Glucose Metabolism and Recycling of Radioactively Labelled Glucose in the Zucker Genetically Obese Rat (*fa/fa*)

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1. The glucose metabolism of conscious lean and obese rats of the Zucker strain was studied by using doubly labelled glucose ($[6\text{-}^3\text{H}, \text{U}\text{-}^{14}\text{C}]\text{glucose}$) given by intravenous injection as a single dose. Fed animals were used, allowing the study to be made in conditions favouring active lipogenesis. 2. At any given prior food intake (consumption during preceding 24 h), the irreversible glucose replacement rate, R_0 , was considerably higher in the growing obese rat (4–6 months old) when both of these variables were scaled in terms of the total body water of the animals. 3. When scaled in a similar way, the minimal mass of glucose ($M_{\min.}$) was also larger in the obese rats. The mean transit time, $\bar{t}$, through the pool did not differ significantly between the two groups, but there was a tendency for this to be shorter in obese rats. 4. There was no difference in the proportion of ^{14}C (derived from metabolized labelled glucose) that recycled as $[^{14}\text{C}]\text{-glucose}$ after passing through the pyruvate pool in the two groups of rats if the rate of recycling of radioactivity (R_c) was expressed as a percentage of R_0 .

The genetic obesity in rats discovered and described by Zucker & Zucker (1961) is due to a single recessive autosomal gene. Homozygous animals (*fa/fa*) become grossly obese, increasing in adiposity particularly up to the age of 6 months. This adiposity is due mainly to hyperplasia, especially of the subcutaneous fat, with cell division continuing for much longer than is the case in normal or heterozygous rats (Johnson *et al.*, 1971). During this phase of growth, lipogenesis in the obese rats proceeds at a very rapid pace, synthesizing more than 2 g of triacylglycerol daily (Zucker, 1975). So great are the demands of lipogenesis that even when the animals are feeding *ad libitum* the general body growth of young obese rats lags behind that of their lean littermates, although they are eating about 50% more food. When pair-fed, with allowance made for the restriction in general body growth of the obese rats, these animals fail to grow normally, but remain in positive energy balance, conserving (principally as lipid) 3 times as much dietary energy as the normally growing lean controls (Zucker, 1975).

Glucose metabolism in these obese rats has been studied mainly in terms of changes in glucose concentration, or plasma insulin concentration, in various circumstances. Working with rats of rather widely differing ages (2–10 months), Zucker &

Zucker (1962) set the pattern for most subsequent reports (Bray, 1970; York *et al.*, 1972; Zucker & Antoniadis, 1972), emphasizing the similarity, rather than the difference (which was just statistically significant), between the glucose concentrations of lean and obese animals. The mean blood glucose concentration of obese animals in their series was some 15–20% higher than that of the controls whether the animals were fed or starved; this small difference was seen as being in sharp contrast with the marked hyperglycaemia of the *ob/ob* obese mouse. Subsequent work has shown that a modest hyperglycaemia does indeed occur in the obese rats, but that it is markedly age-dependent. It is found at about 4 months of age (York *et al.*, 1972; Zucker & Antoniadis, 1972). Hyperinsulinaemia in the obese rat is also particularly marked at this age (Zucker & Antoniadis, 1972).

There is good reason to expect that growing obese rats would have a high glucose requirement; glucose is necessary as a substrate for the very active lipogenesis seen in these animals. There is also an enormous number of adipocytes (Johnson *et al.*, 1971), each of which has been shown to convert glucose into CO_2 at the same rate as do cells from age-matched (6 month) lean controls (Stern *et al.*, 1972) under basal conditions in studies *in vitro*.

In the experiments described in the present paper, glucose metabolism was studied directly, *in vivo*, by using isotopically labelled glucose injections given to conscious fed rats provided with indwelling cannulae at an operation 2 or 4 days previously. The conditions were intended to favour normal metabolic activity, which in the obese rats implies active lipogenesis, insofar as experimental constraints made this possible.

The purpose of these experiments was to obtain information on the glucose metabolism associated with active lipogenesis in genetically obese rats, and also to see whether any differences in the balance of activity among the metabolic pathways converging on the pyruvate pool (which include the Cori cycle) could be detected in these circumstances.

