ON THE RATE OF ABSORPTION FROM INTRAMUSCU-LAR TISSUE.

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PLATES I.–III.

The rate of absorption from muscles has never yet been a subject of scientific investigation. In fact, nowhere in physiological literature do we meet the suggestion that absorption from the muscles might differ from that of any other parenchymatous or subcutaneous tissue. Only from the serous cavities, especially the peritoneal, is it generally assumed that absorption takes place more rapidly than from the subcutaneous tissues. In the recent extensive studies of infections and immunity, in which inoculation of animals with virulent, toxic, or antitoxic material is one of the most extensively employed methods of investigation, this is usually accomplished by subcutaneous or intraperitoneal injections, to which injections into the spinal canal, the brain, or the nerve trunks were recently added. In the latter cases, the injections are carried out rather to demonstrate their localized effect than to cause a general systemic infection or intoxication. Intramuscular injection, however, as far as we know, was never yet employed, at least not consciously, as a method of introducing infectious or toxic products into the circulation.

In therapeutics, however, we now and then come across the practice of intramuscular administration of drugs. It originated in the treatment of syphilis with mercury. When at the beginning of the '80's of the last century it was found that hypodermic injections of any compound of mercury gave considerable pain and favored the development of abscesses at the site of injection, the method developed of giving deep-seated injections,

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especially in the gluteal muscles where it was claimed that they caused neither pain nor abscesses. It was, however, especially stated by certain authorities [1] "that the absorption from the intramuscular tissue with its fewer lymphatics is much slower than from the subcutaneous tissues where the lymphatics are abundant." For the same reason, namely, of avoiding pain and abscess, the practice of injecting into the gluteal muscles extended to some other drugs, such as digitalis, camphor, etc., which cause pain when injected subcutaneously.

OUR EXPERIMENTS.

We came across the question of the rate of absorption from the intramuscular tissues while studying the effect of suprarenal extract upon the pupil when injected peripheral to a ligature applied to an extremity. In studies of the effect of suprarenal extract upon the paradoxical pupil dilatation,[2] the authors stated that in animals from which one superior cervical ganglion was previously removed, a subcutaneous injection of adrenalin caused a long and lasting dilatation of the pupil on the side without ganglion. The dilatation set in about fifteen minutes after the injection. In order to demonstrate that the suprarenal extract is not oxidized by the tissues, the authors ligated a leg and injected adrenalin peripheral to the ligature. When the ligature was removed after some time, the pupil on the side without ganglion dilated. In this case, however, the dilatation appeared a minute or two after removal of the ligature. The problem which the present writers set out to study was the cause of this rapid onset of the effect of the extract after the use of the ligature. We soon made the observation that in introducing the extract into the part of the extremity peripheral to the ligature, the injections were almost unavoidably made intramuscularly. We then began to study directly the rate of absorption after intramuscular injections, and we reached the remarkable result that, for the substances we have studied so far, the effect of an intra-

[1] Neumann und Finger, *Wiener Medizin. Presse*, 1885, xxvi., 80.

[2] S. J. Meltzer and Clara Meltzer Auer, *American Journal of Physiology*, 1904, xi, 28.

muscular injection stands nearest to that of an injection into the circulation, and is far above that of a subcutaneous application.

The substances we have studied so far are: adrenalin, curare, fluorescein, and morphine. In order to obtain clear results it was desirable to employ substances which give distinct reactions, and at the same time permit a comparison of the different modes of application in the same animal. The most available substance for our purpose was again suprarenal extract, as its absorption into the blood is capable of giving us three distinct reactions: the rise of blood-pressure, the dilatation of the pupil, and the characteristic prostration. The effect upon the blood-pressure has, as a method of investigation, an advantage over the other reactions mentioned in that as it permits a graphic presentation of the results.

THE EFFECT OF INTRAMUSCULAR INJECTIONS OF ADRENALIN UPON THE BLOOD-PRESSURE.

The blood-pressure experiments, as well as all other experiments recorded in this paper, were made exclusively on rabbits.

In the experiments on blood-pressure the carotid artery was connected with a mercury manometer, by means of which the variations in the pressure were recorded on a slowly revolving smoked drum. During the operations the animals were anæsthetized with ether; during the further course of the experiments, in some cases the animals were kept under mild anæsthesia by ether, or a small dose of morphine was injected. In a few cases curare was given intramuscularly.

It is worth while mentioning that, in studying the effect of suprarenal extract upon the blood-pressure in rabbits, we were greatly hampered by the favoring effect of the extract upon blood-clotting.[3] As soon as the extract was absorbed into the circulation we could hardly obtain two consecutive tracings without being compelled to free the cannula and connecting tubing from clots. In some cases a clot ended the tracing before the entire effect of the extract was over. In other cases the

[3] Vosburgh and Richards, *American Journal of Physiology*, 1903, xi, 30.

cleaning of the tube was of no avail, as the clot was formed far down in the carotid artery.

On the other hand, a *saturated* solution of magnesium sulphate, with which cannula and connecting tube were filled, proved to be a source of great danger to the animal. When, after a struggle, the pressure sank for a few seconds, the solution of magnesium sulphate rushed backward through the central end of the carotid and reached the aorta, the animal was liable to die within a few seconds without any asphyxia and with practically no struggle. We preferred using less concentrated solutions of magnesium sulphate, and contending with the difficulties of clotting rather than risk the effect upon the circulation. We lost a number of animals in rapid succession, due to this effect of the magnesium salt. We bring out this point here because we believe that some physiological experimenters are not fully familiar with the eminently toxic effect of magnesium sulphate when brought directly into the circulation.

In studying the effects of intramuscular injections of suprarenal extract upon the circulation, we had to compare them with the effects of other modes of administration, i. e., with the effects of subcutaneous, intraperitoneal, and intravenous injections of the extract. This comparison extended to the questions of the time of the onset, of the effect after injection, the character of the development, and the degree of the increase of the pressure which is caused by each mode of injection. For various reasons we had to neglect in this study the question as to the duration of the effect due to each mode of injection.

