Obesity and Atherosclerosis as Consequences of Early Weaning

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I hope to demonstrate in this chapter that early pre- and postnatal nutrition and other factors have lasting effects on the further development of the individual. Finally, I shall marshall the meager evidence pertaining to humans to show that possibly the same, or at least similar, responses can be found in our species.

I shall deal with two pathological states thought to be possibly affected by early nutrition: atherosclerosis and obesity.

The rat fetus lives 22 days in the uterus. During this time it is fed a high-glucose diet with very little fat and cholesterol. Logically, and as confirmed by experiments, the fetus does not make glucose; its liver does not contain the necessary enzymes (Table 1). On the other hand, the fetal liver makes both large amounts of fatty acid and cholesterol-synthesizing enzymes (Tables 1 and 2). Fatty acids are not oxidized to any large extent; hence, ketones are not released by the liver and the requirements for carnitine are minimal (2,3).

In the life of the rat there are two events that cause a sudden change in the above situation: first, delivery, which suddenly changes not only the route via which food reaches the blood but also the composition of the food; second, premature weaning, when overnight milk is replaced by the solid laboratory diet, the composition of which is controlled by the experimenter.

Table 1 shows the changes that occur within 12 hr after birth. They are conditioned by the high-fat, low-carbohydrate milk diet, which leads to an increase in glucose formation by the liver and possibly by the intestinal mucosa, as well as to a considerable rise in the rate of fatty acid oxidation. The sequence of events is probably hypoglycemia → release of catecholamines → release of glucagon → lipolysis, leading to a rise in both plasma glycerol and fatty acid levels, breakdown of liver glycogen, and increased synthesis of the gluconeogenic enzymes phosphoenal pyruvate carboxykinase (PEPck) and glucose-6-phosphatase. Within 12 hr the rate of fatty acid oxidation is increased so that plasma levels of ketones increase by more than 10-fold (2,3).

In humans similar changes occur; however, they are frequently modified by medical or maternal interference immediately after birth. Perhaps the most important
TABLE 1. Metabolic changes occurring at birth and at weaning in the rat*

<table>
<thead>
<tr>
<th>Fetus</th>
<th>Newborn</th>
<th>Weaned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluconeogenesis</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>PEPcK</td>
<td>0</td>
<td>↑</td>
</tr>
<tr>
<td>Glucose-6-phosphatase</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>FA synthesis</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>FAS</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Malic enzyme</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Citrate cleavage enzyme</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td>FA oxidation</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Ketone formation</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Carnitine synthesis</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td>CAT</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>CPT</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Transamination</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Urea</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma cholesterol</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma TG</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Plasma FA</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma glycerol</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma carnitine</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma insulin</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Plasma glucagon</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>HMGCoAR</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>7α-Hydroxylase</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td>Bile acid pool</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

* (PEPcK) phosphoenolpyruvate carboxykinase; (FA) fatty acid; (FAS) FA synthetase; (CAT) carnitine acetyltransferase; (CPT) carnitine palmitoyltransferase; (TG) triglycerides; (HMGCoAR) hydroxymethyl glutaryl coenzyme A reductase.

TABLE 2. Effects of diet changes on rats*

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
<th>White Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HF</td>
<td>HC</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>77.3 ± 3.5</td>
<td>96 ± 7.5*</td>
</tr>
<tr>
<td>Fatty acid synthetase</td>
<td>9.4 ± 0.4</td>
<td>10.6 ± 1.2</td>
</tr>
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*Male rats were fed either a high-carbohydrate diet or a high-fat diet during postnatal days 18 to 30, and a Purina chow diet from day 30 to 40. They were then fed a high-fat diet for 2 more days: (HF) high fat; (HC) high cholesterol. (From ref. 1).

*p < .05.

*p < .01.
difference between a baby rat and a newborn human baby is the fact that the latter can survive without breast milk, while the former cannot. The other important difference is the source of plasma fatty acids and glycerol. These are derived from milk fat in the newborn rat, but from body fat in the newborn infant. We shall return to this difference later.