Methods

Animals

Seven lean (*fa/+* or *+/+*) and eight obese (*fa/fa*) male rats were studied. Details of age and weight are given in Table 1. The animals were fed, in the sense that they had eaten up to the time of the experiment, and still had partially digested food in the gut at post-mortem. The experiment was conducted at a time of day at which rats normally sleep, and do not normally consume food; food was not, therefore, provided during the experiment.

Surgery

Either 2 or 4 days before the experiment, the right jugular vein and carotid artery were cannulated with tip-plugged dry-bore cannulae (Wade, 1979). At the same operation a curved blind-ended polythene tube was tied into the neck wound; this was used as a thermocouple sleeve during the experiments.

Recovery period

During recovery from surgery, food intakes were monitored daily, and body weight was recorded. All but two rats were still below their pre-operative weights on the day of experiment; median values of the deficit were -12 g for lean and -16 g for obese rats.

Experimental protocol

A strict timetable was employed, the essentials of which were as follows.

11:15–11:30 *h*. Extension catheters and the thermocouple were connected and each rat was placed in an open-topped Perspex [poly(methyl methacrylate)] cage. It was not handled again. Cannulae were kept patent by the slow infusion of saline (0.9% NaCl).

13:10 *h* (time 0). The rats were injected intravenously with D-[6-³H,U-¹⁴C]glucose (supplied by The Radiochemical Centre, Amersham, Bucks.,

U.K.) in saline. Twelve 0.1 ml samples of arterial blood were collected, at 1, 3, 5, 10, 20, 40, 60, 80, 100, 120, 150 and 180 min.

16:10 *h*. A 1 ml blood sample was collected from each rat for haematocrit measurements. The animals were killed by intravenous injection of pentobarbitone sodium.

Processing of samples

After addition to 0.5 ml of preweighed chilled 0.085 M-ZnSO₄ solution, sample size was measured by weight. Deproteinization was completed by adding 0.5 ml of 0.083 M-Ba(OH)₂ (Somogyi, 1945). Glucose concentration was measured immediately in two 0.1 ml samples of the supernatant (Huggett & Nixon, 1957). Biochemical reagents were obtained from Sigma Chemical Co. (Poole, Dorset, U.K.). Labelled glucose was extracted for scintillation counting of radioactivity as glucose penta-acetate (Jones, 1965), 0.5 ml of supernatant plus 200 mg of carrier glucose being used. Glucose penta-acetate was also prepared from a 1:1000 dilution of the injection solution. Chemical reagents were supplied by BDH Chemicals (Poole, Dorset, U.K.).

Analysis of results obtained with radioactively labelled glucose

After being weighed, glucose penta-acetate crystals were dissolved in NE250 scintillant fluid (Nuclear Enterprises, Edinburgh, Scotland, U.K.) and counted for ³H and ¹⁴C radioactivity. Observed radioactivities (c.p.m.) were corrected for channel overlap, background, yield of glucose penta-acetate, sample size, blood water content and dilution during deproteinization. Correction for efficiency was not necessary, as all vials counted with closely similar efficiency. Eventually, radioactivity for either isotope was expressed as the fraction of the dose injected per 100 g body wt. remaining in 1 mmol of blood glucose at the time of sampling (fractional residual radioactivity).

As glucose pool size was found to be essentially constant during these experiments (see the Results section), a steady-state method of analysis was chosen. Fractional residual radioactivity was plotted against time on linear graph paper. The area under each curve for ³H and ¹⁴C radioactivity was determined by weight, and the rate of replacement of glucose was calculated; the theoretical basis for this method, which does not assume a multicompartmental model, has been thoroughly explained by Katz *et al.* (1974). *R*₀, as calculated from the disappearance of [6-³H]glucose, was taken as the best estimate of irreversible glucose replacement rate, in preference to [2-³H]glucose (Dunn *et al.*, 1967, 1975). When tritium is attached to C-6, it remains attached throughout glycolysis, but is dislodged during gluconeogenesis; the ways in which it is lost

have been explained most concisely by Judson & Leng (1972). By looking at the ratio of ^3H to ^{14}C found in positions C-1–C-3 of glucose resynthesized *in vivo* from glucose injected with both labels on C-6, Dunn *et al.* (1967) provided experimental evidence that there was (in their own words) virtually complete loss of tritium during recycling.