Of the modes of administration of the extract, we have compared the intramuscular most extensively with the subcutaneous injections from which they are generally but little distinguished. We made but few comparisons with intravenous injections, considering this comparison of no particular importance in the present study; and we also made but few comparisons with intraperitoneal injections, for reasons which we shall state later. Of the results which were obtained, the greatest value had to be attached to those which were derived from comparisons made on one and the same animal, as in comparisons between the

results obtained from different individuals the element of individuality might come into play. But in the comparisons on the same animal the question of sequence had to be taken into consideration, since a preceding injection always has a better effect than the following one.[4] We have therefore, in some experiments, varied the sequence of injections, i. e., in some experiments a subcutaneous injection was given first and this was followed by an intramuscular one; and in others we reversed the order. However, since a preceding intramuscular injection impairs incomparably more the effect of a subsequent subcutaneous injection than a subcutaneous could effect a following intramuscular one, we began the majority of experiments with a subcutaneous injection.

Between two injections we usually permitted intervals of fifteen to thirty minutes to elapse, sometimes letting the drum run continuously or obtaining short curves every two minutes. Although in most of the experiments we waited with the second

[4] It has been stated by many observers that in consecutive intravenous injections of suprarenal extract the effect upon the blood-pressure is gradually diminished. This gradual decrease in the effect was looked upon as a sort of process of adaptation or immunization. In previous unpublished experiments with subcutaneous injections of the extract we have noticed that by this mode of administration we rarely obtained an effect from a second and certainly not from a third injection, although they were given each time in another place and the effects of subsequent intravenous injections were in no way impaired. The above given explanation of adaptation, etc., will not hold good in this case. In our present studies we also found that in repeated intramuscular and peritoneal injections of adrenalin the effect upon the blood-pressure is rapidly decreased. Our interpretation of this phenomenon is as follows: In a previous paper (Meltzer and Auer, *Transactions of the Association of American Physicians*, 1904, xix, 207) we have demonstrated that the introduction of suprarenal extract into the circulation retards the absorption from the tissues into the blood, and also the transudation from the blood into the tissues. When, therefore, a subcutaneous, an intraperitoneal, or an intramuscular injection of suprarenal extract once produces an effect upon the blood-pressure, it has then of course reached the circulation and causes therefore a retardation of the further absorption of the extract from the tissues; hence the smaller effect of a second injection. Possibly the same explanation might also hold good for the gradual reduction of the effect of repeated intravenous injections of the extract, since transudation also becomes retarded, and, since even in intravenous injections, the vascular intima has to be permeated before the extract can exert its influence upon the muscle fibres of the media.

injection until the blood-pressure reached its original level or fell below it, we cannot claim that even in those cases the effect of the preceding injections had actually passed off, since the frequent cleanings of the cannula and the necessity of letting blood escape in order to drive out a deep-seated clot, might have interfered with the absolute pressure. For this reason we refrained, as stated above, from utilizing the data regarding the duration of the effects of these injections.

We did not attempt to make an exhaustive study of the effects of subcutaneous and intraperitoneal injections of the suprarenal extract upon the blood-pressure, since the chief purpose of our present investigation was a study of intramuscular absorption, and not of the effect of suprarenal extract upon blood-pressure. However, we have in the present and in previous studies acquired a few data regarding the effects upon blood-pressure of subcutaneous, as well as of intraperitoneal, injections of suprarenal extract which we are about to report briefly.

SUBCUTANEOUS INJECTIONS.

In the physiological and the pharmacological literature upon suprarenal extract we frequently find the brief statement that subcutaneous injections of the extract exert no influence upon blood-pressure. In the medical literature, however, some scattered remarks are met that subcutaneous injections do increase the blood-pressure. We are not aware that any definite data on the subject accompanied by tracings or figures have been published anywhere. From our present studies we know that if special care is not taken, the hypodermic needle will sometimes get under the fascia of muscles and the result will be a definite effect upon the blood-pressure, but it is then not from a subcutaneous, but from an intramuscular injection of the extract. In the light of our present experience we have reason to distrust therefore not only the statements of others, but also our own previous observations when made while we had no idea of the necessity of sharply distinguishing between subcutaneous and intramuscular injections. However, as will presently be shown,

there is something characteristic about the blood-pressure curve obtained from a subcutaneous injection which assists in identifying it.

From our experiments we may state in a general way that subcutaneous injections of suprarenal extract in rabbits will undoubtedly influence the blood-pressure, but the degree of the effect is in no way comparable to that obtained by intravenous injections. Furthermore, the effect is very variable; while sometimes even a comparatively small dose will bring out a relatively powerful effect, a large dose cannot always be relied upon to cause a noteworthy rise of pressure. As a rule, a dose of 1.5 cc. of commercial adrenalin (1 :1000) will cause the characteristic prostration of the animal and the ears will show an absolute blanching, while at the same time the general blood-pressure may show a gradual rise not exceeding perhaps ten millimetres of mercury. On the other hand, doses of 0.4 or 0.5 cc. of adrenalin per kilo animal will, as a rule, exert no influence whatsoever upon the blood-pressure of the rabbit. (See Figs. 4, and 6.) But in some exceptional cases even such a small dose might unexpectedly produce a comparatively powerful influence. Figure 1, presents such a powerful effect of a first subcutaneous injection of 0.8 cc. adrenalin in a rabbit weighing 2200 grams. In a series of experiments on more than thirty rabbits such effects were obtained only twice.

