catheter could be withdrawn leaving the polyethelene tube in place. Two fine wire ligatures were tied around the carotid artery to secure the tubing and stitched through either side of the incision in such a way as to externalize the cut end of the artery.

Results. Wound healing was found to occur within about 10 days provided penicillin was infiltrated in the incision during the operation. Seven dogs were prepared with indwelling catheters in the pulmonary artery and lived in apparent health and good spirits. Three of these animals retained these tubes for 41, 50 and 56 days, respectively. No clotting occurred in the tubes provided the heparin was changed at least once or twice a week. Blood samples could be withdrawn at any time and the pressures measured. At various times after successful healing in of the pulmonary arterial tubes, the catheterizations of the pulmonary veins were made. Contrary to the successful results on the pulmonary arterial side apparently considerable trauma is caused by the pulmonary venous catheters. In spite of all possible therapeutic measures wound healing was slow. The dogs lost their spirit and usually succumbed within 10 days unless the catheter was withdrawn. Autopsies revealed interlacing antemortem clots, raised hard plaques lining the vessel walls and inflammation of heart valves. The evidence strongly indicates that death was a consequence of the placing of the pulmonary venous catheter.

Summary. A method is described for placing permanent polyethelene catheters into the pulmonary artery and vein of dogs through the jugular vein and common carotid artery, respectively. The pulmonary artery catheter seems to cause little trouble to the animals and has been kept in place up to 56 days for sampling blood and measuring pressures. The pulmonary vein catheters, however, cause considerable trauma and animals succumb within 10 days after placement of the tube.

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Further Investigation of Effect of Colloidal Materials upon the Shwartzman Phenomenon.* (19837)

IVAN L. BENNETT, Jr.†

From the Department of Medicine, Emory University School of Medicine.

When the Shwartzman phenomenon is elicited at two-day intervals in rabbits, successive skin lesions rapidly diminish in intensity and animals soon become completely non-reactive (1,2). The production of hemorrhagic skin lesions is not necessary for the development of resistance, repeated parenteral administration of bacterial materials being effective in inducing the state of non-reactivity(2,3). This type of acquired resistance to the Shwartzman reaction resembles closely the tolerance to the pyrogenic action of bacterial endotoxins which develops in the course of repeated injections of these materials in animals or humans(4), one similarity being that both types of resistance are abolished promptly by injection of thorotrast or trypan blue(1,5). This has been interpreted as indicating a role of the fixed phagocytes of the "reticulo-endothelial system" in the removal of bacterial toxins from the blood stream(1).

In the original studies of Beeson on the Shwartzman phenomenon, thorotrast was administered 16 hours before the intravenous provocative injection of bacterial toxin(1). The present report describes experiments designed to determine the effect of giving thorotrast at varying times before the provocative injection in resistant animals as well as observations on the effect of administration of a colloidal iodide preparation upon non-reactivity to the Shwartzman reaction.

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† Present address: Department of Internal Medicine, Yale University School of Medicine.

TABLE I. Effect of Administration of 9 ml of Thorotrast at Varying Times Before I.V. Provocative Injection of *S. marcescens* Filtrate in Shwartzman-Resistant Rabbits.

No. animals	Interval before provocative injection	Results Pos.	Results Neg.
4	30 min.	3	1
5	2 hr	5	0
2	4	2	0
2	8	2	0
2	16	2	0
4	24	4	0

TABLE II. Effect of Administration of 3 ml of "Angiopac" at Varying Times Before I.V. Provocative Injection of *S. marcescens* Filtrate in Shwartzman-Resistant Rabbits.

No. animals	Interval before provocative injection	Results Pos.	Results Neg.
5	30 min.	3	2
6	2 hr	5	1
2	4	2	
2	8	2	
3	16	3	
2	24	2	

Experimental. Material used to elicit the Shwartzman reaction was a filtrate of agar-washings from a culture of *Serratia marcescens*. The dosage employed (0.5 ml of 1:10 dilution intradermally and 1.0 ml of 1:25 dilution intravenously 24 hours later) produced typical hemorrhagic lesions in about 90% of normal animals. White male rabbits of mixed breed weighing 2000-3000 g were used. Hair was removed from the abdomen with electric clippers and intradermal injections were given in alternate sides of the abdomen beginning in the right upper quadrant and moving the sites of successive injections posteriorly. The general plan of experiments was to induce resistance in animals by eliciting the Shwartzman reaction on alternate days. After at least two negative results, animals were again prepared for the reaction by intradermal injection of filtrate and, at varying intervals before the provocative injection 24 hours later, one of the colloidal materials under study was injected. The two colloids used were thorotrast, a suspension of approximately 25% thorium dioxide (Heyden Co.), and Angiopac (lot No. 115 D.G., S.A. Union Chimique, Belge, N. V. Brussels), a colloidal organic iodide preparation which has been used in Europe for radiographic demonstration of the liver and spleen.

Results. The administration of a single injection of 9 ml of thorotrast immediately following skin preparation or at any time up to 30 minutes prior to the provocative injection of filtrate regularly abolished resistance to the Shwartzman phenomenon. Animals thus treated developed large areas of hemorrhagic necrosis at the prepared skin area. Table I presents a summary of results obtained with thorotrast.