[U- ^{14}C]Glucose provided another estimate of glucose replacement, R_a , which is known to be too low because the specific radioactivity of blood glucose is raised by recycling ^{14}C returning to the glucose pool from the pyruvate pool. It should be stressed that the difference between R_a and R_0 does not measure recycling of glucose through lactate and pyruvate in a truly quantitative fashion; the specific radioactivity of ^{14}C in the carbon pool in glucose is always much higher than that in the pyruvate pool, and consequently some substitution of ^{12}C for ^{14}C occurs during the recycling process (Krebs *et al.*, 1966; Streja *et al.*, 1977). The difference $R_0 - R_a$ is described in the present paper as R_c , the rate of recycling of radioactive glucose, and may be expressed either in molar terms or as a percentage of R_0 . The transit time and the minimal mass ($M_{\min.}$) of glucose were also calculated from the specific-radioactivity curve for [6- ^3H]glucose, by using the second graphical method described by Katz *et al.* (1974).

Scaling factors

An important conceptual decision must be taken before scaling metabolic rates of lean and obese subjects in order to make comparisons between the two groups. Scaling corrections to allow metabolic rates to be compared between animals of differing body size are usually best made by using the exponential function of body weight, $\text{kg}^{0.75}$ (Schmidt-Neilson, 1970). This scaling factor fails to eliminate the 'dead weight' of a massive triacylglycerol store, however. To make this correction, total body water has been used as a measure of metabolically active tissue. When comparison is made over a narrow range of body weight, there is no particular virtue in using $(\text{total body water})^{0.75}$, although if interspecies comparison is foreseen this would be preferable. For the present study, the simpler unit of 100 g of total body water has been used to scale results in lean and obese rats, but sufficient information is provided in Table 1 to allow rescaling to $(\text{total body water})^{0.75}$ to be performed.

Determinations of total body water

In a single acute experiment tritiated water (as saline) was given by intraperitoneal injection to four lean and five obese fed anaesthetized male rats with body weights covering most ranges used in experiments on glucose metabolism. ^3H in the water of blood taken from the heart 45 min after injection was used to estimate the dilution into total body water.

Previous experience with this technique in the rabbit (Wade, 1976) had shown that distribution of the labelled water should be complete within 45 min.

Results

Total body water

Tritiated water distributed into 0.692 ± 0.020 s.d. of the body weight of lean rats, and into 0.429 ± 0.030 s.d. of the body weight of obese rats. Lean rats ranged in weight from 320 to 482 g, obese rats from 540 to 723 g. The mean factors derived were used to calculate total body water in the lean and obese rats (respectively) used in experiments on glucose metabolism.

Glucose metabolism

A single experiment is illustrated in Fig. 1, showing data points for subcutaneous temperature, glucose concentration and fractional specific radioactivity.

Descriptive data and results for the 15 individual experiments are summarized in Table 1.

Fig. 1. Specific radioactivity, glucose concentration and body temperature during a single experiment (rat no. Z14, obese)

Experimental details are given in the text. An intravenous injection of [6- ^3H ,U- ^{14}C]glucose was given at time zero. (a) Subcutaneous temperature; (b) concentration of blood glucose; (c) fractional residual radioactivity in blood glucose (Δ , [6- ^3H]glucose; $\circ$, [U- ^{14}C]glucose).

Table 1. *Descriptive data and results from individual experiments*
 Experimental details are given in the text. Total body water is given by $0.692 \times$ body weight for lean rats and by $0.429 \times$ body weight for obese rats.

(a) Lean rats

Rat no.	Body wt. (g)	Age (days)	Total body water (g)	Concn. of blood glucose (mmol/l)	R_0 ($\mu\text{mol}/100 \text{ g of total body water}$)	R_a ($\mu\text{mol}/100 \text{ g of total body water}$)	R_c ($\mu\text{mol}/100 \text{ g of total body water}$)	R_c (% of R_0)	M_{min} ($\mu\text{mol}/100 \text{ g total body water}$)	Transit time (min)	Food intake during 24 h preceding experiment (g/100 g of total body water)
Z3	314	180	217	4.82	7.67	6.47	1.20	15.7	223	29.1	4.2
Z4	362	184	251	5.41	14.22	13.41	0.81	5.7	563	39.6	10.3
Z6	346	192	239	5.72	9.75	8.54	1.21	12.4	366	37.6	10.2
Z8	385	169	266	5.07	6.17	4.85	1.32	21.3	298	48.3	4.3
Z10	302	175	209	4.66	5.69	4.77	0.92	16.2	274	48.2	3.3
Z17	384	245	266	4.88	5.62	4.71	0.91	16.2	263	46.9	4.6
Z18	311	134	215	4.93	6.75	5.71	0.98	14.6	284	42.1	7.6
Mean	343	182	238	5.07	7.98	6.93	1.05	14.6	324	41.7	6.4
S.E.M.	± 12	± 12	± 8	± 0.13	± 1.08	± 1.1	± 0.07	± 1.6	± 40	± 2.4	± 1.0

