XVIII. THE EARLY ACTION OF INSULIN IN THE DIABETIC.

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EVEN in the case of the normal animal opinion is divided as to the effect of insulin on the metabolism of carbohydrate. Macleod [1922] and others believe that the first action of insulin is to cause the storage of sugar as glycogen. Dudley and Marrian [1923], as the result of experiments on normal small animals, came to the conclusion that insulin does not cause glycogen to be stored.

The object of the present investigation was to attempt to throw some light on this subject as affecting the diabetic. It was planned to study the respiratory exchange and blood sugar levels in the diabetic as influenced by the administration of food with and without protection from insulin.

For this purpose we investigated the respiratory exchange of four severe cases of diabetes, three of whom were adult males and one a youth of 19 years of age.

That they were cases of a severe type is shown by blood sugar curves obtained from each of them after the administration of 25 grams of glucose. As judged by the trend of the curves, Case IV was the most severe, Cases I and II reacted similarly, Case III was the least severe of the series. The results obtained by the administration of glucose were on the whole confirmed by clinical examinations of the patients.

The general plan of the experiments was to administer a certain meal after a basal metabolism determination and blood sugar estimation had been made. The metabolism and blood sugar levels were followed at intervals of 15 to 30 minutes. The effect of insulin was determined by repeating the control experiment, except that 30 minutes before a given meal a dose of insulin was injected. We thus have comparative experiments which show the effect of insulin on meals of various components in cases of diabetes of varying severity. All experiments were performed in the morning, the patients having abstained from food for 12–14 hours previously. The basal metabolism determinations were made with the open circuit apparatus of C. V. Bailey [1921]. In order that the samples of air could be examined at leisure, they were collected in gas pipettes over mercury, as was done by Wolf and Hele [1914], and analysed at the close of the experiment. Over 100 basal metabolism estimations were performed on the four patients. The results are, on the whole, very uniform

and allow us to draw some conclusions regarding the early influence of insulin on the diabetic.

Case I. The urine on admission to the hospital contained 7·6% of glucose and gave strong qualitative tests for acetone and acetoacetic acid. The experiments were commenced after a period of nine days, in which time the patient was given sugar-free and fasting regimens. With a daily diet of five eggs, ten ounces of green vegetables, and 1¾ ounces of butter, the urine contained traces of sugar, not estimable quantitatively. Acetone was present. The first experiment, after a 14 hour fast, was done with a meal containing 12·04 grams of protein, 20·0 grams of fat, with a total heat value of 238·3 Calories. The ketogenic-anti-ketogenic ratio, applying Woodyatt's formula [1922], was 2·5 : 1·0. This high ratio asserted itself in the increase in acetone compounds after the meal. From Exp. 1 it will be seen that the basal metabolism was 13 per cent. below the Dubois [1916] normal. The effect of the protein and fat was to raise the metabolism 17 per cent. within three-quarters of an hour after the meal; in two hours and a quarter the metabolism began to fall. The CO_2 was also increased, but not proportionately to the O_2 absorbed. The lung ventilation followed somewhat closely the execretion of CO_2.

The respiratory quotient in the basal state was 0·754 but with the administration of food the quotient fell, to resume its higher value at the end of the morning. The consumption of 12 g. of protein and 20 g. of fat did not materially alter the quotient.

The effect of insulin and a similar meal given to this patient is seen in Exp. 2. The experiment was performed six days after the preceding. The higher sugar concentration in the urine is explained by the fact that the patient surreptitiously obtained some bread the day before, and this was not discovered until the tests had been commenced.

The basal metabolism starts practically from the same level as in the previous experiment, namely 12 %. There did not appear to be the same influence on the metabolism due to the carbohydrate consumed the day before, as the respiratory quotient was 0·705. Lusk [1922] has recently shown that the effect of a carbohydrate meal may be traced for over 20 hours, and our findings appear to corroborate those of the American worker.

