# THE RELATION OF THE RATE OF ABSORPTION OF ADRENALIN TO ITS GLYCOSURIC AND DIURETIC EFFECTS.*

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## INTRODUCTION.

Deep or intramuscular injections have been practised by physicians for many years. This was not done, however, with the expectation that it would favor absorption; on the contrary, some writers (1) state especially, "that the absorption from the intramuscular tissue with its fewer lymphatics is much slower than from the subcutaneous tissues where the lymphatics are abundant." The intramuscular injection was recommended because of the assumption that "deep injections give rise less often to the formation of abscesses." About nine years ago Meltzer and Auer (2) showed experimentally for the first time that the effects of active drugs appear after intramuscular injections earlier and with greater intensity than after subcutaneous injections. The experiments were made with adrenalin, curare, fluorescëin, and morphin. Doses of curare, for instance, which practically had no effect in subcutaneous injections, brought on paralysis and death when injected intramuscularly. In recent experiments by the same authors (3) in which the previous results regarding the blood pressure action of adrenalin were especially studied and confirmed, potassium cyanide was added to the list of substances which act more profoundly by intramuscular injection. They also found that acute anaphylactic shock can be brought on in highly sensitized guinea pigs by injecting one cubic centimeter of horse serum into the lumbar muscles; whereas such a prompt result is never obtained by a subcutaneous

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injection. Eggleston and Hatcher (4) studied recently the seat of the emetic action of apomorphin, and found that for intramuscular injections the minimum dose of this drug is half that which produces a similar effect upon subcutaneous injection. Of practical importance are the experiments of Morgenroth and Levy (5) on the absorption of diphtheria antitoxin. They found that the intramuscular injection of a small dose of antitoxin, together with a fatal dose of toxin, prevented even induration at the seat of injection, while a much larger dose of the antitoxin administered subcutaneously (again together with a fatal dose of toxin) was incapable of preventing the early death of the animals. It seems therefore to be now a well established fact that substances, whether crystalloidal or colloidal, producing definite effects upon the animal body, manifest these effects earlier and with greater intensity when administered by intramuscular than by subcutaneous injection.

The earlier experiments of Meltzer and Auer with adrenalin dealt with three of its known effects: (*a*) rise of blood pressure; (*b*) dilatation of the pupil on the side in which the superior cervical ganglion has been removed; and (*c*) manifest muscular weakness which follows the injection of larger doses of the drug. These three different manifestations appeared in an unmistakable manner quite rapidly after an intramuscular injection of adrenalin, while after subcutaneous injection of a similar dose of that drug, either no effect at all followed, or the effect was comparatively insignificant and appeared late. Adrenalin, however, is capable of producing another quite important effect upon the animal body, namely, the production of glycosuria. Since the discovery of adrenalin glycosuria by Blum (6), the subject has been studied by many investigators. The influence of the place of injection upon the intensity of the glycosuria has also been variously investigated. For dogs it was stated by Herter and Wakeman (7) that intravenous injections give better effects than subcutaneous, and that intraperitoneal injections give the best effects. For the rabbit the glycosuric effects of subcutaneous injections were compared with those of intravenous injections by Ritzmann (8). According to him the glycosuric effect of adrenalin is similar to that of the same drug upon blood pressure; in both cases intravenous injection of the

drug is more effective than subcutaneous. However, among the numerous recent communications on adrenalin glycosuria no mention is made of the glycosuria after intramuscular injection of an adrenal preparation.

The foregoing brief review brings out the following points. It is now quite safely established that active crystalloidal and colloidal substances are pharmacologically more effective when administered by intramuscular than by subcutaneous injections. This fact has been established especially for the several effects produced by adrenalin when injected into the animal body. The glycosuric action of drugs, however, has not been studied as yet by the method of intramuscular injection. This gap we have tried to fill in the present investigation. We have studied the effect of intramuscular as compared with the subcutaneous injection of adrenalin upon the production of glycosuria.

## EXPERIMENTAL DATA.

*Method.*—The experiments were performed on rabbits. There were forty-nine experiments with two rabbits for each, one of which received the adrenalin intramuscularly and the other subcutaneously. The intramuscular injections were given in the lumbar muscles since, as Auer and Meltzer (9) have shown for rabbits, the absorption is better from these muscles than from any other mass of muscular tissue; the subcutaneous injections were made in one of the lower quadrants of the abdomen. The adrenalin[1] was employed in the usual solution of 1:1,000. Many of the rabbits were not fed for twenty-four hours previous to the experiment. Most of the animals received, immediately before the injection of adrenalin, 100 or 150 cubic centimeters of water through a stomach tube. None of the rabbits were fed during the time of observation after the administration of adrenalin, which usually was twenty-four hours. During the observation the animals were kept in metabolism cages, the bladder being emptied at the beginning and at the end of the period of observation. No experiment was considered as finished until the urine was sugar-free. The urines were always preserved with toluene. The analysis for sugar was made by the Pavy-

[1] The adrenalin employed was prepared by Parke, Davis and Company.

Ramsden method,[2] the reduction being calculated as dextrose. Although rabbit urine always contains some substance which slightly reduces the ammoniacal copper solution, the inaccuracy resulting from it is too insignificant to impair the results in any degree, since our object was not to ascertain the absolute amount of reducing substances present in the urine, but merely a comparison of the amounts of these substances brought about by two different methods of administration of adrenalin.

