glucose is the sole substrate. When supplemented with 3 carbon compounds such as lactate, glycerol, alanine, there occurs a simultaneous formation of glucose and glycogen at the expense of the 3 carbon substrates; b) lactate is a much better precursor than glucose for hepatic lipogenesis in vivo and in vitro; c) in animals and in man fructose (which is metabolized via triose phosphate) is a better precursor of hepatic glycogen than is glucose; d) after the administration of glucose by mouth or intravenously, it is difficult to demonstrate in animals and in man net uptake of glucose by portal-hepatic vein analysis. Net glucose uptake occurs in animals conditioned to a high carbohydrate diet or upon administration of heavy glucose loads in the presence of a low glucagon/insulin ratio, but the uptake of glucose is substantially less than the deposition of glycogen; e) after administration of U-¹⁴C glucose, the specific activity of glycogen glucose is less than that in the circulation, indicating production of glycogen from non-glucose carbon; f) when rats are injected with glucose labelled with ¹⁴C in carbon 1 or 6, an extensive scrambling of ¹⁴C in the glucose carbon skeleton occurs. When glucose is labelled with ¹⁴C and tritium there is a preferential loss of tritium relative to ¹⁴C in glycogen. These findings indicate a cleavage of glucose to a 3-carbon compound prior to conversion to glycogen; g) when glucose and ³HOH are administered, there is incorporation of tritium on carbon 1 and 6 of liver glycogen, which must occur in the synthesis of glucose from pyruvate.

There is presently controversy as to the relative contribution of the direct and indirect pathway to glycogen synthesis. The majority of studies is that in rats, half or more of liver glycogen is formed indirectly. The effect of hormonal and dietary conditions, pathways of glucose administration (intragastric, intraportal, intravenous) and of species differences remains to be investigated. A possible reason for the limited capacity of liver to utilize glucose is the relatively low rate of hepatic glucokinase, combined with the concurrent activity of glucose-6-phosphatase, causing futile cycling and hydrolysis of glucose 6P back to glucose. So far no effectors of the rate of glucokinase and glucose-6-phosphatase have been found. Several unresolved problems remain: a) The hepatic uptake of the lactate or other 3-carbon compounds appears inadequate to account for the synthesis of glycogen by the indirect path. The site of formation of such putative 3-carbon precursors is obscure; b) the synthesis of hepatic glycogen by the indirect path occurs in the presence of high levels of fructose-2,6P. This compound is known to activate phosphofructokinase and inhibits fructose-6-phosphatase, thus presumably blocking synthesis of hexose from triose phosphates.

To resolve the questions it has been proposed that gluconeogenesis and glycogen synthesis by the indirect path occurs predominantly in the cells of the periportal zone of the liver, whereas glycolysis and glycogen synthesis from glucose occurs in cells of the perivenous zone of the liver. According to this concept the metabolic pattern of liver metabolism is heterogeneous, and in effect different or even opposing reactions and processes occur simultaneously in different zones of the liver. Current studies in our laboratory on the distribution of enzymes and fructose-2,6P through the liver will be described.

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THE UTILIZATION OF SUBSTRATES AND O₂ BY THE MAMMALIAN FETUS: CHANGES DURING DEVELOPMENT

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In the past two decades a great deal of information has been acquired with respect to the metabolism of the mammalian fetus. For the better part, the data have been collected in chronically catheterized animals, representative of steady state conditions. Thus, meaningful interspecies comparisons have become possible. The species studied include the horse, cow, pig, goat, guinea pig and rabbit. But by far the most data have been collected in the sheep.

Several features of fetal metabolism have been well established by these studies. Among these are: a relatively high rate of fetal O₂ consumption, which, when viewed across species, appears relatively constant on a per kg basis, in the order of 8 ml/kg/min. In all species, the placenta has a high rate of lactate production under aerobic conditions, and the lactate is consumed by the fetus. A similar pattern has been shown for placental production and fetal consumption of NH₃. In the fetal lamb aminoacids transported across the placenta provide the bulk of the carbon and nitrogen required by the fetus.

More recently, the utilization of nutrients within the fetus has been studied. Two different lines of investigation have been pursued. First, individual organ uptakes and release of substrates and O₂ have been studied. In the fetal lamb, data are now available for brain, heart, kidney, GI tract, liver and hind limb, all studied under chronic steady state conditions. Secondly, tracer methodology has been used to investigate the utilization of aminoacids and carbohydrates by the fetus (1).

However, until recently, all such studies of fetal metabolism had been carried out in the latter part of gestation. In man, the advent of techniques permitting us to obtain fetal blood samples at any stage of gestation from 17 weeks to term, has made it imperative to acquire knowledge of the biology of the early or mid gestation fetus. We have now been able to catheterize the mid gestation fetal lamb permitting studies under steady state conditions, when the fetus is only approximately 200 gms. These studies have shown a higher O₂ saturation and lower hemoglobin concentration in the fetus, coupled with a much higher metabolic rate, when expressed on a dry weight basis (2,3). Fetal rates of protein synthesis and leucine oxidation have been studied using (¹⁴C)leucine. The protein synthetic rate is higher than at term, but, expressed as a fraction of O₂ consumption, is unchanged from late gestation (4). The increased use of fetal blood sampling in man for diagnosis of congenital infections or genetic disorders in mid pregnancy as well as for assessment of fetal well-being in late pregnancy has provided an opportunity to obtain a similar description of the fetal environment in man from mid to late gestation. Studies conducted jointly by the University of Colorado and the University of Milano have provided a description of some of the changes in oxygenation and acid base balance as well as transplacental glucose gradients of the latter half of gestation in man. The data from these studies are now being organized for publication.

