Man can live fairly comfortably on 30 grams of carbohydrate along with unlimited protein and fat. If a case of severe diabetes be given enough insulin to ensure his utilizing 30 grams of carbohydrate he will escape the symptoms of diabetes mellitus, but his blood sugar will be above 0.15 per cent. during the greater part of the twenty-four hours, which will cause overstimulation of the small amount of pancreas which he still possesses and gradual deterioration. The final stage will be total destruction of the pancreas; then the patient will have to rely for all the sugar-burning material on supplies from the outside. In case these fail, life would be extremely short. This is the danger which should be avoided by strictly correlating the diet with the amount of insulin available from the pancreas of the patient together with that injected.

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OBSERVATIONS ON THE INFLUENCE OF INSULIN ON NORMAL METABOLISM IN MAN.

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THE study of the respiratory exchange in diabetic patients and in depancreatized dogs by Banting and his co-workers¹ has shown that the injection of insulin, either alone or combined with the administration of sugar by the mouth, causes a pronounced rise in the respiratory quotient. This rise has been generally interpreted as indicating increased consumption of glucose, the ability to burn carbohydrate being temporarily restored by the action of insulin. Dudley, Laidlaw, Trevan, and Boock² have recently failed to find any direct evidence of such an action of insulin in normal mice and rabbits, the diminution of circulating sugar being attended by a profound fall in both oxygen consumption and output of carbon dioxide, although they observed in some experiments a marked rise in the respiratory quotient which evidently could not be attributed to increased combustion of glucose.

So far as we are aware, no observations on the influence of insulin on normal metabolism in man have been recorded, and it seemed worth while to record two such experiments, which Miss M—, a medical graduate, very kindly allowed us to make upon her. We made three series of observations, and on each occasion the subject had no food and only water to drink for the preceding fifteen hours, and during the experiment. She was kept at rest in a bed which was screened off in a corner of a ward. A number of six-minute samples of expired air were collected in a Douglas bag at approximately hourly intervals, some before and some after the injection of insulin. Before the collection of each sample the subject breathed for five minutes through the mouthpiece containing inspiratory and expiratory valves, in order to ensure respiratory equilibrium. Observations of the pulse and respirations were made during this period and during the collection of the sample. A half-hourly record of the rectal temperature was kept throughout the day of each experiment.

The insulin used in these experiments was made under Professor Drummond's direction in the Biochemical Department at University College, and was tested for us by Dr. Babkin. We have expressed the dose used in multiples of the amount required to reduce the blood sugar of a rabbit weighing 2 kilos sufficiently to cause convulsions. The injections were made subcutaneously, and changes in the blood sugar were followed, using Maclean's method for 0.2 c.cm. of blood.³

A preliminary experiment in which we took a series of eight samples of expired air, four before and four after the injection of two rabbit doses of insulin, gave the subject the necessary training in breathing and furnished an indication of the amount of insulin which could be used in our later experiments. The fall of blood sugar in four hours after this dose of insulin was from 0.123 per cent. to 0.108 per cent., and there were no significant changes in the metabolism. We give condensed protocols of our two subsequent series of observations.

In both these experiments there was a marked rise in the respiratory quotient associated with the fall in blood sugar

caused by insulin. In Experiment 2 the blood sugar fell from 0.125 per cent. to 0.080 per cent. in one and a quarter hours, and, allowing a quarter of an hour for insulin to be absorbed in sufficient amount to affect the blood sugar, there was a fall of 0.045 per cent. in an hour. If we assume, with Keith, Rowntree, and Geraghty,⁴ that the blood volume in man is 85 c.cm. per kilo of body weight, this represents a loss of $0.045 \times 76 \times 85 = 2.9$ grams of glucose. This is a conservative estimate of the amount of sugar lost from the blood, because the low level of blood sugar was maintained at 0.080 per cent. for the succeeding two hours, which suggests the attainment of an equilibrium between the sugar disposed of by insulin and that which is in all probability mobilized from the liver during the time of its action.

