cities and from flies collected in widely separated areas. Subclinical infection may be produced in chimpanzees by oral administration of the virus. A laboratory worker has been accidently infected with the virus.

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17187. Effect of Phenergan (N-Dimethylamino-2-Propyl-1-Thiodiphenylamine, 3277 RP) on the Arthus Reaction in Rabbits.

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The so-called antihistaminic compounds have been of great value in that they have made possible the study of various biological phenomena, principally those related to histamine reactions, and the treatment of histamine-like allergies. As yet, none of the antihistaminics have been found to be effective in modifying the necrotizing type of allergic reactions. The lack of effect of pyribenzamine on the Arthus phenomenon and bacterial allergic reactions has been reported.[1] The present study is presented because an unusually potent antihistaminic, possessing, in addition, properties apparently unrelated to its antagonism to histamine, has been found effective in inhibiting the Arthus reaction.

The Fourneau compounds[3,4] and antergan[2] were modified to produce phenergan, N-dimethylamino - 2 propyl - 1-thiodiphenylamine, (3277 RP) which was extensively studied by Halpern.[5,6,7] In addition to being 30 times more effective than antergan in protecting guinea pigs against histamine, phenergan apparently protects capillaries against injury by various noxious stimuli.[8-12] The drug was kindly given for this study by Dr. B. N. Halpern. A quantitative technic for the induction of the Arthus reaction with known quantities of a single antigen and its homologous antibody has been described.[1,13] This method was employed in the present study.

Experimental. Arthus reactions were simultaneously induced in untreated control rabbits and in those treated with varying amounts of phenergan (25 to 100 mg/kg). In preliminary experiments, the Arthus reaction was induced in multiple sites in 9 albino rabbits by the local injection of antibody and of antigen as previously described.[1] It was found that 75 mg/kilo of phenergan in saline intramuscularly prevented the development of a severe Arthus reaction. The technic for producing the Arthus reaction was then modified by the administration of the antigen intraven-

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TABLE I.

Effect of Phenergan on Severity of the Reverse Arthus Reaction Induced Passively in Animals Injected Intravenously with 1.5 to 2.0 mg of Crystalline Egg Albumin Nitrogen, and 30 Minutes Later Injected Intradermally with Known Amounts of Anti-Egg Albumin. Number of reactions of different severity related to total reactions in each group.

Severity of the reaction	Phenergan 100 mg/kg	Phenergan 75 mg/kg	Phenergan 50 mg/kg	Phenergan 25 mg/kg	Control animals
		0.22 mg AbN.			
0	0	0	0	0	0
±	0	2/26	0	0	0
+	1/20	20/26	3/20	0	4/38
++	18/20	4/26	13/20	4/4	5/38
+++	0	0	4/20	0	3/38
++++	1/20	0	0	0	26/38
		0.025 mg AbN.			
0	1/4	2/18	0	0	0
±	3/4	8/18	4/4	2/4	5/14
+	0	8/18	0	2/4	8/14
++	0	0	0	0	1/14

ously and the subsequent injection of antibody intracutaneously.[13] This procedure was found to result in a more rapidly developing and more hemorrhagic reaction than did the local administration of both antigen and antibody. The antigen was administered intravenously to 45 rabbits in amounts of 1.5 to 2.0 mg egg albumin nitrogen (EaN); 30 minutes later the antibody was injected intracutaneously in amounts of 0.22 and 0.025 mg antibody nitrogen (AbN). Untreated controls were injected simultaneously with phenergan treated animals. The treated group of animals received 2 doses of phenergan in amounts of 25, 50, 75 or 100 mg/kg intramuscularly. The first dose was given at the time the antigen was administered; and the second dose, 4 hours later. One of 6 animals given 100 mg/kg phenergan had convulsions after the second dose and died. The other animals showed some drowsiness, muscular incoordination and occasional muscular twitchings with the dosages of 75 or 100 mg/kg but recovered completely in a few hours. The skin reactions were observed at 6 and 24 hours. In this series of rabbits the most acutely severe reactions appeared at 6 hours after the injections of the antibody. The reactions were graded as follows:

0 = no reaction; + = petechial hemorrhages of an area less than 1 cm in diameter with minimal edema; ++ = less than 1 cm of confluent intracutaneous hemorrhage or 1 cm of petechial hemorrhage with edema over a somewhat larger area (2 cm); +++ = 1 cm of confluent hemorrhage or 2 cm of petechial hemorrhage with moderate edema; ++++ = 1.5 cm or more of confluent hemorrhage, with moderate to severe edema. The results are presented in Table I.

