CXXX. RESPIRATORY QUOTIENT IN OBESE SUBJECTS.

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INTRODUCTION.

A LONG series of determinations of the B.M.R. in cases of obesity under treatment, accumulated over many months, showed that while the B.M.R. was generally within normal limits, the R.Q. was usually low, and often below 0.70. Quotients below 0.70 are by no means unknown in the work of Benedict on healthy subjects during fasting [*cf.* Benedict and Higgins, 1912]. Lehmann and his co-workers [1893], in the study of a fasting individual, observed low values of the R.Q. which, during several days, averaged 0.67. Bernstein and Faltz [1916] obtained average quotients of 0.657 and 0.653 while feeding a normal individual on oatmeal, wheat, and butter; and on two different days quotients as low as 0.631 were recorded. Heinbecker [1931] has reported similarly low values in his study of the metabolism of Eskimos, and it is noteworthy that he specially remarks the relative absence of acetonuria in association with these abnormal values. The very low quotients encountered in diabetes, starvation or after administration of a ketogenic diet are undoubtedly due, in part at least, to ketosis, which means, in effect, the storage of oxygen. This is undoubtedly a factor in the low values reported by Means [1915]. Such an explanation of the results in our non-diabetic obese patients is, however, inadmissible, since the urine of these patients never contained more than a trace of ketones.

There is no doubt, however, that a value for the R.Q. below 0.69 in a diabetic subject, or 0.72 in a normal, is regarded with suspicion as due to faulty technique [*cf.* Lusk, 1928, p. 671], and we therefore considered it essential to institute a rigorous testing of the method by which our low values had been obtained.

METHOD.

The method used for the determination of the B.M.R. and R.Q. was the open method, using Haldane's face mask and Douglas bags, and analysing the collected expired air with the aid of the Haldane apparatus. This technique was employed simultaneously for the routine hospital work and for other metabolic investigations, in the course of which the very few low values of

the R.Q. found were associated with an unexpectedly low B.M.R., and could well be explained by a leak in the apparatus. In the case, however, of the obese patients on a sub-caloric diet, the very low R.Q. was encountered with a considerable degree of constancy, and was not associated with a reduced metabolic rate.

The points at which technical errors may enter into the determination of the R.Q. are:

- (1) the fit of the mask,
- (2) leakage from the bags,
- (3) faulty analytical technique,
- (4) the subject.

(1) *The fit of the mask.* The fitting of the mask was carefully carried out in every case, and tests were always made for leaks before and after the collection of expired air. The subjects co-operated intelligently, themselves pointing out any tendency to leakage between the cushion and the face. The obese person, moreover, has just that type of physiognomy to which a mask may be accurately fitted. Although there is thus no *a priori* reason for any error from this source being confined to obese people, in a series of 28 experiments the R.Q. was determined by means of a mouthpiece and noseclip, with which any leak is practically impossible. The average value was 0.014 higher than the value obtained from the same subjects, on the same occasions, with the mask. Nearly all the patients complained of greater discomfort from the mouthpiece and noseclip, and this in itself is probably sufficient to account for the slight discrepancy between the two methods—especially as the average B.M.R. was also 2.5 % higher with the mouthpiece than with the mask. In any case, a difference of 0.014 is insufficient to bring many of the low values of the R.Q. within the normal range.

(2) *Leakage from the Douglas bags.* The Douglas bags were filled with expired air from a spirometer, itself rigorously tested for leaks, samples being removed during the filling. Ten minutes later—the maximum time which ordinarily elapsed between their being filled and measured—samples were again removed, and still further samples were obtained after 30 minutes. On each occasion three samples were taken, and analysis was done in duplicate. The results showed that in 10 minutes there was insufficient leakage to cause appreciable fall in the R.Q., though in 30 minutes enough CO₂ had been lost to lower the R.Q. by 0.01 to 0.02. Evidently our procedure of emptying the bags within 10 minutes of their being filled was safe but must be rigorously adhered to. In confirmation of this was the fact that samples of expired air collected from the side-tube of the Douglas bag during the course of actual respiration experiments gave, on analysis, results practically identical with those from the same bag after standing for 10 minutes.

