ON THE FORMATION OF PRECIPITATES AFTER THE INTRAVENOUS INJECTION OF SALVARSAN.*

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During the past year there have appeared in the literature several reports of serious results—in a few cases even of death—following the intravenous injection of salvarsan. It was some time, however, before the chemical reaction of the salvarsan solution used was considered in connection with certain of these fatal cases. Fraenkel and Grouven (1), for instance, reported the death, within a few hours, of a patient who received intravenously 0.4 gram of salvarsan dissolved in fifteen cubic centimeters of water. These authors considered the symptoms following the injection to be those of arsenic poisoning, and concluded that death was due to a special hypersensitiveness of the patient to the drug. Ehrlich (2), commenting upon the case of Fraenkel and Grouven, agrees with them that the death of their patient was due to a pre-existing hypersensitiveness of the individual. He refers to other cases, in which, as in the case of Fraenkel and Grouven, there were advanced degenerative changes in the central nervous system, and in which there seemed to be a special susceptibility to the drug. Willige (3), however, thinks that death was due in the case of Fraenkel and Grouven to the use of a solution of too high concentration and suggests that only solutions of much lower concentration should be used intravenously.

H. E. Hering (4) first called attention to the dangers of using acid solutions of salvarsan. In experiments upon rabbits and dogs he determined the lethal dose of a one half per cent. solution. For rabbits he found it to be from four to five milligrams per kilo of body weight, and for dogs, from ten to twenty milligrams per

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kilo of body weight. From the fatal doses in rabbits he calculated an average fatal dose for man, and came to the conclusion that the fatal result in the case of Fraenkel and Grouven may have been due to the chemical reaction of the acid solution. He warned against the use of the acid solution intravenously in man.

Auer (5), in a paper which is in press, has shown, however, that the concentration of the acid solution of salvarsan is a definite factor in the survival of an animal, and that much larger doses of salvarsan can be given in a dilute solution, without fatal results, than in a more concentrated solution. Auer's experiments were carried out upon rabbits. His results from the use of a one half per cent. solution of acid salvarsan agree with those of Hering already mentioned; i. e., he found that very small doses of this solution were fatal. However, when a one tenth per cent. solution was used, as much as twenty-two milligrams per kilo of body weight produced no apparent harmful effect. There was not even a fall of blood pressure during the injection. Moreover, after a period of from two to four weeks, several of these animals were reinjected (in a few cases two or three times) with doses of twenty milligrams each, per kilo of body weight, using a one tenth per cent. solution. No injurious effect was ever seen.

The cause of the fatal results following the intravenous injection of acid solutions of salvarsan has been discussed in the literature. Some writers have considered that the acidity was the real cause. Most writers at present agree, however, that the amount of acid present in a lethal dose is too small to produce death.

For some time it has been a well known fact that a precipitate is formed upon the addition of an acid solution of salvarsan to blood in vitro. Miessner (6) showed that the acid solution produces a heavy precipitate when added to defibrinated blood or to bovine or horse serum. If an alkaline solution of salvarsan was used, he failed to obtain this precipitate. Schottmüller (7) has reported the same results from mixtures in vitro of acid and of alkaline solutions of salvarsan and blood plasma. Both Miessner and Schottmüller suggest that these precipitates are formed within the body.¹

¹ Michaelis (8) made a similar statement before either Miessner or Schottmüller.
as well as in the test-tube, and that the formation of a precipitate may have been the cause of death in certain of the cases which have been reported in man following the intravenous injection of the acid solution of salvarsan. These were, however, as stated, mere suggestions and no experiments were made by these or other writers to determine whether a precipitate is actually formed within the animal body. Such experiments have now been made, and the results are given in this paper.

METHOD.

