STUDIES OF CARBOHYDRATE METABOLISM IN CASES OF INSULIN RESISTANCE.

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In the treatment of diabetic patients it is usual to think of five different aspects of carbohydrate metabolism which must be controlled if proper regulation of diabetes is to be obtained. The first of these is acidosis due to ketosis; the second is the adequacy of the diet, not merely in respect to total calories but in its content of vitamins and minerals and its proportion of carbohydrate, protein and fat; the third is the blood sugar, for the obvious reason that one must avoid hypoglycemia, and most of us feel that persistent hyperglycemia is equally to be avoided; the fourth is the efficiency of the action of insulin; and the fifth is the respiratory quotient relationship, that is, that the respiratory quotient itself should be maintained as nearly normal as possible.

We have been studying the carbohydrate metabolism of diabetic patients at the Deaconess Hospital by means of determinations of the oxygen consumption and the respiratory quotient. We have studied the effects of giving glucose to diabetic patients and also to some non-diabetic patients with and without insulin. Most of the patients with insulin resistance have been, at the time of the experiment, somewhat under the influence of protamine insulin in that they had received protamine insulin twenty-four hours previously, although unless otherwise stated they did not receive insulin on the morning of the experiment. In these resistant cases the question of what happens under conditions where the efficiency of insulin action has been impaired is the chief point.

The questions we are hoping to find some light upon are: First, can insulin resistance be explained? Second, can it be so treated that acidosis and coma can be avoided? Can it be so treated that the respiratory quotient can be made normal? And obviously the old question: How does insulin act?

Insulin and the Respiratory Quotient in the Previously Untreated Diabetic.

First one should remember the behavior of the respiratory quotient under normal circumstances. The respiratory quotient (the ratio $\frac{CO_2}{O_2}$) is around 0.80 fasting if the subject has taken a normal diet in the preceding days. When glucose is given by mouth or vein, and it is true that glucose in the normal behaves the same when administered by mouth as when administered by vein, the respiratory quotient first drops in a few minutes and then promptly rises to a level of 0.90 or more, which persists.

Fig. 1—Case 19493, Age 56 Years. October 16, 1940.

Period	Time a.m.	R. Q.	O_2 per minute, cc.
1	8:40	0.710	244
2	8:50	.689	253
3	9:00	.725	243
	50 gm. dextrose intravenously (9:55-10:20 a.m.)		
4	10:40	.746	242
5	10:55	.739	237
6	11:10	.760	240
7	11:25	.754	239
8	11:40	.766	244

Fig. 2—Case 19493, October 22, 1940.

Period	Time a.m.	R. Q.	O_2 per minute, cc.
1	9:15	0.764	223
2	9:25	.775	220
3	9:35	.763	222
	50 gm. dextrose intravenously (9:54-10:23 a.m.)		
	50 units insulin intravenously—10:29 a.m.		
4	10:40	.730	258
5	10:55	.829	245
6	11:10	.887	234
7	11:25	.918	223
8	11:40	.896	227
9	11:55	.885	226

Figure 1 presents the picture in the untreated diabetic patient. The data were obtained in the last two weeks in a woman who came to the hospital without treatment previously, blood sugar between 300 and 400 milligrams, 8.0 per cent sugar in the urine, who was given glucose solution, 50 grams by vein. Without any treatment her

respiratory quotient started at 0.71, a typical diabetic quotient, and rose to a maximum of 0.766. It is notable that a slight rise in quotient occurred, indicating that even in the untreated diabetic there is some ability to utilize glucose.

When that patient was given insulin and the same dose of glucose, 50 grams intravenously, on October 16, the fasting quotient was 0.767, presumably because the patient had been treated with insulin for a few days. Although the fasting quotient starts at a higher level, the rise to 0.918 is an increase of 0.151. It is evident that in this patient, the use of insulin and diet for 6 days resulted in a rise in the fasting respiratory quotient and also the response to glucose administered intravenously was greatly increased. The assumption seems justified that the effect of insulin was to increase the proportion of carbohydrate oxidized in the metabolic mixture. So much for the picture of the untreated diabetic bearing on the question of what insulin does in the body.

Insulin Resistance.