*Results.*—As mentioned before, ninety-eight rabbits were injected with adrenalin, one half intramuscularly and the other half subcutaneously. The injections were made in pairs; that is, in each experiment two rabbits were employed at the same time and under

TABLE I.

*Adrenalin, 1.0 Cubic Centimeter; Water per Os, 100 Cubic Centimeters. All Animals Fasted Twenty-Four Hours Previous to Injection.*

| Intramuscular injection. | | | | | Subcutaneous injection. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. | No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. |
| A 109 | 1,430 | 68 | 1.48 | 24 | A 110 | 1,440 | 160 | 1.43 | 24 |
| A 111 | 1,480 | 174 | 1.10 | 24 | A 112 | 1,555 | 160 | 0.34 | 24 |
| A 113 | 2,085 | 143 | 0.35 | 24 | A 114 | 2,110 | 131 | 1.38 | 24 |
| A 115 | 2,310 | 104 | 0.13 | 24 | A 116 | 2,325 | >167 | 1.18 | 24 |
| A 117 | —— | —— | —— | Died | A 118 | 1,435 | 109 | 2.02 | 24 |
| A 119 | 1,840 | 101 | 2.85 | 24 | A 120 | 1,520 | 88 | 1.77 | 24 |
| A 121 | 1,425 | 53 | 0.00 | 24 | | | | | |
| A 123 | 1,085 | 58 | 0.00 | 24 | A 124 | 1,020 | 129 | 0.64 | 24 |
| A 125 | 1,390 | 98 | 0.83 | 24 | A 126 | 1,340 | 147 | 0.65 | 24 |
| A 127 | 1,290 | 137 | 1.09 | 24 | A 128 | 1,225 | >179 | >3.07 | 24 |
| A 129 | 1,430 | 120 | 0.76 | 24 | A 130 | 1,350 | 139 | 1.98 | 24 |
| Average | | 106 | 0.86 | | Average | | 141 | 1.45 | |

the same conditions, each being injected with a like quantity of adrenalin, the one receiving it intramuscularly and the other subcutaneously. The two sets of results are therefore comparable. Different doses of adrenalin were tested, one cubic centimeter of a 1 : 1,000 solution being the highest and 0.3 about the lowest dose which was systematically tested. The forty-nine experiments consist therefore actually of several series of experiments, which run as fol-

[2] Vernon, H. M., *Jour. Physiol.*, 1902, xxviii, 164.

lows. Ten pairs of rabbits received 1 cubic centimeter per animal, seven pairs received 0.7 of a cubic centimeter, ten pairs received 0.5, eight pairs received about 0.4, and eight pairs received 0.3 of a cubic

TABLE II.

*Adrenalin, 0.7 to 0.8 of a Cubic Centimeter; Water per Os, 100 Cubic Centimeters. All Animals Fasted Twenty-Four Hours Previous to Injection.*

| Intramuscular injection. | | | | | Subcutaneous injection. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. | No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. |
| A 73 | 1,820 | 100 | 1.15 | 24 | A 74 | 2,060 | 132 | 0.99 | 24 |
| A 75 | 2,220 | 149 | 1.53 | 24 | A 76 | 2,410 | 102 | 1.13 | 30 |
| A 77 | 1,070 | 103 | 1.00 | 48 | A 78 | 1,160 | 96 | 0.75 | 48 |
| A 79 | 1,530 | 90 | 0.77 | 24 | A 80 | 1,550 | 121 | 1.76 | 24 |
| A 85 | 1,920 | 111 | 0.00 | 24 | A 82 | 1,360 | 124 | 1.02 | 24 |
| A 89 | 1,160 | 48 | 0.00 | 24 | A 84 | 1,580 | 175 | 1.10 | 24 |
| Average | | 100 | 0.74 | | Average | | 125 | 1.13 | |

centimeter. In addition there were six pairs in which the injected dose varied from 0.7 to 0.8 of a cubic centimeter per animal. The results are given in detail in tables I to VI, each table containing

TABLE III.

*Adrenalin, 0.7 of a Cubic Centimeter; Water per Os, 150 Cubic Centimeters. Animals Not Previously Fasted.*

| Intramuscular injection. | | | | | Subcutaneous injection. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. | No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. |
| A 29 | 2,170 | 176 | 1.05 | 24 | A 30 | 2,140 | 145 | 1.33 | 24 |
| A 31 | 1,750 | 175 | 0.36 | 49 | A 32 | 2,170 | 179 | 1.74 | 49 |
| A 33 | 1,595 | 171 | 0.83 | 48 | A 34 | 1,860 | 203 | 1.80 | 48 |
| A 35 | 1,550 | 49 | 0.00 (Trace?) | 24 | A 36 | 1,500 | 206 | 3.08 | 24 |
| A 37 | 2,170 | 222 | 2.69 | 48 | A 40 | 1,990 | 276 | 1.96 | 48 |
| A 41 | 1,820 | 176 | 0.21 | 48 | A 42 | 1,720 | 228+ | 0.00 (Trace?) | 48 |
| A 43 | 2,920 | 282 | 2.23 | 48 | A 44 | 2,890 | 265 | 3.01 | 48 |
| Average | | 179 | 1.06 | | Average | | 215 | 1.86 | |

the data obtained with a given dose of adrenalin, and all six tables are summarized in table VII. In every case the results of two injec-

tions which are placed opposite one another in the tables were done at the same time.