Dogs and rabbits were used in these experiments. The dogs were etherized by means of the intratracheal insufflation method of Meltzer and Auer (9), and cannulas were inserted into a jugular vein and a femoral artery. Moderate ether anesthesia was maintained usually throughout the injection of salvarsan. The salvarsan was infused from a burette into the jugular vein. A sample of blood was drawn from the femoral artery before starting the infusion of salvarsan (sample 1—control), and another (sample 2) at the end of it. Then by means of a pipette inserted through the ventricular wall, samples were taken from the left ventricle (sample 3), and from the right ventricle (sample 4). One or more lobes of lung were snipped off and as much blood as possible was squeezed out (sample 5). To prevent coagulation, each of these samples of blood was collected in a small amount of a 0.03 per cent. solution of hirudin in saline solution. The samples were examined by spreading a film of blood over a glass plate, when the presence or absence of a precipitate could be made out either with the naked eye or with a fairly strong hand lens.

Most of the rabbits were treated in essentially the same way as the dogs. They were etherized, tracheotomized, and cannulas were inserted in one jugular vein and in one carotid artery. The salvarsan was injected into the jugular vein from a burette and blood samples were drawn from the carotid artery. During the injection, ether was discontinued in most cases. Then at the end of the salvarsan injection, or sometimes shortly before, ether was again used and the chest opened under artificial respiration to obtain samples of blood from the heart. Artificial respiration was maintained
in order to prevent stoppage of the heart during the taking of the blood samples, since it was desired to obtain the blood in a condition as nearly normal as possible. In all cases, the heart continued to beat efficiently until artificial respiration was discontinued. The method of taking samples of blood corresponded exactly to those described above for dogs.

In a number of experiments, portions of the control blood (sample I) were mixed in vitro with different quantities of either acid or alkaline salvarsan solutions of different concentrations.

The acid and alkaline solutions of salvarsan were used in both dogs and rabbits, and the dosage in practically all cases was, in proportion to body weight, as large as that usually employed in man or even larger.

The acid solutions were prepared by grinding up the salvarsan in a mortar with a 0.9 per cent. solution of sodium chlorid which was added slowly in small amounts until the required dilution of salvarsan was obtained.

The alkaline solutions were prepared by adding to an acid solution of salvarsan in saline solution, normal sodium hydroxid (4 per cent.) in the proportion of one cubic centimeter of normal sodium hydrate to 0.1 gram of salvarsan. This is the minimum amount of alkali which will redissolve the precipitate that is thrown down when the acid solution approaches the neutral point. The acid and alkaline solutions were perfectly clear when injected. They were made up shortly before being used.

The concentrations of acid salvarsan used were, in dogs 1:200 (one half per cent.), and in rabbits 1:500 (one fifth per cent.). Of the alkaline solutions, the concentrations used were, in dogs 1:200 and 1:500, in rabbits 1:500. It might be mentioned in this connection that the solution usually employed in man for intravenous injections is a 1:500 solution.

EXPERIMENTAL RESULTS.

THE EFFECTS OF ACID SOLUTIONS OF SALVARSAN IN DOGS.

It will be recalled that the concentration of the acid solutions used in dogs was 0.5 per cent. By referring to table I, it will be seen
that seven experiments were performed. The dose of salvarsan varied between fourteen milligrams and thirty-three milligrams per kilo of body weight. There was also some variation in the rate of injection, as indicated in column 6.

TABLE I.
Acid Solutions of Salvarsan Given Intravenously to Dogs.

