THE RELATION BETWEEN METHOD OF ADMINISTRATION AND EFFECT OF A DRUG.*

BY H. B. CORBITT.

In a previous publication dealing with the connection between skin and the effect of insulin on the blood-sugar content, Müller and Corbitt[1] described observations showing that the results of insulin injections differ according to the route of administration. Animals injected with the same amount of insulin, per Kilogram of body weight, showed different decreases in the lowering of the blood-sugar content, depending upon whether the injection was intradermal or subcutaneous.

After a subcutaneous injection of 0.5 unit of insulin, the general effect is: A decrease of the blood-sugar content to approximately fifty per cent. of the initial value at the end of the two-hour period following the injection, a recovery to within fifteen or twenty per cent. of the original content at the end of the four-hour period, and a further recovery to within ten per cent. or less of the initial sugar level at the end of the six-hour period.

As was shown in the paper mentioned above, the intradermal method gave quite different results in that while the initial percentage decrease was practically the same as with the subcutaneous method, the blood-sugar level at the end of four and six hours was much lower. This indicated that by the intradermal route a greater hypoglycemic action was obtained from a given amount of insulin. Further experiments along this line will be published soon. These results obtained by carefully controlled experiments on a greater number of animals will show in detail the difference in the effects resulting from different methods of administration.

Just what may be the complete explanation of this difference in action is not apparent. The possibility of difference in animals was suggested and has been controlled as will be described. The difference in absorption does not seem to offer an adequate solution of this problem since if such occurred, the common low level would not be the same irrespective of the method of administration. The conclusion was reached that there is some unknown special property of the skin responsible for this difference in effects after insulin injection. This hypothesis becomes the more plausible when it is considered that the skin is an organ having close relationship to the involuntary nervous system and through it to the blood cells and plasma by means of which it may produce certain reactions in the body. It is known, for instance, that 0.1 cc. of Aolan, a non-specific lactalbumin preparation, which is germ- and toxin-free and, therefore, not tissue irritating, is a stimulant to the involuntary nervous system if given intradermally, while the subcutaneous, the intramuscular and even the intravenous administration of the same quantity of Aolan is not followed by any measurable change in the organs controlled by the involuntary nervous system.

It is possible, therefore, that the skin may have a special property, hitherto unknown, through which specific agents act upon the body. If so, this would correspond to a property already known whereby the action of nonspecific substances is made manifest through the skin.

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* Read before the Scientific Section of the American Pharmaceutical Association, Buffalo, N. Y., August 27, 1924.

[1] E. F. Müller, and H. B. Corbitt, *J. Lab. Clin. Med.*, 9, 608–17 (1924).

In previous work in this laboratory, as in the work of others elsewhere done, the variability of animals has been recognized. This, as well as other factors, enters into the accurate determination of the effects of the hypo- and hyperglycemic producing substances. Because of the differences in reaction of individual rabbits, each animal was injected both intradermally and subcutaneously. In addition, intravenous injections have been made in some of them in order to study further the properties of the skin as shown by the mechanism of the action of insulin.

Macleod and Orr[1] in a recent article have mentioned certain variables which, it is believed, have been controlled in this work. There is another factor, however, which is to be considered, namely, the condition of the animals at the time of securing a sample of the blood. Usually, there is little manifestation of excitement or irritation. Yet some animals struggle at times and it was thought advisable to investigate the effect of struggling upon the blood-sugar level.

Animals were bled (*a*) without injection and without forced exercise; (*b*) without injection and with forced exercise; (*c*) with an injection of insulin and with forced exercise. Struggling was induced by holding the animal by the hind legs and allowing it to walk with its fore legs. This form of exercise was longer and more severe than would be produced by the usual procedure of obtaining blood from the aural vein. Little difficulty in bleeding animals has been encountered with the use of mixture of xylene and ether.

TABLE I.—THE EFFECT OF FORCED EXERCISE ON THE BLOOD SUGAR CONTENT OF A NORMAL RABBIT. RABBIT 76.

Time after initial bleeding. Hrs.	Blood sugar mg. per 100 cc.	Change in sugar content per cent.	Remarks.
0	130	...	No exercise.
2	133	+2.3	
4	126	−3.1	
6	125	−3.8	
0	107	...	
2	180	+68.2	Given forced exercise 5 min. before bleeding.
4	133	+24.3	No forced exercise but some struggling.
5.9	116	+ 8.4	Exercised 2 min. after this bleeding.
6.0	143	+33.6	

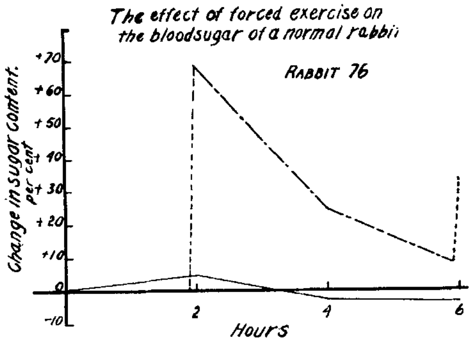

Chart A.

