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Hemorrhagic Skin Reactions in Rabbits with Cutaneous Sensitization to Streptococci and Pneumococci (Shwartzman Phenomenon).*

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When intravenous injections of living or heat-killed bacteria were given to skin-sensitive rabbits within 48 hours after an intracutaneous injection of either a homologous broth-filtrate or a heat-killed suspension of microorganisms, hemorrhagic reactions frequently occurred within 24 hours at the site of the skin-test. These lesions varied considerably in intensity, were usually purple or violet and closely resembled the hemorrhagic lesions described by Shwartzman.¹

Such local hemorrhagic reactions in rabbits have been more often induced by bacterial filtrates than by suspensions. Streptococci usually contain little preparatory factor.¹ Antopol² produced hemorrhagic reactions with extracts of various microorganisms, including Type 3 pneumococcus, but Witebsky and Neter³ reported that intravenous injections of living or dead pneumococci were incapable of eliciting hemorrhage at the site of a previous intracutaneous injection of pneumococcal culture.

Sensitization may influence the development of this reaction.^{4, 5} Freund pointed out that hemorrhage develops in the skin and peritoneum of tuberculous but not of non-tuberculous guinea pigs. Fabiani elicited a Shwartzman phenomenon in rabbits that became Arthus positive after the third subcutaneous injection of horse serum but not in rabbits that required 5 injections before they became sensitive to horse serum. Zander⁶ demonstrated that capillary fragility is greater in areas of allergic inflammation in the skin of rabbits sen-

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¹ Shwartzman, G., *Phenomenon of Local Tissue Reactivity*, Paul Hoeber, Inc., New York, 1937.

² Antopol, W., *J. Inf. Dis.*, 1937, **61**, 330.

³ Witebsky, E., and Neter, E., *Proc. Soc. Exp. Biol. and Med.*, 1938, **38**, 187.

⁴ Freund, J., *J. Exp. Med.*, 1934, **60**, 669.

⁵ Fabiani, G., *Compt. Rend. Soc. Biol.*, 1938, **127**, 536.

⁶ Zander, E., *J. Exp. Med.*, 1937, **66**, 637.

sitized to streptococci than in control rabbits. Because of the possible relationship of these hemorrhages to hypersensitivity, further investigations seemed desirable.

Sensitization was induced by a variable number of intracutaneous injections of 0.1 cc of heat-killed indifferent streptococci,⁷ or Type 1 pneumococci, or formalin-killed hemolytic streptococci (Strain AB 13)⁸ given over periods of from 6 to 140 days. Intracutaneous injections were given daily for 6 days and repeated after an interval of 1 to 2 weeks.

The degree of skin-sensitivity was tested by an intracutaneous injection of 0.1 cc of homologous filtrate or vaccine. The average diameter and height of the reactions at 48 hours are recorded in millimeters.

Provocative Injection. In the experiments with indifferent streptococci, heat-killed vaccine was injected intravenously 48 hours after the intracutaneous test-injection. In the experiments with hemolytic streptococci and pneumococci, an 18-hour broth-culture was injected intravenously 24 hours after the intracutaneous test-injection. The degree of hemorrhage 24 hours after the provocative injection was recorded as $\pm$ to ++++.

Agglutinin and precipitin tests were performed close to the time of the intracutaneous test-injection. There was no correlation between circulating antibodies and the degree of hemorrhage in lesions 24 hours after the provocative injection.

Experiment 1. Of the rabbits sensitized with repeated intracutaneous injections of heat-killed indifferent streptococci, only No. 1 (Table I) showed a hemorrhagic lesion after the first provocative injection. A second intravenous injection one week later induced a considerably greater hemorrhagic lesion at the site of the last intracutaneous test-injection. Rabbits No. 2 and No. 6 that did not react to the first provocative injection also gave strongly positive skin-reactions after the second intravenous injection. There was no definite correlation between skin-sensitivity and degree of hemorrhage in these animals. However, the most intense reactions were observed in the 2 animals that had the highest degree of cutaneous sensitivity at the time of the second test.

