The duration of anoxemia was seldom more than 4 minutes. Analysis of respiratory air showed that within this period carbon dioxide was absorbed and that oxygen tension (corrected) was progressively reduced to between 52 and 90 mm. of mercury. Blood gas analysis indicated marked anoxemia. After about 4 minutes of this gradually induced anoxemia a secondary increase in intrapleural pressure was usually observed, accompanied by a mean decrease in thoracic girth and marked slowing of respiration. This corresponds to Loevenhart's secondary depression of the respiratory center as a result of continued oxygen want. It is to be noted that anoxemia like excess carbon dioxide tension seems first to stimulate the inspiratory mechanism and then later that concerned with expiration.

The initial increase of thoracic girth with more negative intrapleural pressure under the influence of mild anoxemia offers an explanation of the mechanism by which emphysema develops during continued residence at high altitudes.

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Phenomenon of Local Skin Reactivity to Serum Precipitates.

GREGORY SHWARTZMAN.

From the Laboratories of the Mount Sinai Hospital, New York.

Phenomenon of local skin reactivity to serum precipitates is elicited as follows:

The abdominal skin of a rabbit is injected with 0.25 cc. of undiluted *B. typhosus* "agar washings" filtrate.[1] Twenty-four hours later the rabbit receives a single intravenous injection of a suspension of serum precipitate prepared in the manner about to be described. Four to 5 hours after the intravenous injection there appears at the prepared skin site a severe hemorrhagic and necrotic lesion characteristic of the phenomenon of local skin reactivity to bacterial filtrates.[2]

The serum precipitates with which the phenomenon could be consistently reproduced were obtained from the following mixtures:

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

[2] Shwartzman, G., PROC. SOC. EXP. BIOL. AND MED., 1928, **25**, 560; *J. Exp. Med.*, 1928, **48**, 247.

1. Normal horse serum with anti-horse rabbit serum.
2. Antimeningococcus horse serum with anti-horse rabbit serum.
3. Antimeningococcus horse serum with anti-horse goat serum.
4. Antimeningococcus anti-human horse serum with normal human serum.

The mixtures were made in proportions yielding maximum amount of precipitate, incubated in water bath at 37° for 2 hours, kept in the refrigerator over night and centrifuged at high speed. The supernatant fluid was removed and the sediment taken up in 0.85% NaCl solution in volume equal to ¼ of the volume of horse serum used.

A dose of 1 cc. of the suspension per kilo of body weight injected intravenously elicited severe reactions in a high percentage of rabbits. The reacting potency could be easily titrated by testing various dilutions of a suspension. Each dilution was tested in a group of 3 rabbits. The titer usually varied between 1:5 and 1:50 dilutions. The toxicity of the serum precipitates was quite stable since almost identical results were obtained on retests after a lapse of several weeks and months.

There was no apparent relationship between the amount of precipitate obtained in various preparations and their reacting potency. Some abundant serum precipitates proved totally inactive, while other slightly turbid suspensions were highly potent.

Furthermore, for the same ingredients the reacting potency of a mixture did not depend on the amount of precipitate obtained in it. By employing different proportions of ingredients there were obtained gradations in the amount of precipitate. If with a certain proportion there was obtained maximum precipitation the precipitate was potent and the supernatant fluid inactive. However, if the ingredients were mixed in a proportion which gave only partial precipitation, then both the precipitate and the supernatant fluid proved potent. The potent supernatant fluid was usually clear at the time of the injection, and produced some precipitation in the refrigerator after several days. Thus, it was possible to obtain severe reactions with serum containing no visible precipitate as well as with serum showing abundant precipitate—both derived from mixtures of the same ingredients.

When a *B. typhosus* culture filtrate is mixed in the necessary proportions with an immune anti-typhoid horse serum, complete neutralization of *B. typhosus* reacting factors can be obtained.[3] The mixtures usually form abundant precipitates. These precipitates

[3] Shwartzman, G., *J. Exp. Med.*, 1931, **54**, 1.

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*.

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On the Local Inhibition of the Shwartzman Phenomenon.

HERBERT M. KLEIN.* (Introduced by Gregory Shwartzman.)

From the Laboratories of The Mount Sinai Hospital, New York.

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.

* Moses Heineman Research Fellow.

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

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