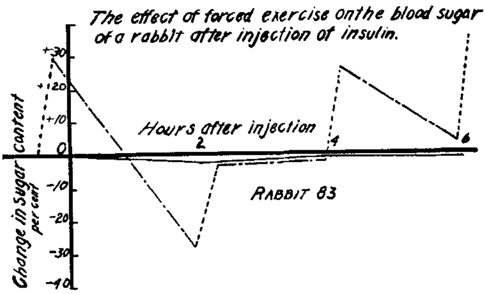

Chart B.

Chart A (from Table I) shows the variations in blood sugar with and without forced exercise. This animal was difficult to bleed at the four-hour period and

[1] Macleod and Orr, *J. Lab. Clin. Med.*, 9, 591–608 (1924).

struggled to some extent. The dotted lines indicate the increase due to forced exercise. Chart B (from Table II) shows the effect on the blood sugar level of a rabbit given intradermal and subcutaneous injections of insulin and the effect of a subcutaneous injection of the same agent given at a different time, together with four periods of forced exercise. It is evident that the effect of considerable struggling is to counteract the hypoglycemic effect of insulin. This explains the increase in blood sugar sometimes recorded after convulsions. It may be concluded, therefore, that while the struggling of animals should be avoided, if it occurs, it will tend to decrease the effects of insulin rather than to magnify them.

TABLE II.—THE EFFECT OF FORCED EXERCISE ON THE BLOOD SUGAR OF A NORMAL RABBIT AFTER INJECTION OF 0.5 UNIT OF INSULIN. RABBIT 83.

Time after injection. Hours.	Mins.	Blood sugar content mg. per 100 cc.	Change in sugar content per cent.	Remarks.
−0	31	126	....	Exercised 2 minutes after this bleeding.
−0	17	164	+30.2	
0	0	..	....	Injected subcutaneously with 0.5 unit insulin.
+1	55	92	−27.0	Exercised 2 minutes after bleeding.
+2	16	122	−3.2	
+3	56	125	−0.8	Exercised 2 minutes after bleeding.
+4	8	158	+25.4	
+5	54	130	+ 3.2	Exercised 2 minutes after bleeding.
+6	4	169	+34.2	
0	..	115	....	Control experiment.
2	..	112	−2.6	No injection or exercise.
4	..	114	−0.9	
6	..	113	−1.7	

The experimental results which are presented here have been obtained with these factors in mind. They are given in the form of tables and, to render them more clear, a graphic presentation in the form of charts is made.

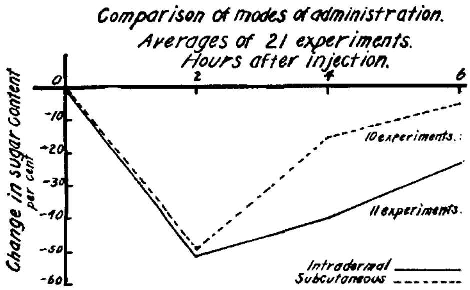

Chart C.

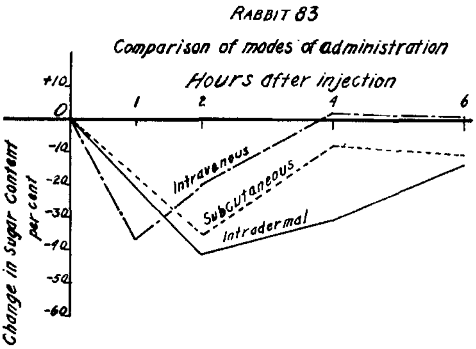

Chart D.

TABLE III.—SUMMARY OF TWENTY-ONE EXPERIMENTS COMPARING THE INTRADERMAL AND SUBCUTANEOUS INJECTION OF INSULIN. THE EFFECT ON THE BLOOD SUGAR OF NORMAL RABBITS.