<table>
<thead>
<tr>
<th>Number of experiment</th>
<th>Body weight in gm.</th>
<th>Concentration of salvarsan used</th>
<th>Amount of salvarsan given in c.c.</th>
<th>Amount of salvarsan in mg.</th>
<th>Duration of injection in minutes</th>
<th>Arterial at end of salvarsan injection</th>
<th>Direct from right ventricle.</th>
<th>From lungs and pulmonary artery.</th>
<th>Direct from left ventricle.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4300</td>
<td>1:200</td>
<td>17½</td>
<td>20</td>
<td>18</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5600</td>
<td>1:200</td>
<td>23</td>
<td>20</td>
<td>7</td>
<td>Definite moderate ppt.</td>
<td>No ppt.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4600</td>
<td>1:200</td>
<td>13</td>
<td>14</td>
<td>22</td>
<td>Definite moderate ppt.</td>
<td></td>
<td>Direct from right ventricle.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4400</td>
<td>1:200</td>
<td>26</td>
<td>30</td>
<td>12</td>
<td>Definite moderate ppt.</td>
<td>At least as much ppt. as from right ventricle.</td>
<td>Trace of ppt. (†).</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4300</td>
<td>1:200</td>
<td>23</td>
<td>26</td>
<td>5</td>
<td>Large amount of ppt.</td>
<td>At least as much ppt. as from right ventricle.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4800</td>
<td>1:200</td>
<td>32</td>
<td>33</td>
<td>6½</td>
<td>Fairly heavy ppt.</td>
<td>About same as from right ventricle.</td>
<td>About same as from right ventricle.</td>
<td>Very slight ppt.; much less than from right ventricle.</td>
</tr>
<tr>
<td>14</td>
<td>5100</td>
<td>1:200</td>
<td>22</td>
<td>21</td>
<td>4</td>
<td>Heavy ppt.</td>
<td>About same as from right ventricle.</td>
<td>No ppt.</td>
<td></td>
</tr>
</tbody>
</table>

In six experiments, samples of blood were taken from the femoral artery at the end of the injection of salvarsan. In four of these there was no precipitate whatever to be seen. Two contained a moderate but definite precipitate.

In four of the seven experiments, samples were obtained from the right and left ventricles and from the lungs. In all four samples from the right ventricle there was a perfectly definite precipitate present in the blood. In three of the four cases, the right ventricle blood contained a heavy precipitate.

In each of the four experiments, a precipitate was obtained from the vessels of the lungs in at least as large a proportion as was found in the blood from the right ventricle. In the four experi-
Formation of Precipitates after Injection of Salvarsan.

ments in which samples of blood were taken from the left ventricle, two contained no precipitate at all, one a doubtful trace, and one a very slight amount of precipitate—markedly less than was found in the blood from the right ventricle.

In these experiments, then, we find that there was in each sample studied a precipitate in the blood from the right ventricle and also in the blood from the lungs; but that in only two out of six cases was there any precipitate in the arterial blood, and that in only two out of four was there a precipitate in the blood from the left ventricle, one of these two being doubtful. In other words, the precipitate was much less frequent in the arterial blood than in the blood from the right ventricle and lungs.

Portions of control (normal) blood were mixed with some of the 0.5 per cent. acid solution of salvarsan in the test-tube or on a glass plate. The proportions varied from one part of salvarsan to thirteen of control blood, to one part of salvarsan to fifty-four parts of blood. In all cases a precipitate was formed, concerning the existence of which there was no question even to the naked eye.

THE EFFECTS OF ACID SOLUTIONS OF SALVARSAN IN RABBITS.

Nine experiments were performed. The concentration of the salvarsan solutions used was 1:500. It will be seen from table II that the dose of salvarsan injected into rabbits (varying from nineteen milligrams to seventy-one milligrams per kilo of body weight) was relatively larger than that given to dogs.

In five of the nine experiments, samples of blood were obtained from the carotid artery at the end of the injection of salvarsan. In not a single case was any precipitate found, though in one of these animals the dose of the drug was seventy-one milligrams per kilo of body weight.