TABLE IV.

*Adrenalin, 0.5 of a Cubic Centimeter; Water per Os, 100 to 150 Cubic Centimeters.*

| Intramuscular injection. | | | | | Subcutaneous injection. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. | No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. |
| A 45[3] | 1,610 | 196 | 1.44 | 24 | A 46[3] | 1,540 | 198 | 3.62 | 24 |
| A 47[3] | 1,820 | 74 | 0.00 | 24 | A 48[3] | 1,640 | 114 | 0.27 | 24 |
| A 89[4] | 1,300 | 151 | 0.34 | 24 | A 90[4] | 1,310 | 181 | 0.75 | 24 |
| A 91[4] | 1,400 | 154 | 0.38 | 24 | A 92[4] | 1,410 | 160 | 1.01 | 24 |
| A 93[4] | 1,750 | 87 | 1.16 | 24 | A 94[4] | 1,800 | 193 | 0.33 | 24 |
| A 95[4] | 2,185 | 63 | 0.34 | 24 | A 96[4] | 2,290 | 184 | 0.45 | 24 |
| A 105[4] | 1,500 | 157 | 0.26 | 24 | A 106[4] | 1,555 | 165 | 1.09 | 24 |
| A 107[4] | 1,630 | 150 | 0.80 | 24 | A 108[4] | 1,675 | 213 | 2.57 | 24 |
| A 101[4] | 1,175 | 89 | 0.00 | 24 | A 102[4] | 1,300 | 165 | 0.00 | 24 |
| A 103[4] | 1,415 | 103 | 1.44 | 24 | A 104[4] | 1,550 | 124 | 1.02 | 24 |
| Average | | 122 | 0.62 | | Average | | 170 | 1.11 | |

On glancing through the various tables, we are confronted, in the first place, with a discouraging element; the method does not lend itself to the obtaining of uniform quantitative results. Under ap-

TABLE V.

*Adrenalin, 0.4 of a Cubic Centimeter; Water per Os, 100 Cubic Centimeters. Animals Not Previously Fasted.*

| Intramuscular injection. | | | | | Subcutaneous injection. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. | No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. |
| A 49[6] | 2,070 | 89 | 0.00 | 24 | A 50[5] | 1,970 | 136 | 0.88 | 24 |
| A 53 | 1,630 | 148 | 0.87 | 24 | A 54 | 1,395 | 159 | 0.00 | 24 |
| A 55 | 1,750 | 104 | 0.62 | 24 | A 56 | 1,670 | 182 | 0.43 | 24 |
| A 63 | 1,500 | 101 | 0.48 | 24 | A 64 | 1,380 | 141 | 2.30 | 24 |
| A 65 | 1,670 | 103 | 0.00 | 24 | A 66 | 1,510 | 102 | 0.84 | 24 |
| A 67 | 1,820 | 171 | 2.46 | 24 | A 68 | 1,720 | 154 | 1.44 | 24 |
| A 69[6] | 1,530 | 117 | 0.00 | 24 | A 70 | 1,360 | 102 | 1.73 | 24 |
| A 71[7] | 1,250 | 87 | 0.24 | 24 | A 72[8] | 1,220 | 146 | 0.13 | 24 |
| Average | | 115 | 0.58 | | Average | | 140 | 0.97 | |

[3] Not previously fasted. Received 150 c.c. of water *per os.*

[4] Fasted twenty-four hours before experiment. Received 100 c.c. of water *per os.*

[5] Received 150 c.c. of water *per os.*

[6] Adrenalin, 0.45 c.c.

[7] Adrenalin, 0.38 c.c.

[8] Adrenalin, 0.37 c.c.

TABLE VI.

*Adrenalin, 0.3 of a Cubic Centimeter; Water per Os, 100 Cubic Centimeters.*

| Intramuscular injection. | | | | | Subcutaneous injection. | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. | No. of animal. | Weight in gm | Urine in c.c. | Dextrose in urine in gm. | Hours. |
| A 51[9] | 1,270 | 112 | 0.00 | 24 | A 52[9] | 1,080 | 155 | 1.88 | 24 |
| A 57[9] | 1,650 | 87 | 0.43 | 24 | A 58[9] | 1,600 | 99 | 0.79 | 24 |
| A 59[9] | 1,820 | 69 | 0.16 | 24 | A 60[9] | 1,700 | 89 | 0.00 | 24 |
| A 61[9] | 2,270 | 122 | 2.32 | 24 | A 62[9] | 1,940 | 94 | 0.20 | 24 |
| A 97[10] | 1,400 | 72 | 0.00 | 24 | A 98[10] | 1,505 | 149 | 0.54 | 24 |
| A 99[10] | 1,525 | 86 | 0.00 | 24 | A 100[10] | 1,525 | 162 | 0.11 | 24 |
| A 131[10] | 1,490 | 99 | 0.17 | 24 | A 132[10] | 1,480 | 118 | 0.12 | 24 |
| A 133[10] | 2,070 | 161 | 0.29 | 24 | A 134[10] | 2,050 | 106 | 0.27 | 24 |
| Average | | 101 | 0.42 | | Average | | 122 | 0.49 | |

TABLE VII.