(b) Obese rats

Z5	525	186	225	4.51	13.29	12.08	1.21	9.1	368	27.7	8.8
Z9	525	170	225	7.13	15.73	12.40	3.33	21.2	473	30.1	6.8
Z11	515	176	221	5.76	12.24	10.65	1.59	12.9	352	28.7	8.2
Z12	524	177	225	11.37	16.62	13.03	3.59	21.5	849	51.1	8.0
Z14	712	145	305	6.04	13.24	11.61	1.63	12.3	378	28.6	6.7
Z19	459	131	197	5.00	17.32	14.27	3.05	17.7	350	20.2	11.7
Z22	505	151	217	5.67	15.01	11.75	3.26	21.7	409	27.2	7.6
Z23	530	164	227	5.30	9.37	7.58	1.79	19.2	350	37.4	2.9
Mean	537	163	230	6.47	14.10	11.67	2.43	17.0	441	31.4	7.6
S.E.M.	± 24	± 7	± 10	± 0.70	± 0.70	± 0.65	± 0.32	± 1.6	± 56	± 3.1	± 0.8

Subcutaneous temperature

In all but one experiment, a complete record of subcutaneous temperature was available for analysis. Although a slight upward drift in temperature occurred, particularly within the first hour, no serious pyrexial reactions were seen; consequently glycogenolysis due to this experimental hazard was avoided.

Glucose concentration

To obtain the mean glucose concentration during each experiment without introducing a bias due to the relatively frequent sampling during the early stages, the glucose concentration was averaged at seven points: 1 min, 30 min (interpolated value, based on the values at 20 and 40 min), 60 min, 90 min (interpolated value, based on the values at 80 and 100 min), 120, 150 and 180 min. This average then included information drawn from nine of the 12 samples collected during the experiment.

The glucose concentration did not vary systematically; this is shown in Fig. 2. The glucose concentration was not significantly higher in the obese rats than in the lean (Mann-Whitney U-test; Siegel, 1956), but it was clearly higher in some individual obese animals (see Table 1). Minor fluctuations in glucose concentrations during individual experiments showed no consistent trend. The smoothness of all the specific-radioactivity curves (see, e.g., Fig. 1) also supported the choice of an analytical technique based on the assumption of a steady state of glucose metabolism during the sampling period.

Glucose replacement rate

The calculated values of R_0 are listed in Table 1, expressed on the basis of 100 g of total body water as the scaling factor. It was soon apparent that rats had variable post-operative appetites, and it was decided to allow them to eat *ad libitum*, and to make allowance for differences in food intake in the analysis of results.

There was a clear separation between the glucose metabolism (R_0) in lean and obese rats at any given food intake (Fig. 3). There was no significant

difference in slope for the two regressions, but their intercepts differed significantly ($\alpha_1 = 2.552 \mu\text{mol/min}$ per 100 g of total body water for lean rats, $\alpha_2 = 8.041 \mu\text{mol/min}$ per 100 g of total body water for obese rats; $F = 30.06$, degrees of freedom = 1, 12, $P < 0.001$). This difference indicates

Fig. 3. Regressions of food intake on glucose replacement rate, R_0 , in lean and obese Zucker rats

Experimental details are given in the text. Regressions of food intake on the glucose replacement rate, R_0 , in lean ($\square$) and obese ($\circ$) rats are shown. The equations of the lines were: for lean rats, $y = 2.552 + 0.854x$; for obese rats, $y = 8.041 + 0.799x$. The slopes were the same, but the intercepts differed greatly ($F = 30.06$, degrees of freedom 1, 12, $P < 0.001$). The correlation coefficients for lean and obese rats respectively were 0.819 and 0.755. Both are significant ($P < 0.05$).

