ON ABSORPTION FROM INTRAMUSCULAR TISSUE.*

BY J. AUER AND S. J. MELTZER.

(From the Department of Physiology and Pharmacology of the Rockefeller Institute for Medical Research, New York.)

About five years ago we published the results of a series of experiments upon a comparison of the rate of absorption of solutions from within the muscles and the subcutaneous tissue. We tested the rate of absorption with substances which give a definite reaction; for instance, the effect of adrenalin upon blood-pressure and upon the pupil in animals in which the corresponding cervical ganglion was removed, the effect of curare, and of fluorescein.

The effect of adrenalin upon blood-pressure was studied especially on account of the objective graphic evidence which it furnishes. The investigation brought out the definite result that the absorption after intramuscular injections is far superior to that after injections into subcutaneous tissue, approaching in its effectiveness that of an intravenous injection. Our experiments were made on rabbits and the results obtained were constant. We discussed in our paper the possibility of the intramuscular injection being in reality an intravenous one and brought forward a number of facts which seemed to us to be sufficient to refute such an assumption.

Since the appearance of our communication statements have been published on the subject of intramuscular absorption of adrenalin in which the authors arrived at conclusions different from ours. Patta states that in his experiments neither the intramuscular nor the subcutaneous injection of adrenalin ever produced a rise of blood-pressure, and that in his opinion our favorable effects with intramuscular injections resulted from the fact that our hypodermic needle was inserted accidentally into a vein. In a communication

* Received for publication, January 6, 1910.
2 Patta, Arch. ital. de biol., 1906, xlvi, 463.
before the New York Academy of Medicine, Wallace stated that in his experiments an intramuscular injection of adrenalin in rabbits acts indeed practically like an intravenous injection, but he was of the opinion, "that the injection was in truth an intravenous one, that the manipulation resulted in the tearing of a small vein and that some of the adrenalin gained entrance into a vein."

We have recently gone over the subject again and carried out a series of experiments under conditions which, in the first place, exclude the possibility of the needle having entered the lumen of a muscle vein. Our results furnish at the same time a possible explanation for the surprising failure of Patta to obtain an evident effect of adrenalin upon blood-pressure by intramuscular injection. As in the previous investigations, we experimented chiefly upon rabbits, using the rise of blood-pressure after injection of adrenalin as an indicator for the absorption. The injections were made, as in the previous experiments, into the lumbar muscles.

At the outset we may say in general that in employing these lumbar muscles there is no difficulty whatsoever in demonstrating the superiority of the absorption from the muscles over that from the subcutaneous tissue. This was easily accomplished by the simple method of injecting adrenalin with a hypodermic needle. It practically never failed to bring out an immediate definite rise of blood-pressure when the injections were made into the lumbar muscles, while after a subcutaneous injection the effect is inconstant and insignificant. We may mention here that in the present investigation this difference came out in a striking manner also in using potassium cyanide. A minimum dose was found which killed rabbits in a short time by an intramuscular administration, while by subcutaneous injection, the same dose was not fatal, and sometimes not even manifestly toxic. We may refer here also to the experiments of Joseph and Meltzer with magnesium salts, in which the difference between the intramuscular and the subcutaneous injection was very evident.

In order to exclude the possibility of the needle being in a muscle vein, a number of experiments were carried out in the following:

---


*Joseph and Meltzer, Jour. Pharm. and Exper. Therapeutics, 1909, i, 373.
Absorption from Intramuscular Tissue.

manner: we exposed in rabbits the sacro-lumbar muscles and made a small slit in them, through which a large glass cannula was bored slowly and gradually into the muscle tissue where it was safely secured by means of needle and thread. The cannula was usually one of the largest which we employ in the laboratory for the jugular veins of dogs, that is of about five millimeters diameter; it surely could not have entered into the lumen of a muscular vein. A feather was introduced to the bottom of the cannula, to test for the presence of blood; in most instances not even a stain of blood was brought back. The cannula was kept open and free for some-

Fig. 1a. During the interval marked by crosses on the tracing, 1 c.c. of adrenalin was injected into a cannula which had been tied into the lumbar muscles of a rabbit. The injection was given at 2:05 p.m. Note prompt and considerable rise of blood-pressure.