In eight of the nine experiments, samples of blood were obtained from the right ventricle. In six of these, there was a definite precipitate present which varied in amount in the different animals from "moderate" to "heavy." In two, no definite precipitate could be found. In one of these two (experiment 9, table II), the injection was made rather slowly—fifteen cubic centimeters in ten
<table>
<thead>
<tr>
<th>Number of experiment</th>
<th>Body weight in gm.</th>
<th>Concentration of salvarsan used</th>
<th>Amount of salvarsan injected in c.c.</th>
<th>Amount of salvarsan per kilo of body weight in mg.</th>
<th>Duration of injection in minutes</th>
<th>Blood samples examined for precipitate</th>
<th>Mixtures of blood and salvarsan in vitro</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arterial at end of salvarsan injection</td>
<td>Direct from right ventricle</td>
</tr>
</tbody>
</table>
Formation of Precipitates after Injection of Salvarsan.

minutes. In the other experiment in which no precipitate was found in the blood of the right ventricle (experiment 17, table II), about ten minutes elapsed between the end of the injection and the taking of the sample. In this case, a large amount of precipitate could be demonstrated in the blood from the pulmonary vessels. It is possible, therefore, that the precipitate had passed on out of the right ventricle in this instance. At any rate in only one of the nine animals was no precipitate found in the blood from the right ventricle or the lungs.

In six of the nine experiments, samples of blood were obtained from the lung. In four of the six, a definite precipitate was found. The amount of precipitate present was at least as great as that contained in the blood from the right ventricle.

In eight of the nine experiments, samples of blood were obtained from the left ventricle. In six of the eight samples, there was no precipitate whatever. In the other two, there may have been a trace, though this was doubtful.

Stated briefly, the results of the injection of acid salvarsan solutions intravenously in rabbits were as follows: The arterial blood (carotid) at the end of the injection contained in no case a precipitate; blood from the left ventricle almost never; while blood from the right ventricle and lungs contained in nearly all cases a definite, and in some cases a very heavy precipitate.

It should be mentioned that in the right ventricle of one animal (No. 19, table II) at autopsy there were large masses of precipitate mixed with clotted blood clinging to the chordae tendineae. These masses occupied one half or more of the cavity of the ventricle. Similar masses were found in another rabbit and in one dog of this series.

ANIMALS SURVIVING THE INJECTIONS OF ACID SOLUTIONS OF SALVARSAN.

Experiments were performed upon four rabbits to observe the after-effects, if any, of the injections. These rabbits received doses of acid solutions of salvarsan which would surely have produced a precipitate within the blood-vessels in the experiments already described. The injections were made into the ear vein without any
operative procedure and the animals were allowed to live. Two of the four rabbits received twenty milligrams of acid salvarsan per kilo, and another received twenty-five milligrams per kilo. In all three, a one fifth per cent. solution of salvarsan was used. The fourth rabbit received ten milligrams per kilo of body weight of a one half per cent. solution of acid salvarsan. No ill effects whatever were observed in any of the four rabbits. Two were killed after forty and forty-one days respectively, and two after six days. Nothing abnormal was found at autopsy in any of them. It may be recalled here that the experiments of Auer already mentioned showed also that large doses of acid solutions of salvarsan could be given intravenously without any harmful effect if introduced in a dilute form, and that these large doses might even be repeated several times in the same animal with impunity.

THE EFFECTS OF ALKALINE SOLUTIONS OF SALVARSAN IN DOGS.

Injections of alkaline salvarsan solutions were made into six dogs (see table III). The concentrations of salvarsan used were 1:200 and 1:500.

Blood was obtained from the carotid arteries of six animals, from the right ventricles of seven, from the lungs of three, and from the left ventricles of seven; but in none of the samples was a precipitate found. Moreover, these alkaline solutions were injected at a rate considerably in excess of that employed with the acid solutions already described, a procedure which should have favored the appearance of a precipitate, if there was a tendency to precipitate formation.

As indicated in table III, mixtures of control blood and salvarsan solutions of different concentrations and chemical reactions were made. Not all these tests are recorded here. It will be seen in experiment 13 that a mixture of one part of a 1:500 acid solution of salvarsan to four parts of control blood gave a heavy precipitate, while one part of blood and one part of a one per cent. solution of alkaline salvarsan—a solution five times as strong as the former—gave no precipitate even upon standing. After some time, hemolysis took place in this latter mixture.
### TABLE III.

