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DEVELOPMENT OF LIPID METABOLISM

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Eighty years ago Babak (5) reported that very soon after delivery the respiratory quotient (RQ) of the neonate dropped from about 1.0 to below 0.8. This was confirmed 15 years later by Talbot & Benedict (9) and by many others after them. Thus it has been known for some time that the newborn mammal utilizes fat for energy purposes apparently to a greater extent than the fetus and in many cases the adult.

Since space is at a premium only the aspects listed in the table of contents will be covered.

Fatty Acids

In contrast to triglycerides (TG), phospholipids (PL), and cholesterol, there is no doubt that some fatty acids (FA) must be able to cross from mother to fetus in all species since otherwise the newborn would be devoid of essential fatty acids. A persuasive study demonstrated that in a rabbit doe fasted for 2 days between the 26th and 28th day of pregnancy maternal plasma levels of FA and glycerol doubled; the same was found for the fetus, which appeared to deposit the extra fat received from the mother (35, 36, 37, 38, 41). Even more striking is the rapid transfer of FA in the guinea pig (12), in which C^{14} labelled palmitate injected into the maternal circulation

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appears within 3 min in the fetal blood. The calculated rate of transfer of free fatty acids (FFA) was about 2.2–3.2 μmoles/min to the combined fetuses. FA transfer from mother to fetus could provide all of the triglycerides in the liver (1 g TG for 4 g of liver).

Shapiro et al (140, 141) showed that in post-term rabbits placental transport is impaired; consequently, fetal liver lipid levels decreased and fetal plasma free fatty acid levels increased, suggesting mobilization of fetal fat stores.

Using in vivo techniques, Hudson & Hull (84) showed that fetal rabbit brown fat takes up 8.5 μmoles/g/hr of labelled fatty acids. Rates were much slower in liver and placenta. FA were oxidized to CO_2 in brown fat and incorporated into TG. In liver most of the FA were in TG. In placenta PL also contained the labelled acids.

Hummel et al (86, 87, 88) and Zimmermann & Hummel (162, 163) have quantified the amounts of FFA crossing from mother to fetus in the rat and have estimated the rate of oxidation. They report that fetuses synthesize 0.16 μmoles FA/min/litter and that hence about 50% of the FA are derived from the mother. FA oxidation proceeds at a rate of 0.12 ± 0.03 μmoles/min/litter. They conclude that about equal amounts of FA are synthesized, oxidized, and transferred from the mother. For a review of FA transport up to 1975 see Hull (85).

The rabbit placenta also possesses a lipoproteinlipase that aids in the transfer of fatty acids derived from maternal TG (38).

The situation is different in sheep. In this animal, transfer of FA is limited (40) as are transfers of ketones (7) and carnitine (72). On the other hand, acetate appears to supply 10% of the energy to fetal lambs (21). However, Noble et al (110, 111) report that transfer of ^{3}H-palmitic acid is fast, whereas that of ^{14}C-linoleic acid is slow. The same 2 acids were used by Elphick et al (40), but their experiment was an acute one using anesthesia, while Noble et al used chronically implanted catheters in unanesthetized ewes. Thus the latter group's results are probably more reliable.

In dogs, starvation of the pregnant animal just before delivery resulted in increased hepatic triglyceride content in the fetal and neonatal liver (103), suggesting increased release and transfer of FA and their esterification in the liver.

Feeding pregnant rats a fat-free diet from the 16th to 22nd day of gestation resulted in a deficiency of linoleic acid in all tissues, again indirectly confirming transfer of FA from mother to fetus (155, 156). Arachidonic acid content in mother, placenta, and fetus was not altered. Arachidonic acid is transferred more rapidly than linoleic acid (118). However, apparently less than 1% of the fatty acids derived from the mother is transported paraplacentally—i.e. from uterine fluid to yolk sac to fetus (163).

Trans- fatty acids (elaidic and linoelaidic) are transported from mother to fetus in the rat at a slow rate; 0.2–1% was taken up by the placenta and about 0.1–0.4% by the fetus. Incorporation into fetal tissues was greater than for cis- acids. Both cis- and trans- acids were found mostly in TG in maternal plasma, in TG and PL in the placenta, and mostly in PL in the fetus. Both linoleic and elaidic acid, but not oleic or linoelaidic acids, are oxidized in the fetus (105).

