THE ROLE OF VASOCONSTRICTION IN THE LOCAL
SHWARTZMAN REACTION

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The phenomenon of local tissue reactivity was first described by Shwartzman in
1928 (cited in reference 1) and now is generally known as the local Shwartzman re-
action. It is characterized by dermal hemorrhage and necrosis which develop a few
hours after the second of two injections of a culture filtrate of Gram-negative microor-
ganisms, or of a lipopolysaccharide material from such cultures. The first, or prepar-
atory injection is made intradermally, usually in the abdominal skin of the rabbit;
the second, or provocative injection, is given intravenously about 24 hours later.
Within a few hours after the intravenous injection, purple-black areas of hemorrhage
and necrosis appear at the site of intradermal injection.

Until recently, little was known concerning the mechanisms involved in this phe-
nomenon, and it was considered to be a manifestation of some type of immune tissue
response. Many of the features of this reaction have now been studied, and the im-
portance of several non-antigenic factors in the production of this lesion has been
established (2-5). The initial alterations appear to be confined to the site of intra-
dermal injection, and resemble a mild inflammatory reaction. Concomitantly, bio-
chemical changes occur at the prepared site. These include an increased lactic acid
content, and an increase in aerobic and anaerobic glycolysis. These changes become
maximal 24 hours after the preparatory injection, but are generally insufficient, by
themselves, to induce the hemorrhagic lesion. If, however, the provocative dose of
bacterial polysaccharide is given at this time, there can be seen the development of
progressive damage at the prepared site. Thrombi of platelets and leucocytes appear
in the blood vessels, intravascular clotting occurs, and there is hemorrhage into the
area and, in time, necrosis develops.

Vasoconstriction, which occurs in rabbits following administration of bacterial
polysaccharides (2, 6), may contribute to the local damage by impairment of the blood
supply to the area. Peripheral vasoconstriction would predispose to thrombus for-
mation, and, in turn, local thrombosis would tend to intensify and prolong circulatory
deficiencies. Development of hemorrhage and necrosis could result from the cumulative
effect of altered metabolism of the skin, of less efficient removal of metabolic products,
and of anoxia.

These studies were undertaken to obtain information which would help to
evaluate the importance of peripheral vasoconstriction during the provocative
phase of the Shwartzman reaction. This report presents data which indicate that peripheral vasoconstriction is involved in the Shwartzman phenomenon, and, indeed, may be a major factor in its development.

Materials and Methods

Previously untreated, young albino rabbits of both sexes weighing 1.2 to 2.0 kg. were used in these experiments. The hair was removed from the injection sites with electric clippers on the day the intradermal injections were made. A polysaccharide preparation from Serratia marcescens (Perrault and Shear, Lot No. P-35) was used in all experiments (7). It was administered in solution in commercial, sterile, pyrogen-free saline. The preparatory dose was given intradermally, and the provocative dose was given by ear vein 24 hours later. Development of an area of purple-black necrosis at the prepared site within 6 hours after provocative injection, and persisting for 24 hours, was considered a positive reaction. No attempt was made to grade the intensity of response. Differences between experimental and control groups of rabbits were evaluated by the chi square test.

The following drugs were used:—

Dibenamine (Smith, Kline and French Laboratories, Philadelphia)
SY-28(N-ethyl-N-[2-bromoethyl]-1-naphthalenemethylamine)(Courtesy of Dr. A. C. Bratton, Parke, Davis and Co., Detroit)
Dihydroergotamine (Sandoz Pharmaceuticals, New York.)
Epinephrine, synthetic (Winthrop-Stearns, Inc., New York)
l-Norepinephrine, synthetic (Winthrop-Stearns, Inc., New York)
5-Hydroxytryptamine (Courtesy of Dr. R. K. Richards, Abbott Laboratories, North Chicago)
Diphenhydramine (benadryl) (Parke, Davis and Co., Detroit)
Tripelennamine (pyribenzamine) (Ciba Pharmaceutical Products, Inc., Summit, New Jersey)
Mechlorethamine (mustargen) (Merck and Co., Inc. Rahway, New Jersey)
Heparin (Hynson, Westcott and Dunning, Inc., Baltimore)

EXPERIMENTAL RESULTS

1. Site of Intradermal Injection:

In most experiments the local Shwartzman reaction has been elicited in high percentage only in the abdominal skin of rabbits (1, 2). If this phenomenon occurs preferentially in abdominal skin, it would argue against the importance of peripheral vasoconstriction in the development of the reaction, because polysaccharide-induced vasoconstriction occurs in all skin areas. In order to obtain definite information on this question, therefore, other skin areas were tested.