There is a small but unmistakable rise in the oxidation of carbon-rich substances, probably carbohydrate, following the injection of insulin, but the blood sugar remains constant indicating that the carbohydrate consumed was drawn from other sources than the sugar of the blood, or that a constant replacement of sugar was being effected, resulting in the glucose level in the blood being maintained. The dynamic rise in metabolism as a result of food protected by insulin is not as great as without the hormone, nor does the lung ventilation follow so closely the CO_2 elimination. There is again a definite drop in the respiratory quotient following the ingestion of food, but what is of greater interest is that metabolism is transferred almost entirely to the combustion of protein and fat, since in the triangular diagrams of

Case I. Computed oxygen absorption in the basal state: *217 cc. per min.*

	Time	Per min. O₂ c.c.	B.M.R. %	CO₂ cc.	R.Q.	Litres Lung vent.	Blood % sugar	Urine % sugar	acetone	Remarks
Exp. 1	9.30	—	—	—	—	—	0·223	Trace	+	} Absolute rest
	10.15	187	− 13	141	0·754	5·19	—	—	—	
	10.30	—	—	—	—	—	—	—	—	P. 12 g., F. 20 g., C. 0 ingested
	11.0	—	—	—	—	—	0·206	—	—	
	11.20	226	+ 4	166	0·735	5·79	—	—	—	} Patient quiet
	12.40	215	− 1	161	0·750	5·75	—	—	—	
	12.45	—	—	—	—	—	0·203	Trace	+ + +	
Exp. 2	9.10	—	—	—	—	—	0·262	0·2	3·7	} Absolute rest
	9.40	191	− 11	135	0·705	5·02	—	(g. per 1000 cc.)		
	10.0	—	—	—	—	—	—	—	—	*Insulin* U. 10
	10·25	199	− 8	149	0·749	5·40				
	10.30	—	—	—	—	—	0·260			
	10.40	—	—	—	—	—	—	—	—	P. 12 g., F. 20 g., C. 0 ingested
	11·10	217	± 0	155	0·715	5·23				
	11.30	—	—	—	—	—	0·208	—	—	
	11·45	222	+ 2	166	0·740	5·43	—	—	—	} Patient quiet
	12.15	219	+ 1	166	0·760	5·42	—	—	—	
	12.35	215	− 1	165	0·765	5·35	—	—	—	
	12·45	—	—	—	—	—	0·162	0·2	1·9	
Exp. 3	9.10	—	—	—	—	—	0·195	0	6·8	} Absolute rest
	9.45	181	− 16	129	0·710	5·05	—	—	—	
	10.0	—	—	—	—	—	—	—	—	P. 16·4 g., F. 24·7 g., C. 27 g., ingested
	10.45	223	+ 3	157	0·705	5·63	—	—	—	
	11.0	—	—	—	—	—	0·187	—	—	
	11.15	233	+ 7	171	0·735	6·20	—	—	—	} Patient quiet
	11.40	241	+ 11	182	0·755	6·37	—	—	—	
	12.20	232	+ 7	183	0·790	6·38	—	—	—	Becoming a little restless
	12.30	—	—	—	—	—	0·270	1·58	7·5	
Exp. 4	9.10	—	—	—	—	—	0·165	0·37	1·06	} Absolute rest
	9.45	171	− 21	121	0·710	5·09	—	—	—	
	10.0	—	—	—	—	—	—	—	—	*Insulin* U. 10
	10.25	189	− 13	139	0·735	5·20	—	—	—	
	10.30	—	—	—	—	—	0·285	—	—	P. 16·4 g., F. 24·7 g., C. 27 g., ingested
	11.15	225	+ 3	160	0·710	5·54				
	11.30	—	—	—	—	—	0·221			
	11.45	220	+ 1	173	0·785	5·31				
	12.10	219	+ 1	172	0·783	5·37				
	12.30	212	− 2	160	0·755	5·32				
	12.45	—	—	—	—	—	0·247	0·43	0·87	
Exp. 5	9.10	—	—	—	—	—	0·115	0	0·096	} Absolute rest
	9.40	173	− 20	125	0·721	4·93	—	(g. per 1000 cc.)		
	9.50	—	—	—	—	—	—	—	—	*Insulin* U. 15
	10.15	189	− 13	143	0·755	5·18				
	10.20	—	—	—	—	—	0·100			
	10.30	—	—	—	—	—	—	—	—	P. 16·4 g., F. 24·7 g., C. 27 g., ingested
	11.10	214	− 1	144	0·673	5·39	—	—	—	
	11.25	—	—	—	—	—	0·141	—	—	
	11.40	232	+ 7	165	0·711	5·61	—	—	—	} Patient quiet
	12.5	231	+ 7	167	0·723	5·67	—	—	—	
	12.35	226	+ 4	165	0·732	5·64	—	—	—	
	12.40	—	—	—	—	—	0·146	0	0·119	

