THE INTRANASAL APPLICATION OF INSULIN, EXPERIMENTAL AND CLINICAL EXPERIENCES.

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Since the discovery of insulin investigators have attempted to introduce it into the body by various methods. Woodyatt[1] in 1922 says, "experiments were conducted with oral, rectal, vaginal, intranasal, intravenous, and subcutaneous administrations. Inunctions were also tried. Many variations were attempted in connection with each. Positive effects were obtained with subcutaneous and intravenous injections, very weak, doubtful or frankly negative results with the others." Up to the present time intravenous and subcutaneous administrations have been employed to the exclusion of all other methods.

Telfer[2] in 1923 reported that insulin could be introduced into the blood stream by means of inunction. Harrison[3] in 1926 repeated this work and found that the inunction of insulin was useless even in very large doses. Peskind, Rogoff and Stewart[4] in 1924 found that insulin when injected per rectum into rabbits was absorbed, and produced lowering of the blood sugar; in dogs, negative results were obtained. Heubner, de Jongh and Laquer[5] in 1924 describe the lowering of blood sugar in diabetics by inhalation of insulin. Fisher[6] in 1924 found some absorption of insulin by the intestine, vagina and scrotal sac. Gänsslen[7] in 1925 described lowering of the blood sugar in diabetics by inhalation of an insulin spray. Miller[8] in 1926 reported that insulin given in absolute alcohol, or 95 per cent alcohol solution in keratinized capsules, lowered the blood sugar of diabetic patients. Stephan[9] in 1929 described lowering of blood sugar following the administration of insulin by mouth. This work was not confirmed by Wahncau and Bertram[10] or by Bertram, Horwitz and Wahncau.[11] Bollman and Mann,[12] working with intestinal catheters and with ileac loops, found that large amounts of insulin might be instilled into the duodenum, jejunum, or ileum without any appreciable effect on the

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blood sugar of normal dogs. Similar results were found with administration into the ileac loop.

A summary of these results bears out the initial statement of Woodyatt that with methods other than subcutaneous or intravenous injection "very weak, doubtful or frankly negative results" have been obtained.

Recently we have repeated some of these experiments with variations, and, in the course of our work, studied the problem of intranasal absorption. We have obtained undoubted evidence of the activity of insulin, either when sprayed or when instilled into the nostrils in normal rabbits, normal dogs and in diabetic patients, under certain conditions.

Preliminary experiments indicated that the instillation or insufflation of insulin in the nose produced either frankly negative or doubtful results. We studied next various solutions which might possibly increase absorption through the mucous membrane. Finding several solutions which apparently had this effect, we chose first ethylene glycol as a medium. We have mixed equal quantities of ethylene glycol and insulin, using a highly concentrated solution of insulin containing 1000 units per c.c. The solutions employed for instillation contained 500 units per c.c. With such a solution .1 c.c. contains 50 units and .2 c.c. 100 units of insulin.

The following are a few typical protocols on rabbits and dogs:

Date	Animal	Time	Blood Sugar mg.
3/13/35	Rabbit No. 1	8:50 a.m.	247
		8:55 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		10:28 a.m.	177
		11:47 a.m.	149
3/15/35	Rabbit No. 2	9:05 a.m.	105.5
		9:08 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		10:40 a.m.	62.5
		12:40 a.m.	55.2
3/20/35	Dog	9:50 a.m.	96
		9:55 a.m.	.4 c.c. insulin-ethylene glycol mixture (200 units) intranasally.
		10:50 a.m.	58.8
		11:45 a.m.	58.3
		12:45 p.m.	44.2

The effects of this solution when applied intranasally in diabetic patients is shown in the following tables:

Date	Patient	Time	Blood Sugar mg.
3/18/35	No.1	7:30 a.m.	150
		8:15 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		9:15 a.m.	149
		10:15 a.m.	122
		11:15 a.m.	83
		12:15 p.m.	110
3/19/35	No. 2	7:30 a.m.	135
		8:15 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		9:15 a.m.	87
		10:15 a.m.	94
		10:15 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		11:15 a.m.	69
		11:15 a.m.	Slight reaction.
		11:30 a.m.	More marked reaction.
		11:40 a.m.	Orange juice.
		12:15 p.m.	115
3/21/35	No. 3	8:00 a.m.	225
		8:50 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally (spray).
		9:50 a.m.	197
		10:50 a.m.	172
		11:50 a.m.	148
		12:00 noon	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally (spray).
		1:00 p.m.	137
		2:00 p.m.	116
3/21/35	No. 4	8:00 a.m.	256
		8:50 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally (spray).
		9:50 a.m.	154
		10:50 a.m	125
		11:50 a.m.	115
3/29/35	No. 5	8:30 a.m.	188
		9:30 a.m.	180
		9:40 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		10:30 a.m.	144
		11:30 a.m.	142

Date	Patient	Time	Blood Sugar mg.
3/30/35	No. 6	12:15 p.m.	158
		12:20 p.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		1:15 p.m.	106
		2:15 p.m.	65
		3:15 p.m.	66
4/3/35	No. 7	10:45 a.m.	286
		10:50 a.m.	.2 c.c. insulin-ethylene glycol mixture (100 units) intranasally.
		11:45 a.m.	112
		12:45 p.m.	67
		1:45 p.m.	73

We next made observations employing trimethylene glycol instead of ethylene glycol. These solutions were prepared so that 0.1 c.c. of the solution contained 75 units. The Ph of the solution employed was 2.5. These solutions were apparently more active than those made with ethylene glycol.

