mainly in the form of bile acids. Specific activity of the excreted bile acids was 2.5 times higher in EE-treated rats than in untreated controls.
Similar results were obtained using liposomes as artificial vehicles for ^{3}H-CO. Thus, large multilamellar vesicles (MLV), composed of cholesterol, sphingomyelin, phosphatidylserine and ^{3}H-CO in a 49½:40:10:½ molar ratio, were cleared very rapidly by Kupffer cells ($t_{½}$~1 min). After 3 hours only 1.9±0.2% of the injected radioactivity had appeared in bile. Small unilamellar vesicles (SUV; cholesterol: phosphatidylcholine: phosphatidylserine: ^{3}H-CO, 49½:40:10:½) were directed predominantly to hepatocytes ($t_{½}$~10 min) and the 3 hours biliary recovery was 6.5±1.2%. Again, biliary radioactivity was mainly in the form of bile acids. SUV-derived radioactivity was found markedly enriched in the muricholic acid fraction; MLV-Co was mainly converted to cholic acid.
In conclusion: newly synthetized hepatic cholesterol is quantitatively the main source for bile acid synthesis in the rat, although a specific bile acid, β-muricholic acid, is highly dependent on pre-existing cholesterol. Uptake of CO by hepatocytes is followed by a relatively efficient excretion of its derivatives, i.e. bile acids, into bile. Kupffer cell uptake is less efficiently coupled to biliary excretion, and probably depends on the rate of cholesterol transport from Kupffer cell to hepatocyte.

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KETOGENESIS AND CARBOHYDRATE AVAILABILITY

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It is now well-established that ketone bodies are important alternative substrates to glucose in mammalian tissues, in particular the brain (1). Under normal conditions, as the availability of glucose decreases (e.g. during fasting) the level of ketone bodies in the circulation increases and their utilization , which is concentration-dependent, is enhanced. When carbohydrate is made available again, the concentration of ketone bodies rapidly falls. The key question is how this reciprocal relationship between these respiratory substrates is achieved? The available evidence indicates that it is brought about by changes in concentration of plasma hormones which in turn alter metabolism in adipose tissue and liver (2). As the blood glucose decreases there is a concomitant decrease in plasma insulin which in turn results in a stimulation of lipolysis in adipose tissue. One of the most potent effects of insulin being its antilipolytic action in this tissue. Increases in plasma glucagon or catecholamines (e.g. as a consequence of hypoglycaemia) relative to the prevailing insulin concentration will also increase lipolysis and flux of fatty acids from adipose tissue.
Long-chain fatty acids derived from adipose tissue are the major precursors of ketone bodies and therefore whenever the flux to the liver increases the rate of ketogenesis might be expected to increase. However, the fate of fatty acids within the liver is finely regulated by the hepatic carbohydrate availability as well as to external signals (insulin versus glucagon) (2). Thus long-chain fatty acids can either be esterified and secreted as VLDL (high carbohydrate state) or enter the mitochondria for oxidation to ketone bodies or CO_2 (low carbohydrate state).
The integration of fatty acid and carbohydrate metabolism in the liver is brought about by changes in the concentration of malonyl-CoA, an intermediate in the de novo synthesis of fatty acids from glucose (or lactate) (2). This metabolite inhibits the activity of carnitine acyltransferase I (CAT I) which initiates the entry of long-chain fatty acids into the β-oxidation pathway. Insulin can increase the concentration of malonyl-CoA by activation of the enzyme, acetyl-CoA carboxylase, which controls its synthesis.
Glucagon has the opposite effect. Recent studies indicate that CAT I is less sensitive to malonyl-CoA inhibition in insulin-deficiency or fat feeding, which are associated with increased ketogenesis. Glucagon can also activate CAT I by covalent modification (phosphorylation) (3) and it is possible that this may be responsible for the decrease in sensitivity to malonyl-CoA.
This overview of the integration of ketogenesis and carbohydrate availability will be discussed in relation to two inborn errors of hepatic carbohydrate metabolism, namely glycogen synthetase deficiency (4) and glucose-6-phosphatase deficiency (5) which are associated with hypoglycaemia but widely different concentrations of blood ketone bodies.

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THE GLUCOSE PARADODX: IS GLUCOSE THE PRECURSOR OF LIVER GLYCOGEN?

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The consumption of carbohydrate after a fast is followed by glycogen deposition in the liver, and carbohydrate feeding induces hepatic lipogenesis. Common sense suggests that glucose is the precursor for glycogen and fat; and indeed the direct conversion of glucose into glycogen via hexose phosphate and UDP glucose is depicted in most textbooks. However, a large body of experiments shows conclusively that a major part of glycogen is not directly derived from glucose but from 3 carbon precursors formed by glucose cleavage. Such a pathway appears energetically wasteful, and hence has been designated the "glucose paradox". I present here the experimental evidence for the occurrence of the indirect pathway, and I dwell upon the unsolved problems in the area. Relevant literature references are found in two recent reviews (1,2).
The evidence in vivo and in vitro for the limited capacity of liver to take up glucose even in the presence of a substantial glucose load and to convert it directly to glycogen is as follows: a) Isolated perfused liver and hepatocytes have a high capacity for gluconeogenesis, but show very little net uptake of glucose at physiological concentrations (below 15 mM), and form virtually no glycogen when