Case I (continued)

Time	O₂ cc.	B.M.R. %	CO₂ cc.	R.Q.	Litres Lung vent.	Blood % sugar	Urine % sugar	Urine % acetone	Remarks
Exp. 6 9.10	—	—	—	—	—	0·187	0	0	Absolute rest
9.45	198	− 8	144	0·730	5·23	—	—	—	
9.55	—	—	—	—	—	—	—	—	Insulin U. 20
10.20	190	− 12	147	0·776	5·57	—	—	—	
10.25	—	—	—	—	—	0·171	—	—	
10.30	—	—	—	—	—	—	—	—	P. 6·6 g., F. 6·6 g., C. 40·5 g., ingested
11.0	218	+ 1	159	0·730	5·65	—	—	—	
11.5	—	—	—	—	—	0·265	—	—	
11.30	212	− 2	167	0·788	5·60	—	—	—	Patient quiet
12.0	213	− 2	164	0·772	5·55	—	—	—	
12.40	201	− 7	161	0·800	5·63	—	—	—	
12.45	—	—	—	—	—	0·216	0	0	
Exp. 7 9.10	—	—	—	—	—	0·156	0	Trace	Computed B.M.R. 223 cc. O₂
10.10	229	+ 3	165	0·723	6·57	—	—	—	
10.15	—	—	—	—	—	—	—	—	P. 6·6 g., F. 6·6 g., C. 40 g., ingested
10.55	—	—	—	—	—	0·174	—	—	
11.0	220	− 2	150	0·685	5·52	—	—	—	
11.30	247	+10	188	0·763	6·41	—	—	—	Patient quiet
12.0	244	+ 9	206	0·846	6·39	—	—	—	
12.30	239	+ 7	186	0·780	6·52	—	—	—	
12.45	—	—	—	—	—	0·266	1·2	Trace	

Case II. Computed oxygen absorption in the basal state: *204 cc. per min.*

Time	O₂ cc.	B.M.R. %	CO₂ cc.	R.Q.	Litres lung vent.	Blood % sugar	Urine % sugar	Urine % acetone	Remarks
Exp. 10 9.20	—	—	—	—	—	0·090	0	Trace	Absolute rest
10.5	186	− 9	135	0·726	5·74	—	—	—	
10.20	—	—	—	—	—	—	—	—	P. 16·4 g., F. 24·7 g., C. 27 g., ingested
11.0	210	+ 3	147	0·701	6·02	—	—	—	
—	—	—	—	—	—	0·130	—	—	
11.40	214	+ 5	159	0·743	6·77	—	—	—	Patient quiet
12.15	213	+ 4	165	0·777	6·70	—	—	—	
12.50	218	+ 7	165	0·756	6·63	—	—	—	
1.0	—	—	—	—	—	0·232	Trace	Trace	
Exp. 11 9.10	—	—	—	—	—	0·114	0	0	Absolute rest
9.45	187	− 8	134	0·715	5·51	—	—	—	
9.50	—	—	—	—	—	—	—	—	Insulin U. 15
10.15	174	− 14	128	0·732	5·27	—	—	—	
10.25	—	—	—	—	—	0·106			
10.35	—	—	—	—	—	—	—	—	P. 16·4 g., F. 24·7 g., C. 27 g., ingested
11.15	201	− 1	144	0·714	5·48	—	—	—	
11.20	—	—	—	—	—	0·115	—	—	
11.40	199	− 2	147	0·738	5·53	—	—	—	Patient quiet
12.10	202	− 1	156	0·775	5·59	—	—	—	
12.40	202	− 1	157	0·779	6·01	—	—	—	
12.45	—	—	—	—	—	0·116	0	0	

Dubois the oxidation of carbohydrate takes very little part in a metabolism the respiratory quotient of which is 0·715. It will be noticed, however, that the respiratory quotient rose steadily, the final figure being above that found in the companion experiment without insulin.