The amount of transport of FA from mother to fetus in the rat is small, as evidenced by the fact that a 15% corn oil diet, which suppresses maternal hepatic lipogenesis, had no effect on the high rate of FA synthesis in the fetus (104). Nevertheless, the linolenic acid content of *both* fetal and maternal livers trebled. Fasting also raised the polyunsaturated content of fetal and maternal liver. However, maternal fasting does decrease fetal FA synthesis (104). Essential fatty acid deficiency during pregnancy resulted in retarded brain development and a profound reduction in some myelin components (galactolipid, proteolipids) (100). The brain of the fetal rat appears capable of converting linolenic acid to docosahexaenoic acid (22:6 ω3), which may also explain why the fetal brain is not protected from the adverse effect of an imbalance in the linoleic/linolenic acid ratio in the maternal diet (33, 34).

Infusion of glucose into rabbits on the 28th day of pregnancy increased insulin levels in both mother and fetuses and decreased maternal FFA plasma levels without having a strong effect on fetal levels; hence in the infused groups the FFA level in the umbilical vein was twice that in maternal blood, suggesting another source of acids (perhaps the placenta) under these conditions (41).

In humans less is known. Sabata et al (131) reported some dependence of fetal FA plasma levels on maternal levels. As a rule it appears that the rate at which FFA are transferred from mother to fetus is slow (52), although according to Hull (85) all the fat accumulated by the fetus towards the end of gestation may be derived from a transplacental supply of FFA. There is no doubt that some essential fatty acids must be transferred, since they cannot be made by the fetus (50, 51).

That the blood levels of FFA and glycerol rise rapidly after birth, a fact first reported 20 years ago, is still attracting attention. Evidence shows that even in humans the concentration of FFA in the umbilical vein is positively correlated with that in the maternal blood (e.g. 39) and that adipose tissue development in the fetus is dependent on the maternal blood level of FFA (144). In all cases there is a postnatal rise, apparent immediately after delivery (22; but see 3)

Many years ago, Hahn & Koldovsky (74) reported that hepatic levels of glycogen increased in newborn rats fed TG or FFA only. This finding was

ascribed to the glycerol in the TG, even though FA had the same effect. Ferre et al (45, 46, 47) have now confirmed this finding and, to a large extent, explained it. They showed that in newborn rats hepatic FA oxidation increases gluconeogenic flux by providing acetyl CoA for pyruvate kinase and NADH to direct the glyceraldehyde-3-phosphate dehydrogenase reaction towards glucose formation. This, of course, brings us back to the importance of carnitine in the peri- and neonatal periods. Apparently the glycogen content of the liver is also important, since if it is high the FA oxidation rate is low (129, 161) and vice versa.

In confirmation of the work of Ferre et al (45, 46), Sabel et al (132) showed that the hypoglycemia of small-for-date newborns could be raised by "fat injection." Feeding milk was only useful if ketones in the serum had attained a certain value. Hence gluconeogenesis could proceed only if fat was being oxidized.

There is thus consensus that fetal levels of FFA are lower than maternal ones but that the actual rate of transfer depends on (*a*) chain length, (*b*) desaturation, and (*c*) the species and age of the fetus (73). Little has been reported between 1975–1980 that alters these conclusions arrived at in the mid-1970s. Similarly, few new reports have appeared concerning the postnatal changes in blood levels of FFA [see (71, 72, 73, 85) for details].

Ketones

It has long been known that pregnant mammals are more prone to ketosis than nonpregnant ones [for review see (136)] and that in human, rat, rabbit, and guinea pig they readily cross the placenta (72). The sheep is the exception. Transplacental passage of β-hydroxybutyrate or acetoacetate in this species is slow or nonexistent (7). The finding that ketogenesis is low in fetal rat liver (26) and that the brain of the newborn rat utilizes ketones in preference to glucose (27) has generated considerable interest. For review of earlier work see (73, 154).

Of particular interest is the fate of ketones produced by the mother and transported to the fetus. Seccombe et al (136) investigated this in some detail and showed that (*a*) labelled DL-β[3–^{14}C] hydroxybutyrate is rapidly passed from mother rat to her fetuses, (*b*) it is used for lipid synthesis, and (*c*) different tissues incorporate it at different rates. Brown adipose tissue contained by far the highest radioactivity, mostly in the triglyceride (75%) fraction (202093 dpm/g against the second highest, lung: 38324 dpm/g). In all other tissues most of the activity was in the phospholipids (44–65%).

Indirect evidence also suggests increased sterol synthesis from acetoacetate in the suckling rat's brain (120, 157, 160). The cytosolic 3-hydroxy-3-methyl-glutaryl CoA synthase in the brain decreases during days 0–21 (119). Ketone utilization by the infant rat brain in vivo has also been

demonstrated (19, 24). Benavides et al (8) suggest that the inhibition of 3-hydroxybutyrate dehydrogenase and 3-oxoacid CoA transferase activities by phenylalanine and its metabolites in the suckling rat brain may affect mental development in phenylketonuria. Utilization of ketone bodies for cholesterol and FA synthesis in different parts of the brain is highest in very young rats and greater than that of glucose. The greatest rate of synthesis was found in the brain stem (16).