Natural weaning in the rat occurs gradually between the 14th and 30th postnatal days (4), with milk intake decreasing and solid food intake increasing (5). However, rats can be weaned prematurely between days 14 and 18.

The immediate effects of early weaning to the usual high-carbohydrate Purina chow diet are numerous and can be compared to the response of adult rats whose diet is suddenly changed from a high-fat to a high-carbohydrate diet. The rate of fatty acid synthesis in white adipose tissue increases rapidly, as evidenced by a rise in the activities of fatty acid synthetase citrate cleavage enzyme, glucose-6-phosphate dehydrogenase, and malic enzyme (6).

The rate of gluconeogenesis is decreased, as indicated by the fall of PEPck activity in the liver and in brown adipose tissue, where this enzyme serves for the synthesis of glycerophosphate rather than of glucose (2,3). The above is valid for liver and also for brown adipose tissue (2); as far as fatty acid synthesis goes, it is also valid for white adipose tissue. The rate of fatty acid oxidation, high during the suckling period, also falls rapidly at the time of premature weaning to the Purina chow diet. This is evidenced by the precipitous fall at weaning of the very high plasma levels of ketones found in the suckling period (3). Plasma hormone levels also change suddenly in premature weaning. The very high level of glucagon found in the infant rat drops rapidly, while the low insulin level rises suddenly (2). Thyroxine levels apparently do not change with weaning, although they rise throughout the suckling period (7).

Knowledge of the development of cholesterol metabolism is crucial to an understanding of the later appearance of hypercholesterolemia and all the disadvantages this state entails. The rate of cholesterol synthesis is high in fetuses, falls after birth, and rises again at weaning, more rapidly so on premature weaning. This has been shown both for the incorporation of labelled precursors into cholesterol and also for 3-hydroxy-3-methyl-glutaryl Coenzyme A (CoA) reductase (HMGCoAR) (8), the rate-limiting enzyme of cholesterol synthesis; it is true for liver, brown adipose tissue, and intestinal mucosa (9,10), but not for white adipose tissue (9).

Cholesterol is the precursor of bile acids. The rate-limiting enzyme for this process is 7α-hydroxylase. The activity of this enzyme is low in suckling rats and rises at weaning (11); as expected, the formation of $^{14}\text{CO}_2$ from cholesterol labelled in the side chain with $^{14}\text{C}$ is also low in suckling rats. Bile flow and bile acid formation are also low (12). However, no one has looked at the effects of premature weaning on these processes.

Most of these changes, but not all, can be prevented by weaning to a high-fat diet, which quantitatively, at least, is similar to the high-fat breast milk (2–4).

Another interesting feature of the prematurely weaned rat is its inability to handle
excess protein. An 18-day-old rat, weaned to a diet of protein and vitamins only, will cease growing and die within 2–3 days. In contrast, a 30-day-old rat weaned normally to the same protein diet will live at least 150 days, even though the rate of growth is slowed down (4). These age differences are probably related to (a) immature kidney function on day 18 and (b) the postnatal development of some transaminases, specifically alanine transaminase.

An important tissue from the nutritional point of view is the intestine. Its development is well documented (13). Recently interesting facts have been reported concerning the development of fat absorption. Both a lingual lipase and one found in milk have been found to play an important role in fat absorption (14), a compensation for the low pancreatic and intestinal lipolytic activity found in the newborn (13). The rate of fatty acid synthesis as judged from mucosal acetyl CoA carboxylase activity is low in the suckling animal and rises at weaning (15). The rate of glycolysis is low in the suckling period (16). Finally, we have recently been able to show that both PEPck and fructose diphosphatase activities are very high in intestinal mucosa of suckling rats (17,18). The same has been found for glucose-6-phosphatase (19). All three enzymes are rate limiting for gluconeogenesis, and the activity of all three enzymes drops rapidly on day 18. In the case of fructose diphosphatase this fall can be slowed down, but not prevented, by feeding a high-fat diet (18).