In Table I, it is apparent that phenergan has a definite inhibitory effect on the severity of the reaction at the higher concentrations of antibody (0.22 mg AbN). When only 0.025 mg AbN was employed, there did not appear to be any significant difference between the control animals and those receiving phenergan. It is much more difficult to compare minimally severe reactions employing the criteria used in this study. In consideration of the sedative and anesthetic side effects of phenergan, two animals were given respectively procaine and pentobarbital intramuscularly and were given both antigen and antibody locally. The severity of the reactions in these animals, although not tabulated, was similar to that of untreated control animals. In Table I, with the maximum amount of antibody (0.22 mg AbN), 29 out of 38 reactions, or 75%, in the control group were graded +++ or more. In the treated group, only 5 of 70 reactions, or 7%, were similarly graded. Since the dose of phenergan administered here is far greater than the dose of pyribenzamine used in the previous study (10 mg/kg),[1] it seemed relevant to determine whether pyribenzamine given in comparable amounts would affect the Arthus reaction.

Two rabbits were given 25 mg/kg and 75 mg/kg respectively of pyribenzamine intramuscularly in a single dose and died shortly thereafter with severe convulsions. To investigate further the activity of phenergan, the effect of the drug was studied on the skin reaction of the rabbit to the streptococcal erythrogenic toxin. Two control animals observed 24 hours after the injection of 2 skin sites with 550 skin test doses of toxin showed areas of edema and erythema 1.5 cm in diameter. Milder edema and erythema resulted after the injection of 55 skin test doses into two other sites. In contrast, 2 other animals treated with 75 mg/kg of phenergan every 4 hours for 3 doses showed no reaction to either the 55 or the 550 skin test doses of erythrogenic toxin. The observation that phenergan inhibits the effect of the erythrogenic toxin is consistent with the view that the drug appears to protect the capillary bed from injury.

Discussion. The severity of the Arthus reaction can be related to the amount of precipitin available for union with antigen locally.[13,14] The primary site of the injury due to the antigen-antibody reaction is probably the small blood vessels and capillaries.[15] Certain observations indicate that the action of phenergan is on these small blood vessels. Halpern and his associates have shown that the drug, in doses of 20 mg/kg, can protect rabbits against pulmonary edema induced by the injection of such unrelated agents as epinephrine and chloropicrin, a war gas.[8-10] Furthermore, Hamburger *et al.*[11] have studied the effect of phenergan on experimental orthostatic albuminuria and hematuria in rabbits, and found that the animals were completely protected by doses of 20 mg/kg. The inhibition of the Shwartzman reaction in rabbits has been noted recently.[12] These observations suggest that the effect of the drug on the Arthus reaction may well be a consequence of its ability to decrease capillary damage in the presence of nonspecific irritants. As such, the mechanism of action would be on the vascular bed and have little relation to the occurrence of an antigen-antibody reaction.

The dosages of phenergan employed in this study (25 to 100 mg/kg of body weight) were not lethal for the rabbit except for the highest dose, 100 mg/kg, which caused death in 1 of 6 rabbits. These doses are far greater than the amounts used therapeutically in humans, and, indeed, are the highest reported in animals. Halpern and Hamburger used 20 mg/kg effectively against experimental pulmonary edema and orthostatic albuminuria. The dose of phenergan which is effective as an antihistaminic is still smaller.

Summary. The effect of phenergan on the Arthus reaction was investigated, employing a quantitative method for the induction of the reaction. In large but non-lethal doses, the drug was found to inhibit appreciably the development of the more severe Arthus reactions. It is suggested that the action of the drug on the Arthus reaction is related to its effect on capillary permeability. A limited study of the inhibition by phenergan of the toxic effect of a large quantity of streptococcal erythrogenic toxin appears to support this view.

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