Our resistant cases may be described briefly. The first (17162) was a young clergyman, 33 years of age, who came to the hospital in 1938, and proved to be a simple case requiring 30 units of insulin a day. That was in September. In December he returned in diabetic coma. Two weeks after discharge he returned with his second attack of diabetic coma, this time requiring 700 units of insulin, and he remained in the hospital because to our surprise he now required 400 units a day, even under hospital conditions. One morning we were surprised to be called at seven o'clock with the news that he was unconscious. He was now in profound diabetic coma, having received the preceding day 400 units, and this day he required 2200 units of insulin given in large doses, including one of 300 units intravenously. He recovered from that coma, and during the next few weeks continued to require from 1500 to 1800 units a day. Now the experiments with him were carried on at a period a few weeks later when already the peak of this insulin resistance had begun to subside. He was then requiring only 800 units a day, and those experiments are summarized in Figure 3.

The second case of insulin resistance (15761) was a nurse about 40 years of age who similarly had required a few years ago 30 units of insulin a day, but who at home had found that her requirement

had risen to 500 units a day. During a period of two or three months in the hospital we found that her insulin requirement at its maximum was 2000 units a day. The experiments with her were carried on at a time when the condition was at its peak. It is notable in both these cases that in the fasting state glucose produced almost no response, whereas fructose and galactose gave almost normal responses.

Each of these two patients during the two years since have gradually come down so that in the case of the young clergyman when the second series of experiments were carried on the insulin requirement was 100 units, and the nurse's is now 150 units a day.

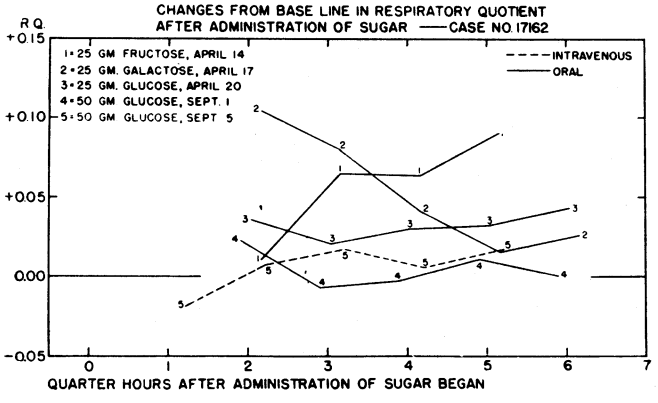

FIG. 3. RESULTS OF SUGAR ADMINISTRATION TO CASE NO. 17162.

With this patient 25 grams each of fructose, galactose, and glucose were given in April. The fructose produced a rise which was slow in reaching its maximum effect. With a normal we would expect a maximum at the third quarter hour. With galactose, however, the rise was very marked (over +0.10) and followed the course that it might with a normal. The two lots of 50 grams of glucose orally and intravenously in September show but little, if any, definite rise.

The third case, Fig. 5 (18425), is a young Jewish salesman whose insulin requirement had been very slight, and in the course of a few weeks rose to 500 units a day. He has begun, although he is a somewhat more recent case, to show this same subsidence in the severity of the resistance.

A fourth case (19110), Fig. 6, was a woman whose diabetes began last February, and at the same time she was found to have

jaundice. Between February and June when she came to the Deaconess Hospital her insulin requirement had risen to 150 units. She had jaundice; carcinoma was suspected; operation was carried out and two stones in the common duct were removed. At the time of operation she was taking 600 units a day. Within a few days her insulin requirement was 1000 units. The jaundice gradually subsided. That was July. On September 18 her blood sugar was 180 milligrams after a meal, her urine sugar free, and she is now taking no insulin.

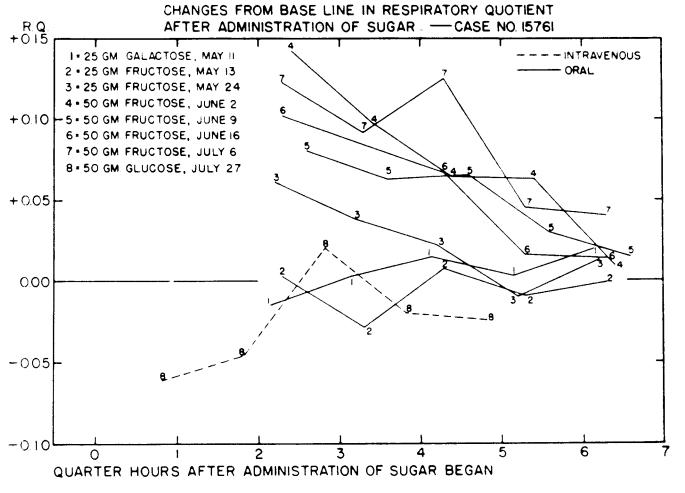

FIG. 4. RESULTS OF SUGAR ADMINISTRATION TO CASE NO. 15761.