Four sites (right ear, left costovertebral angle, right upper quadrant of abdomen, and right hind leg) were prepared by intradermal injection of 0.25 mg. of polysaccharide in 0.125 ml. saline. Twenty-four hours later, a provocative dose of 1 mg. polysaccharide was administered intravenously.

The high incidence of positive reactions (Table I) which was obtained in all sites indicates that the ability of the skin to develop the characteristic local
lesion is not restricted to one area. This finding is consistent with the concept that generalized peripheral vasoconstriction may play an essential part in the development of the local Shwartzman phenomenon.

2. Action of Autonomic Blocking Agents:

Certain adrenolytic drugs have been reported to block, at least in part, the vasoconstriction induced by intravenous administration of pyrogenic bacterial polysaccharides (6). Indication that vasoconstriction is important in the Shwartzman reaction was obtained indirectly in the following experiments in which the incidence of positive reactions was reduced by administration of adrenergic blocking drugs just prior to the provocative injection of polysaccharide. The results obtained when SY-28, dibenamine, or dihydroergotamine were given are summarized in Table II. The percentage of positive reactions was reduced in those groups of rabbits given either 2.5 to 4.0 mg./kg. SY-28 intraperitoneally, or 20 to 30 mg./kg. dibenamine intraperitoneally. The reason for the failure of the highest dose levels of SY-28 to reduce the number of positive responses is unknown. Dihydroergotamine at the level of 2 mg./kg. has no effect on the number of positive reactions, and this drug may have a weaker adrenolytic action than the others (8). Although both SY-28 and dibenamine, in suitable doses, reduced the number of Shwartzman reactions significantly, about 40 per cent of the animals still developed the characteristic lesion. This may be related to the inability of these drugs to block completely certain cardiovascular reflexes which seem to be dependent primarily on nerve impulses mediated through the sympathetic nervous system. These agents are highly effective against circulating epinephrine or norepinephrine, but are less effective against nerve mediated vasoconstriction (8, 9).

3. Action of Antihistaminic Drugs:

Since SY-28 and, to a lesser extent, dibenamine have an antihistaminic action (8, 10) the effect on the Shwartzman phenomenon of two drugs with

<table>
<thead>
<tr>
<th>Skin area tested</th>
<th>Positive reactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen (right upper quadrant)</td>
<td>7</td>
</tr>
<tr>
<td>Ear (right)</td>
<td>6</td>
</tr>
<tr>
<td>Costovertebral angle (left)</td>
<td>8</td>
</tr>
<tr>
<td>Hind leg (right)</td>
<td>11</td>
</tr>
</tbody>
</table>

* 12 rabbits given 0.25 mg. polysaccharide intradermally in each site, followed in 24 hours by 1 mg. intravenously.
strong antihistaminic activity, diphenhydramine, and tripelennamine, was studied.

The preparatory and provocative dose schedule of polysaccharide in these experiments was the same as that used to test the autonomic blocking agents. The antihistaminic drugs were given subcutaneously 5 minutes before, and at 1, 2, and sometimes 3 hours after the provocative dose of polysaccharide. As indicated in Table III, these two antihistaminic drugs had no statistically significant effect on the number of positive Shwartzman reactions elicited by bacterial polysaccharide.

TABLE II
Effect of Adrenergic Blocking Drugs on the Shwartzman Reaction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (i.p.)</th>
<th>Time*</th>
<th>No. of rabbits</th>
<th>Positive reactions</th>
<th>Significance §</th>
</tr>
</thead>
<tbody>
<tr>
<td>SY-28</td>
<td>mg./kg.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4</td>
<td>1 hr.</td>
<td>10</td>
<td>100</td>
<td>None</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>5.0</td>
<td>1 &quot;</td>
<td>18</td>
<td>78</td>
<td>&quot;</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>4.0</td>
<td>1 &quot;</td>
<td>16</td>
<td>50</td>
<td>&quot;</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>3.2</td>
<td>1 &quot;</td>
<td>22</td>
<td>36</td>
<td>&quot;</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>2.5</td>
<td>1 &quot;</td>
<td>20</td>
<td>60</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>1 &quot;</td>
<td>15</td>
<td>87</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Dibenamine</td>
<td>30.0</td>
<td>1 hr.</td>
<td>10</td>
<td>50</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>20.0</td>
<td>1 &quot;</td>
<td>20</td>
<td>55</td>
<td>P &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>15.0</td>
<td>1 &quot;</td>
<td>7</td>
<td>57</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>1 &quot;</td>
<td>13</td>
<td>85</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine</td>
<td>2.0</td>
<td>5-10 min.</td>
<td>8</td>
<td>88</td>
<td>None</td>
</tr>
<tr>
<td>0.7</td>
<td>5-10 &quot;</td>
<td>8</td>
<td>75</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>—</td>
<td>—</td>
<td>123</td>
<td>88</td>
<td>—</td>
</tr>
</tbody>
</table>

* Expressed as time before intravenous injection given.
† Three abdominal sites were prepared on each rabbit by intradermal injection of 0.125 mg., 0.25 mg., and 0.50 mg. polysaccharide respectively.
§ Comparisons made with control group not given blocking drug. P value by chi square test corrected for continuity.

