treated in the same manner as the serum precipitates described above have no reacting potency.

In order to test whether whole sera by themselves or colloidal suspensions are capable of eliciting the reaction, the following substances were tested in rabbits prepared with *B. typhosus* "agar washings" filtrate and found totally devoid of reacting potency, namely:

Normal human, rabbit, horse, guinea pig, chicken and rat sera.
Immune rabbit, goat and horse sera.
Normal and immune chicken plasma.
Heparinized chicken plasma.
4% suspension of charcoal, 2% suspension of infusorial earth.
4% suspension of silicic acid and 10% gelatine.

According to Sickles[4] reactions can be obtained by intravenous injection of agar into rabbits prepared with meningococcus toxic filtrate but not by intravenous injection of galactose, gelatin, serum and India ink. This observation is corroborated by the author of this paper.

Observations reported here seem to demonstrate liberation of a toxic principle from blood serum by production of some disturbance in its colloidal state. This principle is capable, then, of eliciting severe injury in a tissue made vulnerable by a bacterial filtrate. It remains to be seen whether the reacting potency of agar[4] is due to some toxic principle carried by it or whether the agar liberates a toxic principle from the blood *in vivo*.

5795

On the Local Inhibition of the Shwartzman Phenomenon.

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If an intradermal injection of a potent bacterial filtrate is followed 24 hours later by an intravenous injection of the same or another potent bacterial filtrate, there occurs a hemorrhagic, necrotic lesion at the site of the preparatory skin injection, generally reaching its maximum 4 to 5 hours after the intravenous injection. This phenomenon was described by Shwartzman [1, 2] and is known as the Shwartzman phenomenon.

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[4] Sickles, G. U., *J. Immun.*, 1931, **20**, 169.

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[1] Shwartzman, G., PROC. SOC. EXP. BIOL. AND MED., 1928, **25**, 560.

[2] Shwartzman, G., *J. Exp. Med.*, 1928, **48**, 267.

A number of observations[3] were reported by Shwartzman which indicate that the phenomenon is not anaphylactic in nature. On the contrary, it seems to represent a transient state of vulnerability of the prepared tissue which makes it highly susceptible to injurious factors present in the blood stream for a period of 4 to 48 hours after the preparatory injection.

Burnet[4] was able to prevent the occurrence of the phenomenon in a portion of the prepared skin site by making a local injection of active material immediately before the intravenous injection. Because, in his experiments, toxin and toxoid were more effective than immune serum or saline, the inhibition was considered by him to have been due to local "desensitization". According to him, then, "the reaction is certainly not anaphylactic in any ordinary sense of the term, but it has some suggestive similarities to the classical anaphylactic phenomena." Before accepting his immunological explanation for the inhibition, it seemed necessary to determine whether the increased tension in the skin created by the second skin injection might mechanically collapse the local blood vessels and thus shield a portion of the prepared tissue from the injurious agents circulating in the blood stream. With this aim in view the following experiments were performed on domestic rabbits.

A. Five-tenths cc. of *Meningococcus* and *B. dysenteriae* (Shiga) "agar washings" filtrate, as described by Shwartzman,[5, 6] were injected into the abdominal skin. Twenty-four hours later, from 0.15 to 0.20 cc. of the substances used to produce inhibition were injected into the center of the prepared skin sites. Immediately thereafter, 50 reacting units of meningococcus toxin were injected intravenously. The results were read 4 to 5 hours after the intravenous injection. The first skin injection elicited a variable degree of local edema. Consequently, the tension produced by the second skin injection varied, being less pronounced when the edema was more marked. There was recorded inhibition when a purpuric lesion occurred at the prepared skin site except for the area infiltrated by the second skin injection.† One could frequently prognosticate the

[3] Shwartzman, G., *J. Exp. Med.*, 1930, **51**, 571.

[4] Burnet, F. M., *J. Path. and Bact.*, 1931, **34**, 45.

[5] Shwartzman, G., PROC. SOC. EXP. BIOL. AND MED., 1929, **26**, 843.

[6] Shwartzman, G., *J. Inf. Dis.*, 1929, **45**, 232.

† At the site of inhibition there is an area of tissue relatively normal in appearance, which is surrounded by a zone of intense hemorrhage, necrosis, and polymorphonuclear infiltration, as in the histological picture of a Shwartzman reaction.[2]

elicitation of inhibition when the second intradermal injection produced a wheal with blanching of the skin.

TABLE I.

Skin Preparatory Factors	Inhibiting Substance	Intravenous Reacting Factors	No. of Rabbits Showing	
			Phenomenon	Inhibition
0.5 cc. meningococcus "agar washings" filtrate	Undil. pituitrin 0.2 cc.	50 units of meningococcus toxin	6	6
"	5% sterile egg white solution 0.1 cc.	"	3	2
"	Adrenalin (1-1000) 0.15 cc.	"	2	2
"	Meningococcus "agar washings" filtrate 0.2 cc.	"	4	1
"	Histamine (0.2 mgm.) 0.2 cc.	"	1	0
"	Normal NaCl 0.15 cc.	"	2	1
"	Formalinized (0.5%) NaCl 0.2 cc.	"	2	0
"	Phenolized (0.4%) NaCl 0.2 cc.	"	2	0
0.5 cc. *B. dysenteriae* (Shiga) "agar washings" filtrate	Normal human serum 0.2 cc.	"	3	2
"	Phenolized (0.4%) NaCl 0.2 cc.	"	2	2
"	Formalinized (0.5%) NaCl 0.2 cc.	"	2	2
"	Immune rabbit serum 0.2 cc.	"	3	3
"	Pituitrin, undil., 0.2 cc.	"	2	2
"	Pituitrin, dil. 1:3, 0.2 cc.	"	5	2
"	*B. dysenteriae* (Shiga) "agar washings" filtrate 0.2 cc.	"	2	2
"	Histamine (0.2 mgm.) 0.2 cc.	"	1	1
"	Adrenalin (1-1000) 0.2 cc.	"	2	1
"	Meningococcus "agar washings" filtrate 0.2 cc.	"	3	2

