Exercise by means of bilateral stimulation of the sciatic nerves at rates of 1/s and 5/s did not significantly increase the removal of acetoacetate nor did it increase the release of 3-hydroxybutyrate.

Exercise increased the uptake of glucose (5mM) in the absence of insulin, confirming the findings of Szabo, Mahler & Szabo (1969). In contrast with the findings with perfused rat heart (Williamson & Krebs, 1961) addition of acetoacetate to the perfusion medium containing 5mM-glucose did not inhibit the increased uptake of glucose in the presence of insulin, nor did it inhibit the increased uptake of glucose during exercise in the absence of insulin.

Although the rate of removal of acetoacetate by this preparation was less than 10% of that reported for the perfused rat heart, sufficient acetoacetate was removed to account for 70–80% of the fuel of respiration at rest.

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Activity of Ketone-Body Utilization Pathway in Brain of Suckling and Adult Rats*

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The capacity of brain to utilize ketone bodies has been measured in suckling and adult rats by determining the activities of 3-hydroxybutyrate dehydrogenase (EC 1.1.1.30), 3-oxo acid CoA-transferase (EC 2.8.3.5) and acetoacetyl-CoA thiolase (EC 2.3.1.9). The activity of 3-hydroxybutyrate dehydrogenase in brain at birth was about two-thirds that of adult brain. The activity rose throughout the suckling period and at the time of weaning (20–22 days) reached values about three times higher than those for the adult. Similar findings have been reported by Klee & Sokoloff (1967). The changes in 3-oxo acid CoA-transferase paralleled those of 3-hydroxybutyrate dehydrogenase. The transferase activity at birth was about 1 U/g fresh wt. of brain, rose to 6 U at 21 days and then gradu-

ally declined to the adult value of 2.5 U. In contrast, brain acetoacetyl-CoA thiolase remained virtually constant at 4.0 U for 30 days after birth, which is higher than the adult activity of 2.5 U. The activities of these enzymes in kidney and heart gradually increased but did not reach the adult values until 3–4 weeks after birth. Thus during the suckling period rat brain, because of its size in relation to kidney and heart, is potentially the most important site of ketone-body utilization.

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Metabolic Effects of Propionate Administration to Normal and Vitamin B₁₂-Deficient Rats*

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Oberholzer, Levin, Burgess & Young (1967) reported that an oral load of propionate caused hypoglycaemia in a patient with congenital deficiency of methylmalonyl-CoA mutase (EC 5.4.99.2), which interconverts methylmalonyl-CoA and succinyl-CoA. To investigate possible reasons for this effect, propionate was administered to normal and vitamin B₁₂-deficient rats. The latter are unable to utilize propionate effectively (Weidemann, Hems, Williams, Spray & Krebs, 1970) because vitamin B₁₂ is an essential cofactor for the mutase. The rats were starved for 48 h and were killed 30 min after intraperitoneal injection of either propionate (1mmol) or 0.9% NaCl. The liver was freeze-clamped and blood collected from the aorta.

Propionate caused a slight increase (about 1 μmol/ml) in blood glucose in both normal and vitamin B₁₂-deficient rats. The concentration of lactate in blood was not significantly altered in control animals given propionate, but rose from 1.26 ± 0.44 μmol/ml (s.d.; n = 9) to 3.05 ± 1.77 (10) μmol/ml in the deficient group. The changes in blood pyruvate followed a similar pattern.

The lactate concentrations in livers from normal and vitamin B₁₂-deficient rats were the same at 0.39 μmol/g. After propionate the lactate concentration did not change significantly in the control livers, whereas in the deficient livers it increased to 1.20 ± 0.71 (12) μmol/g. Similarly, hepatic pyruvate concentrations did not alter in normal animals

* Dedicated to Professor H. A. Krebs, F.R.S., on his seventieth birthday.

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treated with propionate, but increased threefold in the deficient group. These changes were accompanied by a dramatic fall in the hepatic acetyl-CoA content from 0.109 ± 0.17 (11) $\mu\text{mol/g}$ to 0.016 ± 0.006 (12) $\mu\text{mol/g}$ after propionate loading. The corresponding values for normal livers were 0.086 ± 0.012 (7) $\mu\text{mol/g}$ and 0.053 ± 0.029 (7) $\mu\text{mol/g}$ respectively.

The decrease in acetyl-CoA, an activator of pyruvate carboxylase, together with a probable increase in methylmalonyl-CoA, a potent inhibitor of this enzyme (Utter, Keech & Scrutton, 1964) provide an explanation for the accumulation of lactate and pyruvate in these experiments and for the hyperlactataemia and lactate intolerance that can accompany methylmalonic acidemia in humans (Lindblad, Lindblad, Olin, Svanberg & Zetterström, 1968).

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Uptake of Ketone Bodies by Rat Brain *in vivo**

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Measurements of metabolite concentrations in blood sampled from the internal jugular bulb and the aorta of human subjects undergoing prolonged starvation indicate that ketone bodies are utilized as a fuel of respiration (Owen *et al.* 1967). However, it is not clear whether this is due to an enhanced ability of the brain to utilize ketone bodies or to raised ketone-body concentrations. The enzymes necessary for ketone-body utilization are present in rat brain but their capacities are unaltered by starvation (D. H. Williamson, M. A. Page, M. Bates & H. A. Krebs, unpublished work).

Ketone-body utilization by rat brain was investigated by simultaneous sampling of femoral-artery and cerebral-sinus blood. During starvation arteriovenous differences of ketone bodies rose in proportion to circulating ketone-body concentrations from negligible values to $0.16 \mu\text{mol/ml}$ at 48 h.

* Dedicated to Professor Sir Hans Krebs on his seventieth birthday.

When acetoacetate was infused into fed rats the same arteriovenous differences as for starved rats were observed at corresponding concentrations. Thus ketone bodies may be used by rat brain whenever they are present in blood. Control of cerebral ketone-body utilization operates through change in blood concentrations, at least in the rat.

The mean arteriovenous difference of glucose across brain was $0.51 \mu\text{mol/ml}$ in fed rats and decreased to $0.43 \mu\text{mol/ml}$ after 96 h starvation. Lactate production rose on starvation from 0.04 to $0.2 \mu\text{mol/ml}$ after 48 h and decreased thereafter. The oxygen calculated to be necessary to oxidize glucose and ketone bodies was $3.08 \mu\text{mol/ml}$ in fed rats, and remained constant throughout starvation. Ketone bodies accounted for 3% of the oxygen consumption in fed rats and 20% after 48 h starvation.

In 16–22-day-old suckling rats, which are normally hyperketonaemic, the capacity of the enzymic pathway of ketone body utilization is threefold greater than that of adults (Page & Williamson, 1971). Brains of suckling rats also extracted ketone bodies in proportion to circulating concentrations but arteriovenous differences were three times those of adult rats at a given concentration. Arteriovenous differences for glucose were similar to, or lower than, adult values and a greater proportion was converted into lactate. Ketone bodies could account for 25–70% of the oxygen consumption.

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The Metabolism of Homoanistic Acid in Man and Guinea Pigs

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Although the metabolism of phenylacetic acid and its substituted derivatives have been extensively studied in man and other animal species (Williams, 1959), there is no information on the fate of *p*-methoxyphenylacetic acid (homoanistic acid). In man, phenylacetic acid is almost exclusively conjugated with glutamine, the halogeno derivatives with glycine, and the hydroxy acids are excreted free (Ambrose & Sherwin, 1933), whereas benzoic acid is excreted as hippuric acid, the