(3) *The analytical technique.* The accuracy of the analytical technique was proved by satisfactorily accurate determinations of the R.Q. of absolute alcohol

combusted in glass vessels. Of course, samples of the laboratory air were analysed each day, and no experimental work with the apparatus was undertaken until such analysis gave satisfactory results.

(4) *Errors due to the subject.* Errors in the observed R.Q. may, of course, be due to the subject not being in a strictly basal condition, though any such errors would probably tend to raise rather than to lower the R.Q. In all our subjects, however, the strictest precautions were taken to ensure basal conditions, and they were all well habituated to the technique before serious observations were started. Careful observations were made of the subject's respiratory movements before and during the experiment, and we are satisfied that in all the results recorded there was no error from alteration in the type of respiration during the collection of the sample.

The R.Q. of normal individuals.

Any systematic error, leading to a general lowering of all our values of R.Q. was unlikely in view of the results obtained in routine hospital determinations. These, however, were not from healthy individuals, and we therefore thought it desirable to compare our value for the R.Q. of normal healthy subjects with that given by other workers.

Seven normal healthy women students, accustomed to breathing through a mask, were chosen for this experiment. After an ordinary mixed supper in hospital at 7 p.m., the subject remained fasting and in bed from 9 p.m. until the test was made shortly after 8 a.m. the next morning. Two determinations of the B.M.R. were made on each subject (all were within normal limits) and four samples of air were analysed from each bag. The quadruplicate analyses agreed, and an average basal R.Q. of 0.797 was obtained over the whole series, the lowest individual value being 0.760.

Du Bois [1927] states that after ordinary mixed fare the normal basal R.Q. lies between 0.80 and 0.84, and an average quotient of 0.83 was calculated by Joslin [1923] from the results obtained in 236 out of 239 normal individuals in the Harris and Benedict series [1919]. On the other hand, a study of 61 readings in Benedict's famous Squad A [Benedict *et al.*, 1919] shows an average R.Q., when the subjects were on normal diet, of 0.795—a figure which is identical with our own. We may mention that all our subjects were under the strictest possible basal conditions at the time of the test. Under these circumstances we believe that our mean value for the R.Q. in normal subjects is correct, and does not indicate any general artificial lowering of our determinations such as would invalidate the results obtained from the obese subjects.

General treatment of the subjects.

On entering the ward for the investigation of metabolism, the subject was at first given what would normally be a maintenance diet of about 2500 Cals. Most of the subjects, however, had been accustomed to eating considerably

more than this, and even so were only maintaining their weight and not increasing it. To them, therefore, the supposedly maintenance diet was in reality sub-caloric, and they almost invariably lost weight on it. This diet was continued for some days during which repeated determinations of the basal B.M.R. and R.Q. were made, and the patient was thus habituated to the technical procedures.

The patient was then given a diet of, usually, 1000 Cals. This was normally made up of 66 g. of protein, 38 g. of fat, and 100 g. of carbohydrate, but occasionally the amount of carbohydrate was reduced with compensatory addition of fat. Finally, the effect of the sub-caloric diet was reinforced by administration of thyroid extract.

Throughout the whole of this time, along with frequent determinations of the B.M.R. and R.Q., and estimations of the urinary nitrogen, the presence or absence of acetonuria was noted daily. In a number of instances, when acetone was present, the total excretion of ketones was determined quantitatively, but was never found to exceed 0.5 g. daily.

In this note on the treatment of the subjects, as in the discussion which follows, we have included only those points relevant to our present purpose. A fuller account, from the therapeutic aspect, is given by Lyon and Dunlop [1932].

RESULTS AND DISCUSSION.

Table I gives the results of the determinations of the B.M.R. and R.Q. in a number of typical cases, and the total number of determinations has been summarised in Table II.

The average of 34 estimations of the R.Q. in obese persons receiving a diet of 2000 to 2500 Cals. is 0.755, which is significantly below the normal average. As has been pointed out, however, this diet, normally sufficient for maintenance, is actually sub-caloric for the obese subject who was losing weight on it.

When the patient was receiving a more definitely sub-caloric diet of 1000 to 1200 Cals. daily, the average basal R.Q. was still lower—0.721—but still just within the range of normal metabolism. Addition of thyroid extract made little difference to the average basal R.Q., but it is evident, from the fact that in the thyroid group relatively few values below 0.70 were obtained, that there is, in individual cases, a tendency for the R.Q. to rise when thyroid is administered (*cf.* records of individual patients in Table I). Indeed, many of the unduly low values, which depress the average of the thyroid group were probably obtained before the full effect of the hormone had appeared.