The results of these experiments are summarized in Table I. Only the rabbits which showed positive reactions are included, the negative ones being omitted from these protocols. It is possible that some of the latter were really negative because of complete inhibition. It is seen that, using *Meningococcus* and *B. dysenteriae* (Shiga) preparatory factors, local inhibition was produced by

adrenalin, pituitrin, normal saline, phenolized saline, formalinized saline, sterile egg white solution, immune rabbit serum, normal human serum, and *Meningococcus* and *B. dysenteriae* (Shiga) toxins. The most marked and constant inhibition was produced by pituitrin.†

B. A band of the abdominal skin was infiltrated with 1 cc. of *Meningococcus* or *B. dysenteriae* (Shiga) "agar washings" filtrate. Twenty-four hours later, 3 injections of 0.15 cc. of normal saline, or one of these toxins, or combinations of these were made into different areas of the same prepared skin site. Immediately thereafter, 50 reacting units of *Meningococcus* toxin were injected intravenously. In these experiments, from 1 to 3 areas of inhibition were produced. Inhibition seemed best obtained at the ends of the band infiltrated with preparatory factors. This may have been due to the fact that there was least toxin and least edema at the periphery of the prepared skin site. The results in this type of experiment are not so clear-cut as they are when only one inhibiting agent is used, as in A.

C. Five-tenths cc. of *Meningococcus* "agar washings" filtrate were injected into the abdominal skin. Twenty-four hours later, padded clamps, 5 mm. wide at the edge, were applied to the centers of the prepared skin sites and left attached for 60 minutes. Immediately after the application of the clamps, 50 reacting units of *Meningococcus* toxin were injected intravenously. The clamps, themselves, caused no apparent injury to the skin. Of 6 rabbits tested, only 2 showed reactions and in each there was definite inhibition at the site of attachment of the clamps.

Conclusions. Local inhibition of the Shwartzman phenomenon can be produced by injecting into the prepared skin site a number of various substances immediately before the intravenous injection of the reacting factors. "Desensitization" can also be obtained by clamping off a portion of the prepared area for one hour after the intravenous injection. It becomes evident, therefore, that the inhibition described by Burnet cannot be considered as anaphylactic desensitization. It seems also of interest to point out that Burnet in his own experiments did not observe any specificity of inhibition because, as he says, "Meningococcal material can desensitize a typhoid reaction and *vice versa.*" In one of the experiments cited even saline effected a weak "desensitization". It seems more likely that the inhibition is due to diminished blood supply to the prepared

† Pituitrin, injected alone, often causes intense blanching of the injected area with a peripheral band of purpura.

area at the time of introduction of reacting factors into the blood stream.

Summary. A number of experiments are described which demonstrate that local inhibition of the Shwartzman phenomenon can be achieved by treating the prepared skin area with a variety of substances immediately prior to the intravenous injection of reacting factors or by clamping off a portion of the prepared skin area for one hour after the intravenous injection. It is believed that these agents produce their effects by creating a local ischemia which shields the prepared skin tissue from the injurious agents circulating in the blood stream.

5796

Effects of Diet and Fasting on Plasma Phosphatase.

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Increased plasma phosphatase has been reported by Kay[1] and others in v. Recklinghausen's disease, in Paget's disease, in active rickets and in other pathological bone conditions. These results were confirmed by ourselves in our clinical material. Kay suggested that increased plasma phosphatase in these conditions was due to leakage of the enzyme from bone at more than the normal rate. However, in view of the presence of large amounts of phosphatase in other tissues than bone (kidneys, intestinal mucosa) it seems that variations in plasma phosphatase might be due to other causes, and that the state of nutrition of an animal might influence the plasma phosphatase in bone diseases found clinically or produced experimentally. The latter possibility had to be considered by us in studies of plasma phosphatase changes in experimental hyperparathyroidism, in view of the diminished appetite which is observed in animals treated with parathormone for long periods.[2, 3] (In other experimentally produced conditions asso-

[1] Kay, H. D., *J. Biol. Chem.*, 1930, **89**, 249.

[2] Jaffe, H. L., and Bodansky, A., *J. Exp. Med.*, 1930, **52**, 669; Jaffe, H. L., Bodansky, A., and Blair, J. E., *Arch. Path.*, 1931, **11**, 207.

[3] Bodansky, A., Jaffe, H. L., and Blair, J. E., *J. Biol. Chem.*, 1930, **88**, 629; Bodansky, A., and Jaffe, H. L., *J. Exp. Med.*, 1931, **53**, 591.