LATE EFFECTS OF EARLY NUTRITIONAL CHANGES

These can be divided into three categories, depending on when the nutritional change has occurred: (a) at weaning (usually early weaning), (b) the suckling period, and (c) gestation, which is not relevant to this chapter.

Weaning

Rat pups are born blind and without fur. By day 14 to 15 they are capable of independent existence. However, they will lose weight for a day or two. If weaned on day 18, they will continue to grow as long as an adequate diet is supplied. They are fully weaned on day 30 after birth. Premature weaning to a high-carbohydrate diet (Figs. 1–3) has late effects which, to some extent, can be prevented by weaning to a high-fat diet for the crucial time between days 18 and 30 after birth. The most striking effects have been found in the area of cholesterol metabolism. Early weaning to a high-carbohydrate diet (2–4) for 12 days, followed by a prolonged period of feeding the laboratory Purina chow diet and then by 2 months of an atherogenic diet, resulted in plasma cholesterol levels that were much higher than in normally weaned rats. This effect of early weaning could be annulled by feeding a high-fat diet for these crucial 12 days. We could show that on day 50 after birth, the same results could be obtained (Table 2) (1).

Serum cholesterol levels are also permanently elevated in prematurely weaned rats fed a diet high in animal fat, whereas premature weaning to a vegetable oil
fat-containing diet did not have this effect (20) (Fig. 4), indicating that the type of fat is of importance. Similarly, a high sucrose diet, fed from 3 days before birth to day 29 postnatally will cause a doubling of the serum cholesterol level on day 213 in male rats (21). This is due to the sucrose, since feeding a diet containing glucose instead of sucrose does not have this effect (22).

**Suckling Period**

Another way of using nutrition to change the further development of an individual is over- or underfeeding during the suckling period. The effects of severe under-
nutrition have been described repeatedly and we shall not discuss them here, except to stress that during rapid development, severe undernutrition can obviously have permanent effects, e.g., on bone and brain development (23–25). Here we are concerned with more subtle effects. On raising rats from day 3 after birth in litters of three, nine, or 14 we can note differences in several parameters only 2 days later (Fig. 5). Particularly striking are the differences in plasma cholesterol and insulin levels (9,10) (Figs. 6,7). However, hormone and enzyme activities are also affected (25) (Figs. 8–11). Sixty to 200 days later these differences are still apparent (26,27) (Figs. 12–19). It appears that the breakdown of cholesterol to bile acids is also conditioned by early nutritional experience (30–37). Thus, feeding guinea pigs cholestyramine (1.1% of diet) for 6 weeks after birth, resulted in increased resistance to a high-cholesterol diet at ages 105–259 days (37). Both HMGCoAR and 7α-

FIG. 4. Body weight (B.wt) on day 30 and plasma triglyceride (TG) and cholesterol levels on day 213 in rats fed a high-fat (HF) or high-sucrose (HSU) diet early in life. (From O'Brien et al, ref. 20.)

FIG. 5. Body weights of rats raised in litters of 4 (closed circles) or 14 (open circles). (From Hahn and Walker, ref. 10.)
hydroxylase activities and the bile acid pool were increased (3). This suggests that animals that learn to deal with cholesterol early in life are more efficient in getting rid of excess exogenous cholesterol later in life. This would also explain the negative effect of early weaning. The sudden removal of a large portion of dietary cholesterol (change from milk to Purina chow) may prematurely cut off factors necessary for a permanent adaptation to extradietary cholesterol.