It is possible that in experiments of short duration the observed R.Q. bears no true relation to the oxidative metabolism actually proceeding, even though it accurately represents the gas exchange during the experimental period. Theoretically, this must be the case in an experiment of infinitesimally short duration, though in a long one of, say, 24 hours the R.Q. undoubtedly represents the net result of metabolism during that time. Hence it is necessary to enquire

Table I.

Case	Date	Diet, Cals.	Acetonuria	R.Q.	O ₂ used per hour, litres	B.M.R.
Mrs A. S.	27. xi. 31	2700	-	0.77	20.85	+18
	1. xii. 31	.	-	0.78	20.08	+14
	3. xii. 31	1000	-	0.74	20.62	+18
	7. xii. 31	.	-	0.70	19.74	+11
	10. xii. 31	.	-	0.68	19.59	+10
	14. xii. 31	.	+	0.78	18.40	+5
	17. xii. 31	.	-	0.70	20.19	+13
	22. xii. 31	.	+	0.69	18.55	+4
	24. xii. 31	.	-	0.69	18.63	+5
	28. xii. 31	.	-	0.77	17.80	+3
	31. xii. 31	.	-	0.67	18.75	+5
	4. i. 32	.	-	0.69	20.25	+15
	8. i. 32	.	-	0.76	19.37	+11
	11. i. 32	.	+	0.73	20.31	+8
	14. i. 32	.	-	0.75	18.35	+6
	18. i. 32	.	-	0.69	18.01	+4
	21. i. 32	.	-	0.70	19.47	+13
	22. i. 32	.	Trace	0.74	18.16	+6
	25. i. 32	.	Trace	0.70	18.55	+9
	28. i. 32	.	-	0.72	18.65	+9
	29. i. 32	.	Trace	0.75	16.81	+3
	5. ii. 32	.	-	0.69	16.17	-5
	8. ii. 32	.	-	0.74	17.45	+4
	13. ii. 32	.	-	0.68	17.56	+4
Mrs M.	5. xii. 30	1800	-	0.77	14.80	-7
	8. xii. 30	2000	-	0.78	14.63	-4
	14. i. 31	1000	-	0.74	14.47	-11
	21. i. 31	.	Trace	0.74	13.03	-11
	28. i. 31	1000 + thyroid	-	0.76	16.75	+15
	3. ii. 31	.	-	0.76	17.92	+18
	10. ii. 31	.	-	0.76	.	+15
	12. ii. 31	1000	-	0.68	18.32	+19
	13. ii. 31	.	-	0.66	17.83	+17
	14. ii. 31	.	-	0.64	16.10	+9
Mrs O.	27. ix. 28	1000	-	0.75	15.84	+14
	3. x. 28	2000	-	0.76	.	-8
	10. x. 28	.	-	0.81	10.76	-19
	18. x. 28	800	-	0.74	13.30	-1
	25. x. 28	1000	-	0.76	12.90	-3
	31. x. 28	.	-	0.77	13.44	+1
Miss M.	12. viii. 29	2000	-	0.77	15.76	-9
	30. viii. 29	1000	-	0.76	.	+4
	31. viii. 29	.	-	0.69	17.93	+4
	22. x. 29	.	+	0.68	18.65	+13
	10. ii. 30	.	-	0.67	13.98	-4
	11. ii. 30	.	-	0.67	12.76	-3
	18. ii. 30	1000 + thyroid	-	0.75	15.38	+13
	10. iv. 30	1000	-	0.67	18.03	-4
	11. iv. 30	.	-	0.67	15.42	-6
	18. v. 30	1000 + thyroid	-	0.75	.	+14

Table II.