As shown earlier (26), hepatic ketone production is high in the suckling period of the rat (10, 47) while incorporation of C^{14}-palmitate into lipids is decreased. Blood levels of ketones can be further raised by feeding medium-chain triglycerides (MCT), or long-chain TG (158). In adults rats, MCT feeding is more effective and leads to hypoglycemia.

In sheep, ketones do not cross the placenta (7). However, the fetal liver produces acetoacetate at ever increasing rates as gestational age increases, and there is considerable postnatal rise. This is matched by blood β-hydroxybutyrate levels, which rise from 0.037 pre- to 0.133 μmol/l postnatally and continue rising to high levels (0.4 and higher).

In contrast to adult liver, fetal rat liver (also the brain, placenta and fetal carcass) can oxidize ketones supplied from the mother when the latter is starving (159). Isolated fetal hepatocytes also oxidize ketones. The enzyme 3-oxoacid CoA transferase is present in newborn liver but has little activity in the adult organ (44). Thus the fetal liver is geared to utilize ketones, the suckling liver to make them. The ability of the rat fetus to utilize ketones, *depending on their concentration,* spares glucose and lactate when these are in short supply—e.g. during maternal starvation (138). Similar conditions prevail in baboons (122).

If pregnant rats are fed a 45% corn oil diet for the last 8 days of gestation, ketonemia develops in both mother and fetuses; this has profound effects on the metabolism of the neonatal brain (23). Fetal rat tissues can oxidize ketones in the order placenta, brain, liver, carcass. This is of particular importance during a maternal fast, when a 30–60-fold rise in fetal plasma β-hydroxybutyrate levels can be observed (137, 138, 139). Ketones are also used in preference to glucose for lipid synthesis by the brain of newborn rats (150, 157). In neonatal hypothyroid rats the development of ketone metabolizing enzymes is delayed; the rise and the subsequent decrease occur later (120, 121). In the liver of suckling rats the major site of regulation of ketogenesis involves the disposal of long-chain acylCoA between the esterification and oxidation pathways. The authors suggest that the high levels of cycle AMP in the liver inhibit esterification, thus making possible a maximum rate of ketogenesis (10). The rise in plasma ketone levels after birth starts 4 hr after birth, while plasma FFA and liver carnitine levels rise within 2 hr after birth as soon as the pups consume milk (129).

Twenty-four-hour starvation of the pregnant guinea pig, whose fetuses represent up to 50% of maternal body weight, causes a 5-fold rise in FFA and 8-fold rise in blood ketone levels (56).

Incorporation of ketones into brain lipids (cholesterol, lecithin, gangliosides) develops more slowly in hypothyroid rats than in normal pups and decreases later in life (30). The postnatal rise in blood ketone levels seen in the rat has also been described in man (123). Recently it has been suggested that in man this perinatal rise is due to starvation and can be eliminated by early feeding (3).

Cholesterol

Feeding of cholesterol or cholestyramine to pregnant rats has no effect on fetal cholesterol synthesis (104). It is well established that plasma levels of triglycerides, phospholipids and cholesterol rise rapidly after birth. Considerable attention has been paid recently to the lipoproteins and their cholesterol content (14, 15, 17, 63). At birth, total cholesterol content of the blood is higher in premature than full-term neonates; the same is true for high-density lipoprotein (HDL)- and very low density-low density lipoprotein (VLDL-LDL)-cholesterol content (58, 59, 60). The postnatal rise in total cholesterol content is the same in both groups. Values attained 10 days after birth reach 3.1 mmoles/l or 118 mg/dl regardless of the food consumed, but after that time they increase to higher values in breast fed infants than in babies fed cow's milk or other formulas (86). The cholesterol content of breast milk was not affected by the amount of cholesterol consumed by the mother or the plasma level of this sterol. However, linoleate content of milk was directly proportional to plasma linoleate levels. The plasma cholesterol content of babies decreased as the linoleate content of the milk rose (124).

Feeding a high-cholesterol diet raised maternal plasma cholesterol levels but had no effect on milk or infant serum values. In contrast, phytosterol content of the diet was reflected in both maternal serum and milk and newborn serum (102). At birth, white girls had the highest cholesterol, β-, and α-lipoprotein levels; values were higher for white than for black neonates (18). Thus basic values are already established at birth (49). For discussion see (2, 14, 17).