*Summary of Tables I to VI.*

| | Manner of injection. | No. in which no glycosuria occurred. | Urine in c.c. | Dextrose in urine in gm. |
|---|---|---|---|---|
| Table I. 1.0 c.c. adrenalin..... | Intramuscular | 2 | 106 | 0.86 |
| Fasted—10 pairs..... | Subcutaneous | 0 | 141 | 1.45 |
| Table II. 0.7–0.8 c.c. adrenalin..... | Intramuscular | 2 | 100 | 0.74 |
| Fasted—6 pairs..... | Subcutaneous | 0 | 125 | 1.13 |
| Table III. 0.7 c.c. adrenalin..... | Intramuscular | 1 | 179 | 1.05 |
| Not fasted—7 pairs..... | Subcutaneous | 1 | 215 | 1.85 |
| Tables II and III. 0.7–0.8 c.c. adrenalin | Intramuscular | 3 | 142 | 0.91 |
| 13 pairs..... | Subcutaneous | 1 | 172 | 1.52 |
| Table IV. 0.5 c.c. adrenalin..... | Intramuscular | 2 | 122 | 0.62 |
| 2 pairs not fasted, 8 pairs fasted —10 pairs..... | Subcutaneous | 1 | 170 | 1.11 |
| Table V. 0.4 c.c. adrenalin..... | Intramuscular | 3 | 115 | 0.58 |
| Not fasted—8 pairs..... | Subcutaneous | 1 | 140 | 0.97 |
| Table VI. 0.3 c.c. adrenalin..... | Intramuscular | 3 | 101 | 0.42 |
| 4 pairs fasted, 4 pairs not fasted —8 pairs..... | Subcutaneous | 1 | 122 | 0.49 |
| Tables I to VI. 0.3–1.0 c.c. adrenalin. | Intramuscular | 13 | 120 | 0.73 |
| All experiments—49 pairs..... | Subcutaneous | 4 | 152 | 1.20 |

[9] Not previously fasted.

[10] Fasted twenty-four hours previous to experiment.

parently similar conditions and by the same mode of administration a given dose of adrenalin gave rise to very variable quantities of dextrose in the urine. This held true for both modes of injection. Under these circumstances we might readily expect that in one experiment it would be an intramuscular injection of adrenalin, which would give rise to a larger quantity of dextrose in the urine, while in another experiment the larger quantity of dextrose would follow a subcutaneous injection. Evidently a small number of experiments would not permit one to draw any definite conclusions. However, the number of experiments is great enough to bring out the differences produced by the two modes of injection even under these discouraging circumstances. Hence an analysis of the various data given in the tables shows unmistakably that subcutaneous injections of adrenalin give rise more often to the appearance of large quantities of dextrose in the urine than do intramuscular injections,—a conclusion quite opposite to that which we had reason to expect. When we take, in the first place, the amount of sugar eliminated by all the forty-nine animals of each set, we find that the average amount for each animal is 1.2 grams for the subcutaneous and 0.73 of a gram for the intramuscular injections. *The glycosuria produced by intramuscular injection is less than two thirds of that produced by the same dose of adrenalin administered subcutaneously.* The difference in favor of the subcutaneous injection remains constant for every dose of adrenalin tested. But with such a small, practically minimum dose, as 0.3 of a cubic centimeter per animal (table VI), the difference in favor of the subcutaneous injection is so small as to be within the limits of experimental error.

The same holds true in general when the dose of adrenalin administered is calculated per kilo of body weight of the animal (table VIII). Here again the average amount of dextrose appearing in the urine after an intramuscular injection of adrenalin is tangibly less than that which follows a subcutaneous injection. The difference in favor of the subcutaneous injection is manifest for every dose of adrenalin used, except for doses below 0.2 of a cubic centimeter per kilo of body weight.

Another instructive fact is the number of failures occurring with both modes of administration. With each mode of administration

there were rabbits which did not react with a glycosuria after an injection of adrenalin; but out of the forty-nine intramuscular injections there were thirteen failures, while of the same number of

TABLE VIII.

*Summary of Results with Dose Calculated to Body Weight.*

| Adrenalin in c.c. per kilo. | No. of experiments performed. | Manner of injection. | Urine in c.c. | Dextrose in urine in gm. |
|---|---|---|---|---|
| 0.70 and over | 6 | Intramuscular | 89 | 0.69 |
| | 5 | Subcutaneous | 141 | 1.67 |
| 0.50–0.69 | 5 | Intramuscular | 103 | 1.23 |
| | 7 | Subcutaneous | 132 | 1.32 |
| 0.40–0.49 | 8 | Intramuscular | 118 | 0.39 |
| | 4 | Subcutaneous | 183 | 1.43 |
| 0.35–0.39 | 5 | Intramuscular | 147 | 0.85 |
| | 6 | Subcutaneous | 186 | 1.13 |
| 0.30–0.34 | 7 | Intramuscular | 158 | 0.93 |
| | 10 | Subcutaneous | 149 | 1.49 |
| 0.25–0.29 | 4 | Intramuscular | 103 | 0.63 |
| | 5 | Subcutaneous | 150 | 1.07 |
| 0.20–0.24 | 9 | Intramuscular | 121 | 0.65 |
| | 8 | Subcutaneous | 169 | 0.87 |
| Below 0.20 | 5 | Intramuscular | 106 | 0.64 |
| | 4 | Subcutaneous | 97 | 0.32 |

subcutaneous injections there were only four failures. Whatever the factor may be which interferes with the production of glycosuria, it is manifest that it operates more frequently when the adrenalin is administered intramuscularly than when it is administered subcutaneously, which is in harmony with the finding that the glycosuria occurring after a subcutaneous injection of adrenalin is generally greater than after an intramuscular one.