Disregarding any calculations as to the relationships between the blood sugar levels and the respiratory quotient, one may only say that the acetone concentration in the urine was less at the end of the experiment, indicating a more efficient combustion of fat, possibly due to the utilisation of carbohydrate as the result of the use of insulin.

Comparing the results obtained in the two experiments, it will be seen that the immediate effect of insulin is to increase the combustion of carbohydrate in the post absorptive state. Following the ingestion of the diet, the combustion is apparently transferred to the combustion of protein and fat, since the respiratory quotient falls at first, reaching a higher level at the end of 2½ hours when assisted by insulin than without it. What also is noteworthy is that the total metabolism following the ingestion of food and insulin is lower than without the hormone.

The next three experiments are concerned with the metabolism of the diabetic consuming meals containing protein, fat and carbohydrate. The effect of varying the amounts of insulin injected was investigated. The protocols are given under Expts. 3, 4 and 5. The meal contained protein 16·4 grams, fat 24·7 grams, carbohydrates 27·0 grams. Total calories 408. Ketogenic-anti-ketogenic ratio 0·75 : 1. Exp. 3 shows the simple experiment where no insulin was administered. That the patient was incapable of catabolising the available carbohydrate in the meal is shown by the fact that while the urine was sugar-free at the commencement of the experiment, the concentration of glucose at the end was 1·58 %. The effect of the meal containing all three principal food components is to raise the total metabolism 7 % above the level obtained with fat and protein alone. That this increase does not result from an increased combustion of the carbohydrate is shown by the fact that the rise in the total metabolism is not coincident with the highest respiratory quotient. One may therefore conclude that it is due to the promoting action of the carbohydrate on the combustion of protein and fat. The rise in the blood sugar level does not take place until the final specimen, when a value, of 0·27 % was obtained. This corresponds to the finding of sugar in the urine of 1·58 %. In spite of the ketogenic-anti-ketogenic ratio of the food being 0·75 : 1·0, the excretion of acetone bodies was increased after food, due doubtless to the inefficiency of carbohydrate utilisation.

Exp. 4 was done six days later and demonstrates the effect of 10 units of insulin upon the metabolism after the ingestion of protein, fat and carbohydrate. The basal metabolism on this morning was—21·0 % with a respiratory quotient of 0·71. There was a trace of sugar in the urine in spite of the fact that the blood sugar was 0·17 %.

The immediate effect of the injection of 10 units of insulin was to increase

the combustion of carbohydrate as shown by the elevation of the respiratory quotient from 0·71 to 0·735. The drop in the respiratory quotient as the result of giving food is well seen and the rise to a value of 0·785 is thereafter rapid. As the lowest respiratory quotient is coincident with the greatest oxygen absorption it is evident that carbohydrate can have taken little part in the elevation of the metabolism.

The amount of insulin administered was not sufficient to protect the patient from a characteristic rise in blood sugar, which reaches its highest point in the final blood sugar estimation $2\frac{1}{2}$ hours after the patient received food. Whether insulin has an effect on the absorption of carbohydrate from the alimentary canal, which seems unlikely, or whether some step in the intermediary fate of the food stuff is accelerated, there appears to be a more immediate rise in the level of blood sugar with than without insulin, and this phenomenon we have seen in others of our experiments. As the commonly accepted ratio between the amount of sugar capable of being catabolised per unit of insulin used is as 2 : 1 and the food contained in all 39 g. of available carbohydrate from the bread, 9·52 from the protein, and 2·47 from the fat, the rise in blood sugar and increase in urinary sugar was to be anticipated with only 10 units of insulin given.

In order to see if an increase in insulin dosage would alter the type of curve, another experiment was performed seven days later (Expt. 5). The daily diet had been increased until the patient was receiving 1153 Calories per day, of which 56 Calories were contributed by carbohydrates. The same meal as in the previous experiment was administered, preceded, however, by 15 units of insulin. In this experiment the amount of insulin was sufficient to keep the blood sugar below the threshold for this case and there was, therefore, no sugar excreted in the urine. As will be seen, the trend of the total respiratory exchange and respiratory quotients is similar to that in the previous experiment, the respiratory quotient falling as the result of the administration of food. There is no late depression in total metabolism. Viewing this experiment as a whole it seems that the organism was able to utilise the greater part of 39 g. of carbohydrate. That the low respiratory quotients were not due to a retention of CO_2 by the liberated alkali on the disappearance of the ketonic acids from the blood, as Davies and his co-workers suggest, is negatived by the fact that the concentrations of acetone compounds in the urine at the beginning and end of the experiments are not in harmony with this idea. If large quantities of lactic acid were formed, there would be a tendency to an increased lung ventilation. There was, as a matter of fact, a decrease. The only theory therefore which appears to satisfy the condition is a transformation of the carbohydrate into glycogen or into a substance of unknown composition.