Figure 1 might serve also as prototype for the character of the normal curves, which are obtained after a subcutaneous injection, no matter whether the effect be small or large. While the rise of pressure after intravenous injections is characterized by a very short latent period, steep rise and gradual descent, the entire effect lasting only from four to six minutes, we see in subcutaneous injections the effect only beginning minutes after the injection, the pressure rising slowly, remaining at the maximum for some time, and then gradually descending to the original level, the entire course frequently extending over a period of twenty to thirty minutes.

The original height of the blood-pressure seems to be an influential factor upon the effect of a subcutaneous injection. When

the blood-pressure is low we may reasonably expect a noteworthy rise after such an injection. However, a rise of more than 25 to 30 millimetres of mercury is under all conditions rather an exception.

We have already stated above that, as a rule, only the first injection is distinctly effective; the effect of a second injection, if there is any, is already perceptibly reduced, and there is rarely any effect after a third injection. However, after an interval of a few hours an injection might again become effective.

A struggle of the animal seems to have a tendency to bring out the effect of a subcutaneous injection. In normal conditions, struggle, as a rule, causes a fall of short duration, and if there is sometimes a moderate rise of pressure, it returns after a few seconds to the previous level. After a subcutaneous injection of an ineffectual dose of adrenalin we noticed, however, in a few instances that a struggle was followed by a sudden moderate but long-lasting rise of pressure (see Fig. 10.) Possibly struggle is instrumental in causing rapid absorption of some of the injected adrenalin.

INTRAPERITONEAL INJECTIONS.

Our experience with the effects of intraperitoneal injections of suprarenal extract were a surprise and a puzzle to us. In the majority of the experiments we have seen either no effect or a rise of only 10 or 20 millimetres. (See Figs. 13 and 14.) We met only with two exceptions; but in these two instances the rise which followed immediately after the injections was so powerful and so very like the effect of an intravenous injection, as to raise the doubt whether the injections were not indeed made intravenously. At first we made the injections by means of a hypodermic syringe through the intact abdominal wall. We soon discarded this method and carried on the injections either through a small nick in the abdominal wall or through wide incisions, trying at the same time to carry the adrenalin to different parts of the peritoneum, with the above stated results. Of the two exceptions mentioned, one was obtained by plunging a hypodermic syringe through the intact wall,

the other by pushing a hard catheter through a small abdominal incision, between liver and diaphragm. In the first instance the needle might have entered a blood-vessel, and in the second the catheter might have injured the surface of the liver, thus facilitating the entrance of the extract directly into the circulation.

How are these results to be explained? Can it indeed be a fact that suprarenal extract enters but little into the circulation when applied directly to the peritoneum, possibly on account of its intense local action on the blood-vessels of the peritoneum, thus preventing its absorption into the blood? We intend to take up this question again in an investigation specially devoted to it, and shall therefore refrain from discussing it here any further.

INTRAMUSCULAR INJECTIONS.

Our experience with intramuscular injections of suprarenal extract has been more extensive and more varied than with the other methods. The results, however, were so precise and uniform that they can be stated briefly. The effect of an intramuscular injection of adrenalin upon the blood-pressure approaches in every respect that caused by an intravenous injection. The rise sets in a few seconds after the injection and reaches within a fraction of a minute its maximum, which can be considerable. A dose of 0.3 or 0.4 cc. of adrenalin may produce a rise of 40 to 50 millimetres of mercury. Figures 5, 9, 15, will illustrate these effects better than they can be described by words. These curves were obtained from intramuscular injections of such small doses of adrenalin that if applied subcutaneously they exerted an insignificant influence or none at all upon the blood-pressure. The effect of an intramuscular injection differed from that of an intravenous only in degree; the rise of pressure was not as large and not entirely as sudden as after intravenous injections. Furthermore, an intravenous injection still responded with a fairly good rise when, after repeated intramuscular injections, no reaction could any longer be obtained. We have, however, to state that in intramuscular injections the response was not exhausted until three or more consecutive

injections had been made, although each consecutive reaction became distinctly smaller.

A feature of our intramuscular curves is the frequent appearance of so-called "vagus-pulse," i. e., the heart-beats become larger and often less frequent, as was ascribed by Biedl and Reiner [4] (in tracings from intravenous injections) to a stimulation of the vagus centre in the medulla. From a comparison of the blood-pressure tracings in the experiments of many writers on intravenous injections with the tracings obtained by us after intramuscular injections, it would appear to us that the vagus-pulse is a much more frequent phenomenon after an intramuscular administration of suprarenal extract than after an intravenous one. We record here our observations without further comment as to the possible nature of this difference. Sometimes the vagus-pulse sets in before the pressure has reached its maximum; then the pressure will rise still higher after the cessation of the vagus-pulse (see Figs. 5 and 14); or the large pulsation sets in after the rise has attained its maximum, and it will then be accompanied by a slight fall of pressure (see Fig. 15), or there will be large vagus-pulses throughout the entire effect following the injection, the rise of pressure in this case not being very high (see Fig. 7).

In some instances it seemed that also after an intramuscular injection a struggle would increase the rise of blood-pressure, or cause a second rise after there was already a tendency to drop.

As to the duration of the rise we cannot, for reasons mentioned, make any positive statements. We may, however, remark that the general impression received from a survey of our tracings is that the effect upon the blood-pressure lasts somewhat longer after intramuscular injections than after intravenous ones.

In the majority of the experiments the injections were made into the muscles of the back, in the lumbar region, and we had not a single failure. We have, however, established that the effect is the same if the injections are made in any other muscle.[5]

4 *Pflüger's Archiv*, 1898, lxxviii., 385.

5 Among the tracings in our possession from previous studies on the effects

In injecting into other muscles of the rabbit's body 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 groups of muscles, in which case the effect will be the same as from the subcutaneous tissue.

EXPERIMENTS WITH THE PARADOXICAL PUPIL REACTION.