**Alkaline Solutions of Salvarsan Given Intravenously to Dogs.**

<table>
<thead>
<tr>
<th>Number of experiment</th>
<th>Body weight in gm.</th>
<th>Concentration of salvarsan used</th>
<th>Amount of salvarsan per kilo of body weight in mgm.</th>
<th>Amount of salvarsan injected in c.c.</th>
<th>Duration of injection in minutes</th>
<th>Blood samples examined for precipitate.</th>
<th>Direct from right ventricle</th>
<th>Direct from lungs and pulmonary artery</th>
<th>Direct from left ventricle</th>
<th>Mixtures of blood and salvarsan in vivo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>4550</td>
<td>1:500</td>
<td>53</td>
<td>23</td>
<td>3½</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>1 part blood + 1 part 1:500 alkaline salvarsan = no ppt.</td>
</tr>
<tr>
<td>9</td>
<td>4400</td>
<td>1:200</td>
<td>31</td>
<td>35</td>
<td>8</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>1 part blood + 1 part 1:200 alkaline salvarsan = no ppt.</td>
</tr>
<tr>
<td>10</td>
<td>3700</td>
<td>1:500</td>
<td>53</td>
<td>28</td>
<td>4</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>3 parts blood + 1 part 1:200 acid salvarsan = heavy ppt.</td>
</tr>
<tr>
<td>11</td>
<td>4400</td>
<td>1:500</td>
<td>80</td>
<td>36</td>
<td>7</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>1 part blood + 1 part 1:500 alkaline salvarsan = no ppt.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>6400</td>
<td>1:200</td>
<td>40</td>
<td>31</td>
<td>3½</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>1 part blood + 1 part 1:100 alkaline salvarsan = no ppt.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>3700</td>
<td>1:200</td>
<td>24</td>
<td>32</td>
<td>2½</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>No ppt.</td>
<td>4 parts blood + 1 part 1:100 acid salvarsan = heavy ppt.</td>
<td></td>
</tr>
</tbody>
</table>

**Formation of Precipitates after Injection of Salvarsan.**
Table IV.

Alkaline Solutions of Salvarsan Given Intravenously to Rabbits.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No ppt.</td>
<td>1 part blood + 1 part alkaline salvarsan 1:500</td>
</tr>
<tr>
<td>10</td>
<td>1450</td>
<td>1:500</td>
<td>15</td>
<td>21</td>
<td>7</td>
<td>No ppt.</td>
<td>= no ppt.</td>
</tr>
<tr>
<td>11</td>
<td>1320</td>
<td>1:500</td>
<td>15(\frac{1}{2})</td>
<td>24</td>
<td>8(\frac{1}{2})</td>
<td>No ppt.</td>
<td>= no ppt.</td>
</tr>
<tr>
<td>12</td>
<td>1050</td>
<td>1:500</td>
<td>25</td>
<td>50</td>
<td>12</td>
<td>No ppt.</td>
<td>= no ppt.</td>
</tr>
<tr>
<td>13</td>
<td>1350</td>
<td>1:500</td>
<td>22</td>
<td>34</td>
<td>9(\frac{1}{2})</td>
<td>No ppt.</td>
<td>2 parts blood + 1 part alkaline salvarsan 1:100</td>
</tr>
<tr>
<td>14</td>
<td>1130</td>
<td>1:500</td>
<td>30</td>
<td>54</td>
<td>9</td>
<td>No ppt.</td>
<td>= no ppt.</td>
</tr>
<tr>
<td>15</td>
<td>1070</td>
<td>1:500</td>
<td>32</td>
<td>64</td>
<td>10</td>
<td>No ppt.</td>
<td>= no ppt.</td>
</tr>
<tr>
<td>16</td>
<td>1510</td>
<td>1:500</td>
<td>32</td>
<td>43</td>
<td>10</td>
<td>No ppt.</td>
<td>= no ppt.</td>
</tr>
</tbody>
</table>

Don R. Joseph.
THE EFFECTS OF ALKALINE SOLUTIONS OF SALVARSAN IN RABBITS.

