On the Action of Cocaine upon the Blood Vessels of the Frog.

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The action of cocaine upon the blood vessels has very often been examined by many investigators. But the results have not been the same. Anrep[1], Beyer[2], Kobert[3] and Full[4] found that cocaine caused the contraction of the blood vessel, while Mosso[5], Brodie and Dixon[6], O. B. Meyer[7] and Kuroda[8] found the effect to be its dilatation. Ando[9] reported that it first dilatated and then contracted the vessels. Why is it that the results of their experiments are so various?

It is generally known that the same substance may produce different effects according to the species of animals experimented on. They performed their experiments on animals of different species. It can therefore be suspected that the above mentioned disagreements may be due to the fact that animals of different species were experimented on.

I therefore made an investigation of the reports of experiments on the blood vessels of the frog. Anrep[1] subjected a frog to a hypodermic injection of cocaine and found a considerable contraction of the capillary of the web. Kuroda[8] by the perfusion test of the blood vessels of legs noticed a manifest dilatation of the blood vessels. Ando[9] reported that, in his perfusion test of the blood vessels of legs, he found that cocaine caused dilatation and that when it was washed away contraction followed. Thus we see that, even when experiments were made on frog only, the results were not the same. But we must remember that there are various species in the frog family. Those which are most frequently used in experiment are Rana esculenta, L. and Rana temporaria, S. Although those two kinds of frogs react in the same way to many drugs, they show different reaction to certain substances. For instance, caffeine increases mainly the reflex irritability in the case of Rana esculenta, while the same substance brings about mainly a stiffness of the muscles in the case of Rana temporaria (Schmiedeberg[10]). The difference in the results may be due to the difference in the species of the frogs.

I chose Rana esculenta and Rana temporaria and made preparations for the perfusion of the blood vessels of the legs according to Läwen-Trendelenburg. In the experiment 0·25 c.c. of cocaine solution, dissolved in Ringer's, was injected into the inflow cannula. The state of the blood vessels was observed by measuring the change in the quantity of the liquid flowed out.

Rana temporaria. When a 0·5 % cocaine solution was injected, no noticeable change occurred. When a 1·0 % solution used, for the first time, a noticeable change was seen, but was not marked (Fig. 1). When a 5·0 % solution was injected, a remarkable change appeared (Fig. 2). Although the degree of change varied with the concentration, in the increase in the rapidity of the flow or the dilatation of the blood vessels, there was an agreement with the experiment of Kuroda[8].

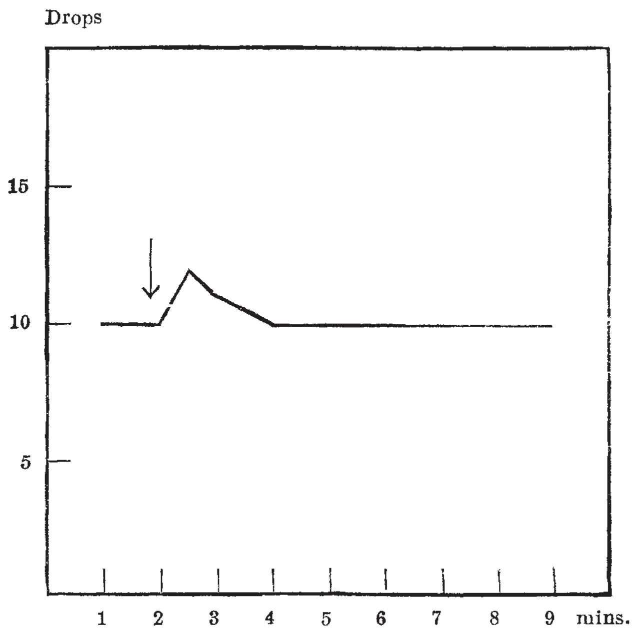

Fig. 1. Rana temporaria, 1·0% cocaine.

Rana esculenta. The sensibility of Rana esculenta to cocaine was the same as that of Rana temporaria. But in this case, as may be seen

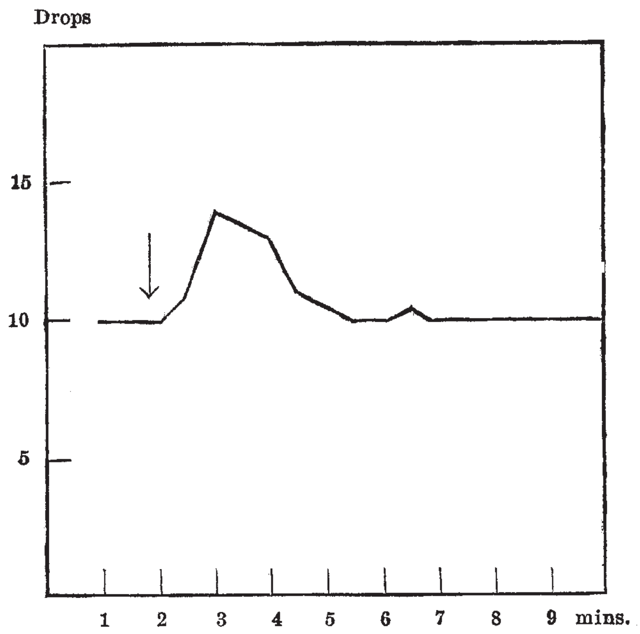

Fig. 2. Rana temporaria, 5·0% cocaine.