As was already stated above, S. J. Meltzer and Clara Meltzer Auer [6] have found that some time after removal of the superior cervical ganglion (twenty-four hours in rabbits and forty-eight hours in cats) a subcutaneous injection of adrenalin caused a dilatation of the pupil on the side without the ganglion, which would last for hours. The doses of adrenalin employed were about 1.2 to 1.5 cc. for a "large rabbit," and the reaction appeared "a few minutes" after the injection. In some instances even such a small dose as 0.6 cc. caused some dilatation. The authors had at that time, of course, no reason for distinguishing between subcutaneous and intramuscular injections.

We now resected the superior cervical ganglion in a number of animals and studied the effect of the extract according to the tissue injected, with the following results:

When a dose of adrenalin of 0.4 cc. per kilogram of animal was injected intramuscularly, the pupil on the operated side began to dilate within a fraction of a minute and reached the maximum within two minutes. Such a small dose has nearly no effect upon the pupil in subcutaneous application. When a large dose was injected subcutaneously, the pupil on the operated side dilated ten to fifteen minutes after the injection. When the pupil once became dilated *ad maximum*, the dilatation lasted apparently just as long after intramuscular injection as after an effective subcutaneous one. Doses smaller than 0.4 cc. per kilo

of subcutaneous injections of suprarenal extract there was one from a "subcutaneous" injection of a small dose of adrenalin made into the pectoral muscle (Fig. 2). It looked exactly like the following tracing (Fig. 3), which was obtained with a still smaller dose from an intravenous injection. We know now that it was not due to a subcutaneous but to an intramuscular injection.

[6] S. J. Meltzer and Clara Meltzer Auer, *Amer. Journ. of Phys.*, 1904, xi, 28.

given intramuscularly would often cause only a moderate dilatation of the pupil, which would set in later and disappear sooner. In no case have we observed that an effective intramuscular injection has ever caused any dilatation of the pupil on the normal side. This fact distinguishes the intramuscular application from the intravenous, after which even the pupil on the normal side becomes dilated for a fraction of a minute.

THE EFFECT OF THE SUPRARENAL EXTRACT UPON THE SKELETAL MUSCLES.

The early writers on the influence of suprarenal extract have noticed its general prostrating effect upon the animal. Oliver and Schaefer [7] have observed that ten minutes after a subcutaneous injection of the extract into a frog "its movements have usually become languid," and after another 5 minutes" its voluntary power over the muscle is greatly diminished." In the rabbit, "half-an-hour after a large subcutaneous dose, the animal may become listless, and may, when interfered with, move languidly." In our experience a dose of about 2 cc. of adrenalin, when given to a medium-sized rabbit subcutaneously, would produce a distinctly prostrating effect. The animal would lie on its belly, all four extremities stretched out, the chin resting on the table and the head turned sideways by its own weight, and would move only with great effort. This effect appeared fifteen to twenty minutes after the injection. After intramuscular administration, however, the prostrating effect already appeared a minute or two after the injection of o.6 or o.8 cc. per kilo, a dose which exerts hardly any effect in subcutaneous injections. We have to add that doses larger than o.8 cc. can be fatal to the rabbit when given intramuscularly; the animal may die even within a few minutes after the injection, while we have never met with such accidents in the practice of subcutaneous injections even after larger doses.

EXPERIMENTS WITH CURARE.

The experiments with curare were very instructive. They brought out the difference between subcutaneous and intramus-

7 Oliver and Schaefer, *Journal of Physiology*, 1895, xviii, 227.

cular injections in a striking manner. We succeeded in finding the doses which in subcutaneous injections brought out no perceptible effect, while after intramuscular injection all the voluntary muscles were paralyzed, at least all except the respiratory muscles. We shall illustrate with a few protocols.

Experiment I. Nov. 15. 1904.—1. Gray male rabbit, 1300 grams injected subcutaneously with 0.25 cc. of a 1 % solution of curare (0.2 cc. per kilo). Rabbit quiet at first. Practically no effect.

2. White and gray male rabbit, 1560, injected intramuscularly, (right thigh) 0.3 cc. of above solution of curare (0.2 cc. per kilo). (The same solution was used in all experiments.) After seven minutes the paralysis developed to such degree that artificial respiration was necessary. Animal used for a blood-pressure experiment.

Experiment II. Nov. 16.—1. Rabbit number 1 of Experiment I was again given subcutaneously 0.25 cc. of curare (0.2 cc. per kilo). Practically no effect.

2. Black and white male rabbit, 1320, received intramuscularly in right thigh, 0.25 cc. curare (0.2 cc. per kilo); paralyzed; artificial respiration necessary. Used for a blood-pressure experiment.

Experiment III. Nov. 17.—Rabbit number 1 of the two previous experiments, during which it had twice received subcutaneously 0.2 cc. curare per kilo with no effect, was now given intramuscularly (thigh) 0.25 cc. of curare (0.2 cc. per kilo). After six minutes practically paralyzed.

Experiment IV. Nov. 30.—1. Brown female rabbit, 1540, injected intramuscularly (back) with 0.29 cc. of the 1 % solution of curare (0.19 cc. per kilo). After five minutes animal unable to move, all voluntary muscles profoundly affected except the muscles of the respiratory mechanism. Two hours later still paretic, but able to move again.

2. Brown female rabbit, 1435, received subcutaneously (back) 0.27 cc. of the solution of curare (0.19 cc. per kilo). Watched for two hours; no effect whatsoever.

The effect of an intramuscular injection of curare resembles

greatly that of an intravenous one. The effect sets in quite rapidly and lasts for some time, perhaps even longer than after an intravenous injection. We have employed doses so small as would hardly be sufficient to ensure absolute rest even in intravenous injections. When at the end of a blood-pressure experiment, for which some of the rabbits with intramuscular injections of curare were utilized, the animal was permitted to die, the asphyxia would bring out perfunctory convulsions. Even during the experiment one or the other animal would show once in a while a faint struggle, especially when the dose was only 0.18 cc. per kilo; and we have never added any more curare during the experiment to ensure absolute rest, as is frequently done in intravenous injections. We believe that the intramuscular injections of curare will prove to be a practical method in experimentation on animals, as it is much more convenient and less dangerous than intravenous injection.

