on the blood pressure than its optical levo-isomer ephedrine(1-4). This compound, dextro-ephedrine (1-phenyl, 2-methylamine propanol-1-hydrochloride) is reported to cause approximately one-half as much elevation in blood pressure as ephedrine(2-3) and some differences in pharmacologic properties have been reported(5). Further information concerning its effect on the cardiovascular system in general, however, is limited and the drug was accorded no significance in a recent extensive review of the circulatory effects of sympathomimetic amines (6).

Materials and methods. The present study was done in 11 anesthetized mongrel dogs varying in weight between 15 and 30 kg with an average weight of 23.2 kg. These dogs were anesthetized by administration of 3 mg/kg of morphine sulfate subcutaneously followed one hour later by 0.25 ml/kg of veterinary pentobarbital and dial-urethane‡ intravenously. In the ensuing hour after establishment of anesthesia cardiac catheters were inserted through the jugular veins and manipulated fluoroscopically into the pulmonary artery, coronary sinus, and right atrium and a needle was placed percutaneously in the femoral artery for recording of pressures and drawing of blood specimens. Pressures were recorded by way of Statham strain gauge pressure transducers on a Sanborn 4-channel Poly-Viso. Mean pressures were determined by electrical damping. Expired air was collected through an endotracheal tube and low resistance large-bore tubing in a Tissot spirometer. Expired air was analyzed for oxygen and carbon dioxide by the method of Scholander. Blood specimens were analyzed by the Van Slyke-Neill manometric method. Analyses for arterial blood oxygen content were required to check within 0.2 ml. Cardiac output was measured by the direct Fick principle and coronary blood flow by the nitrous oxide saturation method utilizing the partition coefficient one. Cardiac work was calculated by the usual Starling formula.

After control observations had been made, pseudoephedrine was infused at a rate of one or two mg/kg body weight/minute. Approximately 7 minutes after onset of the drug in-

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‡ Dial-urethane contains Dial 100 mg/ml, monoethylurea 400 mg/ml, and urethane 400 mg/ml. Veterinary pentobarbital contains 60 mg/ml of pentobarbital.