Calorific value of diet	Number of deter- minations	Average R.Q.	Range	Number below 0.70	
					%
2000 and above*	34	0.755	0.67-0.86	3	9
1500-2000	30	0.722	0.65-0.86	11	36
1000-1200 standard	117	0.721	0.63-0.87	51	44
1000 low carbohydrate	15	0.678	0.63-0.76	12	80
1000-1200 + thyroid	70	0.727	0.66-0.84	14	20

* These diets were sub-caloric for the patients receiving them, and the patients were losing weight.

whether, in our experiments of 6 minutes, the observed data (granting their accuracy) can be accepted as expressing the oxidative metabolism during that period. Our experimental evidence bearing on this point falls into three categories. Firstly, as a routine measure, two successive independent determinations of the R.Q. were made at an interval of about 10 minutes, but without any attempt at regulating the interval exactly. Secondly, in a number of cases, the interval between the two determinations was exactly half an hour. Lastly, in a few cases, four independent determinations were made, one after the other, the patient wearing the mask throughout. These three procedures would expose any haphazard variations, or any accidental tendency in the routine treatment to hit off a possible periodicity in the R.Q. In the vast majority of the results the successive estimations of the R.Q. and of the oxygen consumption agreed very closely, and in only a very few cases was there any marked and unaccountable discrepancy. Since the agreement of duplicate or quadruplicate determinations was the rule, it could not be ascribed to coincidence, and, consequently, the 6-minute determinations may justifiably be regarded as giving a true expression of the metabolism at that time. Nevertheless, it must always be realised that reliance on the technique of indirect calorimetry is dangerous, and that our results, together with the interpretation to be placed on them, must fall if any technical error (which, however, we have failed to detect) can be shown to account for them.

Our discussion and tentative interpretation of our results is based on the supposition that individual determinations of the R.Q. are reliable, and that therefore the subjects were at times exhibiting an abnormal type of metabolism. (It is to be noted that patients varied in the results they yielded; some gave a low R.Q. more frequently than others, though none invariably gave results below 0.70.) The fact that the averages in Table II are so near the normal minimum interests us only as showing that, with a distribution similar to that of healthy individuals, many values must have been below 0.70—if the average is correct. Of that there is no reason to doubt in view of the value obtained for the average R.Q. in normal healthy subjects.

An R.Q. below 0.70 can only mean that oxygen is being used without production of a corresponding amount of carbon dioxide—*i.e.* for some incomplete oxidation. It has already been pointed out that the ketonuria occasionally observed was inadequate to account for the low values of the R.Q. even in the patients who showed it. It might be objected, however, that in the special case of the obese subject, ketosis might occur without corresponding ketonuria, the excess keto-acid being stored in the fatty tissues by virtue of preferential solubility in fat. According to this hypothesis, ketosis would occur during starvation without ketonuria but with a low R.Q., and after a carbohydrate-containing meal the stored ketones would be oxidised with production of an abnormally high R.Q. We have measured the R.Q. in our obese subjects at regular intervals for 4 hours after a meal, but have never found evidence of this occurring.

We have, moreover, shown by direct *in vitro* experiments that there is no preferential solubility of ketone substances in fat as compared with Ringer's solution or serum. In a typical experiment, Ringer-Locke solution containing 60 mg. of acetoacetic acid per 100 cc. (p_H 7.40) was shaken with an equal volume of olive oil for 90 minutes. The two layers were then separated by centrifuging, and acetoacetic acid was determined by Van Slyke's method in the aqueous layer and in the original solution. The results were: before shaking, 59.75 mg. acetoacetic acid per 100 cc.; after shaking, 60.50 mg. per 100 cc. A similar experiment with acetone (*a priori* more likely to show solubility in fat than sodium acetoacetate) gave a similar result: before shaking, 244 mg. acetone per 100 cc.; after shaking, 216 mg. per 100 cc.

The only other incomplete oxidation of which one can conceive as taking place in significant amount is the conversion of protein or fat into carbohydrate. Evidence from the urinary D/N ratio of 3.65 in severe diabetes and in depancreatized or phlorhizinized dogs indicates that about 58 g. of carbohydrate may be formed from 100 g. of protein. This figure is derived from study of the fate of ingested protein, of which a small part of the nitrogen is lost in the faeces. When the body is metabolising its own protein exclusively, so that the whole of the nitrogen appears in the urine, this figure may be slightly altered. However, any error introduced by its use is a very small one. Even if, on this basis, it be supposed that all the protein metabolised is converted to carbohydrate which is stored, it appears that the R.Q. for the remainder is frequently below 0.70. This, in the absence of incomplete oxidation of fatty acid to keto-acids, and after allowance for the possible conversion of glycerol to glucose, strongly suggests the formation of carbohydrate from fatty acid.