Seven rabbits were injected with alkaline solutions of salvarsan of a concentration of 1:500 (see table IV). Here again, as in the case of the rabbits which received injections of acid salvarsan, the dosage given was large—from twenty-one to sixty-four milligrams per kilo of body weight. The rate of injection was between two and three cubic centimeters per minute.

After the injection of salvarsan, samples of blood were obtained from the carotid arteries of six animals, from the right ventricles of seven, from the lungs of three, and from the left ventricles of seven; but in none of these was a precipitate found. We see, therefore, that in rabbits as well as in dogs no precipitate was found, even after injections of fairly large doses of alkaline solutions of salvarsan.

Mixtures of control rabbit blood and alkaline salvarsan solutions of concentrations of 1:100, 1:200, 1:500 were also examined in vitro for precipitate, but in no case was any found, even though equal parts of a one per cent. solution of salvarsan and blood were mixed.

Usually after standing for some time, a mixture of control blood and an equal amount of one half per cent. or 1 per cent. alkaline solution of salvarsan showed hemolysis.

SUMMARY AND DISCUSSION.

The results of these experiments are definite. There is, in the first place, a very striking difference with regard to precipitate formation between the acid and alkaline solutions of salvarsan when injected intravenously. Intravenous injections of alkaline solutions of salvarsan produce no precipitate in the blood, while injections of the acid solution nearly always give a precipitate. Furthermore, after injections of the acid solution, there is a striking difference between the blood from the right side of the heart and that from the left side. At the end of injections of an acid solution of salvarsan, a precipitate was seldom present in the arterial blood. Blood taken from the left ventricle at this time (at autopsy) also showed no precipitate in a large majority of cases; in eight experi-
ments there was no precipitate, in three a doubtful trace of precipitate, and in one a definite small amount. On the other hand, blood obtained from the right ventricle and the lungs showed a very different condition. In ten out of twelve animals (rabbits and dogs), blood from the right ventricle contained a definite precipitate, and in a number of these cases the amount of precipitate was large. Blood squeezed from the lungs showed in eight out of ten cases at least as much precipitate as was found in the blood from the right ventricle.

The results of injections of alkaline solutions of salvarsan, as pointed out before, are quite different from those produced by the acid solutions. In thirteen experiments upon dogs and rabbits, no trace of a precipitate was found in the arterial blood, the blood from the left ventricle, the right ventricle, or the lungs.

There is no apparent difference in the process of precipitate formation whether salvarsan solutions and the blood are mixed in vivo or in vitro. In both mixtures the acid solutions produce a precipitate, while the alkaline solutions of salvarsan do not.

These experiments have demonstrated the fact that a precipitate is present in the blood after an injection of an acid solution of salvarsan. One would expect that such a precipitate, consisting as it usually does of rather coarse particles, would, if brought to the medulla, cause immediate death by producing emboli. However, the freedom from such occurrences may be explained by the fact that the precipitate, which is abundantly present in the right ventricle, is only rarely seen in blood taken from the carotid or femoral arteries or even from the left ventricle itself. The fact itself, however, is quite difficult to interpret. It might perhaps be assumed that the precipitate is filtered out during its passage through the lung capillaries. If this is the case, we might expect intravenous injections of salvarsan to produce embolism in the pulmonary vessels with consequent fatal results.

As a matter of fact, we have in the recent literature an instance which seems to point to such a result. Miessner (6) tried the effects of salvarsan in cattle which had foot and mouth disease. He used at first the acid solution, and though the dose was small, seven milligrams per kilo of body weight, all the animals (four) died in
from ten hours to two days after the injection. They all showed labored respiration during or soon after the injection of salvarsan.