It might be supposed that the diminished averages of the urinary sugar output and the larger number of failures after intramuscular injections of adrenalin are not two separate facts, but that the lower averages after intramuscular injections are merely caused by the greater number of failures, and that the actual glycosurias, when they occur, are as severe as those, or perhaps even more severe than

those produced by subcutaneously administered adrenalin. That this is not the case may be seen from table IX, which gives the actual glycosuria for each dose. In making up the averages, the animals which did not react with glycosuria were excluded from

TABLE IX.

*Summary of Actual Glycosurias.*

| | Manner of injection. | No. in which no glycosuria occurred. | Average excluding the cases having no glycosuria. Urine in c.c. | Average excluding the cases having no glycosuria. Dextrose in gm. |
|---|---|---|---|---|
| Table I. 1.0 c.c. adrenalin..... | Intramuscular | 2 | 118 | 1.07 |
| Fasted—10 pairs..... | Subcutaneous | 0 | 141 | 1.45 |
| Table II. 0.7–0.8 c.c. adrenalin..... | Intramuscular | 2 | 111 | 1.11 |
| Fasted—6 pairs..... | Subcutaneous | 0 | 125 | 1.13 |
| Table III. 0.7 c.c. adrenalin..... | Intramuscular | 1 | 200 | 1.23 |
| Not fasted—7 pairs..... | Subcutaneous | 1 | 212 | 2.15 |
| Table II and III. 0.7–0.8 c.c. adrenalin | Intramuscular | 3 | 164 | 1.18 |
| 13 pairs..... | Subcutaneous | 1 | 169 | 1.65 |
| Table IV. 0.5 c.c. adrenalin..... | Intramuscular | 2 | 133 | 0.77 |
| Not fasted—2 pairs, fasted—8 pairs..... | Subcutaneous | 1 | 170 | 1.23 |
| Table V. 0.4 c.c. adrenalin..... | Intramuscular | 3 | 120 | 0.93 |
| Not fasted—8 pairs..... | Subcutaneous | 1 | 138 | 1.11 |
| Table VI. 0.3 c.c. adrenalin..... | Intramuscular | 3 | 108 | 0.67 |
| Fasted—4 pairs, not fasted—4 pairs..... | Subcutaneous | 1 | 126 | 0.56 |

the calculations. The proportion of the average glycosuria for the subcutaneous and intramuscular injections after this exclusion is 7.63 to 5.78 grams or 100:76. A difference in favor of the subcutaneous injection after exclusion of the failures is present also in the averages made up for each dose tested, except for the smallest dose of 0.3 of a cubic centimeter per kilo of body weight.

The experiments clearly indicate that the chances for the production of glycosuria by adrenalin are greater when it is administered subcutaneously than when given intramuscularly, and that, when glycosuria is produced, the amount of dextrose in the urine is likely to be greater after a subcutaneous injection than after an intramuscular one.

*The Volume of Urine after Subcutaneous and Intramuscular Injections of Adrenalin.*—All the forty-nine pairs of rabbits received, as stated above, 100, and, in some experiments, 150 cubic centimeters of water, shortly before the injection of adrenalin. Owing probably to this precaution, the diuresis was sufficient for all the rabbits; there were no failures in this respect. The largest quantity of urine passed in twenty-four hours by an individual animal was 276 cubic centimeters (subcutaneous injection), and the smallest quantity amounted to forty-nine cubic centimeters (intramuscular injection); both animals belonged to the group which received 150 cubic centimeters of water and 0.7 of a cubic centimeter of adrenalin (table III). The average quantity of urine for all animals was about 100 cubic centimeters. Here again the average volume of urine of the intramuscular was less than that of the subcutaneous animals, the proportion being 120:152, or 4:5. The proportion for the dextrose was 2:3. The difference in the quantity of urine in favor of the subcutaneous animals is manifest in each of the groups of animals receiving the same dose of adrenalin.

That the variations in the amount of dextrose in the urine were not due to the variations in the quantities of urine passed, is evident from the fact that there were, as mentioned above, among both classes of animals instances in which there was no dextrose in the urine, while some of the quantities of sugar-free urine which these animals passed were: 228, 165, 117, and 112 cubic centimeters in twenty-four hours. On the other hand, we met with instances showing fairly low volumes of urine containing relatively large quantities of dextrose; for instance, 88 cubic centimeters, 1.77 grams; 68 cubic centimeters, 1.48 grams; 87 cubic centimeters, 1.16 grams. While these figures bear witness to the existence of a considerable independence of the glycosuria from the diuresis, in our experiments a survey of all the figures shows that in a general way a certain parallelism prevails between the two phenomena, so that the larger quantities of urine are often accompanied by relatively larger quantities of dextrose, and *vice versa.*