EXPERIMENTS WITH FLUORESCEIN.

The effects of the subcutaneous injection of fluorescein we have extensively described in our experiments upon the influence of suprarenal extract upon absorption and transudation. The skin and mucous membranes become gradually more or less distinctly yellow. Following larger doses, Ehrlich's line in the pupil appears after some time. By intravenous injection the animal is stained intensely yellow, almost in an instant. We have now tried an intramuscular injection of fluorescein, comparing it with the effect of a subcutaneous administration of a similar dose. We shall quote a protocol of such an experiment.

Nov. 16.—White and gray rabbit, 1050 grams received subcutaneously (back) at 4.05 P.M., 2 cc. of a 5 % solution of fluorescein. At 4.09 2.5 cc. of the same solution of fluorescein was injected intramuscularly (back) into a gray rabbit, 1300 grams (both animals received 1.5 cc. per kilo). At 4.12 conjunctivæ of both animals show yellow tint, but much more intense in the "intramuscular." 4.13, "intramuscular" shows yellow nose, "subcutaneous" still pink. 4.20, "intramuscular" much more

yellow in all parts than "subcutaneous." Ehrlich's line appears at 4.20 in the left, and at 4.25 in the right eye of the "intramuscular"; no Ehrlich line in either eye of the "subcutaneous." 4.29, both pupils of "intramuscular" perfectly green; the pupils of "subcutaneous" black, no tint of green.

Fluorescein is absorbed incomparably more rapidly and in larger doses from the intramuscular than from the subcutaneous tissue. However, it should also be noted that the effect of an intramuscular injection of fluorescein cannot be compared in rapidity with that of an intravenous injection of the same dose and strength.

EXPERIMENTS WITH MORPHINE.

We have finally to record the results of our experiments made with morphine. They are fully in accord with the results obtained with the injection of the other substances recounted in the preceding pages. The symptoms brought on by morphine are inappropriate to show the differences in such a characteristic manner as was observed in the experiments with the other substances, especially the onset and the development of the effects are too slow to permit sharp comparisons. However, when the experiments are made simultaneously on a series of animals, the differences of the two groups are unmistakable and are perceived at a glance. The differences between the effects of intramuscular and subcutaneous injections of morphine presented themselves pronouncedly when both kinds of injections were practised on the same animals, of course after proper intervals. The following protocol will illustrate our statement:

Nov. 11.—Four rabbits received at about the same time 8 milligrams of morphine sulphate per kilo of animal. A and B received it intramuscularly; C and D subcutaneously. Within a few minutes after injection, the difference between the two groups was marked: A and B lying on their bellies, legs stretched out, heads resting on the table, and ears flat on back. C and D quiet, but head and ears erect and body not stretched out. Thirty or forty minutes later the difference in the behavior of the two groups still marked; the respirations, too, are much

slower in the "intramuscular" group. An hour after the injections the difference between the two groups now less marked. Next day animals normal.

Nov. 15.—The same four animals again received 8 milligrams of morphine sulphate per kilo. But now the order was reversed: A and B were injected subcutaneously, C and D intramuscularly. Now C and D after eight minutes became droopy, lying on belly, etc., while A and B (now subcutaneous) show little or no effect. After twenty-four minutes all four animals were put on the floor: A and B hopped off to a corner, C and D remained on the spot where they had been put, in a droopy, somnolent condition. The difference in the behavior of the two groups was well marked, and the contrast in the behavior of each group in both experiments was indeed striking.

By the foregoing experiments we believe to have firmly established, at least for the substances we have experimented with, that absorption from intramuscular tissue is incomparably faster than from subcutaneous tissue. The effect of an intramuscular injection stands in value very near that of a direct injection into the circulation. That these injections into the muscles were not indeed intravenous injections, i. e., that, accidentally, each time the injection was made into a blood-vessel, needs hardly a refutation; the constancy of the results speaks sufficiently against their accidental nature. It could, however, be assumed that, the muscles being provided with many blood-vessels, an intramuscular injection is unavoidably an injection into the blood-vessels. Hence the rapid effect of an injection into the muscles was actually only the effect of an intravenous injection, and does not signify that a rapid absorption from the muscles into the blood-vessels takes place normally; in other words, our experiments do not prove that in the normal metabolic processes within the muscles the rate of absorption is different from that of the subcutaneous tissue. But the following facts speak against such an assumption. The rise of blood-pressure which was caused by an intramuscular injection of suprarenal extract was rarely as great as that which is caused

by an intravenous injection of a similar dose. Furthermore, after repeated intramuscular injections a further injection by the same method would have no effect, while subsequent intravenous injections would still continue to cause a considerable rise of pressure. In the effect upon the pupil there is a distinct difference between the effects of intravenous and intramuscular injections. An intravenous injection of suprarenal extract would always cause a dilatation of the pupil, although of short duration, even when the superior cervical ganglion was intact, while we have not observed that an intramuscular injection ever caused any dilatation of the pupil on the unoperated side of the animal. Finally, the most striking differences between intramuscular and intravenous injections have been observed in our experiments with fluorescein. After intravenous injections, even with much smaller doses than those which we have employed in the present experiments, the effect is instantaneous: the conjunctivæ become orange-yellow, the pupils deep green, etc. within a few seconds after the injection. While with intramuscular injections the pupils did not become green until nearly half an hour after the injection, and the entire animal was by far not so deeply colored as after an intravenous injection.[8]

We therefore entertain the view that in intramuscular injections the fluid does not enter directly into the blood, but is at first deposited between the muscle fibres and is carried thence into the blood by some process of rapid absorption.