The calculation to which the experimental data have been submitted is shown below, and in Table III are given the results for a number of abnormally low values of R.Q., all obtained in absence of ketonuria. The formulae apply to the usage of oxygen and production of CO_2 on the assumption that maximal production of carbohydrate from protein is taking place and that at least as much carbohydrate as this is being stored. Hence if, on solution of the equations, y is zero, the gain of carbohydrate to the body is equal to the production from protein, if y is negative, less than this amount is being stored, if y is positive, additional sugar is being produced and stored from fat. There is no assumption that carbohydrate is not being oxidised—merely that with abnormally low R.Q.'s it is being produced to a greater extent than it is being burnt. Since it is highly probable that some carbohydrate is always being oxidised, a zero value of y still indicates the probability of formation of sugar from fat, and even with positive values of y only the net gain, and not the total production of carbohydrate is calculable.

The values for the non-protein R.Q. in Table III are evidently well below 0.707, even when full allowance is made for maximal carbohydrate storage from protein. If further allowance is made for conversion of glycerol to

Table III.

Case	Date	Total R.Q.	For 1 hour, fasting			Non-protein R.Q. with normal protein oxidation	Assuming maximal carbohydrate from protein		
			Litres O ₂	Litres CO ₂	g. urinary N ₂		Non- protein R.Q.	g. fat. com- pletely oxidised	g. fat. converted to carbo- hydrate
J. McW.	14. v. 31	0.670	14.76	9.89	0.470	0.634	0.673	6.21	1.13
	22. v. 31	0.675	12.31	8.32	0.422	0.643	0.680	5.19	0.77
	8. vi. 31	0.650	13.56	8.82	0.247	0.631	0.651	5.80	1.77
V.	17. vii. 29	0.666	14.27	9.51	0.410	0.638	0.668	6.04	0.89
	19. vii. 29	0.656	14.31	9.39	0.415	0.624	0.652	5.95	1.58
	22. vii. 29	0.678	13.37	9.07	0.380	0.652	0.683	5.78	0.77
A. C.	29. vii. 29	0.668	19.48	13.00	0.450	0.645	0.670	8.42	1.68
	1. viii. 29	0.650	20.28	13.20	0.465	0.626	0.652	8.55	2.56
	20. viii. 29	0.679	19.79	13.42	0.445	0.653	0.683	8.72	1.23
M.	10. ii. 30	0.670	13.98	9.37	0.260	0.653	0.672	6.17	1.14
	11. ii. 30	0.670	12.76	8.55	0.245	0.652	0.672	5.62	1.04
J. H.	12. iii. 30	0.677	17.24	11.67	0.510	0.649	0.683	7.41	1.04
Mn.	12. ii. 31	0.680	20.13	13.67	0.448	0.659	0.682	8.90	1.19
	13. ii. 31	0.665	19.49	12.95	0.482	0.640	0.667	8.35	1.80
	14. ii. 31	0.641	17.22	11.04	0.408	0.614	0.641	7.12	2.54
H.	12. ii. 31	0.683	18.32	12.51	0.448	0.662	0.687	8.09	0.88
	13. ii. 31	0.664	17.83	11.84	0.430	0.640	0.666	7.64	1.67
H. K.	17. ii. 31	0.696	15.81	11.00	0.650	0.661	0.704	6.73	0.07
	25. ii. 31	0.664	12.14	8.06	0.479	0.620	0.632	4.67	1.06
	5. iii. 31	0.700	12.47	8.73	0.576	0.660	0.711	5.25	0.00
E. S.	9. iii. 31	0.682	17.51	11.94	0.684	0.644	0.688	7.34	0.79
	10. iii. 31	0.680	16.22	11.02	0.690	0.636	0.685	6.68	0.79
	19. iii. 31	0.627	15.52	9.74	0.450	0.590	0.625	6.14	2.76
	27. iii. 31	0.630	16.22	10.21	0.390	0.601	0.628	6.56	2.71
A. S.	31. xii. 31	0.670	18.75	12.56	0.304	0.655	0.671	8.33	1.58
	18. i. 32	0.690	18.01	12.42	0.299	0.677	0.693	8.25	0.67
	13. ii. 32	0.680	17.56	11.94	0.320	0.665	0.683	7.87	1.04

I. Data.

Example of calculation.