Date	Patient	Time	Blood Sugar mg.
6/24/35	No. 8	Fasting	206
			25 units insulin in trimethylene glycol (0.05 c.c.) intranasally.
		1st hr.	157
		2nd hr.	146
		3rd hr.	132
6/24/35	No. 9	Fasting	203
			25 units insulin in trimethylene glycol (0.05 c.c.) intranasally.
		1st hr.	222
		2nd hr.	198
		3rd hr.	189
6/24/35	No. 10	Fasting	310
			25 units insulin in trimethylene glycol (0.05 c.c.) intranasally.
		1st hr.	224
		2nd hr.	165
		3rd hr.	158
7/14/35	No. 11	Fasting	240
			25 units insulin in trimethylene glycol (0.05 c.c.) intranasally.
		1st hr.	184
		2nd hr.	156
		3rd hr.	184

Conclusions: The above tables, which are examples of a larger group of similar observations, show that insulin in ethylene glycol and in trimethylene glycol when either dropped or sprayed into the nasal mucous membrane produces an unquestioned and marked fall in blood sugar in normal rabbits, normal dogs, and in diabetic patients. The dosage employed by this intranasal method is considerably greater than that necessary in subcutaneous injection.

Two impressions that we gain may be of some interest. First, in patients who prove later to be mild diabetics, the blood sugar falls very rapidly following intranasal application even when the blood sugar values are very high. Our second impression is that it is relatively difficult to produce a shock. While it is not difficult to lower the blood sugar from a high value to a range of 140 to 160, it is more difficult to lower the blood sugar below this level.

We have treated fifteen patients in the hospital over periods of time varying from two weeks to two months and have been able to keep them relatively sugar free by the intranasal method. Whether this method of administration is practical in the treatment of diabetic patients further observations alone can determine. The treatment may prove too expensive to be practical and we may also discover great variations in absorption in different patients. The fact that insulin under certain conditions can be absorbed from mucous membranes is, however, of more than academic interest.

(We are under obligations to Eli Lilly and Company for the insulin used in these observations.)

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DISCUSSION.

DR. HOWARD F. ROOT (Boston): This is perhaps the first time that we have seen results that are as striking as this in any form of insulin given on any sort of mucous membrane, nasal or otherwise. This is certainly most interesting.

There is at present a great deal of interest in attempts to form and to produce combinations of insulin with other substances which will be effective. There was reported in Copenhagen this June a combination of insulin with another substance which brings about the slowing of the action of insulin. Someone there had combined insulin with adrenalin in a single dose. That is entirely outside of the field of Dr. Major's efforts, I know, but that does show how attempts are being made in many places to improve the methods of administration of insulin, so as to either simplify the actual method of administration, or by prolonging the effect, the injections need not be made so often.

Are these patients those that have been taking the insulin regularly, that is, are they patients that have been taking insulin for periods before in this form, or is this replacing the old form? That seems to me to be a very important point.

DR. FRANCIS M. RACKEMANN (Boston): I would like to ask Dr. Major if, when patients have repeated the dosages of intranasal injections, do they develop any local nasal symptoms?

DR. C. SIDNEY BURWELL (Boston): Do these special substances improve the absorption? I do not know enough about the substances to know what they do, but does it make the absorption better when they are used?

DR. RALPH H. MAJOR (Kansas City): In response to the question by Dr. Root, almost all of these patients were patients who had been under observation in the Diabetic Clinic for considerable periods of time.

I think there is no question about the absorption in these patients or the possibility of getting absorption with this combination almost any place, although the amount of dosages employed seems to vary. Some patients show a very marked fall with 25 units, while with others it is necessary to increase the dose up to 100 to get a fall.

As far as the local results in the nose are concerned, Dr. Rackemann, we have

never seen any irritation whatever. We have had some patients who have taken the drops for periods of nearly six months without any apparent irritation.

As to whether these solutions promote absorption, unfortunately I am unable to answer that question. There are a number of substances of this same general family that do that. We found we could get some absorption, for example, with glycerin. It seemed to be very markedly inferior to the two substances that I have mentioned. I do not know whether it simply increases the permeability of the mucous membrane by the other substance in these solutions.