Fig. 2. Glucose concentration in Zucker rats during the experiments

Experimental details are given in the text. After calculation of the mean glucose concentration within each experiment (see the text), deviations from this mean at each time t were expressed in percentage terms, and then analysed collectively, giving the mean deviation $\pm$ S.D. ($n = 15$) at each point.

that, in obese rats pair-fed on the basis of their metabolically active tissue mass to lean rats given a normal food intake, the glucose replacement would be about 50% higher.

Mean transit time and minimal mass of glucose

The mean transit time, $\bar{t}$, of glucose through the sampled pool was longer, on average, in the lean rats, but there was no significant difference between the groups (Mann-Whitney U-test). In obese rats (only) the transit time correlated positively with the mean blood glucose concentration ($r = 0.846$ with 6 degrees of freedom; $P < 0.01$).

The minimal mass of glucose ($M_{\min.}$; Katz *et al.*, 1974), in μmol per 100 g of total body water, was greater in obese rats, a difference that was statistically significant ($P = 0.02$, Mann-Whitney U-test). As is to be expected, there was also evidence for a correlation between the mean blood glucose concentration and the minimal mass of glucose; values were: for lean rats, $r = 0.678$ with 5 degrees of freedom (N.S.), for obese rats, $r = 0.975$ with 6 degrees of freedom ($P < 0.01$), and for all values (lean and obese rats), $r = 0.893$, with 13 degrees of freedom ($P < 0.01$).

Recycling of radioactively labelled glucose, R_c

When expressed as a percentage of R_0 , there was no difference in R_c between the lean and obese groups. When expressed in molar terms ($\mu\text{mol}/\text{min}$ per 100 g of total body water), on the other hand, both R_0 and R_c were significantly higher in obese rats ($P < 0.01$ for R_0 , $P < 0.001$ for R_c) when tested by the Mann-Whitney U-test; but, whereas R_0 was related to food intake, R_c was not ($r = 0.260$, N.S., for all data). Two other possibilities may be considered. First, R_c may be directly related to R_0 , even though it could not be shown to be dependent on food intake. The results in Table 1 give some support to this suggestion. There is no sign of a relationship among the data for lean rats alone, but there is a relationship for obese rats alone ($r = 0.765$, $P < 0.05$). If it is assumed that the metabolic differences between lean and obese animals do not directly affect a postulated relationship between R_c and R_0 , data for lean and obese rats might be considered together for analysis. On this assumption, the correlation for data for lean and obese rats taken together is significant at the 1% level ($r = 0.955$). Secondly, R_c might be related to the glucose concentration. R_0 itself was weakly correlated with glucose concentration ($r = 0.514$, $P = 0.05$). There is no correlation between R_c and glucose concentration for lean rats alone (which had closely similar glucose concentrations; see Table 1), but there was a tendency for a relationship among the obese rats ($r = 0.601$, N.S.), and, if again the assumption is made that the metabolic differences

between lean and obese animals do not directly affect a postulated relationship between the concentration of glucose and R_c , and data for lean and obese rats are taken together, the correlation is significant ($P < 0.01$, $r = 0.658$).

Discussion

The measurement of glucose replacement rate in fed animals includes an element of glucose movement through the sampled pool that is associated with the assimilation of food and its conversion into storage forms. By comparison of the regressions of food intake on glucose replacement rate (R_0) for lean and obese animals, it was clear that there was a higher underlying rate of glucose turnover in the obese animals (Fig. 3); there was therefore a higher rate of entry of glucose into the pool, and of utilization of glucose, which was independent of food intake. It is important to realize that this underlying element of glucose turnover, an estimate of which may be extracted from the data as the value of R_0 at a notional food intake of zero, is obtained in animals that were all metabolically and hormonally in the fed state; the intercept value is not to be regarded as an estimate of R_0 in the fasted state.

The increased glucose metabolism reported here, taken together with published findings from studies *in vitro* made in other laboratories, makes clear the importance of this substrate during the phase of growth and fat accretion. Thus, despite the presence of some of the characteristic features of insulin resistance (euglycaemia or hyperglycaemia combined with hyperinsulinaemia, insensitivity to exogenous insulin) that have been clearly demonstrated by Zucker & Antoniades (1972) and York *et al.* (1972), the ability of the obese rat to utilize glucose is actually raised; the replacement rate is higher, the pool size is larger and the transit time tends to be shorter. The increased ability to use glucose was not apparent in recent studies of glucose tolerance, which showed that, whereas the obese rat responded as effectively as its lean littermate to the challenge of a sudden intravenous load of exogenous glucose, the load was not cleared more rapidly from the blood (Triscari *et al.*, 1979). During such a response, however, both glucose and insulin concentrations are greatly disturbed, and, since it is unlikely that the clearance of glucose would remain constant in these circumstances, such an experiment cannot provide direct evidence about the underlying glucose replacement rate.