(a) The figures given by Lusk [1928, p. 69] have been used for the consumption of oxygen and production of carbon dioxide during the normal oxidation of fat and carbohydrate:

1 g. fat requires 2.019 litres O₂ and gives 1.427 litres CO₂.

0.9 g. glucose, or 1 g. glycogen, requires 0.828 litres O₂ and gives 0.828 litres CO₂.

(b) In dealing with protein, Lusk's figures for the elementary composition of meat protein have been used, but it has been assumed that as body protein is being metabolised there is no loss in the faeces. This assumption may not be correct, but if anything it weighs the balance against the conclusion of fat conversion to carbohydrate, since it increases slightly the amount of protein carbon available for similar conversion.

	C	H	O	N
	g.	g.	g.	g.
100 g. meat protein contain	52.88	7.27	22.68	16.65
Of this there appear in the urine	9.41	2.66	14.10	16.65
For respiration	43.17	4.61	8.58	—
Deduct water equivalent	—	1.07	8.58	—
	43.17	3.54	—	—

Hence 100 g. protein require 100.4 litres O₂ and give 80.6 litres CO₂.

Thus with normal metabolism,

1 g. urinary N $\equiv$ 6.005 g. protein $\equiv$ 6.025 litres O₂ used $\equiv$ 4.84 litres CO₂ produced.

With maximal conversion of protein to carbohydrate,

1 g. urinary N = 3.65 g. glucose, which, on oxidation, would use 2.72 litres O₂ and give 2.72 litres CO₂.

Hence, with this glucose stored,

1 g. urinary N = 3.305 litres O₂ used, and 2.12 litres CO₂ produced.

(R.Q. = 0.641.)

(c) For the hypothetical conversion of fat into carbohydrate, the fat is taken as having the composition of glyceryl dioleate monostearate, $C_{57}H_{106}O_6$, which represents fairly closely the average composition of body fat. Small differences in composition have, however, no appreciable effect on the result. It is further assumed that all the carbon of the fat molecule is retained in the carbohydrate molecule, the change being represented as:

According to this equation:

1 g. fat requires 0.594 litres O_2 , produces no CO_2 , and yields 1.736 g. of glycogen.

II. Formulae.

From these data, formulae are derived as follows:

Let observed O_2 usage over a given period = a litres
 „ CO_2 production over a given period = b litres
 „ urinary nitrogen over the same period = c g.

With maximal carbohydrate production from protein,

O_2 for non-protein metabolism = $a - 3.305 c$.
 CO_2 from non-protein metabolism = $b - 2.12 c$.

Let x g. fat be oxidised completely,
 y g. fat be converted to carbohydrate.

Then O_2 used = $2.019 x + 0.594 y$ = $a - 3.305 c$.
 CO_2 produced = $1.43 x$ = $b - 2.12 c$.

Whence
$$x = \frac{b - 2.12 c}{1.43}.$$

$$y = \frac{a - 1.41 b - 0.31 c}{0.594}.$$

carbohydrate, the non-protein R.Q. may be as low as 0.695, the fatty acid being completely oxidised. Values below this figure must then indicate incomplete combustion of fatty acid. The figures given in the last two columns of Table III represent the amounts of fat oxidised and stored as carbohydrate, on the assumption that such a conversion takes place, and that its equation is that postulated by Zuntz. Other calculations, based on other hypothetical equations, such as that of Chauveau, give higher figures for the amount of fat converted to carbohydrate, since they involve the simultaneous production of a little CO_2 , and, in the case of Chauveau's equation, an R.Q. of 0.29 for the conversion. No stress is laid on the figures given in these two columns; they are merely intended to show that if conversion of fat into carbohydrate is taking place, it is proceeding to an appreciable extent, and to emphasise the difference between the observed R.Q. and the minimal value possible on the assumption of normal and complete oxidation of fatty acid.

On the assumption of carbohydrate formation from fat with conservation of all the carbon, Table III shows that the glucose production accounts for about 1/10 to 1/5 of the fat metabolised. These amounts are appreciable, but even if they be added to the amounts supposed to be formed from protein, they would not cause a very rapid increase in the glycogen reserves, and could therefore be conceived of as continuing for some hours.