Both under- and overnutrition in infancy can lead to later obesity. Since in obesity there is a greater tendency towards heart disease and hypercholesterolemia, it is logical to consider it as one of the negative consequences of early inadequate nutrition. However, we must underline here that a large percentage of obesity is
genetically conditioned. In genetically obese mice, plasma levels of cholesterol are elevated and hepatic HMGCoAR activity is reduced (38). In humans this relationship between plasma cholesterol and obesity is less evident. Nevertheless, when body weight is decreased by ileojejunal bypass surgery, plasma cholesterol levels fall (39). Again, as in the case of plasma cholesterol levels, obesity can be the result of early nutritional overeating. Rats or mice fed in small litters for the first 2 or 3
weeks of life are usually larger and have more body fat than those breast-fed in litters of 8 to 14 (6,40–42). As mentioned above, the late effects of early overnutrition are also evident in some levels of enzyme activities (26,43) in adult animals. Thus, both early overfeeding and early weaning seem to have a negative effect on later life. It seems that early overnutrition may also result in a larger number of adipocytes in adult animals (44), even though this is not generally...
accepted and seems to depend on the site from which adipocytes were taken (3,41), as well as on early nutrition (Figs. 17 and 18).

One of the mechanisms that may play an important role in early overnutrition is insulin, which when given to male rats in infancy, causes them to overeat, be heavier, and show both hypertriglyceridemia and hypercholesterolemia when adult (45) (Fig. 20). This is analogous to the overweight newborn from diabetic mothers. Surprisingly, early undernutrition has a similar effect. The adult animal under-
nourished in infancy contains more fat and a larger number of fat cells than a normally fed rat (28).

All of the above sounds very interesting to a zoologist, but may cause an exasperated shrug in a clinician. However, it appears that humans are not exempt from the effects of early nutritional changes. It has been suggested for many years that the foundation for adult degenerative disease is laid early in childhood (46). Many investigators have speculated that lack of breast-feeding in the neonate may have deleterious effects later in life (e.g., 47). Unfortunately, it is very difficult to bring positive or negative proof, since a lifetime study would be required. Nevertheless, some progress has been made. It has been shown that the plasma cholesterol level at 30 to 40 years was significantly higher in men that had not been breast-fed than in those that had received breast milk (48). Another report found similar
FIG. 19. Free fatty acid release from epididymal adipose tissue in response to norepinephrine in rats aged 60, 120, and 300 days raised in litters of four (open bars) or 14 (striped bars). (From Macho, ref. 29.)

FIG. 20. Plasma levels of cholesterol and triglycerides in rats treated with insulin during the suckling period (open bars) or not so treated (striped bars). (From Donner and Gorz, ref. 45.)

FIG. 21. Plasma cholesterol levels (in millimoles/liter) in young men and women that were breast-fed (open bars) or were not breast-fed (solid bars). (From Marmot and Page, ref. 49.)

differences in adult women (Fig. 21) (49). An interesting report (50) deals with the early effects of altered feeding. Neonates were fed a high- or low-cholesterol diet for the first 6 months, a low-cholesterol diet only for the next 6 months, and a high-cholesterol diet for the next 3 months. It is apparent from Fig. 22 that infants receiving the high-cholesterol diet early in life were more resistant to this diet at 15 months of age. This is analogous to our older experiments (1) in rats.
More human data are available on the late effects of early overfeeding. It seems that early weaning is frequently accompanied by subsequent overfeeding. In fact it has been suggested that food intake itself is conditioned by early experience (51). However, others have denied any effect of early overeating on later obesity of plasma cholesterol levels (2,52,53). In general, it is suggested that not only later obesity, but also atherosclerosis, are related to the early postnatal (and perhaps prenatal) period of life in humans. It has also been suggested that poor living conditions early in life are a risk factor for heart disease in adulthood (58). Early nutrition has an effect already on 7 to 8-year-old boys (Fig. 23) and in fact, its effect is noted very soon after birth (Fig. 24).

When considering all these data obtained in laboratory animals and humans, we must be careful not to be carried away. We must bear in mind that despite the high incidence of heart disease in Western nations and large number of obese persons, life in these countries has been considerably prolonged. It is possible that with a prudent diet and exercise, we could even live a few years longer, and undoubtedly

![Figure 22](image_url) **FIG. 22.** Plasma levels of total and LDL cholesterol (C) in 15-month-old infants fed a high- or low-cholesterol diet for the first 6 months of their lives, a low-cholesterol diet between months 6 and 12, and then a high-cholesterol diet for months 12 to 15. Note that early feeding of a high-cholesterol diet (striped bars) resulted in a lower total and LDL cholesterol at 15 months. Left ordinate: % of infants with high plasma total and LDL cholesterol levels; right ordinate: mg cholesterol/dL plasma. (From Stein et al., ref. 50.)