The chart shows the effect of giving by mouth, in several different experiments, 25 grams of galactose and fructose, respectively, 50 grams of fructose, and finally of giving intravenously (in July) 50 grams of glucose. The 25-gram experiments with fructose and galactose did not show a very significant rise. This is truer of the fructose than of the galactose. On May 24, however, the same amount of fructose did produce a marked rise of 0.06 or over. The 50-gram doses of fructose all produced very marked rises and were typical of what we might expect with a normal subject. The 50 grams of glucose intravenously shows no definite rise.

These cases are striking in that they show one feature that I want to stress, namely the cyclic character of this phenomenon of insulin resistance. It is not true in all cases of insulin resistance where the requirement is measured in hundreds of units. I am not interested

in cases that take 100 to 200 units a day for a week or two, but patients in whom the requirement is several hundred units a day under hospital conditions for a considerable period of time.

The striking thing about Case 17162 is the contrast between April and September 1939. During that interval, by treating himself at home and taking insulin every one to two hours, this young clergyman had reduced his insulin requirement to about 100 units, but he had not weighed his diet, the composition of the diet had changed, he

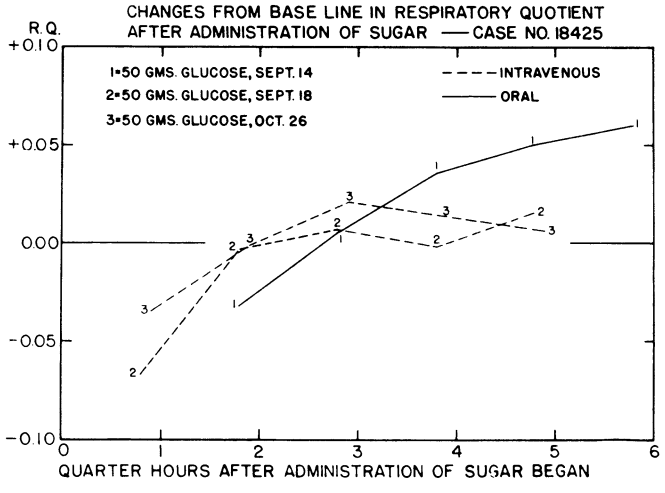

FIG. 5. RESULTS OF SUGAR ADMINISTRATION TO CASE NO. 18425.

There were three experiments with 50 grams of glucose. Two of these, in which the glucose was given intravenously, showed little or no change in the respiratory quotient. In the one experiment in which the sugar was given orally, the change in the respiratory quotient followed somewhat the course that it might take with a normal subject, and it would appear that even at the end of 1½ hours the quotient had not reached the maximum.

had taken a great deal more fat, and his respiratory quotient, even though the diabetes was under reasonably good control, was much lower than in the spring. This case of insulin resistance, then, shows that even with very large amounts of insulin we had not brought about a normal response to glucose under the conditions of this experiment.

FIG. 6—RESPIRATORY QUOTIENT AFTER GIVING 50 GMS. GLUCOSE INTRAVENOUSLY.

Period	Time a.m.	R. Q.	O_2 per minute, cc.
1	8:40	0.736	196
2	8:50	.735	187
3	9:00	.779	195
	Average	.750	193
Glucose injection, 9:28-9:41 a.m.			
4	10:28	.838	200
5	10:43	.818	199
6	10:58	.843	198
	Average	.833	199

In the case of the nurse (15761) we also have a series of curves. Curve No. 1 is galactose on May 11, and it shows hardly anything like normal response with galactose. Curve No. 2 was obtained with fructose on May 13; again no effect comparable with the rapid and prompt rise usually obtained in normal subjects with fructose. Curve No. 3, again fructose on May 24, now beginning to show a normal type of rise; No. 4 again is fructose on June 2, a normal rise in the quotient of 0.15; No. 5, again fructose on June 9, a response well up to normal; No. 7, fructose normal; No. 8, glucose, July 27, in which we have practically no response to glucose at a time when she was taking about 2000 units of insulin a day.