It is obvious that such a storage of carbohydrate cannot continue indefinitely. Accordingly, it is found that after a meal, with the subject still resting, the R.Q. rises above 0.70, sufficiently to indicate usage of carbohydrate during this period. This indicates that the carbohydrate storage mechanism, if it exists at all, is essentially one called into action only during a fast. It is also noteworthy, that even with the patient continuously on the same sub-

caloric diet, the fasting R.Q. is not invariably below 0.70. There is a tendency for the R.Q. to rise and fall in a periodic way, as if the need for storage appeared when the carbohydrate reserve had fallen below a certain level, and disappeared when, by storage from food or synthesis, the reserve had been built up to some higher level.

If, however, it be objected that the actual storage of carbohydrate is so improbable that the assumption of its occurrence must be rejected, we are faced with still greater difficulties, for then we must assume that protein is being oxidised with its normal R.Q. of 0.806. This, of course, leads to still lower values for the non-protein R.Q.—values sometimes below 0.60—which cannot possibly be explained on any known hypothesis.

Without going into the whole of the vexed and still controversial question of the possibility of carbohydrate formation from fat—a question well reviewed by Rapport [1930]—we may mention a few points bearing directly on our interpretation of our experimental data. The obese person whose reserves consist predominantly of fat is evidently more likely than the normal individual to exhibit the phenomenon of fat conversion into carbohydrate under sub-caloric dietary conditions. Moreover, if we reject arguments in favour of such a conversion in diabetes based on observations of abnormally high D/N ratios, there is evidence that exogenous fat can be turned into carbohydrate in animals whose carbohydrate stores have been depleted by a period of starvation, and in which, therefore, the conditions are analogous to those obtaining in our patients. Similarly, Jost [1931] has recently observed increased sugar formation on perfusion of glycogen-poor livers with fatty acids and phosphate. It is significant, too, that in our experiments there was a tendency for a low R.Q. to appear more readily the smaller the amount of carbohydrate in the diet. The absence of ketonuria in our experiments may be reasonably explained by the assumption that part of the fat was oxidised *via* carbohydrate, thus affording a sufficiency of ketolytic material. Such a mechanism may also be the explanation of the fact, known from clinical observation, that fat diabetic subjects show less tendency to ketosis than thin ones.

In conclusion, therefore, we believe that our experimental results afford evidence that in the undernourished obese subject, fat is converted into carbohydrate. This conclusion is, however, tentative, inasmuch as it depends on a technique open to criticism, and becomes liable to revision if and when any more probable mechanism for the storage of oxygen is suggested. Valuable confirmatory evidence of the correctness of our hypothesis might be obtained from measurement of the actual heat production simultaneously with the respiratory exchange. Such a measurement would enable the calculated heat production to be compared with the actual. This technique was, however, beyond our means. Our interpretation does not of course imply that a conversion of fat into carbohydrate takes place ordinarily as an obligate step in the metabolism of fat; but simply that in certain abnormal circumstances the animal body is capable of it. Indeed, experiments on muscular exercise

[cf. Stewart, Gaddie, and Dunlop, 1931] indicate that when fat is used as a source of energy for external work, it is directly oxidised and is not first converted into sugar. In other words, the auxiliary verb for the conversion of fat to carbohydrate is, at most, "may" and not "must."

SUMMARY.

1. In a series of 34 observations on the R.Q. of obese subjects on a sub-caloric diet of 2000 or more Calories loss of weight occurred and the average R.Q. was 0.755. Of these, 3 were below 0.70.

2. When the diet was reduced to 1000 to 1200 Calories the average R.Q. in 117 observations was 0.721 with 51 below 0.70.

3. When the carbohydrate content of these latter diets was reduced, but the total calorific value maintained, the average R.Q. fell to 0.678, 12 out of 15 being below 0.70.

4. Administration of thyroid to the subjects on 1000 to 1200 Calories diet produced a slight increase in the R.Q., the average of 70 determinations being 0.727, with only 14 below 0.70.

5. Ketonuria was usually absent when these observations were made and when present was only slight.

6. These results are discussed with respect to the conversion of fat to carbohydrate.

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