All the tracings represent the carotid blood-pressure in rabbits taken by means of a mercury manometer. The base line is the straight one beneath the time marking. Time is recorded in four second intervals in all tracings.
time, to admit air and hasten the clotting and drying of the blood and thus close the openings in the veins, if any of them were torn; in one case the cannula remained open for forty-five minutes. Then the cannula and the piece of rubber tubing, which was attached to it, were filled with adrenalin and the tubing clamped, after which we again waited a few minutes. The presence of the adrenalin at the bottom of the cannula could assist further, if necessary, in clotting the blood and closing the torn vessels. The simple presence of adrenalin caused no rise of blood-pressure. The carotid and blood-pressure arrangement were prepared in the usual manner. Now one cubic centimeter of adrenalin was injected through the rubber tubing into the lumen of the cannula; in these injections the point of the needle remained in the lumen of the cannula and did not come in contact with the muscle tissue. In experiments so arranged, the cannula could not have been in the lumen of a vein, and if any of the veins were torn by the insertion of the cannula, the openings were closed, at all events at the time when the injection took place. Now as to the results. Practically without exception, soon after the injection was finished, an unmistakable rise of blood-pressure set in, which, in many respects, resembled the rise caused by an intravenous injection of adrenalin (see Fig. 1a). Furthermore, even at the repetition of an injection after half an hour, a similar positive result was obtained, although in his case the effect was somewhat less strong than the one produced by a first injection (see Fig. 3).

In these experiments the observation was further made that the rise of blood-pressure brought on by intramuscular injections of adrenalin, executed in the manner just described, lasted a good deal
Absorption from Intramuscular Tissue.

longer than the usual duration of the rise of pressure following an intravenous injection. We have already called attention to this feature in our first paper. In one case of our present series of experiments more than half an hour passed before the pressure returned to its original level (see Figs. 1a and b).

It is therefore evident that the rapid absorption of adrenaline from the intramuscular tissue in these experiments did not come about from the needle being in a vein or from the entrance of adrenaline into the openings of veins which became torn by the insertion of the needle. Our theory is that adrenaline enters the circulation through the walls of the blood capillaries which are abundantly present in the muscle tissue. The entrance is enforced by the increased pressure which the injection produces within a muscle firmly enveloped in a resistant fascia. Only a small fraction of the quantity of the injected solution present in the muscle tissue enters the circulation at a time, but in such small quantities it continues to penetrate the capillary wall as long as the solution is present in the muscle in a sufficient quantity to maintain the necessary degree

*Loc. cit.*
of additional intramuscular pressure. We would state now that in our opinion the massive structure of the muscle and the resistance of the fascia surrounding the mass of muscle tissue are important.

Fig. 3. Same rabbit. One cubic centimeter of adrenalin was injected again into the cattula tied into the lumbar muscles. A good rise of pressure occurred, in spite of the fact that 1 c.c. of adrenalin had been injected into the same place before.
factors in maintaining the increased pressure and thus favoring the rapid absorption from the muscle tissue. Whether the injected solution passes through the normal stomata of the vascular walls or through abnormal openings artificially produced by the force of the injection, is a question which would be difficult to decide experimentally, and it is not important enough to spend time in a laborious attempt at its solution. We may say, however, that, considering the ever-readiness of the muscle tissue for activity, it is only reasonable to assume that the walls of its capillaries are especially prepared for a rapid and easy exchange of metabolic products.