In small-for-gestational-age newborns, lower values for HDL- and higher ones for LDL-cholesterol were found than in full-term infants (4). Both LDL- and HDL-cholesterol values were higher in prematures. During early postnatal development of normal babies the HDL/VLDL-LDL-cholesterol ratio fell from 1.5 at birth to 0.6 at 3–6 months, with HDL-cholesterol rising by about 60% and VLDL + LDL-cholesterol rising 3.5 times (60). Cord blood has no VLDL (117; but see 17).

Neonatal lipid concentrations have been described in detail for Swedish newborns (77, 78). Others have analyzed lipoprotein and lipid composition in different parts of Norway (64) and have described similar changes in normal newborns (49, 149). A significant correlation was found between the total cholesterol values at birth and values found 3–6 months later; an *inverse* correlation exists between the increase of the first 3–10 days and that in the next 3–6 months for total and VLDL-LDL-cholesterol (60). The conclusion is that in infancy both food and genetic factors control cholesterol levels but that genetic factors predominate later. It was shown many years ago that the postnatal rise in total cholesterol occurs in two steps (114). The first seems to depend on food supply, since it does not occur in infants fed tea with sugar; the second (2–3 days later) occurs even if no food is given.

In postmature rabbit fetuses, blood levels of cholesterol increase from about 90 to 140 mg/dl while in the mother the rise is from about 12 to 40. In normal rabbits blood levels rise to 120 mg/dl in the mother and 180 in the newborn after delivery, whereas TG serum levels are elevated in postmature fetuses only (79, 140).

Serum bile acid levels (lithocholic acid and sulfo-lithocholylglycine) are highest in the newborn (6). They decrease upon the consumption of the first meal in prematures, but rise in full-terms. Adult levels (a 5-fold decrease) are attained only gradually by about one year. In rats there is minimal transfer of bile acids (81).

Newborns of diabetic rats had lower serum cholesterol levels and a smaller cholic acid pool than control pups, whereas the opposite was true for their mothers during pregnancy (80). The strikingly lower serum cholesterol levels in the neonates (13.84 ± 3.3 against 68.38 ± 4.4) deserves special notice.

The postnatal rise in total plasma cholesterol content has been found to occur in all mammalian species examined so far (20, 127) and has been related to the cholesterol content of the milk (125) and of the diet (106, 151). This is probably an oversimplification even though human breast milk contains 20–24 mg/dl while milk formula only 2 mg/dl (59). This is even more strikingly brought home in intravenously fed newborns (and adults) in whom blood total cholesterol content rises up to 500 mg/dl if intralipid is included in the cocktail (63). This occurs within 1–3 days after the start of i.v. feeding. The rise in total cholesterol is directly proportional to the amount of intralipid supplied, whereas HDL-cholesterol levels are decreased and are inversely proportional to the amount of fat infused. The authors calculate that at least 50% of the plasma cholesterol is made by the body. These facts strikingly demonstrate that cholesterol itself, supplied

either orally or intravenously, is not the sole determinant of plasma cholesterol levels. It has been suggested that the ratio of saturated to unsaturated fatty acid might play a role in the regulation of blood total cholesterol levels (63). However, other factors are undoubtedly involved. Thus in rats, total cholesterol levels in 19-day-old animals can be decreased within 24 hr to less than half the suckling value by feeding a high carbohydrate diet (112); these values are significantly lower than those found after 24 hr of starvation. Similarly the quantity of milk consumed affects total cholesterol blood levels. They are elevated in rat pups if only 3 are in the litter compared to litters of 13–14 (69). It should be mentioned that rats over-fed in infancy eat more when adult (116).

Interesting relationships exist in the suckling period between blood levels of total cholesterol and the rate-limiting enzyme of cholesterol synthesis, 3-hydroxy-3-methyl-glutaryl CoA reductase (HMGR). In the rat fetus, hepatic HMGR shows high activity that is not inhibited by feeding cholesterol to the mother (16). Activity decreases after birth (101, 69). It has been suggested that the decrease is due to a factor in milk (101). However, no such factor has been isolated and since it is known that there is an inverse relationship between blood levels of total cholesterol and hepatic HMGR, it seems more probable that cholesterol or one of its metabolites, including VLDL, is responsible. At weaning in the rat, when the high-fat diet of the suckling period is replaced by the high-carbohydrate rat chow, blood total cholesterol falls and hepatic HMGR activity rises (101).