Evidence from many studies *in vitro* strongly supports the view that glucose turnover in the obese rat must be increased (Spydevold *et al.*, 1978; Triscari *et al.*, 1979; Bloxham *et al.*, 1977; Lemonnier *et al.*, 1974; Taketomi *et al.*, 1975; Martin, 1974; Zucker & Antoniades, 1972). These studies, of labelled substrate utilization or of enzyme activity profiles, have

been conducted under a wide variety of experimental conditions, which precludes an exhaustive review here. However, the general outcome of these experiments, and a number of specific points arising from them that bear on the present results, are discussed below.

The overall picture that emerges is consistent with earlier observations made *in vivo*, of very rapid triacylglycerol synthesis and deposition in the growing obese rat, and of continuing lipid deposition even during dietary restriction sufficient to impair normal skeletal and muscular growth (Zucker, 1975). In the adipose tissue of the fed obese rat, all the enzymes of lipogenesis, of the glycolytic route, of the oxidative segment of the pentose phosphate pathway and of the tricarboxylic acid cycle showed increased activity, whether this was expressed per mg of DNA or per whole fat-pad (Spydevold *et al.*, 1978). In the liver, the same authors found the most striking increases in enzyme activity in those enzymes associated either directly or indirectly with lipogenesis.

In the fed obese rat (which is known to be hyperinsulinaemic) there is also an interesting increase in either the total pool size, or the specific activity, of a number of key gluconeogenic enzymes that are normally insulin-suppressible, a situation that resembles that previously described in the *ob/ob* mouse (Herberg & Coleman, 1977). On the other hand, glycolytic enzymes whose activities would normally be depressed by restricted feeding show a persistently high or even a further increased activity in obese rats subjected to restricted food intake (Spydevold *et al.*, 1978).

It is worth noting that the presence of a relatively large liver in the growing obese rat as a fraction of total cytoplasmic mass (or total body water) has not always been discussed by the authors of these studies made *in vitro*. The liver in fed obese rats of 4–6 months of age is more than twice the size of that in lean siblings (A. J. Wade, unpublished work; see also Triscari *et al.*, 1979), although the total body water is similar in the two groups (see Table 1). The evidence for increased pool sizes of many key enzymes related either to the utilization of glucose or to its formation, in either adipose tissue or liver, or both, is conclusive, and is consistent with the increased glucose replacement rate, R_0 , observed in the present study. Part of this increased replacement rate, and of the increased recycling of radioactivity to glucose, R_c , might, of course, be entirely due to intrahepatic metabolism and recycling of glucose in the enlarged liver of the obese rat. The relatively large liver might also contribute to the space occupied by the minimal mass of glucose in the obese rats. It is worth noting that, whereas the minimal mass of glucose was significantly higher in the obese rats, glucose concentration in the blood, though slightly higher, was neither raised significantly, nor,

in percentage terms, to the same extent. By taking median values of glucose concentration and glucose pool size ($M_{\min.}$) for lean and obese rats, it was found that the median glucose concentration was only 16% higher in obese animals, whereas the median pool size was 27% greater. This suggests that part of the larger pool of glucose might lie in tissues that allow both entry and exit of glucose, such as liver and kidney, the masses of both of which are greater in obese rats (Triscari *et al.*, 1979).

The evidence obtained *in vitro* also suggests that in the obese rats the production and utilization of C_3 intermediates (e.g. lactate, pyruvate) should be increased. This is consistent with the relatively constant proportionality of the measure of recycling of radioactivity to glucose, R_c , associated with high values of R_0 in obese rats (see Table 1). This rate of recycling of radioactivity may be taken as an index (though not as a quantitative measure) of the activity of the Cori cycle (Grunnet & Katz, 1978). The present experiments did not, however, reveal any difference in the degree to which recycling occurs between the two groups, if direct comparison of percentage recycling was made. It was not possible to show a relationship between R_c and food intake; consequently, if there is any underlying difference in R_c (as there is in R_0), this could not be demonstrated by the same analytical technique.

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