The striking thing in Case 18425 is that here intravenous administration of glucose did not give any significant rise in respiratory quotient. With orally administered glucose we obtained a better response, first a drop below normal, and then a rise. This clue might be interpreted as suggesting that since glucose taken by mouth goes through the liver first, whereas glucose given by vein goes directly to the muscles, perhaps this may explain the differences in the curves seen in these patients.

In Figure 7 are shown the data from a case who ought to be resistant to insulin, according to all teachings with regard to the pituitary gland, because this patient is a full-blown case of acromegaly in an Italian woman fifty years of age. Here we attempted to see whether acromegaly in its full-blown character would show any characteristic differences in the behavior of the respiratory quotient. Curves 1 and 2 show a slow and moderate rise in quotient following,

practically the same with glucose orally given as with intravenous glucose, which is characteristic of normal individuals. The third curve shows the increased rise in the respiratory quotient obtained by giving 50 grams glucose by mouth and at the same time giving a dose of 30 units of insulin. Whatever else insulin may do, it has the power in acromegalics as well as in non-acromegalic diabetics to raise the respiratory quotient when glucose is given and to increase the rise of the respiratory quotient over what is obtained with glucose alone.

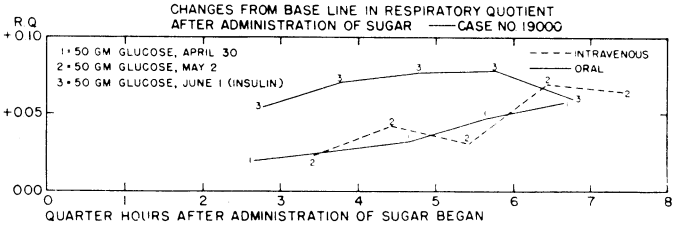

FIG. 7. RESULTS OF SUGAR ADMINISTRATION TO CASE NO. 19000.

With this subject there were two experiments in which 50 grams of glucose were given by mouth. In one of these insulin was also given at the start of the experiment. Both experiments showed definite rises in quotient, the rise in the experiment with insulin being much more marked and showing a definite difference between giving sugar with and without insulin. In a third experiment the intravenous injection of 50 grams of glucose also resulted in a definite and marked rise in the respiratory quotient, particularly after the end of 1½ hours.

That patient is only slightly resistant to insulin and in some twenty-nine cases of acromegaly and diabetes I have been unable to see in the acromegalic diabetic any evidence of any greater variation in insulin resistance than we see very commonly in non-acromegalic diabetics. That is not to say that acromegalics do not at some times show insulin resistance, but in no case that I have been able to find has there been insulin resistance comparable to the degrees of insulin resistance shown in these preceding cases.

In these cases of insulin resistance we did not get any evidence incriminating the liver with fructose determinations. In the patient (Case 19110) with extreme obstructive jaundice associated with common duct stones, in whom the liver section taken at operation incidentally showed normal glycogen distribution, the administration of glucose and insulin during the recovery phase gave an almost nor-

mal response in the respiratory quotient. In summary, untreated and uncontrolled diabetic patients have a very low respiratory quotient, fasting, which will rapidly rise during a few days of insulin treatment; patients under insulin treatment will show a rise in fasting level of the respiratory quotient if the amount of carbohydrate in the diet is increased. When a single dose of insulin and of glucose are given simultaneously intravenously, a striking rise in the quotient can be produced which is greater than will occur if glucose alone is given. This occurred in one acromegalic diabetic as well as in non-acromegalic diabetics. In patients with insulin resistance in whom the efficiency of insulin action is seriously impaired, if sufficient insulin is given the respiratory quotient can be raised to a normal level, indicating at least a partial correction of disturbed carbohydrate metabolism. In two highly resistant cases the response of the quotient to levulose became normal. In one patient when no insulin had been given for twenty-four hours, the administration of glucose by vein was followed by a much smaller increase in respiratory quotient than when glucose was given by mouth, a fact for which we have as yet no explanation.

Have we an explanation for these instances of resistance? There is a certain similarity in this cyclic character of insulin resistance to the cycles in acromegaly. It is a tempting similarity, but so far we have found no evidence in any of these patients of any suggestion of acromegaly or any hyperpituitary state. Roentgenogram of the sella turcica, examination of the eye-grounds and fields of vision were done. The urines have been studied for antipituitary substances without result. We have no explanation except by analogy. We do know that the effect of insulin can be modified greatly by the addition of chemical substances. Certain of the minerals will greatly retard the action of insulin. Certain ferments can be used to modify its action, and then the insulin can be returned to normal by chemical treatment. The patient with jaundice due to common duct stones strongly suggests that the cause is some change internal within the body which results in the production of a chemical substance which, uniting with insulin, slows up and reduces its efficiency. Other possibilities include injuries of the islands of Langerhans either temporary toxic or actually destructive, and disturbed function of the skin muscles or other endocrine glands.