Since HMGR is present in most tissues, enabling them to make cholesterol (and other compounds) necessary for growth and differentiation, the development of its activity in extrahepatic tissues is of interest. Little work has been done in this area. Attention has been paid to the brain, where enzyme activity in the rat reaches a maximum on day 3 after birth when the rate of myelination is at its highest (108, 143) while in the lung activity is highest prenatally (108).

Even though it has been suggested repeatedly that the gut is a large source of cholesterol, developmental changes of intestinal HMGR have not been reported. Results show a steep decline in activity after birth and a rise after weaning in the rat, and similar changes occur in brown adipose tissue. (75).

Recently it has been suggested, that white adipose tissue plays a special role in the maintenance of total plasma cholesterol (67), since HMGR activity in this tissue of obese mice was found to be high, even though the hepatic enzyme showed low activity. Preliminary results indicated that HMGR activity in white adipose tissue of suckling rats in a 3-pup litter was higher than in adipose tissue of suckling rats in a 14-pup litter. Since the enzyme is inactivated by a protein kinase (probably cyclic AMP sensitive),

it is of interest that the low activity in the intestine of suckling rats can be raised by dephosphorylation (75), suggesting that perhaps the postnatal depression in HMGR activity in liver, brown fat, gut, and lung is related to the well-known increase in blood glucagon levels, which, together with the low blood insulin levels (61), results in elevated activity of adenylcyclase, at least in liver and brown fat (113, 142). This is supported by the changes that occur at weaning to different diets. In rats weaned to a high-carbohydrate diet, blood levels of glucagon and cholesterol decrease together with the hepatic content of cyclic AMP and GMP, while insulin levels rise. Maintenance of the picture seen in suckling rats is found on weaning to a high-fat diet (66).

The regulation of hepatic and perhaps extrahepatic HMGR, however, is not the whole picture. Equally important is the rate at which cholesterol is eliminated into the bile. In the newborn guinea pig (98) the pool size of cholic acid is small and so is its rate of synthesis. The enzyme that commits cholesterol to bile acid synthesis is 7α-cholesterol hydroxylase. Little is known of its postnatal development in any species. In rats, activity in the liver is about the same in the newborn and the 21-day-old animal (107). Unfortunately this tells us nothing about the suckling period. Judging from the activity of HMGR, which according to these authors is twice as high on day 21 as in the newborn, one must assume that the 21-day-old rats were consuming considerable amounts of lab diet. Other data from this paper suggest that 7α-hydroxylase is high in the suckling period, since in older animals it is usually elevated whenever HMGR is depressed.

It has also been suggested that the blood level of HDL-cholesterol is inversely proportional to the incidence of atherosclerosis; the higher level of total cholesterol, the more likely is the occurrence of arterial disease.

In 117 neonates HDL-cholesterol was 25.5 ± 0.9, LDL-cholesterol 30.2 ± 1.0, and total cholesterol 72 ± 1.4 mg/dl. HDL-cholesterol rises by 40–50% in older children, but LDL-cholesterol increases 4-fold to adult levels (62). Obviously in the unfed neonate, chylomicrons are not present (74). Because of the conjectured relationship between HDL-cholesterol levels and atherosclerosis, the effect of age and diet have been examined in experimental animals.

In suckling rabbits, Robert et al (127, 128) found an increase in VLDL and intermediate-density proteins; this contrasts with the hypercholesterolemia found when young weaned rabbits are fed a casein-cholesterol-free diet. Most of the cholesterol in these animals was in the intermediate-density lipoproteins. In sheep (95) a different picture is apparent. At all ages, the main lipoprotein is HDL (76% in the adult), while about 20% is LDL. In the suckling animal both fractions increase, together with the cholesterol and cholesterol ester contents. In the suckling lamb, the

transient presence of another lipoprotein in the HDL fraction was reported. In rats (134, 135) HDL-cholesterol levels rise postnatally and rapidly decrease on fat feeding or starvation of prematurely weaned animals. In the suckling rabbit, HDL-cholesterol levels rise from 20 mg/dl two days after birth to 42 mg/dl in the 4th week and fall to 7 mg/dl after weaning. The high VLDL- and LDL-cholesterol levels decreased 10-fold after weaning but rose considerably if casein was added to the diet (127, 128).

In rats, on the other hand, fetal plasma LDL levels were 5-fold higher than in adult animals (135, 136) while VLDL levels were 10-fold lower. HDL levels were 60% those in the adult. About 80% of serum TG are in fetal LDL and 14% in fetal VLDL. Exactly the opposite is true for adult serum.