## THE EFFECT OF DISTRIBUTION OF A SUBCUTANEOUS DOSE OF ADRENALIN.

In the foregoing experiments the fact has been brought out that in two respects the subcutaneous injection of adrenalin proved to be superior to the intramuscular; it caused a more marked diuresis and favored the appearance of dextrose in the urine. As regards the latter, the amount of dextrose was perceptibly higher, and the number of failures to react with a glycosuria was definitely smaller after subcutaneous than after intramuscular injection. These results are diametrically opposite to those previously obtained by Meltzer and Auer in testing some of the other reactions of adrenalin upon the animal body. Here the effects were unquestionably more favorable after intramuscular injections. In these experiments the favorable action was ascribed to a better absorption of adrenalin from the intramuscular tissue. Could the results of the present series of experiments mean that with regard to the effects upon diuresis and the appearance of dextrose in the urine adrenalin is better absorbed from the subcutaneous than from the muscular tissue? Such a conclusion could be accepted only on the basis of an assumption that adrenalin consists of a complex of substances; that, for instance, the action upon the blood vessels emanates from one substance which is better absorbed from the muscle tissue, and that glycosuria is produced by another component of adrenalin which is better absorbed from the subcutaneous tissue,—an assumption not readily acceptable. Or could it be that the favorable effect of the subcutaneous injections in the experiments was due to the fact that absorption from the subcutaneous tissue is less rapid? Were this the case, then any factor which favors absorption in general ought to prove an unfavorable element in the production of glycosuria by adrenalin. The last mentioned point has been tested by us in the following manner. Meltzer (10) showed some years ago that the distribution of a substance over several areas of the body increases its effectiveness. A dose of strychnin, for instance, becomes more effective when injected into several places. We have therefore tested the influence of the distribution of adrenalin over several places upon the production of glycosuria and

diuresis. This series comprised twenty rabbits, of which twelve received 0.7 of a cubic centimeter of adrenalin as a dose, six received 0.75, and two received 0.8 of a cubic centimeter. The adrenalin was given subcutaneously and each dose was distributed over four places. Each animal received 100 cubic centimeters of water previous to the injections of adrenalin. The detailed results are given in table X. Table II contains the results of

TABLE X.

*Subcutaneous Distribution of Adrenalin.*

*Adrenalin, 0.7 to 0.8 of a Cubic Centimeter, Distributed in Four Places Subcutaneously; Water per Os, 100 Cubic Centimeters.*

*All Animals Previously Fasted for Twenty-Four Hours.*

| No. of animal. | Weight in gm. | Urine in c.c. | Dextrose in urine in gm. | Hours. |
|---|---|---|---|---|
| A 142[11] | 1,160 | 105 | 0.00 | 24 |
| A 143[11] | 1,430 | 118 | >0.96 | 24 |
| A 144[11] | 1,390 | 90 | 0.00 | 24 |
| A 145[11] | 1,240 | 89 | 0.00 | 24 |
| A 146[11] | 1,980 | 117 | 0.37 | 24 |
| A 147[11] | 2,100 | 146 | 0.00 | 24 |
| A 148[11, 12] | 1,860 | 59 | 0.60 | 24 |
| A 149[11] | 1,890 | 51 | 0.34 | 24 |
| A 150[13] | 1,900 | 141 | 0.00 | 24 |
| A 151[13] | 1,690 | 151 | 1.12 | 24 |
| A 152[11] | 1,620 | 106 | 1.05 | 24 |
| A 153[14] | 2,260 | 134 | 2.65 | 24 |
| A 154[14] | 2,010 | 80 | 2.09 | 24 |
| A 155[13] | 1,780 | 145 | 1.05 | 24 |
| A 156[11] | 1,310 | 73 | 0.00 | 24 |
| A 157[13] | 1,620 | 69 | 0.35 | 24 |
| A 158[13] | 1,780 | 104 | 1.06 | 24 |
| A 159[11] | 1,380 | 96 | 0.47 | 24 |
| A 160[11] | 1,570 | 88 | 0.00 | 24 |
| A 161[13] | 1,680 | 45 | 0.28 | 24 |

Average of all, 100 c.c. urine, 0.62 gm. dextrose.
Average of 13 glycosurias, 98 c.c. urine, 0.95 gm. dextrose.

similar doses injected into one place. There is a clear difference in the results of the two tables, and the difference is definitely in favor of the single injections. While there were no failures in the subcutaneous injections in table II (and only one failure in table III with single subcutaneous injections of 0.7 of a cubic centimeter),

[11] Adrenalin, 0.7 c.c.
[12] Pregnant.
[13] Adrenalin, 0.75 c.c.
[14] Adrenalin, 0.8 c.c.

we find seven failures in table X; that is, seven rabbits out of twenty failed to show glycosuria after receiving subcutaneously a dose of 0.7 to 0.8 of a cubic centimeter injected into four different parts. Furthermore the average amount of dextrose in the urine after single injections (table II) was 1.13 grams, while the average amount of dextrose for the twenty rabbits in table X was only 0.62 of a gram; and even after deducting the seven rabbits with sugar-free urine, the average amount of dextrose for the remaining thirteen rabbits was only 0.95 of a gram. Finally, the average volume of urine for twenty-four hours, when the adrenalin was given subcutaneously in a single spot, amounted to 125 cubic centimeters, while the average amount of urine for the twenty animals which received their dose of adrenalin subcutaneously, distributed over four areas (table X), was only about 100 cubic centimeters. Evidently the distribution of a dose of adrenalin has the tendency to diminish the quantity of urine voided in twenty-four hours, to increase the number of cases in which no dextrose at all appears in the urine, and, when glycosuria is produced, to decrease the quantity of dextrose in the urine.

If we assume that the above mentioned observation of Meltzer holds good also for adrenalin, namely, that the distribution of an injected substance over several areas favors its absorption, we must come to the conclusion that the better the absorption of adrenalin the less effective are its glycosuric and diuretic actions.