What is the fate of this sugar lost from the blood? Is it consumed, transformed to glycogen and stored in the liver and muscles, or is it transformed to some other complex, such as fat? If it is stored as glycogen, we are left without any

Experiment 2 (Fig. 1). Miss —, aged 26, weight 76 kilos.

Time.	Ventilation per min. in litres.	O ₂ per min. in c.cm.	O ₂ per min. in c.cm.	Respiratory Quotient.	Calories per hour.	Blood Sugar.	Temperature.	Pulse.	Respiration.
10 a.m. ...	4.35	230.6	174.4	0.756	65.7	0.125	99.4°	60	14
11.30 ...	4.25	221.0	166.0	0.741	63.5	—	99.4°	68	15
12.30 p.m. ...	Insulin—10 rabbit doses injected.					0.125			
1.45 ...	5.34	210.5	203.5	0.923	65.5	0.080	99.3°	74	15
2.45 ...	5.17	229.0	197.0	0.860	67.0	0.083	99°	71	19
3.30 ...	4.75	223.3	180.0	0.806	64.2	0.080	—	68	20

FIG. 1.—The effect of ten rabbit doses of insulin on the metabolism of a normal person weighing 76 kilos. R.Q.=respiratory quotient. Calories per hour calculated from observed oxygen consumption and R.Q. on the assumption that the rise in R.Q. is wholly due to increased combustion of carbohydrate.

At 12.30 ten rabbit doses of insulin were administered. There was a definite increase in the ventilation rate one and a quarter hours later, but the patient showed no symptoms till 2.20 p.m., when she commenced to perspire freely. At 2.45 she complained that our voices were unduly loud and that she was feeling drowsy. The drowsiness increased, "coming and going in waves," and the change in mental condition became very striking. The blood pressure was normal and there were no neurological signs. At 4 p.m. 50 grams of glucose were given and the symptoms rapidly disappeared.

Experiment 3 (Fig. 2).

Time.	Ventilation per min. in litres.	O ₂ per min. in c.c.m.	CO ₂ per min. in c.c.m.	Respiratory Quotient.	Calories per hour.	Blood Sugar.	Temperature.	Pulse.	Respiration.
10 a.m. ...	5.04	222.0	172.8	0.778	63.1	—	99.4°	55	12
11.10 ...	5.47	213.3	164.6	0.772	61.0	0.130	99.6°	60	13
11.15 ...	Insulin—8 rabbit doses injected.								
12.15 p.m. ...	5.67	229.6	193.0	0.867	67.3	0.102	99.8°	73	13-14
2.15 ...	5.90	239.0	200.6	0.839	69.3	0.077	99.4°	70	16
3.30 ...	5.38	227.6	171.6	0.754	64.8	0.089	98.2°	72	13

FIG. 2.—The effect of eight rabbit doses of insulin on the same subject as Fig. 1. Calories per hour calculated as in Fig. 1.

At 11.15 a.m. eight rabbit doses of insulin were given. There were no symptoms, though the pulse and respiration rate rose slightly, except a subjective sensation of warmth soon after the injection, and a tendency to perspire at about 2 p.m.

explanation of the pronounced rise in the respiratory quotient. We are therefore confined in our consideration to the first and last possibilities. Let us examine the first of these and assume that the glucose is consumed under the influence of insulin.