![Figure 23](image_url) **FIG. 23.** Plasma cholesterol levels in 7- to 8-year-old boys in different countries. (From Kuniman et al., ref. 54.)
we shall. However, we must be careful not to come to false conclusions. A good example is the paper by Oster (59), who reported that atherosclerosis does not exist among the Tarahumara Indians. Their blood cholesterol levels are also very low. However, they are considerably malnourished and hardly ever reach an age at which heart disease becomes manifest.

**NUTRITION AND WEANING IN HUMANS**

Within 3 hr after birth, plasma levels of free fatty acids and glycerol rise (2–4) and within 24 hr, if insufficient food is given, ketone levels are also increased. All this can be prevented by giving glucose and even amino acids (4). Plasma cholesterol levels also increase rapidly, and their final level in sucklings depends on the kind of food received (Fig. 24). Hormonal changes are less pronounced but are similar to those in the rat.

There is still no agreement on how and when to feed a full-term infant for the first time. There are advocates of very early feeding, while quite a few centers delay the first feed or give only tea with sugar or very diluted milk. It has also been claimed that the early postnatal rise in ketones can be suppressed by early and sufficient feeding. One should probably not overestimate the importance of this problem. We are all alive, even though undoubtedly we were not equally treated postnatally. Nevertheless, I suggest that the normal response to entering this world may be of some significance. We have suggested (60) that perhaps the older practice of giving glucose at birth may be counterproductive, since this suppresses the normal metabolic response and may delay the ability of the newborn to respond adequately to nutritional stimuli.

The other unsolved question is when to wean. Unfortunately it is very easy to not wean an infant at all, by starting it on an artificial diet immediately after delivery. As shown here, early weaning may have deleterious effects in the rat. Whether this is true for humans is a moot point, which was recently again discussed (61). In our nearest relatives, the monkeys, the response of plasma HDL cholesterol depends...
both on whether they were breast-fed or formula-fed and on the current fatty acid composition of the diet (62).

A far larger problem is, of course, the feeding of premature and small-for-gestational-age (SGA) infants. Here much progress has been made, but I do not feel qualified to discuss this in any detail. I think, however, one can state unequivocally that breast milk is the ideal food for the newborn infant. As always, there are riders for a statement like this. Must we add iron and vitamins, and when? How long should one breast-feed? The answers to these questions are not definite, and undoubtedly they will change repeatedly. All I can hope for is that the clinical nutritionist and pediatrician will consider the relatively large volume of pertinent laboratory data when making their decisions, and that perhaps some courageous young epidemiologist will do some longitudinal studies in humans lasting 40 years or more.

ACKNOWLEDGMENT

This work was supported in part by a grant from the British Columbia Heart Foundation.

REFERENCES

DISCUSSION

Dr. Anantharaman: On the small versus large litters: When we reduce the litter size at birth, we often find that either milk production or milk secretion is reduced, but so is the milk intake by the pups. Occasionally, the difference at weaning—i.e., 21 days—from large litters of 14 and from small litters of four in body weight of pups is marginal. We therefore think this technique inadequate to induce so-called marginal undernutrition or overnutrition.

Dr. Hahn: That surprises me! Most laboratories usually reduce the number of pups in the litter to about 8 or 9. Is this the ideal litter size? It is quite possible that some rat mothers do not produce enough milk. Is it better for rats to grow more or less rapidly? I really cannot say. Furthermore, all of us evaluate growth by weight, which of course is not a good indicator either. On the other hand, it has been clearly shown that rats up to day 10 cannot control their intake; they will drink as much as one will give them. After 10 days it is different; this is probably related to cholecystokinin. When we reduce the litter size on day 3, we find that...
we already have a difference 2 days later, not always in weight but most certainly in cholesterol and insulin. So it seems to work.

