

STUDIES OF THE GENERALIZED SHWARTZMAN REACTION PRODUCED BY DIET*

III. PARTIAL PREVENTION BY ANTIBIOTICS

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The generalized Shwartzman reaction can be produced in pregnant rats by the simple addition of oxidized oil to the diet. In spite of the absence of any pathologic evidence of a bacterial infection in 90 per cent of the animals (1), the possibility remains that bacterial products from some endogenous source may be responsible for the development of the reaction under these experimental conditions. The respiratory tract, the vagina, and the gastrointestinal tract normally contain organisms capable of producing bacterial endotoxin. The most likely source of such bacterial products is the gastrointestinal tract since it normally harbors a resident flora of large numbers of Gram-negative rods. In the preceding experiments (1, 2) no evidence was found of any damage to the mucosal cells of the gastrointestinal tract and there was no evidence of an inflammatory reaction in the intestinal wall.

Nevertheless, the demonstration by Fine (3) that animals were protected from the lethal effects of hemorrhagic shock by prior feeding with non-absorbable antibiotics, made it of interest to test the effects of similar antibiotics in the diet-induced generalized Shwartzman reaction.

Materials and Methods

Sprague-Dawley and Columbia-Sherman strain rats were fed on Rockland pellets for a period of 4 months. They were then exposed to male rats for 5 days. At the end of mating they were separated into 5 groups, as follows:

Control Series A.—

Group I: Seven animals were continued on the Rockland diet during gestation.

Control Series B.—

Group II: Forty-five animals were placed on the oxidized cod liver oil diet (1) during gestation.

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Test Series.—

Group III: Twenty animals were placed on the oxidized cod liver oil diet during gestation. A mixture of albamycin and tetracycline in the amount of 15 mg per day was fed to each animal in the drinking water. The antibiotic was started on the 19th day of gestation and continued until the animal died or for 6 days postpartum.

Group IV: Twenty-six animals were placed on the oxidized cod liver oil diet during gestation. In addition 30 mg of neomycin was given each day to each animal in the drinking water, starting on the 19th day of gestation and continuing until the animal died or for 6 days postpartum.

Group V: Ten rats were placed on the oxidized cod liver oil diet to which had been added a mixture of antibiotics containing neomycin, streptomycin, and bacitracin. The animals consumed an average of 15 gm of the diet each day and as a result each received a daily average of 30 mg of neomycin, 15 mg of streptomycin, and 15 mg of bacitracin. These animals received the antibiotics throughout gestation.

The animals in all series were autopsied and examined histologically.

TABLE I
Effect of Feeding Antibiotics

Series (group).....	I (Control A)	II (Control B)	III	IV	V
Diet (during gestation).....	Rockland	OCLO*	OCLO	OCLO	OCLO
Antibiotic.....	0	0	AMC‡ TCC¶	NMC§	NMC, BTC SMC**
Number of pregnant animals..	7	45	20	26	10
Number of deaths.....	0	18	2	3	1
Per cent mortality.....	0	40	10	11	10

* Oxidized cod liver oil.

‡ Albamycin (novobiocin calcium).

§ Neomycin (neomycin sulfate).

|| Bacitracin.

¶ Tetracycline (tetracycline hydrochloride).

** Streptomycin.

RESULTS

The pathologic alterations in the animals that died were the same as those described previously (1). The observations are summarized in Table I. Feeding a variety of antibiotics in three different experiments resulted in a diminution in the incidence of the generalized Shwartzman reaction from 40 per cent to 10 per cent in each group. This reduction in disease was observed whether the antibiotic was fed in the food or drinking water and whether the antibiotic was given for as short a time as 4 days before term or as long as the entire gestation period. The reduction occurred whether the antibiotic was "absorbable" or "non-absorbable." This reduction is significant since $P = <0.01$.

DISCUSSION

The mechanism by which oral antibiotics markedly reduced the mortality rate in the diet-induced generalized Shwartzman reaction requires explanation.

No evidence of a bacterial infection of any organ other than the placenta was ever observed. It is unlikely that the 4-fold reduction was mediated by a prevention of the placentitis since this is found in only 10 per cent of cases. Furthermore, non-absorbable antibiotics produced the effect and could not reasonably have acted on organisms in the uterus.

Since the final event in this disease is an episode of disseminated intravascular coagulation, the beneficial effect may have been the result of an effect of antibiotics on the blood coagulation system. Unfortunately, the reports in the literature on the influence of antibiotics on the blood coagulation system are contradictory and since the non-absorbable antibiotics were effective in our experiments, it does not seem likely that it could have been a direct action of antibiotics on the blood coagulation system.

One possibility for the protective action of the antibiotics lies in the demonstration of the Smiths (4) of an "antitoxic" property of antibiotics. These authors found that antibiotics protected young rats from the lethal effects of a toxic product of tissue catabolism (atypical euglobulin). They demonstrated that this "antitoxic" action was not due to a bactericidal effect. Because of the many similarities of the diet-induced generalized Shwartzman reaction to the changes in toxemia of pregnancy in the human, it is of particular interest to note the Smiths' demonstration of certain beneficial effects of antibiotics on toxemic patients (5). Diuresis and decreased albuminuria were apparent soon after treatment was started and were accompanied by general improvement in those patients with symptoms. Some showed a lowering of the diastolic blood pressure. There was a recrudescence of the disease when antibiotics were discontinued. These results were interpreted as a demonstration of an unspecific antitoxic effect of the antibiotics.

The observation of Fine *et al.* (3) must be considered in evaluating this effect. Although Fine's studies dealt with hemorrhagic shock, they are of interest since the generalized Shwartzman reaction is also associated with shock. Using rabbits that had been in hemorrhagic shock for 90 minutes, it was noted that these animals were exceedingly sensitive to very much smaller doses of bacterial endotoxin than a normal rabbit. They also died when transfused with blood from an animal dying of hemorrhagic shock, but did not die when transfused with the blood of a normal animal. Similar observations were made on dogs. It was then demonstrated that oral administration of polymyxin and bacitracin in advance of the shock, rendered the blood of the donor in prolonged shock free of its lethal effect on the sensitive animal. This protective effect was consistent in rats and rabbits. Since the non-absorbable antibiotics were as effective as absorbable ones, they attributed this effect to their antibacterial properties, acting on the flora of the gastrointestinal tract.

Whether or not the partial protection by antibiotics against the diet-induced Shwartzman reaction is mediated through an action on bacteria in the gastrointestinal tract remains to be proven. It is of major interest to note that

in both the induction of this reaction and the partial prevention of the reaction the gastrointestinal tract plays an important role.

SUMMARY

A 4-fold reduction in the death rate of pregnant rats subjected to a diet capable of inducing the generalized Shwartzman reaction was obtained by the administration of oral absorbable and non-absorbable antibiotics. The possible mechanisms of this partial protection have been discussed.

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