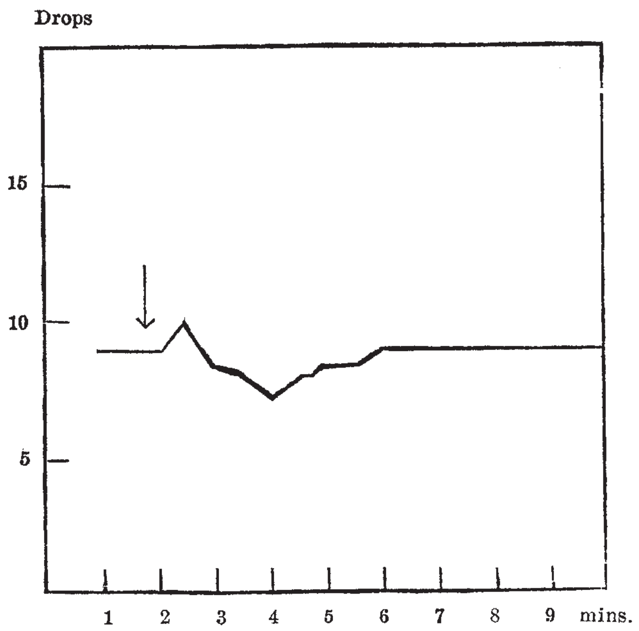

Fig. 3. Rana esculenta, 1·0% cocaine.

in Figs. 3 and 4, after the cocaine injection, the rate of outflow increased only for a while. Gradually the rate decreased until it became slower than before the injection, and then slowly regained the normal rapidity. This means that the blood vessel first dilated and then contracted. The result seems to agree with that of Ando[9]. But in my experiment the dilatation appeared even when the cocaine solution was still in the vessels.

By the reports of the above mentioned investigators, we find that Kuroda[8] used Rana temporaria and Ando[9] Rana esculenta for experiments. Anrep[1] used also Rana esculenta, but he perhaps overlooked the temporary dilatation preceding the contraction. Thus we see that the reaction differed according to the species of the animal which was

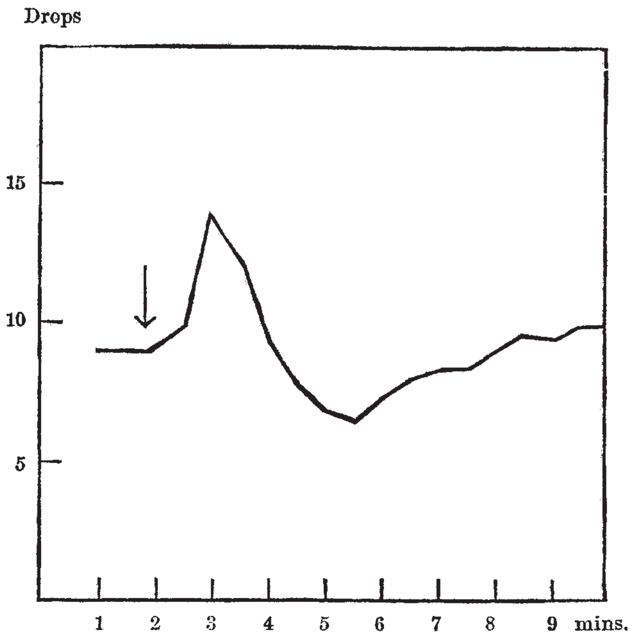

Fig. 4. Rana esculenta, 5·0% cocaine.

employed for the experiments. A great mistake will often be made, if we draw a conclusion regarding the action of a substance on different species of animals from experiments on one or two merely. The reason why there is such a difference in the reports on the action of cocaine upon the blood vessels may be found in that fact. I shall try to make comparative investigations of the action of cocaine upon the blood vessels of different animals and make full reports subsequently.

It is an indisputable clinical fact that when cocaine is applied to a certain part of the body, the local blood vessel contracts and shows a pale color. But the results of experiments on animals are often found to differ considerably. Heinz[12)] ascribed the variation to the difference of the method of application. He asserted that the contraction arises when cocaine is made to act from outside the blood vessel, and the dilatation follows when it acts inside the blood vessel.

For experiment, I made the same preparation as before and applied 1·0 % cocaine solution on the surface of the web and examined the rate of the outflow. But in this case, the result was not different from that which followed when the substance was injected into the inflow cannula. In the case of Rana esculenta the rate of the flow increased and in that of Rana temporaria, the rate first increased and then decreased. Therefore, the theory of Heinz seems to have no ground.

In considering the mechanism of the action of cocaine upon the blood vessels a question may arise, whether the dilatation is the result of the paralysis of the constrictor apparatus or is caused by the stimulation of the dilatator? If it is due to the paralysis, the experiment on Rana esculenta must be explained as a case of paralysis followed by stimulation. But such a phenomenon is contradictory to the general mode of action of the drugs. So it must be regarded as due to the stimulation of cocaine upon the vasodilatator nerve endings. That the contraction of the blood vessels in Rana esculenta is not due to the paralysis of the vasodilatator nerve is clear from the fact that in the stage of contraction, the second injection always produces a typical change. Hence the contraction must also be caused by the stimulation of the vasoconstrictor nerve endings. About the existence of the vasodilatator nerve, there have been various opinions. But the latest reports seem to have proved its existence beyond doubt. The development and distribution of these two kinds of nerve fibres may be different according to the organ or to the species of the animals. Cocaine must stimulate these two kinds of nerve endings. Hence in the case of Rana esculenta first dilatation and then contraction appears. In the case of Rana temporaria since its dilatator nerves are more highly developed than the constrictor nerve, only the dilatation occurs. This may also be the reason why caffeine, while contracting many blood vessels, dilates the coronary vessel alone.

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