In our previous paper we stated that in injecting into muscles
other than those of the lumbar region, "care has to be taken that the needle remains within the muscle, as with the thin muscles of the animal, it might easily happen that the needle enters the loose areolar tissue between layers of muscles, in which case the effect will be the same as from the subcutaneous tissue." In view of the fact that just at present the gluteal muscles are frequently used in practical therapeutics for the purpose of giving "deep injections," we carried out a series of experiments in which the injections into the lumbar region were compared with those given into the gluteal muscles. The injections of adrenalin were given either simply through a hypodermic needle or through a glass cannula carefully tied in the muscles in the manner described above. The comparisons were made on the same animal, the adrenalin being administered first into one group of muscles and later into the other group. Since in our experience the effect of the first injection of adrenalin was always better than that of subsequent injections, the order of the injections was changed in different animals, giving, for instance, in one animal the first injection into the lumbar, and the second into the gluteal muscles, and reversing the order for the next animal. The results were unmistakable and remained the same no matter what the order of the injection was. While the injections into the lumbar muscles, as stated before, practically never failed to bring out promptly a characteristic reaction, the effects produced by intra-gluteal injections were, to say the least, unreliable. Either there was practically no effect at all, or the effect was insignificant compared with that obtained from the lumbar muscles (see Figs. 2 and 4 and compare with Figs. 1a and 5).

The striking difference in the rate of absorption between the two groups of muscles has its origin, we assume, in some anatomical differences. The mass of the lumbar muscles is nearly round, massive, and of a dense texture, and is tightly encased in strong, nearly inelastic fascia. The mass of the gluteal muscles, on the other hand, is arranged in flat layers, consisting of coarse, loosely connected fasciculi. It seems further that the gluteal muscles are only loosely and incompletely covered by their fasciae. The relation of the fasciae to the rate of absorption from the muscles they envelope, may be important for two reasons: first, it may assist in main-
Absorption from Intramuscular Tissue.

taining a higher intramuscular pressure and thus favor a more effective absorption, and secondly, it prevents the escape of the injected solution into the adjacent loose connective tissue. When a solution is injected into the mass of the gluteal muscles, it often fails to be rapidly absorbed because, perhaps, on the one hand, the

![Graph](image)

**Fig. 5.** Same rabbit as in Fig. 4. Eight-hundredths cubic centimeter adrenalin was injected by hypodermic needle into the lumbar muscles of the left side twelve minutes after the injection into the gluteal muscles. The record shows a good and prompt rise of blood-pressure.

injection fails to cause there an effective rise of an intramuscular pressure and, on the other, the solutions, perhaps, frequently escape into the loose connective tissue abundantly present in some parts of the muscles and their neighborhood.

We may record here also the following experiments, based upon the anaphylactic reaction in guinea pigs. In highly sensitized pigs
one cubic centimeter of horse serum, injected into the lumbar muscles either through a glass cannula, as described above, or directly by a hypodermic needle, kills the animal in the same acute manner as an intravenous injection. Such a prompt and rapid result cannot be obtained by a subcutaneous injection, nor was it forthcoming when the injection was given into the gluteal muscles. However, the dose necessary for a prompt effect by an injection into the lumbar muscles is at least twenty times as large as the one which would cause an acute anaphylactic death by an intravenous injection.6

We may mention here briefly that in dogs the favorable effect from injections into the lumbar muscles were obtained only from large animals and only when the muscles were exposed and we made sure that the needle was within the muscle tissue. In these animals the lumbar muscles do not present a large mass.

The results which we obtained in this investigation may perhaps help us to understand the cause of the failure of Patta to obtain a rise of blood-pressure by intramuscular injections of adrenalin. Patta probably did not inject into the lumbar muscles, and in using other muscles he might not have taken special care to inject exclusively intramuscularly, at least he does not mention it especially. The adrenalin which he believed to have injected intramuscularly might have found its way into the connective tissue between the layers of muscles. In fact, in searching for the presence of adrenalin within the muscle, Patta states expressly that in cutting out the muscles into which he believes he had injected it, he took along also some of the adjacent tissue.

CONCLUSIONS.

Injections of adrenalin or other substances into the lumbar muscles of rabbits are followed by a rapid absorption in whole or in part of these substances.

The rapid absorption is not due to the needle being within a vein or to the tearing of veins by the needle during its insertion.

Similar injections into gluteal muscles fail to give reliable results.

6 Gay, Southard and Fitzgerald (Jour. Med. Research, 1909, xxi, 21) who injected horse serum into the lumbar muscles of guinea pigs (see experiment 2, p. 23) believe that the favorable result was obtained because the injection was a "paraneuraxial" one.