**Dr. Nivelon:** With Dr. D. Tenenbaum and Dr. P. Gambert, we have carried out some research in order to evaluate the influence of breast and formula feeding on serum lipoproteins in 43 normal full-term newborns (22 breast-fed, 21 formula-fed). Both groups were comparable on the first day of life. Serum cholesterol concentrations rose very rapidly in both groups but were significantly higher on the sixth day in breast-fed newborns. High density lipoprotein (HDL) cholesterol rose moderately in both groups. Low (LDL) and very low (VLDL) density lipoprotein cholesterol concentrations also increased in the two groups, but reached significantly higher levels in the breast-fed infants. The same was true for the specific LDL apoprotein B, very significantly higher on the sixth day in the breast-fed group. Thus, it is clear that serum lipoprotein concentrations are influenced very early by the type of feeding. The purpose of our future longitudinal research is to determine if, in humans, this effect lasts beyond weaning as Hahn has shown to be the case in rats. My question is: Which diet should be advocated for a newborn in a family with familial hypercholesterolemia—breast-feeding or formula-feeding?

**Dr. Hahn:** Perhaps I should stress one thing. There have been a number of studies on lipoprotein in children from birth until the age of 3, 5, or 10 years old, but in order to prove or disprove our contention that there is a late effect, even this is not long enough. One should study people 30, 40, and 60 years of age for it to show up. In answer to your question, I think Glueck’s group suggests that you should start feeding these newborns as soon as possible. The point, of course, is that you cannot tell prenatally, or when a child is born, whether the gene is lacking for the regulation of blood cholesterol levels. This only shows up later.

**Dr. Anantharaman:** We compared rats weaned early, on day 17 versus day 22, fed either on a moderately low-protein diet (12%) or on a high-protein diet (22%), and found practically no difference in body composition until 200 days of age. We also observed no hyperinsulinemia in these animals.

**Dr. Hahn:** I think we ought to discuss that later, because it really has to be looked at in detail.

**Dr. Boulton:** In relation to babies with familial hypercholesterolaemia (FH), in 1975 I looked at 2000 newborns consecutively,1 to investigate whether low-density lipoprotein could be used as a marker rather than total cholesterol, as Glueck published. One in four of these babies were also followed through the first year of life, and the results showed that FH can be detected at birth with an elevated LDL. There were false-positive results due to perinatal stress (3.7%), and a false-negative rate of 1.1%. Practical constraints and cost limit this screening process. What is the best method of feeding babies with FH? Breast-feeding, and then later using a diet low in fat but rich in polyunsaturated fatty acids. Babies handle cholesterol in a diet very variably, particularly during the first 6 months. Paul Nestel and I looked at the effect of a high-cholesterol diet followed by a low-cholesterol diet given over a period of weeks. During the last weeks we measured their fecal sterol output. Some of these babies, in the first 6 months of life, did not adapt to the normal and mature system of cholesterol handling, decreasing endogenous cholesterol production, but some did.2 During the first year of life in the control population of babies I studied, the serum cholesterol rose

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and fell in an entirely unpredictable way that did not relate to their parents’ cholesterol. Tracking for serum cholesterol became much more evident after 6 months, particularly during the second year of life. By age 1, and particularly by age 2, the variance on serum cholesterol was much greater from genetic factors, as measured by the level of association with the mother’s cholesterol, and in fact, more so than with the father’s.³ Hence, genetic factors become important from late infancy on, as well as the total amount of fat in the diet.

Dr. Hahn: I do not think I have any comment to make. Essentially, you are right. I think that if you have the same genetic group then most certainly you will change the cholesterol level by the way you feed them; there is no doubt about that. All I am saying is that you might alter, to a smaller or greater extent, their response to this different diet, depending on how they were fed when they were very young. I agree completely that this is very difficult to prove in humans, and one has to be very careful in transferring any data from rats to humans in this respect.

Dr. Rey: Dr. Boulton, what is your opinion? Do you think that a high-cholesterol diet during infancy could have any consequence in adult life?