It seemed unlikely, therefore that SY-28 and dibenamine inhibited the Shwartzman phenomenon by acting to block histamine, but rather that they produced this result by virtue of their ability to cause adrenergic blockade.

4. Effect of Vasoconstrictor Drugs:

The use of autonomic blocking agents furnished only indirect evidence in support of the hypothesis that peripheral vasoconstriction is important in the development of the local Shwartzman phenomenon. More direct information was obtained, however, by substituting vasoconstrictor drugs for bacterial
polysaccharide as the provocative agent. These drugs were administered either intravenously or locally at the prepared skin site.

(a) Intravenous Administration.—

In one group of experiments, either t-epinephrine, l-norepinephrine, or 5-hydroxytryptamine was given 24 hours after a preparatory dose of 1 or 4 mg polysaccharide intradermally. They were given by constant venoclysis, or by repeated intravenous injection every 15 minutes over a 2 to 4 hour period.

TABLE III
Effect of Antihistaminic Drugs on Local Shwartzman Reaction*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose mg/kg.</th>
<th>No. of rabbits</th>
<th>Positive reactions</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>10.0</td>
<td>8</td>
<td>62</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>7</td>
<td>71</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>15</td>
<td>73</td>
<td>&quot;</td>
</tr>
<tr>
<td>Tripelenamine</td>
<td>8.0</td>
<td>6</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td>123</td>
<td>88</td>
<td>---</td>
</tr>
</tbody>
</table>

* Three abdominal sites were prepared on each rabbit by intradermal injection of 0.125 mg., 0.25 mg., and 0.50 mg. polysaccharide respectively. 24 hours later, 0.8 mg. polysaccharide given intravenously.
† Total dose; equally divided fractions were administered subcutaneously 5 minutes before the intravenous polysaccharide, and 1, 2, and sometimes 3 hours after the polysaccharide injection.
§ Comparisons made with control group not given blocking drug. P value by chi square test corrected for continuity.

No local Shwartzman reactions were elicited by this procedure, even at toxic dose levels (Table IV).

(b) Intradermal Administration.—

In order to obtain more pronounced vasoconstriction at the prepared skin site, these vasoconstrictor drugs were also injected directly into skin areas which had been prepared in the usual way by intradermal injection of varying dose levels of polysaccharide 24 hours previously. The present experiments in which varying amounts of epinephrine, norepinephrine, or 5-hydroxytryptamine were injected directly into the prepared site, confirm and extend previous reports that local epinephrine can provoke this reaction (11–13). The drugs were prepared in concentrations so that the desired quantity of drug was contained in 0.25 to 0.5 ml. of pyrogen-free saline. The control animals were injected intradermally with the pyrogen-free saline and showed no positive responses. The results have been summarized in Table V.

Epinephrine injected into a polysaccharide-prepared skin site, even at the
relatively low dose levels of 25 μg. provoked positive Shwartzman reactions. Norepinephrine induced a lower incidence of positive reactions; and 5-hydroxytryptamine was essentially ineffective in the dosage used. The differences in results obtained with these three drugs may reflect the degree of their effective-

TABLE IV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total i.v. dose</th>
<th>No. of rabbits</th>
<th>Positive reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>1.0</td>
<td>6</td>
<td>0*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.1</td>
<td>4</td>
<td>0*</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2.0</td>
<td>2</td>
<td>0†</td>
</tr>
<tr>
<td>5-hydroxytryptamine</td>
<td>20.0</td>
<td>4</td>
<td>0*</td>
</tr>
<tr>
<td>5-hydroxytryptamine</td>
<td>50.0</td>
<td>2</td>
<td>0‡</td>
</tr>
</tbody>
</table>

* Received 1.0 mg. polysaccharide intradermally 24 hours previously.
† Received 0.5 mg. polysaccharide intradermally 24 hours previously.