At this point in his treatment the patient received 15 units of insulin daily, administered in three 5-unit doses. His total consumption of food, 57·3 g. as protein and 37·6 g. as carbohydrate, was equivalent in all to 1471 Calories. After seven days of this treatment we estimated the effect of

three ounces of bread in one meal after protection by 20 units of insulin given in one dose (Exps. 6 and 7). As the bread given contained 40·5 g. of carbohydrate, 6·6 g. of protein, and 6·6 g. of fat, the total amount of available glucogenic material was 44·0 g. Assuming the customary ratio between carbohydrate and insulin we should have expected practically complete protection by the hormone. The results of giving the three ounces of bread preceded by an injection of 20 units of insulin were as follows.

Owing, doubtless, to his continued insulin treatment, the basal metabolism on this day was—8·0 %, 12 % higher than that obtained in the previous week. The respiratory quotient was 0·730, indicating a metabolism concerned chiefly with the combustion of protein and fat. The diet even with the amount of insulin given contained an excess of carbohydrate, as shown by the high blood sugar, and the presence of glucose in the urine. After the 14 hour fast the urine was sugar- and acetone-free.

The immediate effect of 20 units of insulin was to depress the total metabolism and elevate the respiratory quotient. This immediate depression of the total metabolism was not seen in the previous experiment with smaller dosages of insulin, but was seen in other of our experiments, notably case II, where 10 units were sufficient to depress the total metabolism. It is not altogether easy to explain this depression. Kellaway and Hughes suggest the transformation of carbohydrate to some substance unknown, the change involving an economy of oxygen and a liberation of excess of carbon dioxide. It is possibly also a protective phenomenon in which the proportion of carbohydrate burnt is increased and thus spares protein and fat. This involves a lower amount of oxygen used and hence is represented in indirect calorimetry as a fall in the total metabolism. It will be noted that during this period the respiratory quotient rose.

The ingestion of three ounces of bread raised the metabolism 9 % above the determined basal level, whereas protein and fat of the same caloric value decreased the level 17 %. The blood sugar rose almost immediately after the ingestion of bread to 0·265 %. With this figure the respiratory quotient rose in the course of the morning to 0·80, the highest obtained with the patient.

Twenty units of insulin in this patient depress the total metabolism and increase the proportion of carbohydrate utilised. The drop in the respiratory quotient after food is again pronounced and does not confirm the observation of Wilder, Boothby and Beeler [1922], who state that the depressor effect is greatest after protein.

Two days after the foregoing series of tests was performed, the daily dose of insulin was increased to 24 units. With this three ounces of bread were given, one after each injection. Sugar was still present in the urine. The dose of insulin was raised to 30 units per day, and finally to 45 units per day. With this dose the patient remained aglycosuric and added 11 pounds to his weight. The effect of giving three ounces of bread without the protection of insulin was now determined. It will be noted (Exp. 7) that the basal metabolism

had risen as the result of treatment from -20% to $+3\%$, confirming Joslin's observations [1918] and lending support to the contention that the basal metabolism is really low in severe cases of diabetes.

In the present experiment the specific dynamic action of the carbohydrate followed on the rise in the respiratory quotient and indeed the total metabolism had already fallen when the respiratory quotient was still on the increase.

There does not seem to have been any increase in carbohydrate tolerance, for, referring to Exp. 3, it will be seen that 39 g. of available carbohydrate raised the blood sugar at the end of $2\frac{1}{2}$ hours to 0.270%, while in the present experiment, the blood sugar rose to 0.266% after three ounces of bread. There was undoubtedly a certain amount of carbohydrate utilised, as the respiratory quotient of 0.846 indicated, but the 20 units of insulin given did not produce a normal catabolism of sugar.

Having discussed in some detail the results obtained with one case of diabetes we now present the results of experiments with three others. These results will be discussed only in so far as they bear comparatively on the first case.

