

A FEW OBSERVATIONS ON THE ACTION OF SALVAR-
SAN UPON THE IRRITABILITY OF NERVE
AND MUSCLE.*

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In the literature upon salvarsan the question has been discussed whether or not salvarsan has a neurotropic action; whether, for instance, affections of the optic, auditory, and facial nerves, which sometimes occur after a salvarsan injection, are due to a neurotropic action of the drug or to a syphilitic manifestation. In this connection the question presented itself: What would be the effect upon nerve and muscle tissue if salvarsan solutions were applied directly to them? This problem was made the subject of a series of experiments performed upon nerve and muscle of the frog. The following is a brief presentation of the results.

Methods.—Leopard frogs (*Rana pipiens*) were used exclusively. The experiments were performed between February 10 and April 12, 1911. They fall into two groups: (A) perfusion experiments and (B) bathing experiments.

(A) PERFUSION EXPERIMENTS.

In these experiments a cannula was inserted in the abdominal aorta, directed distalward, and connected with a burette. The tendo Achillis was freed from its attachment and connected with a muscle lever to register the contractions of the gastrocnemius. From time to time during the perfusion, tests were made of the irritability of the sciatic nerve (indirect irritability) and of the gastrocnemius muscle (direct irritability). For this purpose single break induction shocks were used of such a strength as produced maximal contractions of the muscle.

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Both acid and alkaline solutions of salvarsan were used. In some cases the salvarsan was dissolved in a 0.6 per cent. saline solution; in others, in a Ringer solution the sodium chlorid content of which was isotonic with the tissue fluids of the frog (*i. e.*, 0.6 per cent.). The concentrations of salvarsan in saline or Ringer solution were 1:5000, 1:1000 and 1:500. Salvarsan is a dihydrochlorid and, in making the solutions termed acid, it was simply dissolved in 0.6 per cent. sodium chlorid without the addition of any sodium hydrate.

The alkaline solutions were made by adding one cubic centimeter of normal sodium hydroxid for each tenth gram of salvarsan—the amount of alkali just necessary to produce complete solution of the drug.

Results.—Several attempts were made to perfuse with an acid solution of salvarsan. These were invariably unsuccessful. A precipitate was formed at once when the salvarsan came in contact with the blood of the frog. It plugged the blood-vessels and stopped the solution when one half or one cubic centimeter was injected. Fresh frog's blood mixed with the salvarsan solution on a glass plate gave a heavy yellowish precipitate.

There was no such difficulty, however, with the alkaline solutions. Varying amounts of salvarsan were injected up to eighteen cubic centimeters. In no case was there the slightest alteration in the response of the muscle to direct stimulation. In the majority of cases the perfused salvarsan was equally without effect upon the indirect (nerve) irritability. There was infrequently a moderate reduction in the response through the nerve. This was never greater, however, than that which may be obtained by perfusing with sodium chlorid alone. In brief, then, it may be stated that alkaline solutions of salvarsan, given by perfusion in the amounts and concentrations mentioned, have no immediate effect whatever upon the irritability of nerve and muscle tissue in the frog.

(B) BATHING EXPERIMENTS.

In these experiments muscle-nerve preparations (gastrocnemius-sciatic) were immersed in the salvarsan solutions. Tests were taken

from time to time of the indirect irritability by means of single induction shocks of minimal strength. That is, the changes in irritability were gauged by changes in the threshold stimulus—the weakest stimulus which was capable of producing a response. At the time of stimulation the preparation was lifted out of its bath. The contractions were not registered graphically; they were simply judged by ocular inspection. In those cases in which the indirect irritability was finally abolished, tests were also taken of the *direct* muscle irritability. The following solutions of salvarsan were used for bathing:

- (1) Salvarsan in saline solution (alkaline), 1:1000, 1:500, 1:250.
- (2) Salvarsan in Ringer solution (alkaline), 1:1000, 1:500.
- (3) Salvarsan in saline solution (acid), 1:500, 1:250.
- (4) Salvarsan in Ringer solution (acid), 1:500.

The acid and alkaline solutions are the same as those used above for perfusion.

Results.—The effects of alkaline salvarsan baths will be given first. A solution of one part salvarsan in one thousand parts of 0.6 per cent. sodium chlorid produced only a slight reduction of indirect irritability after four hours.

A solution of salvarsan of the same strength in a Ringer solution was equally without injurious effect.

Alkaline solutions of salvarsan in saline solution (1:500, 1:250) caused almost complete abolition of indirect irritability after two and one half to five hours. During the first two hours the loss of irritability was slight. Toward the end it was more rapid.

The effects of acid solutions of salvarsan were as follows: an acid solution of salvarsan in saline solution (1:500) caused, in some cases, abolition, and in others, a reduction to about one half the previous irritability after five hours in the bath. During the first three hours no effect whatever was observable.

An acid solution of salvarsan in saline solution (1:250) had no effect after one hour, produced slight reduction of indirect irritability after two hours, and nearly an abolition of indirect irritability after two and a half hours.

In practically all cases in which the salvarsan finally caused an abolition of indirect irritability, it was found that the response, when the muscle was stimulated directly, was not better than that through its nerve. In other words both direct and indirect irritability decreased together.

Control experiments were performed by bathing muscle-nerve preparations in a 0.6 per cent. solution of sodium chlorid. It was found that sodium chlorid abolished indirect irritability in from six to eight hours or longer, while the direct muscle irritability still remained fairly good.¹

It should be stated that all the solutions of salvarsan in Ringer solution, whether acid or alkaline, contained a more or less heavy yellow precipitate. The acid solutions of salvarsan in saline also developed gradually a similar precipitate. It appeared first immediately about the muscle and finally spread throughout the solution. Only the alkaline solutions of salvarsan in saline solution remained clear throughout the experiments. It is not impossible that this precipitation, by throwing some of the salvarsan out of solution, reduces the toxicity. It is well-known that either calcium or a carbonate will throw the salvarsan out of solution and this probably explains the precipitate formation in Ringer solutions. The precipitate formed in the acid saline bath was probably due to a decrease in acidity of the solution resulting from the presence of the muscle tissue.

CONCLUSIONS.

These experiments have shown that salvarsan is a comparatively inactive drug when applied directly to nerve and muscle tissue of the frog. In perfusion experiments with alkaline solutions, no detrimental action whatever was to be seen either upon direct or indirect irritability. In bathing experiments, in which the concentration of the salvarsan in the various solutions was surely much higher than that in which it reaches the peripheral tissues in the human subject through the circulation, the loss of irritability occurred only after a long period of exposure to the drug.

¹ This statement applies to the gastrocnemius and not to the sartorius which, according to Locke and others, loses its indirect irritability very quickly in a sodium chlorid solution.