The intestine of the newborn unsuckled rat contains VLDL in its duodenal villus tip cells. Chylomicrons appear only after suckling in duodenal epithelial cells (11). In the mother rat chylomicron cholesterol does not enter the milk (94).

An important enzyme in cholesterol metabolism and its transport is lecithin-cholesterol acyltransferase (LCAT). The enzyme catalyzes the formation of cholesterol esters from cholesterol and lecithin. It is found to be low in the newborn guinea pig (28) and human (28) and to rise quickly after birth if the newborn are fed milk. Thus in the newborn lamb, 6.7% of labelled cholesterol was esterifed; this rose to 9.7% on day 3 but remained unchanged if a nonmilk diet was fed. Similarly, cholesterol esterification in the plasma was 22 μmoles/hr/l in the newborn and 82 three days later if milk was fed, but only 51 on a milk free diet. A large postnatal increase in LCAT in lamb was also reported by Noble et al (111). Frohlich et al (54) found little change in LCAT activity in rats and humans during postnatal development but suggest an inverse relationship between LCAT activity and serum cholesterol.

Adipose Tissue and Obesity

Originally it was proposed that one of the factors causing obesity was the number of cells present in adipose tissue soon after birth (91). This now appears doubtful. Apparently much depends on the origin of the adipose tissue (epidydimal, subcutaneous, abdominal, etc). In rats, evidence suggests that adipocytes (probably preadipocytes) can commence multiplying right into adulthood (55, 90). Thus the idea that the young animal or child soon after birth has a fixed number of fat cells in its adipose tissue is probably no longer tenable (65).

However, feeding in the neonatal period can have immediate effects. Formula-fed infants started on solid food before the age of 2 months had more fat at 3 months than those fed formula or breast milk only (48). Two

months later this difference had disappeared. In infants of diabetic mothers there was a direct correlation between blood levels of insulin and body fat mass and fat cell weight but not fat cell number (42). These data make it difficult to decide whether the greater fat content of newborns from obese mothers is genetically or environmentally conditioned. A high-carbohydrate diet in pregnant women resulted in 20% obesity in their infants (133); 40% of large-for-gestational-age newborns born to diabetic mothers were obese by 7 years (148) and overweight when adolescents; adequate-for-gestational-age newborns from diabetic mothers did not show this tendency. Kramer (92) showed that breast feeding protects against later obesity.

Some light is shed on the differences between species in a report of G. Alexander (1) on adipose tissue development in the fetal sheep. Fat started to be laid down in the fetus before the 50th day of gestation, and brown fat appeared on day 70. White fat could be found 2 weeks later. Surprisingly, fat regressed considerably after the 115th day of pregnancy. The author suggests that the normal fetal lamb is undernourished for the last 5 weeks of gestation. Supporting this view is the fact that in nutritionally restricted ewes fetal fat content was even lower. Perhaps fetal sheep are able to live off their fat to some extent during the last 5 weeks of gestation.

Human adipose tissue had a fat cell weight of 0.05 μg in the newborn, which increased to 0.25 μg by 9 months (115). For the same cell size, basal lipolysis was greater in infants younger than one year than in older ones. Fat cell size and not fat cell number in newborns is significantly correlated to body fat mass and neonatal plasma insulin levels. These authors conclude that during intrauterine development fat mass expansion occurs almost exclusively by fat cell hypertrophy (43).

A controversy exists over whether early weaning of babies leads to obesity (25, 82, 145). Several factors have been shown responsible for early excessive weight gain, an important one being overconcentrated feeds leading to water deficiency, hyperosmolality, thirst, over-feeding, and overweight. All this can be prevented (at least in Sheffield) by adequate feeding either by breast or with formula. Others have suggested (13) that obesity occurs in children only after they have been overfed for a considerable length of time. Thus one-year-old fat babies remain overweight only if they are further permitted to remain fat and to increase their cell number.

Yet how far early feeding is involved in later obesity is still not clear (25, 30, 48). In contrast to the case with mice (31, 32, 146), genetic factors have not been clearly defined for humans. Undoubtedly the density of the milk plays a role. Thus in the musk shrew, fat content of the milk is 17.5% and the young triple their weight by day 5 after birth (29). It seems that excessive carbohydrate intake in pregnancy can also lead to neonatal obesity (134). Similarly, maternal obesity is reflected in the newborn (152, 153).

Female rats allowed to become obese on a highly palatable high-energy diet did not eat more when lactating (as is usually the case), and 44% of their litters died by the 6th postnatal day. The surviving pups grew more slowly than pups from control mothers (79; see also 130). Overeating in infancy (4 rat or mouse pups against 10 or 16 per litter) also has long-lasting effects. In the overfed group, activities of enzymes of FA synthesis were elevated at 20 weeks—i.e. long after weaning (32). Similarly, blood cholesterol levels were higher in the overfed than the normally fed groups 6 months after birth (P. Hahn, unpublished).