Resistant animals given a single injection of 3.0 ml of Angiopac immediately following intradermal preparation or at intervals up to 30 minutes before the provocative injection showed typical Shwartzman lesions at the prepared skin areas, indicating that this colloidal material is also effective in abolishing resistance to the Shwartzman phenomenon. Table II summarizes findings in animals given Angiopac.

An attempt was made to determine the effect of giving thorotrast more than 24 hours before the intravenous provocative dose of bacterial filtrate. Under these circumstances, animals had already received thorotrast when the intradermal preparatory dose of filtrate was injected 24 hours prior to the provocative injection. Difficulty was experienced in interpreting results of such experiments because it was noted that thorotrast treatment prior to skin preparation often resulted in the appearance of significant amounts of hemorrhage 12 to 24 hours after the preparatory injection. Further study of this apparent enhancement of the local injurious effect of *S. marcescens* filtrate was carried out in normal rabbits. In two experiments, 32 animals were given 0.5 ml of 1:10 dilution of filtrate intracutaneously and the resulting lesions were recorded by tracing their extent on x-ray film with colored pencils at intervals up to 48 hours. In no instance was gross skin hemorrhage observed. Sixteen animals were then given 9.0 ml thorotrast intravenously, the remainder serving as controls. Twenty-four hours after thorotrast injection, all animals were again given 0.5 ml of 1:10 dilution of filtrate intradermally, the progress of the inflammatory reaction at the injection site being followed as before. Al-

though hemorrhage was observed in none of the control animals, 11 of the 16 given thorotrast developed gross hemorrhage at the local site within 24 hours. In all thorotrast-treated animals, the edema and redness of the prepared skin area were much more extensive than that in the control group or in the same animals before thorotrast injection. In 8 thorotrast-treated animals, the intradermal injection of *S. marcescens* filtrate was repeated after a 21-day rest period. The resulting skin reactions resembled those observed before thorotrast injection; in no instance was skin hemorrhage seen.

Finally, the observation of Beeson(1) that thorotrast injection potentiates the lethal effect of intravenous injection of Shwartzman toxin was amply confirmed. Of 35 animals which had survived repeated injections of 1.0 ml of 1:25 dilution of *S. marcescens* filtrate, 21 died within 24 hours following injection of the same amount of filtrate after thorotrast treatment. Of 19 animals given Angiopac, 7 died wihin 24 hours after injection of *S. marcescens* filtrate intravenously.

Discussion. The results of the experiments reported here indicate that the injection of colloidal materials profoundly decreases resistance to the Shwartzman reaction within 30 minutes and that this interference is effective for at least 24 hours. Furthermore, both the local injurious and lethal properties of bacterial toxin are strikingly enhanced by these materials. Sickles(6) reported augmentation of the Shwartzman reaction by intravenous injection of India ink 20 minutes before the provocative dose of bacterial toxin.

Particulate substances have long been known to decrease resistance to experimental infections(7,8). Martin and his co-workers (9) have shown that thorotrast interferes with splanchnic removal of bacteria in animals with bacteremia produced by constant infusion of a suspension of organisms and have suggested this as a possible reason for the adverse effect of colloids on infections. Beeson(5) found that the development of tolerance to the pyrogenic effect of bacterial endotoxins in rabbits is accompanied by more rapid clearing of these materials from the blood stream after injection and that thorotrast, which abolishes tolerance, also interferes with the removal of pyrogen from the circulation. The fact that colloids localize in the macrophages of the reticulo-endothelial system after injection and that their effect upon infections and upon resistance to bacterial toxins seems to be related to interference with clearing the blood stream, makes "reticulo-endothelial blockade" a likely and tempting explanation of the effect of colloids upon resistance. However, the controversies surrounding the concept of true blockade of the macrophage system(7,10) and the absence of direct evidence bearing on the matter due to lack of a specific test of reticulo-endothelial function emphasizes a need for further investigation of this problem. It should be mentioned that pyrogen-tolerant rabbits evidence no increase in ability to clear bacteria from the splanchnic circulation(11).

Summary. The injection of thorotrast or Angiopac, a colloidal organic iodide preparation, abolishes resistance to the Shwartzman reaction within 30 minutes and for at least 24 hours. Treatment with these materials enhances strikingly the lethal effect of bacterial toxin and animals given thorotrast manifest increased susceptibility to the local injurious effect of intradermally injected toxin.

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1. Beeson, P. B., PROC. SOC. EXP. BIOL. AND MED., 1947, v64, 146.

2. Cluff, L. E., and Bennett, I. L., Jr., PROC. SOC. EXP. BIOL. AND MED., 1951, v77, 461.

3. Bennett, I. L., Jr., and Cluff, L. E. to be published.

4. Bennett, I. L., Jr., and Beeson, P. B., *Medicine*, 1950, v29, 365.

5. Beeson, P. B., *J. Exp. Med.*, 1947, v86, 39.

6. Sickles, G. M., *J. Immunol.*, 1931, v20, 169.

7. Jaffe, F. H., *Physiol. Rev.*, 1931, v11, 277

8. Maher, F. T., *Illinois Monographs in Med. Sci.*, 1944, v5, 112.

9. Martin, S. P., Kerby, G. P., and Holland, B. C., *J. Immunol.*, 1952, v68, 293.

10. Davis, F. B., Wadsworth, R. C. and Smith, H. P., *J. Exp. Med.*, 1930, v51, 549.

11. Kerby, G. P., and Bennett, I. L., PROC. SOC. EXP. BIOL. AND MED., 1951, v78, 48.

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