Mode of injection.	Initial blood sugar content mg. per 100 cc.	2-hr. blood sugar content mg. per 100 cc.	2-hr. change in sugar content per cent.	4-hr. blood sugar content mg. per 100 cc.	4-hr. change in sugar content per cent.	6-hr. blood sugar content mg. per 100 cc.	6-hr. change in sugar content per cent.
Intradermal	132.9	64.6	−51.57	79.9	−40.2	101.3	−23.75
Subcutaneous	127.7	63.8	−50.07	108.0	−15.52	120.5	−5.6

In Table III is shown a summary of the results of twenty-one experiments in which seven different rabbits were used. Four of these were injected twice intradermally and three of them twice subcutaneously. Usually an intradermal and a subcutaneous injection on different rabbits were made on the same day. For the sake of brevity the values of each separate test and individual rabbit are not given in this paper; instead, the average blood-sugar values and average percentage changes at 2, 4 and 6 hours are presented. These values bring out the well-established difference in the routes of administration. It is noted that the initial decrease is practically the same by both methods, but after the two-hour period a marked difference becomes manifest. This is the more noteworthy when it is considered that these are the average results of experiments on seven different rabbits, in which both methods of injection were used. These results are illustrated graphically in Chart C.

In the study of the action of insulin it now seemed advisable to compare the intravenous method of injection with the two previously described. While this method is known to give quicker results than the others, it was desired to compare the action of all three methods on the same animals. Some of these results are shown in Table IV and graphically in Chart D. It is noted that the decrease in blood-sugar level is neither as great initially nor as lasting as by the other methods although the low level is reached more quickly. Even though the insulin enters the blood stream at a greater concentration than by the other routes, yet it does not produce as large a decrease in the blood-sugar content as when given into or under the skin.

TABLE IV.—A COMPARISON OF THE INTRAVENOUS, SUBCUTANEOUS AND INTRADERMAL METHODS OF INJECTION OF INSULIN. THE EFFECT ON THE BLOOD SUGAR OF A NORMAL RABBIT.
RABBIT 83.

Mode of injection.	Time after injection. Hours.	Blood sugar content mg. per 100 cc.	Change in sugar content per cent.	Remarks.
Intravenous	0	121	....	0.5 Unit of insulin
	1	76	−37.2	
	2	97	−19.85	
	4	123	+ 1.6	
	6	122	+ 0.8	
Subcutaneous	0	128	....	0.5 Unit of insulin
	2	83	−35.2	
	4	118	−7.8	
	6	114	−10.9	
Intradermal	0	129	....	0.5 Unit of insulin
	2	76	−41.2	
	4	89	−31.0	
	6	111	−14.0	

the skin.

These results show that the order of increasing efficacy in administration is intravenous, subcutaneous and intradermal. Without going deeply into the hypotheses which may be advanced as an explanation of this phenomenon, it will for the present suffice to note that there are marked differences in the effect of a specific drug which seem to be dependent upon the mode of administration. It must be expected that the same laws of physical chemistry which have been formulated for actions *in vitro* will apply to actions *in vivo*, when due consideration is given to all the factors involved. At present many of these factors of biologic systems are unknown or little studied and their complexity renders explanations of the reactions extremely difficult. As stated above, it is known that the skin is a factor in the reactions of such preparations of nonspecific proteins as Aolan. The present findings confirm the statements of the previous publication and warrant to a still greater extent the serious consideration of the skin as an organ in specific therapy.

The conclusions from the above work are:

(*a*) Of the three routes for the administration of insulin, a specific therapeutic agent, the increasing order of efficacy is (1) intravenous (2) subcutaneous and (3) intradermal. These results agree with those obtained from the study of certain nonspecific substances.

(*b*) Because of these findings the skin offers a new medium of administration for both specific and nonspecific agents which should engage the attention of investigators.

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THE VALUE OF MICROANALYTICAL METHODS AND EXAMPLES OF THEIR APPLICATION.*

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The microscope continues to increase in importance as a working tool of the analyst, and microanalytical methods are taking a prominent place in the solution of laboratory problems. Unfortunately, the microscope has not always been as important as other instruments of precision and microanalytical methods have not received the recognition which they deserve. As such methods continue to justify their value in the solution of laboratory problems they are being more widely applied, and the trained microanalyst is demonstrating the value of his specialized experience.

In the early history of the microscope the microanalyst's field of activity seemed restricted to the microscopical identification of plant ingredients. For that reason he has needed chiefly a strong foundation in botanical subjects, particularly those relating to plant anatomy and histological structures. The microscopy of vegetable foods and drugs therefore became his largest field of activity. As time went on his field of usefulness broadened to include microchemical technique and the application of optical-crystallographic methods to the identification of small quantities of crystalline material. His expert knowledge became valuable where only small quantities of materials were available and the necessity arose for the conservation of the unknown substance for further tests. In the course of their work microanalysts may often be called upon to employ the following methods of attack.

* Presented at Plant Seminar in Buffalo, 1924.