Early Conditioning for Adult Atherosclerosis

In 1951 Gillman & Gillman (57) suggested that the causes of adult atherosclerosis might be found in early childhood. In recent years increased attention has been paid to this idea. It was demonstrated (74) and confirmed later (76) that premature weaning of female rats made them more susceptible to the effects of an atherogenic diet when aged 8 months. Reiser & Sidelman (125) suggested an inverse relationship between the cholesterol content of rat milk and the plasma cholesterol level in adult male rats that had consumed such milk as pups. Unfortunately milk cholesterol content was examined in 2 mother animals only. Weaning rats prematurely (day 18) to a high-fat diet (HF) fed between days 18 and 30 only made them more resistant to the hypercholesterolemic effect of an atherogenic diet when aged 7 months; whereas feeding a high-carbohydrate diet (HC) for these 12 days had the same effects as premature weaning to the laboratory chow in previous experiments (76). Plasma levels of total cholesterol in the animals weaned to the HF diet remained high until day 30, when Purina Chow was offered, but such levels dropped rapidly in 19-day-old rats weaned to the HC diet on day 18.

Thus again there was an inverse relationship between plasma levels of cholesterol in young animals and those in adult rats challenged with an atherogenic diet. Further studies showed that early weaning (day 18) to the HC diet in the rat results in a rapid decrease in plasma glucagon levels and a slower rise in plasma insulin levels (70). This was reflected 8 months later when rats were fed the atherogenic diet by the fact that plasma glucagon levels were increased more in rats weaned to the HF diet than in those weaned to the HC diet. The effects of feeding a HF or HC diet for 12 days between days 18 and 30 can be revealed much sooner with the right technique. These experiments promoted pediatricians to seek a similar phenomenon in humans. Except in one study (147), no effect of early feeding on subsequent plasma cholesterol levels was found (53, 73, 83, 96, 100). These studies all suffer from the same defects: (*a*) Children were examined between the ages of 1 and 10 years—i.e. they were comparable to very young

rats; and (*b*) they were not challenged with a specific high-fat or high-cholesterol diet. Hence, whether early feeding experience (breast feeding against early weaning) has a late effect in humans has not been effectively examined. [See also (16a) for an evaluation.] Nestel et al (109) also suggest that "the magnitude of the response to dietary cholesterol and fat becomes established early in life."

More recently, Naseem et al (107) showed that even the diet fed to pregnant rats may affect cholesterol metabolism immediately in the fetus and later in the pup. They found that infant rats from mothers fed a high-fat high-cholesterol diet throughout pregnancy and after birth up to day 21 had lower HMGR activity and plasma cholesterol levels than pups from control mothers fed the diet only from day 1 after birth. In other words, prenatal supply of a HF-HC diet had a cholesterol-lowering effect on day 21 postnatally. On the other hand, feeding the control diet from birth to day 21 resulted in *higher* plasma cholesterol levels and hepatic 7α-hydroxylase activity on that day if the experimental diet had been fed during gestation. Note that day 21 is 9 days prior to natural weaning.

The effect of different levels of cholesterol (0–1%) and lard (5–15%) in the diet on maternal plasma and milk cholesterol in rabbit does was examined by Whatley et al (151). In blood, cholesterol levels rose 100-fold (15% lard + 1% cholesterol); in milk they doubled on this diet only. Blood and liver cholesterol levels in suckling pups were elevated but fell to normal after weaning to a low-fat low-cholesterol diet.

The conclusion of a paper by Kris-Elberton et al (93) is definite: "Our work unequivocally refutes the hypothesis that early exposure to exogenous cholesterol protects against subsequent dietary induced hypercholesterolemia in the rats." This is probably a valid conclusion, even though it takes a stand against a premise few investigators have put forward. What has been suggested is that plasma cholesterol levels in infancy are in some way related to these levels in the adult and that early changes in nutrient supply have more permanent effects than was previously thought. This suggestion is borne out in the complex experiments reported by this group. Rat dams were fed 3 diets from the 14th day of gestation: (*a*) fat free (FF), (*b*) high-fat high cholesterol with 2% Na cholate (HFHC), and (*c*) the standard rat diet (S). Milk cholesterol content was more than doubled in the HFHC group but was the same in the other 2 groups (plasma cholesterol in the dams: HFHC, 1120; S, 62; FF, 69 mg/dl). Body weights of the offspring increased more (after weaning) in pups with the HFHC milk than in the other two groups. Feeding a 10% lard diet from days 30–60 resulted in lower plasma cholesterol levels in the group fed the HF diet up to day 30. For reasons that are not clear, a stock diet with 0.5% cholesterol was fed from day 60. On the whole, no differences in plasma cholesterol levels