He then decreased the dose to five milligrams per kilo of body weight, and repeated the experiments. He used also normal animals as controls upon those which had the foot and mouth disease. Both the sick and normal (control) animals showed labored respiration. One died after four days. At autopsy all organs except the lungs appeared to be normal.

The lungs presented the following appearance: There were grayish yellow spots scattered irregularly over the surface. On the cut surface these were seen as grayish yellow spots the size of a pea, which appeared in groups and which sometimes filled a lobule completely. Other spots were surrounded by a small area of dark red lung parenchyma. The affected portion contained no air and felt solid. In adjacent parts the tissue seemed normal. A microscopic examination showed that the larger and smaller pulmonary arteries were filled with uniform, homogeneous, yellow masses. About the vessels there was a serous exudate.

In brief, the changes seen indicated, he believed, that there was a thrombosis of the blood-vessels with inflammatory exudative changes of the lung parenchyma. Miessner states that a similar pathological condition was found in a normal control animal that died.

He suggests that the acid solution of salvarsan might lead in man to a thrombosis of the pulmonary arteries. In support of this suggestion, he mentions a case reported to him by Ehrlich of a man who died following the injection of an acid solution. The lung picture in this case was somewhat similar to that which he had found in cattle.

It may be mentioned in passing that Miessner found that alkaline solutions of salvarsan were far less toxic than the acid solutions. Animals (cattle) which received in an alkaline solution 400 milligrams of salvarsan per kilo of body weight did not show the least symptom of disturbance.

In contrast to Miessner's results seem to stand my observations and those of Auer described in the introduction of this paper. Auer (5) found (in 8 rabbits) that no evident harmful effects
followed the injections of very large doses of the acid solution, if they were given in a highly diluted form (one tenth per cent.). In my own experiments, it was found that a one fifth per cent. acid solution (3 rabbits) and even a one half per cent. solution (1 rabbit) produced no ill effects. The experiments described in this paper make it certain that the doses of the acid solution given to these last mentioned four animals must have produced a precipitate in the right ventricle and in the lungs, and yet the animals survived and showed no symptoms whatever of disturbance following the injection.

This difference between our observations and those of Miessner might perhaps be explained by the assumption that the action of salvarsan in acid solution is more deleterious to cattle than to rabbits. Furthermore, Miessner seems to have injected the salvarsan in high concentrations. In one instance, in which figures are given, the drug was administered in a five per cent. solution. As mentioned before, Auer has shown the importance of the concentration. While in a one tenth per cent. solution twenty and thirty milligrams per kilo of body weight of the acid solution may be injected with impunity, even six or seven milligrams per kilo may prove rapidly fatal when injected in a one half per cent. solution.

Our own results, however, leave us with two puzzling questions: First, if the acid solution of salvarsan causes such a coarse precipitate in the right ventricle and in the lungs, how does it happen that this precipitate does not bring about the death of the animal? Second, what is the real cause of the remarkable fact that this precipitate does not pass over into the arterial side of the circulation? Does the precipitate undergo a profound chemical or mechanical change while it passes through the lung capillaries? In future investigations we may try to answer these interesting questions. For the present, it is necessary to be content with the establishment of the bare facts as they are presented in the conclusions.

CONCLUSIONS.

Acid solutions of salvarsan, injected intravenously into dogs and rabbits, even in the concentrations used in man, produce a precipitate in the blood stream.
Formation of Precipitates after Injection of Salvarsan.

This precipitate, which is easily seen and which is abundantly present in the blood from the right ventricle and lungs, can seldom be demonstrated in blood from the left ventricle and arteries.

Intravenous injections of salvarsan in doses which surely produce a precipitate in the blood stream, are not, at least in rabbits, necessarily fatal to the animal.

Alkaline solutions of salvarsan, even in strong concentration, never produce a precipitate when injected intravenously.

BIBLIOGRAPHY.