

Attempts to Produce Localized Shwartzman Reaction in Seven Species of Animals.* (24230)

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When an intradermal injection of certain bacterial toxins is followed after 24 hours by intravenous injection of a similar toxin, a gross hemorrhage occurs at site of intradermal injection. Since the observation of this phenomenon by Shwartzman(1), the literature(2) on the subject infers that the reaction occurs in many species besides the rabbit. Increased interest in the Shwartzman phenomenon has come from a recognition that a parallel situation may exist in certain human disease states. Topley and Wilson(3) summed up this concept as follows: "The possibility that in natural infections there may be local alterations in the reactivity of tissues, particularly of vascular tissues, induced non-specifically by substances of bacterial origin, cannot be overlooked in our attempts to analyze the phenomena of resistance to infection. Thus the hemorrhagic episodes in certain chronic infections of man may be related to the (Shwartzman) phenomenon. There is ample ground for speculation, but little direct proof."

The purpose of this study was to attempt to induce the localized Shwartzman reaction in several mammalian species.

Methods and materials. The following animals were used: 265 New Zealand albino male and female rabbits weighing 1.8-2.5 kg, 15 *Macacca mulatta* monkeys weighing 4-7 kg, 20 mongrel male and female dogs weighing 12-20 kg, 16 guinea pigs, 16 small swine (Hormel "minipigs") weighing 40-50 kg, 15 Wistar albino rats and 4 Toggenburg goats weighing approximately 30 kg. Three toxins were used to elicit the Shwartzman reaction: (1) meningococcal "agar washings toxin" filtered free of bacteria (supplied by Dr. Greg-

ory Shwartzman), (2) partially purified "polysaccharide toxin" made from a pure culture of *Serratia marcescens*[†] and (3) a crude *Serratia marcescens* agar washing toxin, prepared by us from pure culture of this organism[†] by the same technic used in preparation of the meningococcal toxin(4). Each new preparation of toxin was assayed biologically to determine optimal dose and concentration necessary to give positive reactions in largest percentage of rabbits, while causing minimum lethality from the test itself. After this assay, the toxins were used in our tests. All 3 types of toxin were used in rabbits, monkeys and rats. Only the meningococcal toxin and our own *Serratia marcescens* toxin were used in dogs, minipigs, guinea pigs and goats.

The optimal dosage, previously worked out by biological assay in the rabbit, was given as a 0.50 ml intradermal dose, followed 24 hours later by intravenous dose of 1 ml of toxin. This dosage was used in the rabbits, rats, guinea pigs, goats, and monkeys. Ten dogs and 5 swine received 2.5 and 5.0 ml respectively for their intravenous dose. For further standardization of dosage in large animals, 10 additional dogs and 11 swine received intravenous doses comparable to that given rabbits (0.5 ml of a 1/40 dilution of toxin per kilo of body weight).

Results. Typical positive localized Shwartzman reactions occurred in 165 (62%) of 265 rabbits tested. No such reaction occurred in monkeys, dogs, rats, guinea pigs, goats, or minipigs tested (Table I). One of the goats, a post-partum lactating female, died several hours following intravenous injection of toxin. Although there was no local skin hemorrhage at site of intradermal injection, microscopic sections[‡] of kidneys of this animal revealed a

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[†] Supplied by Dr. Murray Shear, Nat. Inst. Health.

[‡] Dr. George Casarett reviewed the microscopic sections of goat kidney.

TABLE I. Incidence of Positive Localized Shwartzman Reactions in Various Species.

Species	No. of animals tested	Toxin used					
		<i>S. marcescens</i> filtrate		Meningococcal filtrate		<i>S. marcescens</i> polysaccharide	
			%		%		%
Rabbits	265	138/221	62	28/33	85	9/11	82
Monkeys	15	0/5	0	0/5	0	0/5	0
Dogs	20	0/15	0	0/5	0		
Goats	4	0/2	0	0/2	0		
Rats	15	0/5	0	0/5	0	0/5	0
Guinea pigs	16	0/10	0	0/6	0		
Minipigs	16	0/14	0	0/2	0		

"typical generalized Shwartzman reaction" (5), *i.e.* focal hemorrhagic cortical necrosis. Similar renal lesions were not found in animals of other species succumbing as a result of our test. No deaths or other untoward effects occurred in any of the groups of dogs, monkeys, minipigs, guinea pigs, or rats. Although the amount of toxin per kilo of body weight given the goat was markedly smaller than that given to rabbits, one goat which received 1 ml intravenously, developed a generalized Shwartzman reaction.

Discussion. Shwartzman(6) was able to induce the localized reaction in the golden Syrian hamster. He had previously reported (2) some success in inducing the phenomenon in guinea pigs after many unsuccessful attempts with the same species. He also mentions that Gratia and Linz(7) produced the reaction in guinea pigs, using 6-day-old *Vibrio cholerae* culture filtrate. Vassiliadis(8), using both cholera and El Tor vibrios, however, was unable to induce the Shwartzman reaction in guinea pigs. Gross(9) similarly failed, using *B. typhosa* filtrates. Freund(10) was also unable to produce the local hemorrhagic phenomenon in guinea pigs with *B. typhosa* preparations, but reported local skin hemorrhages in this species, if the animals received a skin-preparatory injection of diphtheria toxin, followed in 24 hours by intravenous injection of *B. typhosa* culture filtrate.

Generalized Shwartzman reactions (*i.e.* renal cortical hemorrhagic necrosis) were produced by Apitz(11) by means of a single intravenous injection of meningococcal toxin in pregnant rabbits. Thomas, *et al.*(5) confirmed this finding. Our experiments showed

that a generalized Shwartzman reaction could be produced in a post-partum lactating goat.

Conclusions. 1. The localized Shwartzman reaction was produced in 62% of 265 New Zealand albino rabbits, using 3 different toxins (a meningococcal agar washings toxin, a partially purified "polysaccharide toxin" prepared from a culture of *Serratia marcescens*, and a crude *Serratia marcescens* agar washing toxin). Using these same toxins, localized Shwartzman reactions could not be induced in 15 *Macacca mulatta* monkeys, 20 mongrel dogs, 16 guinea pigs, 15 Wistar albino rats, 16 small swine (Hormel "Minipigs"), and 4 Toggenburg goats. 2. One post-partum lactating female goat developed a typical "generalized Shwartzman reaction" (*i.e.* renal cortical hemorrhagic necrosis).

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