The combustion of 2.9 grams of glucose would require 2.158 litres of oxygen, and would result in the liberation of a corresponding amount of carbon dioxide, since 1 gram-molecule (= 180 grams) requires for its complete combustion 6 gram-molecules of oxygen, or 6×22.33 litres at standard temperature and pressure, according to the equation—

If the glucose lost from the blood were burnt the rise in oxygen consumption per minute should average 36 c.c.m. during the hour of the fall. Actually, the increased consumption of carbohydrate would raise the basal metabolic rate of a starving person and cause a still greater increase in the amount of oxygen used. In this experiment there was no significant rise in the amount of oxygen used, and this, together with the rise of over 30 c.c.m. in the output of carbon dioxide a minute, suggests that the combustion of glucose plays only a minor part in the production of the high respiratory quotient, and that the principal factor in causing this change is the transformation of carbohydrate to some other complex, with economy of oxygen and liberation of excess of carbon dioxide. The metabolism in calories per hour is calculated in these experiments on the assumption that the rise in respiratory quotient is due to the com-

buption of additional carbohydrate, allowing a larger production of heat from a given oxygen consumption at a higher respiratory quotient. Even on this assumption, which we believe to be unsound, the greatest increase in metabolism calculated from the observed oxygen consumption and respiratory quotient—namely, 1.3 calories an hour—does not correspond with that calculated from the combustion of the amount of sugar lost from the blood—namely, 2.9×4.1 calories = 11.89 calories.

In Experiment 3, in which we gave a smaller dose of insulin, the results do not indicate so clearly the nature of the increase in respiratory quotient. The sugar lost from the blood in two and three-quarter hours was $0.053 \times 76 \times 85 = 3.42$ grams. The amount of oxygen

necessary for the combustion of this amount of sugar is 2.530 litres, or an average of 24 c.c.m. a minute. Although the observed increase in the oxygen consumption does not attain to this calculated value, it affords definite evidence of the combustion of glucose. The disproportion between the observed increase in oxygen used—that is, 2,120 c.c.m. (q.p.)—and that in carbon dioxide given out—that is, 3,193 c.c.m. in two and three-quarter hours—supports our contention that the rise in respiratory quotient is due in part at least to transformation of glucose into some complex poorer in oxygen, and that the metabolic rate as calculated from the oxygen used and the respiratory quotient is much above its real value.

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SOME PROBLEMS OF DIABETES MELLITUS.*

BY

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NEARLY forty years ago Mering and Minkowski showed that complete removal of the pancreas resulted in a condition of diabetes. Numerous attempts have since been made to prevent the diabetes following on depancreatization by injection of extracts of pancreas. No real success resulted until the great advance made by Banting and Best. It was found that if the acinous tissue of the pancreas was allowed to degenerate after tying of the duct, an aqueous extract of the gland would diminish the excretion of sugar when injected into depancreatized dogs. This tended to explain the failure of previous workers. Presumably the active principle of the islets of Langerhans, which they termed "insulin," was destroyed by some secretion of the acinous tissue.

The discovery, due to Collip,¹ that an alcoholic extract of normal pancreas is effective, has made possible an extensive trial of the effect of insulin on diabetes in man.² These workers have treated a large number of cases, with successful results. They establish beyond doubt that injection of insulin, in the majority of cases, stops the excretion of sugar and acetone, and enables the patient to utilize an increased amount of carbohydrate.

The action of the pancreas on carbohydrate metabolism has been the subject of much study. The work of Colnheim suggested that the pancreatic secretion caused an increased consumption of glucose by the muscles. Levene and Mayer³ found, however, that the disappearance of glucose was due to the formation of a disaccharide, and that this formation took place only in concentrated solutions of glucose. If the solution was diluted the disaccharide was hydrolysed, and the reducing power showed that the glucose concentration was the same as at the beginning of the experiment. Though it is difficult to determine the precise bearing of these results on diabetes, they tend to show that the action of the pancreas is to activate some enzyme system—for the addition of pancreas or muscle extract alone to glucose was without effect; only when muscle and pancreas were acting together was any effect observed. Clark⁴ showed that the consumption of sugar by the heart was increased when the perfusing fluid was also passed through the pancreas. In a later paper⁵ he established the remarkable fact that perfusion of the pancreas

* Since this was written there has appeared an article by Hewitt (*BRITISH MEDICAL JOURNAL*, April 7th, 1923, pp. 590-591) criticizing some of this work. We propose to reply in detail in the near future.