Experiment 2. In 6 of 9 rabbits sensitized with hemolytic streptococci, intense hemorrhagic lesions were observed after the intravenous injection of 2 cc of homologous broth-culture (Table II). There was no correlation between skin-sensitivity and degree of

⁷ McEwen, C., and Swift, H. F., *J. Exp. Med.*, 1935, **62**, 573.

⁸ Nichols, E. E., and Stainsby, W. J., *J. Clin. Invest.*, 1931, **10**, 325.

TABLE I.
Degree of Hemorrhage in Rabbits Sensitized by Repeated Intracutaneous Injections of Heat-Killed Indifferent Streptococci.

Rabbit No.	No. of injections	Degree of skin-sensitivity to filtrate 143d day	Degree of hemorrhage in lesion 24 hr after i.v. injection of 1 cc of heat-killed streptococci 145th day	Degree of skin-sensitivity to filtrate 150th day	Degree of hemorrhage in lesion 24 hr after i.v. injection of 1 cc of heat-killed streptococci on 152d day
1	50 during	39-2	++	35-2	++++
2	140 days	30-1	None	37-2	+++
3		30-1	"	30-2	None
4		40-2	"	33-1	"
5		23-1	"	29-1	"
6		22-1	"	25-0	++

hemorrhage. Ten normal rabbits were given an intracutaneous injection of streptococcal filtrate; then after 48 hours they were injected intravenously with 2 cc of homologous culture; no hemorrhage was observed at the site of intracutaneous injection.

Experiment 3. The experiments with Type 1 pneumococci are summarized in Table III. After the provocative injection of 1 cc of broth culture, intense hemorrhage was observed in the skin of rabbit No. 24. This was the most sensitive animal of the group. Hemorrhages of lesser degree were observed in rabbits Nos. 19, 22, 23, and 25. In this group the intensity of the hemorrhagic reaction was greater in rabbits which had been sensitized by a larger number of intracutaneous injections, and had reached a higher degree of cutaneous sensitivity to the vaccine.

Summary. When an intracutaneous injection of bacterial filtrates or heat-killed organisms into sensitized rabbits was followed

TABLE II.
Degree of Hemorrhage in Rabbits Sensitized by Repeated Intracutaneous injections of Formalin-killed Hemolytic Streptococci.

Rabbit No.	No. of injections	Degree of skin-sensitivity to filtrate	Degree of hemorrhage in lesion 24 hr after i.v. injection of 2 cc of streptococcal broth culture
7	24 during 42 days	70-3	None
8		67-3	++++
9		60-3	++++
10		46-2	+++
11		40-2	+++
12		40-2	None
13		32-2	++++
14		40-1	++++
15		40-0	None

TABLE III.
Degree of Hemorrhage in Rabbits Sensitized by Repeated Intracutaneous injections
of Heat-killed Pneumococci Type I.

Rabbit No.	No. of injections	Duration of sensitization (days)	Degree of skin-sensitivity to vaccine	Degree of hemorrhage in lesion 24 hr after i.v. injection of 1 cc of pneumococcal broth culture
16	6	6	7-1	None
17	6	6	4-1	"
18	12	20	23-2	"
19	12	20	16-2	+
20	12	20	4-0	None
21	18	34	29-3	"
22	18	34	21-3	±
23	18	34	29-2	±
24	24	48	31-3	+++
25	24	48	28-3	+
26	24	48	18-2	None

by intravenous injections of sufficient amounts of killed or living organisms, a hemorrhagic reaction frequently developed at the site of the intracutaneous injection.

The most intense hemorrhagic reactions were observed in animals with the highest degree of cutaneous sensitization. We did not observe hemorrhagic phenomena in non-sensitized animals treated in a similar manner.

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Blood Pantothenic Acid Values in Multiple Sclerosis.

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Since the discovery and synthesis of pantothenic acid (Williams and Major¹), many attempts have been made to determine its clinical value. Stanbery, Snell and Spies² have shown that in deficiencies of the factors of the vitamin B complex, there is always a decrease in the blood pantothenic acid values. Their normal subjects gave values from 19.0 to 32.0 µg %, with an average of 22.5. The daily varia-

¹ Williams, R. J., and Major, R. T., *Science*, 1940, **91**, 246.

² Stanbery, S. R., Snell, E. E., and Spies, T. D., *J. Biol. Chem.*, 1940, **135**, 353.