Case II, aged 50, was one with a marked family history of diabetes. The urine on admission contained 6.9% of glucose; the blood sugar was 0.245%. He reacted very quickly to fasting, the urine becoming sugar free in two days. Exps. 10 and 11 were performed on this patient. The results go to show that insulin by itself enables the reserve carbohydrate to be catabolised, and at the same time depresses the total metabolism, and furthermore lowers the dynamic action of a given meal when injected 30 minutes prior to the meal.

Case III is presented as that of a diabetic with a history of loss of weight extending over ten years. As will be seen from Exps. 14, 15, 16 and 17, this patient reacted less promptly to insulin. The elevation of the respiratory quotient from insulin alone was present but less marked. The depression of the specific dynamic action of protein was not seen. There was little increase in carbohydrate tolerance even after treatment with insulin for 45 days, showing the refractory nature of the condition. Case IV is presented as a contrast to the foregoing. The patient was a youth of 19 years of age, who had been treated in the hospital about eight months previously, during which time his tolerance had been raised so that he was able to take Graham's full diet with two ounces of brown bread and one ounce of potatoes. His urine at that time was free from sugar and the blood sugar was 0.086%.

On re-admission the urine contained 4.2% of glucose. After 25 g. of glucose the blood-sugar rose to 0.340%. As will be seen from Exp. 18, the effect of nsulin on this patient was very striking. It produced within 25 minutes an elevation of the respiratory quotient from 0.763 to 0.830, with a drop of 7% in the oxygen absorption.

The administration of two ounces of bread increased the metabolic rate 13% above the basal value. The stimulation of metabolism was only transitory.

In two hours, however, the respiratory quotient had risen to 0·890, indicating that a considerable quantity of carbohydrate was being oxidised.

The second experiment with this patient was a control of the foregoing. He received two ounces of bread without the preliminary protection with insulin. The effect of this is strikingly shown in Exp. 19. The basal oxygen absorption had dropped to − 12 % and the respiratory quotient was at the high level of 0·877. The blood sugar level had fallen to 0·114 %, the urine was sugar-free and contained only a trace of acetone. Obviously the patient was reacting promptly to the restricted diet which was that of Graham's third day.

Case III. Computed oxygen absorption in the basal state: *210 cc. per min.*

	Time	O₂ cc.	B.M.R. %	CO₂ cc.	R.Q.	Litres lung vent.	Blood % sugar	Urine % sugar	Urine % acetone	Remarks
Exp. 14	9.15	—	—	—	—	—	0·133	0	2·19	Absolute rest
	9.55	206	− 2	144	0·699	5·59	—	—	—	
	10.20	—	—	—	—	—	—	—	—	P. 16·4 g., F. 24·7 g., C. 27 g.,
	10.55	226	+ 8	151	0·667	5·20	—	—	—	ingested
	11.0	—	—	—	—	—	0·191	—	—	
	11.30	226	+ 7	166	0·735	5·50	—	—	—	Patient quiet
	12.0	242	+15	164	0·676	5·42	—	—	—	
	12.30	247	+18	170	0·687	5·75	—	—	—	
	12.40	—	—	—	—	—	0·195	2·76	2·16	
Exp. 15	9.15	—	—	—	—	—	0·083	0	1·90	Absolute rest
	9.55	210	± 0	142	0·677	4·78	—	—	—	
	10.0	—	—	—	—	—	—	—	—	*Insulin* U. 15
	10.25	208	− 1	144	0·690	4·95	—	—	—	
	10.30	—	—	—	—	—	0·112			
	10.35	—	—	—	—	—	—	—	—	P. 16·4 g., F. 24·7 g., C. 27 g.,
	11.15	235	+12	154	0·656	5·12	—	—	—	ingested
	11.20	—	—	—	—	—	0·178	—	—	Patient quiet
	11.45	243	+15	175	0·719	5·45	—	—	—	
	12.40	248	+18	183	0·739	5·63	—	—	—	
	12.45	—	—	—	—	—	0·170	0	1·30	
Exp. 16	9.10	—	—	—	—	—	0·127	0	Trace	Absolute rest
	9.45	210	± 0	140	0·669	4·56	—	—	—	
	9.50	—	—	—	—	—	—	—	—	*Insulin* U. 20
	10.15	194	− 7	132	0·680	4·55	—	—	—	
	10.20	—	—	—	—	—	0·113			
	10.30	—	—	—	—	—	—	—	—	P. 6·6 g., F. 6·6 g., C. 40 g.,
	11.0	217	+ 3	144	0·680	4·74	—	—	—	ingested
	11.10	—	—	—	—	—	0·210	—	—	
	11.30	239	+14	166	0·696	5·19	—	—	—	Patient quiet
	12.0	232	+10	160	0·692	5·00	—	—	—	
	12.30	234	+11	158	0·674	5·01	—	—	—	
	12.45	—	—	—	—	—	0·182	1·25	Trace	
Exp. 17	9.30	—	—	—	—	—	0·110	0	0	Absolute rest
	10.0	200	− 5	145	0·723	4·70	—	—	—	
	10.15	—	—	—	—	—	—	—	—	P. 6·6 g., F. 6·6 g., C. 40 g.,
	11.20	222	+ 6	166	0·749	6·18	—	—	—	ingested
	11.30	—	—	—	—	—	0·230	—	—	Patient complained of pain on
	12.15	218	+ 4	160	0·736	5·06	—	—	—	
	12.30	—	—	—	—	—	0·232	2·34	0	application of the nose clip

