SOME EXPERIMENTAL DATA ON THE SIGNIFICANCE OF CONCENTRATION AND OF MULTIPLICITY OF AREA IN HYPODERMIC INJECTIONS.[1]

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In the theoretical and practical studies of the effects of bacterial toxins and antitoxins upon the animal body, the subcutaneous method of application is extensively employed. Therefore any contribution to the knowledge of the precise working of this method ought to be of interest to bacteriologists. This is my excuse for bringing before this society a subject which in itself is not an integral part of bacteriology.

In a recent communication by v. Czyhlarz and Donath,[2] the assertion was made that the animal tissue is capable of neutralizing or fixing the poisons of strychnine and venom. The fundamental experiment from which this assertion was derived was as follows: The thigh of a guinea-pig was tightly constricted and a fatal dose of strychnine injected into it at a point peripheral to the ligature. When after an hour or two the ligature was removed, the characteristic effect of strychnine did not set in. In a series of experiments by Langmann and myself,[3] it was shown, as I believe conclusively, that this failure is not due to any capacity of the tissue to neutralize poisons, but to the impairment of the capacity of absorption of the constricted leg. One of the experiments which was made in support of our view was as follows: Instead of injecting the minimum effective dose, which is for a guinea-pig of 250 grammes about 1.5 mgr., into one leg, we divided the dose into three parts and injected them in

[1] Read at the meeting of the Society of American Bacteriologists, Dec. 28, 1900, Baltimore.

[2] *Centralbl. f. innere Med.*, 1900, p. 321.

[3] Meltzer and Langmann, *Medical News*, 1900, lxxvii, p. 685.

three extremities which had been constricted prior to the injections. We had here in comparison to the other experiment a greater amount of tissue to a smaller amount of poison, and if the tissues were capable of neutralizing the poison, there should have been surely in this experiment no effect of strychnine visible. Instead, no sooner were the ligatures taken off than violent convulsions broke out. Our explanation was, that there were for the same amount of poison in the three legs more paths of absorption open than in the one constricted leg, hence the positive result.

One observation which I made in the last-mentioned experiment, gave the stimulus to the new series of experiments, the results of which I shall report here briefly. The tetanus, which followed the removal of the ligatures of the three legs, was more violent and set in sooner than in the case in which the sum of the three quantities was injected into one non-ligatured leg. It was now a question, whether the distribution of the same quantity of the solution of strychnine to several areas of the body does not indeed favor a more rapid absorption. The characteristic effect of the poison appears the more quickly and the more pronounced, the more quickly and the more abundantly it is absorbed into the blood and from there into the central nervous system. The absorption from the subcutaneous tissue takes place either through the blood-capillaries or through the lymphatics or in both ways. Now the distribution of the same quantity to several areas brings the poison, it would seem indeed, into contact with a greater number of capillaries and lymphatics, and it would therefore be quite plausible to assume that such a distribution facilitates absorption. On the other hand, the larger the quantity which is injected subcutaneously into one place, the greater is the pressure which it exerts upon the surrounding tissue. And as pressure facilitates filtration, and filtration is at least one of the factors of interstitial absorption, we might suspect that by the distribution one of the factors favoring absorption becomes impaired. Here was a problem and I tried to solve it by experiment. I employed strychnine again, on account of the characteristic reaction and the short time in which a decisive response can be obtained. In the comparison I noted of

course also the length of the interval which elapses between the injection and the appearance of the tetanus and the degree of violence of the latter, but in my positive conclusions I relied chiefly upon the appearance and non-appearance of a tetanus. The following sample experiments illustrate the result:

Rabbit, 1700 grammes, injected into one leg 1 mgr. of strychnine. No effect. Five days later, injected into the same animal 1 mgr. distributed among three extremities. The first tetanus 23 minutes after injection, followed by a few more; animal survived.

It might be suspected in this experiment that some of the strychnine of the first experiment was not yet absorbed and aided in the result of the second injection. The following experiment is free from such a suspicion:

Rabbit, also 1700 grammes, injected 0.9 mgr., distributed among three extremities. Had a number of tonic and clonic convulsions, the first attack 27 minutes after injection; survived. Five days later, the same animal, injected into one leg 1 mgr. of strychnine. No effect.

In this experiment the single injection was even larger than the divided one. Nevertheless convulsions followed the latter, while the former remained ineffective.

My experiments justify the conclusion that in hypodermic injections the distribution of a certain quantity of poison among several places of the body is more effective than the injection of this quantity in a single dose into one place.

Under the influence of the argument that the larger the quantity, the more effective the filtration and the better the absorption, and in the desire to increase the effectiveness of the distribution by increasing the quantity without increasing the dose, I have attempted to employ greater dilutions of the solution of strychnine, but obtained rather puzzling results. I therefore started out to establish, first, the effect of increasing the bulk without changing the dose in single injections. Here my filtration argument received quite a setback. I shall again illustrate the instructive result by a couple of experiments.

Rabbit, 1300 grammes, injected 0.8 mgr. in a dilution of 1:10,000; no effect. Six days later, the same animal, injected 0.6 mgr. in a

dilution of 1:200. Had convulsions after 11 minutes; survived. Five days later, the same animal, injected 0.9 mgr. in a dilution of 1:20,000. No effect. The same animal again, five days later, injected 0.5 mgr. in a 1 per cent solution; violent tetanus after five minutes and dead. 0.5 mgr. in a 1 per cent solution kills the animal in a few minutes, while nearly twice as strong a dose in a dilution of 1:20,000 remained without any effect.

Guinea-pig, 560 grammes, injected 3.4 mgr. in a dilution of 1:20,000; no effect. Ten days later, injected 2.3 mgr. in a 1 per cent solution. Tetanus and death in a few minutes.

These experiments, which gave uniform results, demonstrate unmistakably that the bulk is nothing and the concentration everything; the doses being equal, the more concentrated the injected poison is, the stronger is the result. The meaning is plain: the osmotic pressure is the most important factor in the process of absorption.

The results of these series of experiments are in brief as follows:

The effect of the subcutaneous injection depends to a considerable degree upon the concentration of the injected solutions, and is materially influenced by a greater distribution of the injected quantity over several areas.