TABLE V

<table>
<thead>
<tr>
<th>Drug, Dose of preparatory polysaccharide</th>
<th>Preparatory dose of polysaccharide, mg.</th>
<th>Positive hemorrhagic and necrotic reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Epinephrine 0.100</td>
<td>—</td>
<td>7/9†</td>
</tr>
<tr>
<td>Epinephrine 0.025</td>
<td>—</td>
<td>5/8</td>
</tr>
<tr>
<td>Norepinephrine 1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Norepinephrine 0.25</td>
<td>—</td>
<td>2/10</td>
</tr>
<tr>
<td>5-hydroxytryptamine 0.50</td>
<td>1/9</td>
<td>0/6</td>
</tr>
<tr>
<td>5-hydroxytryptamine 0.10</td>
<td>1/9</td>
<td>0/18</td>
</tr>
</tbody>
</table>

* Injected intradermally 24 hours prior to vasoconstrictor.
† Numerator refers to number of positive hemorrhagic and necrotic reactions, denominator, to number of rabbits tested.

ness as local vasoconstrictors (14). It is apparent therefore that a typical local Shwartzman reaction can be induced by drugs which are potent vasoconstrictors, presumably through the mechanism of intense local vasoconstriction.

(c) Effect of SY-28, Heparin, and Nitrogen Mustard on the Epinephrine-Induced Shwartzman Reaction.—

In view of these observations, it seemed appropriate to investigate the effect of SY-28, heparin and nitrogen mustard (mechloretamine), drugs which
previously have been shown to block the classical Shwartzman reaction, on the production of the dermal lesion by the local use of vasoconstrictor drugs.

The development of intravascular thrombosis is a prominent feature of the classic Shwartzman phenomenon. Impairment of local circulation, due to severe vasoconstriction, might lead to thrombosis, particularly in an area of inflammation, and the prepared skin site is such an area. In an effort to separate primary vasoconstriction from possible secondary thrombosis, the effects of an adrenolytic agent and of an anticoagulant were tested for their ability to block the epinephrine-induced reaction.

### Table VI

Effect of Heparin and Adrenergic Blocking Drug on Epinephrine Induced Shwartzman Reaction

<table>
<thead>
<tr>
<th>Drugs*</th>
<th>Dose</th>
<th>No. of rabbits</th>
<th>Positive reactions</th>
<th>Significance$\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>25(X 3)</td>
<td>15</td>
<td>80</td>
<td>None</td>
</tr>
<tr>
<td>SY-28</td>
<td>3.5</td>
<td>18</td>
<td>11</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Controls</td>
<td>None</td>
<td>40</td>
<td>55</td>
<td>—</td>
</tr>
</tbody>
</table>

* Heparin was given intravenously 5 minutes before, and 2 and 4 hours after the epinephrine; SY-28 was given intraperitoneally 1 hour before the epinephrine.

† All rabbits given 500 µg. polysaccharide intradermally; 24 hours later 50 µg. epinephrine.

§ Comparisons made with control group not given blocking drug. P value by chi square test corrected for continuity.

Epinephrine, 50 µg., was injected intradermally into sites prepared 24 hours previously by 0.5 mg. of bacterial polysaccharide intradermally in 0.25 ml. saline. Heparin was given at a dose level of 25 mg./kg. 5 minutes before, and 2 and 4 hours after the epinephrine; SY-28 was given at a dose of 3.5 mg./kg., intradermally 1 hour prior to the epinephrine. These dosage schedules will cause a significant decrease in the incidence of positive reactions in response to bacterial polysaccharide.

In the heparinized animals the reactions provoked by epinephrine appeared more intense and were uniformly larger than those in the control animals, and the incidence of positive reactions was not decreased (Table VI). In the animals pretreated with SY-28, almost complete inhibition of the reaction was noted. The effectiveness of the adrenergic blocking drug was not unexpected since it is known to be more active as an inhibitor of circulating epinephrine than of sympathetic nerve mediated impulses (8). These observations support the thesis that vasoconstriction is the primary factor in the epinephrine-induced reaction, at least, and that thrombus formation, as seen in the classic Shwartzman reaction is less important and may indeed be secondary to vasoconstriction.

It has been reported that alterations in the white blood cells, particularly in the polymorphonuclear leucocytes may be of importance in the classic local
VASOCONSTRICTION IN SHWARTZMAN REACTION

Shwartzman reaction since pretreatment of rabbits with granulopenic doses of nitrogen mustard renders such animals incapable of developing the reaction (4). To investigate the role of leucocytes in the epinephrine-induced reaction, a series of animals was rendered leucopenic with nitrogen mustard.

Mustargen was given intravenously, 2.0 mg./kg., to part of a group of rabbits 3 days prior to the intradermal dose of 0.25 mg. polysaccharide and 24 hours later 0.1 mg. of epinephrine was given into the prepared site of each animal. At this time the mean white blood cell count for the rabbits treated with the mustard was 460 WBC/mm.³ with a s.e. of ±120.