Case IV. Computed oxygen absorption in the basal state: *223 cc. per min.*

	Time	Per min. O₂ cc.	B.M.R. %	CO₂ cc.	R.Q.	Litres lung vent.	Blood % sugar	Urine % sugar	Urine % acetone	Remarks
Exp. 18	9.10	—	—	—	—	—	0·210	0	Trace	} Absolute rest
	9.50	215	– 3	164	0·763	4·75	—	—	—	
	10.0	—	—	—	—	—	—	—	—	*Insulin U.* 10
	10.25	200	– 10	166	0·830	5·31	—	—	—	
	10.30	—	—	—	—	—	0·204			
	10.35	—	—	—	—	—	—	—	—	P. 4·4 g., F. 4·4 g., C. 27 g., ingested
	11.5	246	+ 10	192	0·781	5·31	—	—	—	
	11.15	—	—	—	—	—	0·246	—	—	
	11.35	221	– 1	174	0·790	5·38	—	—	—	} Patient quiet
	12.0	211	– 5	164	0·777	5·21	—	—	—	
	12.30	209	– 6	186	0·890	6·19	—	—	—	
	12.45	—	—	—	—	—	0·244	0	Trace	
Exp. 19	9.20	—	—	—	—	—	0·114	0	Trace	} Absolute rest
	10.0	195	– 12	171	0·877	6·41	—	—	—	
	10.15	—	—	—	—	—	—	—	—	P. 4·4 g., F. 4·4 g., C. 27 g., ingested
	10.55	225	+ 1	167	0·741	6·05	—	—	—	
	11.0	—	—	—	—	0·184	—	—	—	
	11.30	217	– 3	164	0·756	5·59	—	—	—	} Patient quiet
	12.0	212	– 5	166	0·783	5·72	—	—	—	
	12.30	211	– 5	165	0·783	5·35	—	—	—	
	12.45	—	—	—	—	—	0·240	Trace	Trace	
Exp. 20	9.15	—	—	—	—	—	0·122	0	Trace	} Absolute rest
	10.0	197	– 11	166	0·847	5·63	—	—	—	
	10.5	—	—	—	—	—	—	—	—	5 *pan-secretin tablets given*
	10.30	194	– 12	164	0·845	5·18	—	—	—	
	10.35	—	—	—	—	—	0·118	—	—	
	10.40	—	—	—	—	—	—	—	—	P. 4·4 g., F. 4·4 g., C. 27 g., ingested
	11.30	224	+ 1	177	0·791	5·52	—	—	—	Patient quiet
	12.0	198	– 11	160	0·807	5·35	—	—	—	
	12.45	201	– 10	158	0·788	5·84	—	—	—	
	12.50	—	—	—	—	—	0·218	Trace	Trace	