We have to add that, in our opinion, the difference between the absorption from intramuscular and subcutaneous tissues is only a matter of degree. We have seen in our previous experiments with fluorescein that one minute after a subcutaneous injection there was already fluorescein present in the serum of the blood. The difference consists only in the quantity which becomes absorbed in a unit of time, and the quantity absorbed is apparently so much larger from the intramuscular tissue than from the subcutis that it produces strikingly different results. Whether some substances are absorbed better from the intramuscular tissue than others, we cannot state for the present.

8 S. J. Meltzer and John Auer, l. c.

The fact that the difference between the effects of intramuscular and intravenous injection is much greater with fluorescein than with, for instance, curare, would speak for such a possibility. Future researches in this direction will throw light on this problem, as well as on many others which are bound to present themselves on the basis of our present investigation.

Why is the absorption from the muscles so much more favorable than from the subcutaneous tissue? Possibly because the unit of space in the muscles contains more blood and more blood-vessels, and is therefore capable of taking up more liquid injected into it in the same unit of time. Possibly the readiness of the blood-vessels of the muscles to respond with vaso-dilatation to local and reflex stimulation is also a factor in this process. It is possible also that the capillary walls of the muscular tissue are much more permeable than the capillary walls of the subcutaneous tissue. We shall, however, for the present not commit ourselves to any theory or enter even into a discussion of the merits of the factors concerned, as this would be premature. Not only has a new fact been observed, but a new field has been opened, which is bound to yield many more new facts capable of throwing more and better light upon the underlying causes. The application of the new point of view may be manifold. In physiology, for instance, we ought to learn in general, from the observations communicated in the preceding pages, that absorption from the tissues of the body is not a single, uniform process, but that the rate and the mode of absorption may vary with each tissue and organ. In particular we might study and come to understand the rapid interchange between the metabolic products of the muscles and the general circulation, the rapid effect which the catabolic products of the active muscles exert upon the mechanisms of circulation and respiration, and many other problems. In pathology we might study and come to understand whether and why infections and intoxications from the muscles occur less readily than from subcutaneous tissue, and why œdema of the muscles is a much less frequent phenomenon than œdema of the subcutaneous tissues. In the experimental studies of infection and immunity, the intramuscular incorporation of virus, toxin,

and antitoxin should present a distinct method of study, and the results should be compared with those of other methods in vogue. In pharmacology the method of intramuscular injection should receive special attention. The action of pharmacological products which are effective in small doses should be tested by intramuscular injection with regard to the rapidity of action as well as the duration of the effect. The permissible dosage should be established. We have seen above that a dose of curare, for instance, which was absolutely harmless in subcutaneous application, was nearly fatal when given intramuscularly. In therapeutics, intramuscular injection might offer the advantages of an intravenous administration without its dangers. On the other hand, a combination of intramuscular and subcutaneous injections might ensure rapidity and intensity together with long duration of action.

EXPLANATION OF FIGURES.

The line on each figure represents variations in blood-pressure written by the mercury manometer. Base lines and time markings were omitted in printing the curves. The tracings were obtained from the carotid artery of rabbits after subcutaneous, intraperitoneal, and intramuscular injections of commercial adrenalin chloride (1:1000).

The first three figures were obtained in previous studies on the influence of adrenalin on the blood-pressure, administered by subcutaneous injection. (The time was marked in five seconds.)

PLATE I.

Fig. 1 represents a part of such a tracing; twenty-eight minutes passed before the elevation reached the original level. Only two curves with such a rise were obtained in an extended series of experiments.

Figs. 2 and 3 were obtained consecutively on the same animal. Fig. 3 was obtained by intravenous injection of 0.3 cc. Fig. 2 was obtained by an injection of 0.4 cc. in the region of the left pectoral muscle. As the autopsy revealed no injury to a blood-vessel, it was then taken for an exceptional effect of a "subcutaneous" injection. It was, however, apparently the effect of an intramuscular injection.

A cross on the curves marks the end of an injection.

Fig. 4.—1375 grams. 1 cc. subcutaneously, upper abdomen. *First* injection.

Fig. 5.—Same animal. *Second* injection; 0.8 cc. intramuscularly, left back, lumbar region.

PLATE II.

Fig. 6.—2500 grams. *First* injection; 1 cc. subcutaneously, left upper abdomen.

Fig. 7.—Same animal. *Second* injection; 0.8 cc. intramuscularly, left back, lumbar region.

Fig. 8.—1500 grams. *First* injection; 0.6 cc. subcutaneously, abdomen.

Fig. 9.—Same animal. *Second* injection; 0.6 cc. intramuscularly, left back, lumbar muscles.

Fig. 10.—Same animal. *Third* injection; 0.6 cc. subcutaneously, right upper abdomen.

(Note that Figs. 8, 9, and 10 are consecutive.)

PLATE III.

Fig. 11.—1320 grams. Curare; artificial respiration; 0.8 cc. intraperitoneally through catheter in abdominal wall. *First* injection.

Fig. 12.—Same animal. *Second* injection; 0.8 cc. intramuscularly, left back, lumbar region.

Fig. 13.—2045 grams. *First* injection; 0.8 cc. intraperitoneally through cut in abdominal wall.

Fig. 14.—Same animal. *Second* injection; 0.8 cc. intramuscularly, left back, lumbar region.

Fig. 15.—1540 grams. Curare; artificial respiration; 1 cc. intramuscularly, left back, lumbar region. *First* injection.