## DISCUSSION.

The starting point for our investigation was the earlier experiments of Meltzer and Auer with adrenalin. For three of the actions of that drug, the raising of the blood pressure, the dilatation of the pupil, and the muscular weakness, the intramuscular injections are more effective than the subcutaneous. Naturally it was anticipated that a similar effect would be found with respect to the glycosuric action of adrenalin. What was obtained was a diametrically opposite result, that is, glycosuria was brought on with greater certainty and, in most instances, with greater intensity by subcutaneous than by intramuscular injection.

The glycosuric action of adrenalin differs from some of its other known

actions in several respects. In the first place, there is the proportion between the injected quantity and the extent of the effect. For the hemodynamic principle it has been shown (11) that under proper conditions the same quantity of the drug can be relied upon to bring about the same degree of effect. The same seems to hold good to a considerable degree also for the dilatation of the pupils, as was recently shown by Joseph (12). Regarding the glycosuric effect Herter (13) stated that "within certain limits the quantity of the sugar excreted appears proportional to the dose of adrenalin." It seems that this is indeed true only "within certain limits." Herter himself says soon after, that "there is reason to believe that when a certain dose is followed by a large excretion of sugar, a larger dose would not have materially increased this output." In our experiments the average amount of dextrose in the urine decreased in general with the decrease of the dose injected, subcutaneously as well as intramuscularly. This is especially the case for the doses of 0.7, 0.5, 0.4, and 0.3 of a cubic centimeter for an animal. At the same time the individual amounts of the urinary dextrose varied considerably for each dose, so that in some instances the dose of only 0.3 has given rise to the presence of a quantity of sugar in the urine which was larger than that of other cases after an injection of 0.7 of a cubic centimeter. Judging by the figures in various protocols, similar conditions apparently prevailed in the experience of other investigators.

We may state here in passing that some of the discrepancies can perhaps be accounted for by the circumstances that the subcutaneous injections of some investigators may have been actually intramuscular, as it may readily happen that inadvertently the point of the needle instead of remaining in the subcutaneous tissue penetrated the muscular fascia and was therefore actually within a muscle. On the other hand, it may also happen that a needle passed through a muscle bundle and the injection was actually subcutaneous (that is, the injected fluid passed into the loose connective tissue), instead of being intramuscular. It was for the purpose of eliminating such errors that in our experiments the solid mass of the lumbar muscles was selected for the intramuscular, and the lower quadrants of the abdominal wall with its loose skin for the subcutaneous injection. However, occasionally such an error may have happened to us, and may perhaps account for one or the other case with a high intramuscular and a low subcutaneous glycosuria.

At any rate, it is evident that the exactness of the relation of adrenalin to glycosuria falls far behind that of the relation of adrenalin to its effects upon blood pressure.

Another striking difference is to be found in the length of the interval between the administration of the adrenalin and the appearance of the effect. The comparatively slow onset of the glycosuria can in no way be compared with the promptness of the rise of blood pressure following an injection of adrenalin or the promptness of the appearance of the dilatation of the pupil after the removal of the superior cervical ganglion.

A further noteworthy difference is the disappearance of the glycosuric effect after repeated injections of adrenalin and the persistence of the effect upon the blood pressure and upon the dilatation of the pupil. This disappearance after repeated injections has been observed and studied by Pollak (17) and others. The persistence of the blood pressure effect is a well known fact noted by various

writers. The persistence of the pupillary reaction to adrenalin has been established by numerous observations in this laboratory. Ganglionectomized rabbits received injections of adrenalin frequently for weeks and months, sometimes every day and sometimes even several times on the same day, without the pupil ever failing to react promptly, and practically with the original intensity.

Evidently the production of glycosuria by adrenalin is a more complicated process than is the rise of blood pressure or the dilatation of the pupil and it is more difficult to control the numerous factors involved.

In view of the foregoing, it should occasion no surprise to find a difference between the glycosuric effect of adrenalin and some of its other effects. We should have found occasion for surprise if we had been compelled to interpret the difference to mean that for the production of glycosuria adrenalin is more readily absorbed from the subcutaneous than from the intramuscular tissue, while with regard to its other effects adrenalin is better absorbed from the muscles. Such an interpretation is, indeed, not indispensable. As we have seen above, our results permit us to assume that even for the production of glycosuria, adrenalin enters the circulation with greater readiness from the muscle than from the subcutaneous tissue. For the understanding of the results we need only to assume further that the production of glycosuria is rather favored by a slow entrance of the injected adrenalin into the circulation. This assumption finds support in the fact that the distribution of the injected dose of adrenalin over several areas, a procedure which favors a more rapid entrance of the chemical into the circulation, tangibly impairs the production of glycosuria. With this as a basis there is no difference between the experience of Meltzer and Auer with regard to the other effects of adrenalin and the present results with reference to its glycosuric action; in both cases adrenalin is better absorbed from the muscular than from the subcutaneous tissues.

The difference which our experiments show to exist between the glycosuric effect and the other effects of adrenalin consists, then, if our view is correct, in the fact that, for instance, the hemodynamic and the pupillodilating actions of adrenalin are the more effective the more rapidly the adrenalin gets into the circulation, while the glycosuric action, on the contrary, manifestly becomes greater with the retardation of the absorption of the drug into the blood.