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FETAL HEPATIC BLOOD FLOW AND METABOLISM

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During fetal life, the liver receives highly oxygenated blood and carbohydrate substrates from the mother across the placenta, via the umbilical veins. The importance of the liver in determining oxygen and substrate delivery to the fetal body has been studied in chronically-instrumented fetal lambs in utero both under normal and acute stress situations. Hepatic blood flow was measured by the radionuclide-labelled microsphere method and hepatic oxygen consumption and carbohydrate substrate uptake or release was calculated using the Fick Principle. Normally, somewhat less than half the umbilical venous blood enters the hepatic circulation; the remainder passes through the ductus venosus directly to the inferior vena cava. Almost all portal venous blood is distributed to the right liver lobe. During fetal hypoxemia, and particularly with reduced umbilical venous return due to cord compression, the proportion of umbilical venous blood entering the liver is greatly reduced. The liver is metabolically very active and accounts for 20-25% of total fetal VO_2 . Hepatic oxygen consumption, particularly of the right lobe, is however reduced during hypoxemia, linearly in relation to oxygen delivery. Normally, glucose is delivered from the placenta, and there is little glucose uptake or release by the liver, but during hypoxemia a considerable proportion of total glucose supply is derived from the liver. Lactate is delivered to the fetal body from the placenta; the liver receives about 1 $\text{mmol} \cdot \text{min}^{-1} \cdot 100\text{g}^{-1}$ and, although it extracts only about 7% of lactate, this accounts for almost 90% of the net fetal lactate uptake.

Although some controversy exists, it is generally agreed little gluconeogenesis occurs in the fetus. However, gluconeogenesis is initiated soon after birth. Possible mechanisms that could initiate hepatic gluconeogenesis after birth have been examined by simulating perinatal events. Hepatic gluconeogenesis was studied by infusing ^{14}C -labelled lactate or alanine and determining the amount of ^{14}C -glucose produced by the liver under steady state conditions. Normally, minimal - if any - gluconeogenesis by the liver can be demonstrated in the fetal lamb. Ventilating the lamb in utero increased arterial oxygen saturation to levels achieved after birth, but did not induce gluconeogenesis. Also gluconeogenesis could not be stimulated by prenatal administration of cortisol for 48 hours, or, in preliminary studies, by thyroid hormone infusion. Acute compression of the umbilical cord produced a marked fall in hepatic

blood flow and oxygen and substrate delivery, but did not stimulate gluconeogenesis. Thus other mechanisms must be responsible for initiation of gluconeogenesis after birth; these are being explored.

PHARMACOGENETICS: ITS RELEVANCE TO INDIVIDUALIZED DRUG THERAPY

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Inherited differences in the handling of and response to drugs, interacting with variables such as age, sex and "environmental" exposures, have a major impact on the wide inter-individual variation in drug efficacy, kinetics and toxicity seen in the human population. Developments in analytical methods and cellular and molecular biology have revealed a wide range of polymorphisms in drug metabolizing enzymes. The gene frequencies for such polymorphisms are not uniformly distributed through the population (1). Thus, while <5% of the Caucasian population are unable to hydroxylate mephenytoin, this abnormality (inherited as an autosomal recessive trait) is present in nearly 25% of Japanese (2). Use of dosing recommendations based on small numbers of Caucasian subjects would be expected to produce blood-level related toxicity in a sizeable portion of Japanese patients. Polymorphic oxidation of debrisoquine has been noted in many ethnic groups. In most populations, inability to metabolize debrisoquine is associated with inability to oxidize sparteine. In Ghana, however, a different allele appears to exist and while the former compound is not recognized by the specific cytochrome P-450, the latter is handled normally (3). Such heterogeneous polymorphisms emphasize the need to individualize therapy, and the difficulty in extrapolating data from one population group to another.

Recently we have found that susceptibility to idiosyncratic "hypersensitivity" reactions to aromatic anticonvulsants results from a heterogeneous group of inherited abnormalities in the ability to detoxify reactive metabolites of the drugs (4,5). The same abnormality in detoxifying metabolites of phenytoin predisposes fetuses exposed to the drug in utero to major birth defects such as congenital heart disease, cleft palate, and microcephaly (6). In the adult, we believe that a major defect (possibly homozygosity for an abnormal epoxide hydrolase) is necessary to alter the balance between production and detoxification of metabolites to result in overt toxicity. In the fetus, the heterozygous state appears sufficient to increase the likelihood of major birth defects. This is an example of interaction between genetically determined predisposition to toxicity and age-dependent development of critical enzyme pathways. Furthermore, minor stigmata of the "fetal hydantoin syndrome" were not associated with defective arene oxide metabolite detoxification. Complex interactions of genetics, pharmacogenetics, and environmental variables ultimately may determine the outcome of in utero exposure to drugs.

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