It seems to me that in these resistant cases we may have a clear indication of one of the very important features of insulin action recently emphasized by Dr. Best, namely, its sparing effect upon the islands of Langerhans. We may assume that in these cases some damage was going on to the islands of Langerhans, but by giving sufficient insulin we have this return to more or less normal insulin requirement, suggesting the mechanism that Dr. Best has brought out when he has shown that one can now produce diabetes and harm the islands of Langerhans by pituitary extract substance in animals and then by giving insulin in sufficient quantities at the right time can produce the actual regeneration of the islands, healing of the process, and cure of the diabetic animal.

REFERENCES.

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2. CAMPBELL, BEST, HORST: New Eng. Jour. Med.

DISCUSSION.

DR. JOHN MINOR (Washington, D. C.): I should like to ask Dr. Root whether he has had occasion to study any cases of hemachromatosis connected with this study, and, if so, how he would relate it to this problem of insulin resistance, they being so notoriously resistant to insulin.

DR. GEORGE A. HARROP (Princeton, N. J.): How commonly in your series, Dr. Root, have these cases of insulin resistance occurred?

DR. BYRON D. BOWEN (Buffalo, N. Y.): I should like to ask the effect of hypoglycemia and whether he has treated any of his patients with X-ray to the pituitary. I mention that because we had a patient within the year who was admitted to the hospital taking 100 units of insulin a day, after several treatments over the pituitary, and the reason treatments were given was that she was thought to be a possible Cushing's syndrome. We have observed her since that time and she has required no insulin.

DR. HOWARD F. ROOT (Boston, Mass.): These are very interesting questions to answer. How common? They are not common; they are very rare. When you limit cases to patients requiring prolonged hospital treatment doses of hundreds of units, excluding patients requiring 300 or 400 units temporarily during acidosis, I can think of three or four others perhaps in some 15,000 or 16,000. However, the occurrence of less severe degrees of insulin resistance is certainly becoming more common. One must be prepared to use doses of 100 to 200 units of insulin a day on short notice and to continue such doses if diabetic catastrophes are to be avoided.

Dr. Herrmann will remember one patient 70 years of age who a year ago required no insulin whatever. She started out with full-blown symptoms, but now, in three or four months, has gone through such a phase requiring 180 units a day.

We have not carried out these studies in hemachromatosis. Hemachromatosis varies tremendously—not always resistant, but resistant when the process is really causing progressive destruction of the islands of Langerhans. In one case a doctor required 1600 units a day, but died in coma with hemachromatosis in spite of 1600 units a day.

Hypoglycemia. I wonder if you have in mind people in whom the respiratory quotients were studied and the conclusion was reached that one could have hypoglycemia without a corresponding rise in quotient, and therefore that insulin wasn't causing carbohydrate combustion. One of our striking cases was a girl of 20 years who had had coma 15 or 18 times, who came to the hospital for exploration. There was a question of tumor. We did a respiratory quotient, because she was such a hopelessly bad case, one hour before the operation. It was started at 6:30 in the morning, finished at 7:00, operation was at 8:00. Her respiratory quotient was 82, a normal quotient, but she had a blood sugar of 40 milligrams at the time. She was operated upon, a liver section was removed at the end of operation and the liver section showed 12 per cent glycogen, higher than the normal glycogen content, but also higher than normal fat content.

I don't know how to explain that except that I assume she had a higher quotient at that time than was normal for her. Her normal quotient is usually 0.71, but she had had protamine zinc insulin 24 hours earlier with a rise in quotient.

X-ray treatment. That young clergyman had a series of X-ray treatments directed both at his pituitary and his parathyroids, not under our direction, but elsewhere. Unfortunately for our thesis the X-ray treatments were carried on at a time after his insulin requirement had fallen from 2000 units to about 500; in other words, the disappearance of resistance had progressed certainly 50 per cent before he had X-ray treatment. In the other cases that we have given X-ray, one of whom was a case suspected of being Cushing's syndrome, we have not been able to show any definite effect from X-ray treatment of the pituitary.