were observed up to day 150, when a diet of 10% lard with 0.5% cholesterol was fed up to day 210. On day 180, but not 210, cholesterol levels were highest in the HF group. Similar results were obtained with a slight variation in the feeding of the infant rats. As a rule, high-cholesterol diets in the suckling periods resulted in lower plasma cholesterol levels in later life (up to day 120); but at day 210, levels were higher in the ones given extra cholesterol when suckling. Finally, some infant rats were artificially reared with or without cholesterol. This resulted in slower growth and (regardless of the cholesterol content of the artificial milk)in higher plasma cholesterol levels than in suckled pups, on days 81 and 111. This experiment supports the unequivocal conclusion of these authors. However, since neonatal undernutrition (artificial feeding in this case) leads to decreased plasma cholesterol levels in infancy (69) it seems possible that perinatal plasma cholesterol levels or some factors other than exogenously supplied cholesterol may be correlated with levels in the adult. This is essentially the conclusion of the authors, who suggest that "the development of a 'normal' metabolic response to exogenous cholesterol in the adult is affected in early life."

It is of interest to note that cholesterol passes from mother rat to fetus only slowly and is without effect on the high rate of its synthesis in fetal liver (16).

It was also shown (107) that hepatic HMGR and 7α-hydroxylase activities may be more sensitive indicators of early nutritional effects than serum cholesterol levels. Thus 52-day-old rats whose dams had been fed a normal diet during gestation and lactation (up to postnatal day 21) were compared with rats from dams fed a HFHC diet during lactation. On day 21 all rats were given this HF diet up to day 52. HMGCoAR was decreased and 7α-hydroxylase activity increased ($p \leq 0.01$) in the group fed the HF diet during lactation, and again the HF diet from day 21 to 52 resulted in higher serum cholesterol and 7α-hydroxylase levels and decreased HMGCoAR activity than when the HF diet was fed during gestation. Thus there remains little doubt that early changes in feeding pattern, even mediated via the mother, can produce long-lasting effects. The question of mechanism remains. Li, Bale & Kottke (97, 99) throw some light on this question using guinea pigs. These are born very mature. They start to eat solid food immediately after birth and hence are not suitable for experiments involving premature weaning. No effect of "early" weaning was noted except a slight ($p \leq 0.05$) decrease in hepatic HMGCoAR in response to a high-cholesterol diet. On the other hand, feeding cholestyramine (1.1% of diet) for 6 weeks after birth made adult animals (aged 105–259 days) more resistant to the hypercholesterolemic effects of a high-cholesterol diet. Such animals, when adult, excreted more bile acids than controls and had higher activities of both hepatic HMGCoAR and 7α-hydroxylase. They also had a larger

bile acid pool. Differences between the 2 groups (with or without cholestyramine for 6 weeks) were more pronounced when a 0.25% cholesterol diet was fed. Feeding cholesterol from the 1st to the 13th postnatal week had little effect on blood cholesterol up to week 25 but did cause a greater excretion of bile acids. Thus it appears that, in guinea pigs at least, cholesterol catabolism is enhanced by treatments in infancy that make the individual more resistant to excessive cholesterol feeding when adult.

Hepatic HMGR activity in adult rats depends on their previous nutritional history (126). Animals fed a semipurified diet up to day 60 (but not 35) maintained low HMGR activity even when they ate a commercial diet for 20 days.

Of course, important differences exist among rats, guinea pigs, and humans. Rats are born very premature and are breast fed for at least the first 14 days of postnatal life, whereas guinea pigs eat solid food nearly immediately after birth. Humans lie between these extremes. They are closer to guinea pigs as far as maturity goes, but closer to the rat as far as dependence on the mother is concerned. In addition guinea pigs hardly ever consume cholesterol after weaning; rats and humans do. It is hence difficult to draw any but the most general conclusions from animal experiments.

J. J. Nora (112) suggests that it is possible to identify during childhood the person who will suffer from coronary disease as an adult. Nora stresses the genetic components of the disease but, of course, underlines the possible role of the environment. By identifying those at risk early in life, such an approach would obviate the reduction of butter, milk, and egg intake for the whole population. This "individualization" of treatment (nutritional and otherwise) will undoubtedly replace current all-embracing condemnations of certain foods.

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