<table>
<thead>
<tr>
<th>Drugs*</th>
<th>Dose</th>
<th>No. of rabbits†</th>
<th>Positive reactions</th>
<th>Significance‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen mustard</td>
<td>2.0</td>
<td>15</td>
<td>67</td>
<td>None</td>
</tr>
<tr>
<td>Controls</td>
<td>—</td>
<td>22</td>
<td>55</td>
<td>—</td>
</tr>
</tbody>
</table>

* The nitrogen mustard was given intravenously 3 days before the preparatory dose of polysaccharide.
† All rabbits given 500 μg. polysaccharide intradermally; 24 hours later 100 μg. epinephrine.
‡ Comparisons made with control group not given blocking drug. P value by chi square test corrected for continuity.

Not only was there a high incidence of positive reactions in the nitrogen mustard group (Table VII) but furthermore it was noted that the reaction in the treated group were more severe than in the controls. These findings suggest that the leucocytes play a less significant role in the epinephrine-induced, than in the classic, Shwartzman reaction.

DISCUSSION

Information concerning the factors involved in the Shwartzman reaction has been derived largely from experiments designed to inhibit this reaction by the use of various drugs. It is convenient to consider some of the factors important in this reaction in terms of their pharmacologic antagonists.

Heparin, as well as certain coumarin derivatives, inhibits the Shwartzman reaction when administered at levels which practically prevent coagulation of blood and thus minimize or abolish the formation of intravascular thrombi (2, 15, 16). The effect of these diverse anticoagulants furnishes strong evidence that thrombus formation is an important factor in the development of the Shwartzman reaction. The thrombosis apparently begins around the leucocyte platelet clumps which occur after the provocative dose. Since nitrogen mustard, which also inhibits the typical Shwartzman reaction, causes thrombocytopenia.
as well as leucopenia (17), it is possible that this compound acts to minimize or prevent the formation of the leucocyte platelet clumps which normally develop after the provocative dose. This would indicate a basic similarity in the mechanism of action of both nitrogen mustard and heparin and might help explain at least, in part, why neither drug inhibits the epinephrine-induced reaction.

The inhibition of the Shwartzman reaction by adrenolytic drugs (Table II) and provocation of a typical lesion by epinephrine (Table V) suggest that a major factor in precipitating the local lesion may be vasoconstriction. Recently bacterial polysaccharide endotoxins were reported to potentiate the action of epinephrine and it was noted that a characteristic lesion of hemorrhage and necrosis could be produced by a single intradermal injection of a mixture of polysaccharide and epinephrine (13, 18). This reaction, also, is intensified rather than inhibited by nitrogen mustard and heparin. These observations suggest the possibility that if small but still significant amounts of polysaccharide remain in the prepared site for some period of time, this residual polysaccharide may act in conjunction with the epinephrine liberated in response to the intravenous injection of polysaccharide and thereby intensify the vasoconstriction produced in the prepared site from the intravenous polysaccharide. This may well be a key factor in the genesis of the local anoxia.

SUMMARY

The local Shwartzman reaction was provoked in the skin of the ear, hind leg, and costovertebral angle of the rabbit, as well as in the ventral abdominal skin. Certain adrenergic blocking drugs reduced the incidence of positive reactions when given prior to the provocative dose of bacterial polysaccharide. Epinephrine and other vasoconstrictor drugs administered intradermally into the prepared skin site produced typical hemorrhagic-necrotic lesions when the usual intravenous injection of polysaccharide was omitted. This reaction could be blocked by adrenergic blocking drugs, but appeared to be augmented by heparin or nitrogen mustard.

A hypothesis has been developed to help explain the mechanism of the local Shwartzman reaction. Following the preparatory dose, tissue metabolic changes occur which lead to increased lactic acid production and render the area particularly susceptible to anoxia. Following the provocative dose, adrenergic vasoconstriction occurs. It is suggested that this vasoconstriction may be intensified at the prepared site by small residual amounts of the preparatory dose of polysaccharide which might potentiate the action of the epinephrine.

The anoxia initiated by the vasoconstriction is prolonged and intensified by the formation of intravascular thrombi around clumps of leucocytes and platelets. This anoxia, superimposed on the local metabolic changes, leads to the characteristic lesion of hemorrhage and necrosis. Thus a combination of factors,
all of causal importance and largely due to known pharmacologic properties of bacterial lipopolysaccharide, occur in specific sequence to lead to the classic local Shwartzman reaction.

BIBLIOGRAPHY