The immediate effect of the food was most striking. The respiratory quotient fell to 0·741 and the oxygen absorption was increased. The specific dynamic action of the carbohydrate was only transitory, for by the end of the morning the oxygen absorption had fallen to – 5 %. The respiratory quotient did not rise to the high figure reached in the experiment with insulin, the quotient generally indicating a restricted use of sugar. The blood sugar curve is typically diabetic, the last point reaching the value 0·24 %. These experiments strongly suggest that the immediate effect of insulin when injected into a fasting diabetic is to depress the total metabolism and at the same time to increase the proportion of sugar oxidised. Probably the former is contingent on the sparing action of the carbohydrate. This, however, is not the only action of insulin, for the final high respiratory quotient reached after the injection of 10 units of insulin and not seen in the experiment without insulin can be explained by assuming that insulin enabled the organism to oxidise a greater proportion of sugar, not, however, immediately after the ingestion of this food, but after the stimulating effect of the carbohydrate on the total meta-

bolism had passed off. This delayed oxidation of sugar may be accounted for by assuming that the first action of insulin after the initial small combustion of sugar is to convert the carbohydrate into some intermediary complex and later to assist in its combustion.

Finally, a preliminary experiment is here reported on the effect of the oral administration of a preparation of the pancreas. The makers do not claim an antidiabetic action except after long continued administration, but it was hoped to demonstrate some effect As will be seen, Exp. 20, five "pan-secretin" tablets given in place of 10 units of insulin produced no immediate effect on the respiratory quotient, the total metabolism or the blood sugar percentage. There is no evidence of an increased utilisation of sugar due to "pan-secretin." Hence this product cannot be substituted for insulin when immediate results are to be anticipated.

DISCUSSION.

The reaction to food and insulin depends on the age and the condition of the patients. The youngest patient of the series reacted quickly to a single dose of insulin. This case showed considerable capacity for oxidising carbohydrate $2\frac{1}{2}$ hours after the injection of insulin. A long standing case of the disease as illustrated by Case III showed very little evidence of any ability to utilise carbohydrate better as the result of diet and insulin. It is notable that the basal metabolic rate of the former case increased as the result of treatment while the rate of the latter remained stationary. As the basal metabolic rate increased, as the result of treatment with diet and insulin, with no corresponding increase in weight of the patient, one may advance this fact in support of the idea that the basal metabolism is really decreased in diabetes apart from any consideration of loss of weight or decreased plane of nutrition. The tolerance of the first case showed a decided improvement during his stay in hospital, while the ability of the second case to utilise carbohydrate was not increased.

The presence and function of a small store of reserve carbohydrate is made evident in these experiments. It is to this store that the metabolism is directed by the injection of insulin. Immediately the reserve carbohydrate commences to be catabolised the protective action on the protein metabolism is manifested and the total respiratory exchange falls, more or less coincidently with a rise in the respiratory quotient.

Once the metabolism has been directed into more normal channels, the organism appears to attempt to preserve the store of carbohydrate and the protein and fat are now attacked. This is the second phase, evidenced by the return of the respiratory quotient to a lower level. In some instances this is paralleled by an increase in the total respiratory exchange.

The experiments do not bear out the theory of Davies, Lambie et al. [1923] that the delayed elevation of the respiratory quotient is due to a retention of carbon dioxide by the liberated alkali on the disappearance of the keto-acids

from the blood, for the curves of acetone excretion in the urine do not correspond with this. Nor do the experiments support the theory of Briggs and Koechig [1924], viz. that the action of insulin is to promote the conversion of glucose into lactic acid, for there is no substantial evidence of an increased lung ventilation, which we would anticipate if such were the case.

The observations seem to fit in rather with the more obvious explanation that the first action of insulin is to convert glucose into glycogen, and as soon as a reasonable demand of the tissue for this substance is satisfied, the insulin enables the organism to mobilise and burn the glycogen in the normal way.

The fact that Dudley and Marrian were unable to demonstrate an increased storage of glycogen in the livers and muscles of normal animals after treatment with insulin does not appear to disprove the theory that the first action of insulin is to convert glucose into glycogen or a similar substance and later to assist in its combustion, but rather tends to confirm it. In the normal animal there is already a sufficiency of glycogen in the tissues. The action of insulin in the normal would be to bring about a combustion of this glycogen rather than a polymerisation and storage of glucose. Hence the experiments on the normal animal only apply with reserve to the processes taking place in the diabetic.

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