Fig. 16.—Same animal. *Second* injection; 1 cc. intraperitoneally, through catheter.
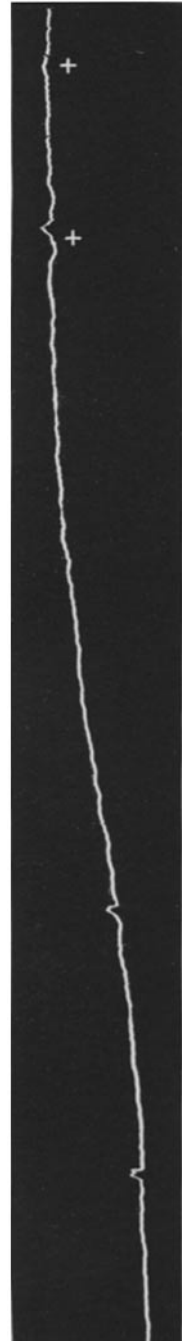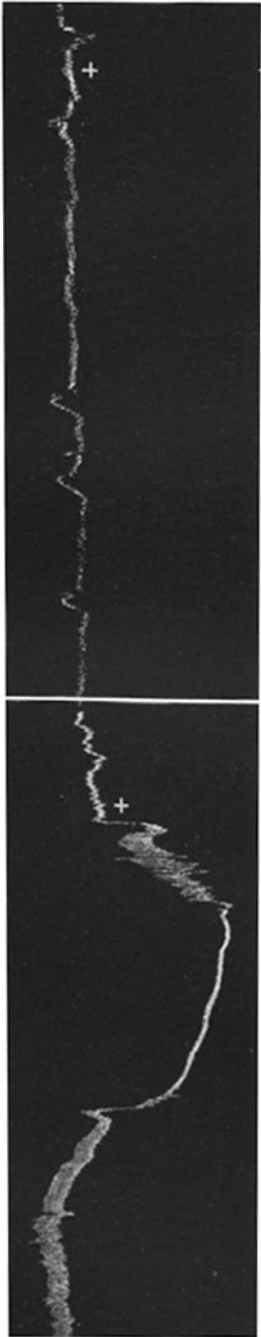
Subcutan., 0.8 cc.   Massage.

FIG. 1 × ⅓.
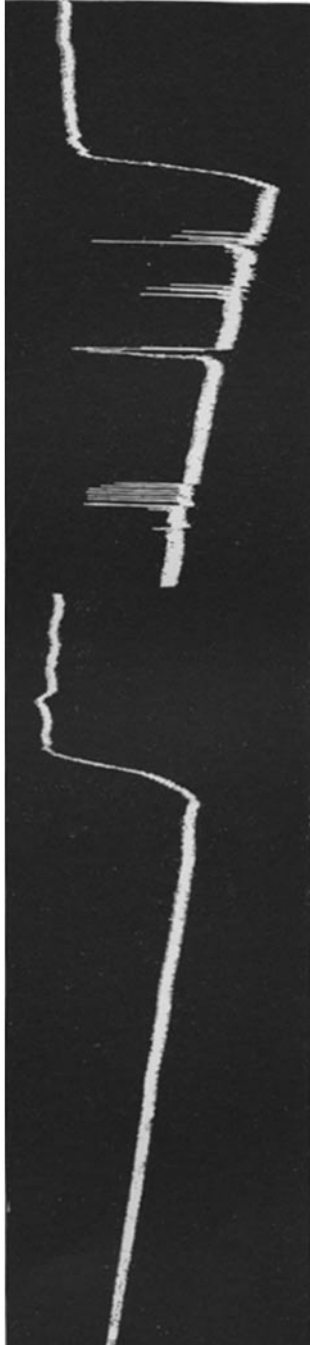
Subpectoral.
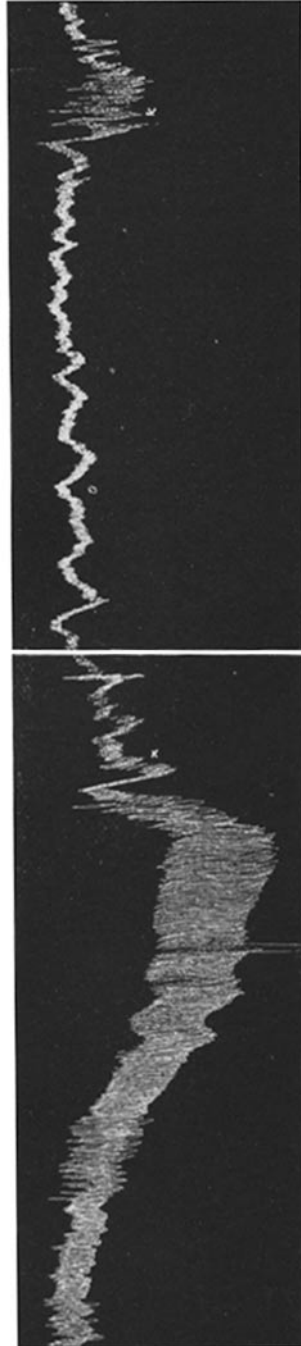0.4 cc.   FIG. 2.

Intravenous.
0.3 cc.   FIG. 3.

Subcutan., 1 cc.
4.17.

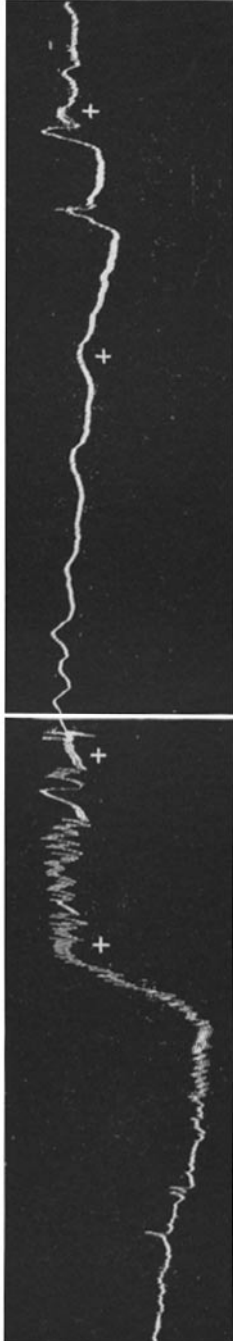FIG. 4 × ⅛.