Is this view probable, and is there any other evidence in favor of it? In the experiments of Meltzer and Auer with the hemodynamic action of adrenalin, it was found that an intramuscular injection of adrenalin acts nearly as well as an intravenous administration. Is a subcutaneous injection of adrenalin more favorable to the production of glycosuria than an intravenous one? The above mentioned and frequently quoted investigations of Ritzmann (14) seem to speak against such a conclusion. Adopting the method of Kretschmer (15) which the latter used for the study of the blood pressure-raising effect of adrenalin, Ritzmann infused intravenously very dilute solutions of adrenalin and found that not only does this method produce glycosuria, but the amount of dextrose in the urine produced by it exceeds considerably the amount of dextrose in the urine produced by a subcutaneous injection of a much larger dose of adrenalin. Underhill (16) who repeated Ritzmann's experiments found that the intravenous infusion of adrenalin in unanesthetized rabbits causes no glycosuria at all, and that the glycosuria observed by Ritzmann was produced by the simultaneous use of urethane as an anesthetic. Underhill further noted that a subcutaneous injection of adrenalin is more likely to cause glycosuria than an intravenous dose of the same size. Pollak (17) stated that the experience of the pharmacological laboratory of the University of Vienna is that a single intravenous injection of adrenalin, in doses ranging from 0.1 to 1 milligram, does not produce glycosuria, while, as we have seen, some of these doses readily produce glycosuria by subcutaneous injection.

Hence, our conclusion that the favorable effect which we obtained by subcutaneous injection of adrenalin was due to the slow absorption, and that any means which promotes absorption may impair the production of glycosuria finds, therefore, ample support in the statements of Underhill and of Pollak. Moreover it is not contradicted by the findings of Ritzmann which were influenced, as is shown by Underhill, by the use of urethane.

The many failures in our experiments to produce a glycosuria after the intramuscular injections and the still larger number of failures from the subcutaneous injections distributed over several

areas find their ready interpretation in the view that in both instances the absorption into the circulation was so rapid as to imitate an intravenous injection.

Pollak found that intravenous injections, which fail to cause glycosuria, nevertheless cause hyperglycemia, the degree of the latter being insufficient to produce glycosuria in the absence of increased diuresis. He observed further that the hyperglycemia produced by the subcutaneous injection of a certain dose of adrenalin exceeds that caused by a similar dose administered intravenously. Pollak calls attention to the diuretic action of adrenalin and believes that the following rules regulate the relation of glycosuria to hyperglycemia and diuresis. When a hyperglycemia in rabbits is more than 0.15 per cent., but not above 0.25 per cent., and is not accompanied by an increased diuresis there will be no glycosuria. If this moderate hyperglycemia is accompanied by an increased diuresis or if the hyperglycemia exceeds 0.25 per cent., without diuresis, glycosuria results. Our experiments show that subcutaneous injection, which favors glycosuria, also generally favors an increase in the diuresis. At the same time it is quite evident that both processes are independent of each other to a considerable extent.

To the above we wish to add the following remark. While we are sure that a theory which attempts to explain completely the reasons why subcutaneous injections, which have to act through the circulation, are superior to direct intravenous injections, would be premature at present, since our knowledge of the facts in question is still too scant, we nevertheless believe that an analysis of the phenomena should also take into consideration the action of adrenalin upon the process of elimination. Meltzer and Auer (18) previously pointed out that adrenalin restricts absorption as well as elimination, and they indicated that it may interfere with the eliminating power of the kidney. Drummond (19) has shown that adrenalin causes a (reversible) cloudy swelling of the kidney epithelium. Ritzmann (20) stated that when the intravenous infusion of the adrenalin solution took place too rapidly, no sugar appeared in the urine and there was, indeed, little or no urine. When the animal recovered from the effects of such an infusion it passed

some urine which often contained blood. From our personal experience we are confident that larger doses of adrenalin interfere with the elimination of sugar as well as of urine. For this reason we did not employ doses exceeding one milligram of adrenalin. The most satisfactory results relating to the presence of dextrose and to the volume of urine were obtained by us from doses of 0.7 of a cubic centimeter of the adrenalin solution. We believe, therefore, that beyond a certain point the increase of the dose of adrenalin lessens the elimination of the dextrose and restricts the diuresis. The size of the restricting dose is probably not the same for both functions. The influences of adrenalin upon diuresis and upon glycosuria (both the stimulating and restricting influences) are, we think, two essentially independent processes.

Without offering any theory of our own, we wish merely to state our belief that any theory which attempts to explain the phenomena under discussion should take into consideration the influence of adrenalin upon elimination of dextrose, as well as of urine.

## SUMMARY.

Subcutaneous injections of adrenalin are, in contrast with its behavior in the production of the other effects of that drug, more favorable to the production of glycosuria in rabbits than intramuscular injections; the failures are fewer and the quantities of dextrose in the urine are generally larger. In general, as regards the stimulation of diuresis by adrenalin, a subcutaneous injection exerts generally a greater effect than an intramuscular one.

Subcutaneous injections of a certain dose of adrenalin distributed over several areas are far less effective than the administration of that dose in a single injection; they fail frequently to produce any glycosuria, the quantity of dextrose in the urine, when present, being less, and the quantity of urine being generally diminished.

Apparently the more slowly the injected adrenalin reaches the blood, the greater is its effect in producing glycosuria and generally, also, the greater its diuretic action.

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