Intramuscular, 0.8 cc.
4.26½.

FIG. 5 × ⅛.

Subcutan., 1 CC.
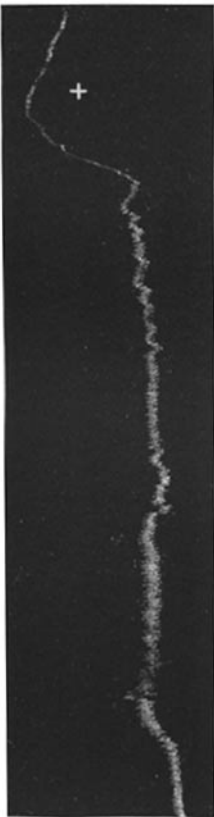3.43.

FIG. 6.

Intramuscular, 0.8 CC.
3.49.

FIG. 7.

Needle inserted.

Subcutan., 0.6 CC.
10.43.
FIG. 8 × ⅙

Needle inserted.
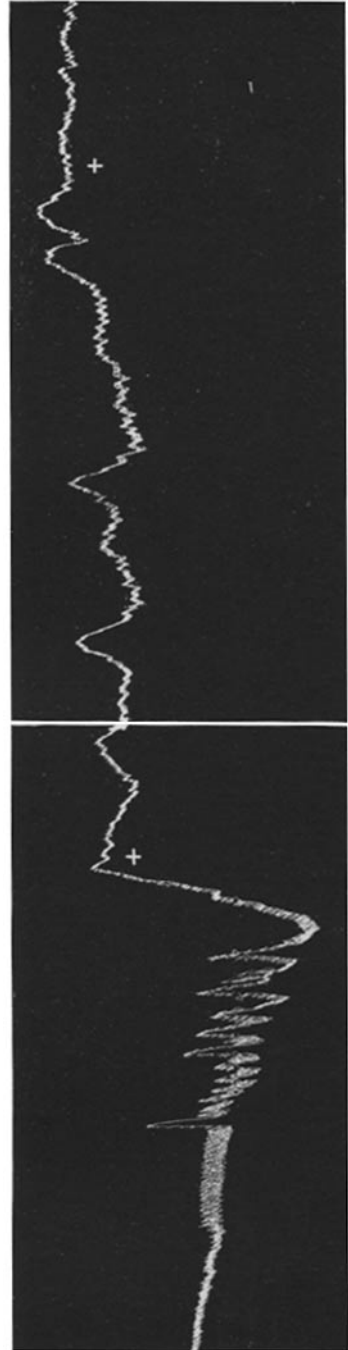
Intramuscular, 0.6 CC.
11.02.
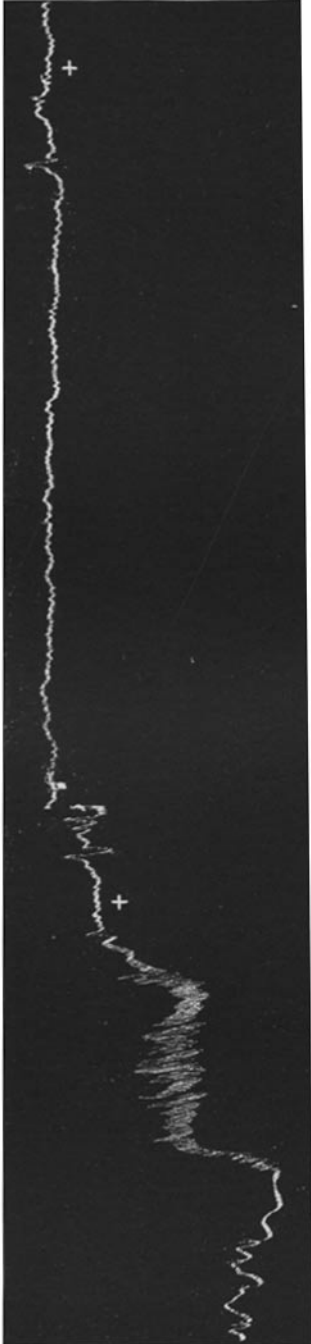
FIG. 9 × ⅙

Subcutan., 0.6 CC.   Struggle.
11.21.

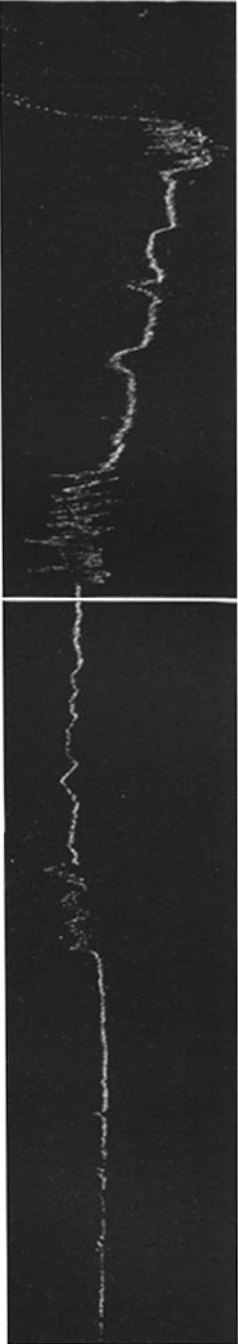FIG. 10.

Intraperitoneal, 0.8 cc.
5.20.   FIG. 11.

Intramuscular, 0.8 cc.
5.35.   FIG. 12.

Intraperitoneal, 0.8 cc.
3.55.   FIG. 13.

Intramuscular, 0.8 cc.
4.16.   FIG. 14.

Intramuscular, 1 cc.
5.10.   FIG. 15 × ⅙.

Intraperitoneal, 1 cc.
5.27.   FIG. 16 × ⅙.