Dr. Boulton: No.

Dr. Hahn: There are species, including monkeys, guinea pigs, pigeons, rats, and mice, in which it has been shown that both early feeding and the composition of food early in life have an important effect. In other words, the animals learn to handle cholesterol in different ways. Of course in humans it might be completely different.

Dr. Poskitt: The rat is not a very good model for studying obesity in humans. We were led astray in the mid 1960s about the adipose tissue theory, partly by looking at what happened to rats when they were overfed. We should examine the research carried out on humans. The worries we had in the early 1970s about creating a race of very fat people in America and Britain due to overfeeding in early infancy just haven’t been confirmed. I myself looked at a group of overfed infants when they were about 5 years old. It was quite clear that 80% of the fat infants had slimmed down naturally to perfectly normal weights, a success rate never achieved in obesity clinics with older fat individuals. The 20% remaining overweight were largely children who had a family history of obesity anyway. I suspect our attribution of adult and childhood obesity to obesity that starts in infancy comes from the fact that if a child is genetically very strongly primed to become fat and has the right environment, then obesity will present early. That is probably the main link, rather than diet in infancy predisposing to becoming fat without necessarily a genetic predisposition. In these children we also looked at cholesterol levels, and there was no tie at all with method of infant feeding and whether they had been overfed in calories, breast-fed, or bottle-fed.

Dr. Davies: I should like to ask a general question about the extrapolation to humans from these experiments in rats. Dobbing has constantly urged us to bear in mind that 3 weeks in the life of a rat brain is equivalent to about 5 years in the life of a human brain. I just wonder if exposing a rat, or a mouse, to a dietary change over a couple of days might not be equivalent to exposing a human to a similar situation over, let us say, 6 months?

Dr. Hahn: I don’t think I can answer that question. I am very much against this assumption of models. A rat is a model for nothing—a rat is a rat. But I am looking for general rules or general laws, which then have to be tested in different species. I have no idea whether any of this applies to humans; the only thing I do know is that the rat lives for a much shorter period, that it has a much shorter gestation period, and that it is weaned much more

rapidly. However, I think that has nothing to do with what we want to know. All I can say is that if you really think that what you observe in rats is of any importance, then you should look at it in humans.

Dr. Ballabriga: In your experiments, after weaning you gave your rats a very high-fat diet. What was the distribution of fatty acids n3, n6, and n9 in these diets?

Dr. Hahn: It was a corn oil diet, so it was exactly the composition of corn oil. As you know there is no cholesterol in corn oil. It was not the cholesterol in the diet that induced the changes we observed. If you feed a high-cholesterol diet without any fat you do not get any hypercholesterolemia. The fat and the proteins are much more important.

Dr. Narasinga Rao: You said that feeding of a high-fat diet early on for a longer period will result in a better response to fat in later life. You know that large population groups in developing countries subsist throughout their life on high-carbohydrate diets containing very little fat. In such populations, would it help to wean at an early stage and give a high-carbohydrate diet in order to better utilize carbohydrate in later life?

Dr. Hahn: I don’t see why. On the contrary, I don’t think that early weaning could be helpful at all for babies that have been essentially underfed. I also do not think that in the developing world, where babies are not well fed, you have any problem with hypercholesterolemia, unless it is of genetic origin. Hypercholesterolemia only appears when you overfeed children with our type of diet. Perhaps I should make one point more: In the rat, when you wean early—on day 18—to a high-carbohydrate diet, within 24 hr the blood cholesterol level drops by nearly 50%. But if you wean them and don’t feed them for those 24 hr, the decrease in cholesterol level is much less. These are influenced by carbohydrates in the diet.

Dr. Rey: You say that a rat is a rat, but not all rats behave in the same way. Some recent work has shown that different strains may respond in different ways to a cholesterol or a sodium load, for example. These data sometimes clearly do not corroborate yours. Some studies, for example, have confirmed that early weaning led to elevation in the activities of hepatic enzymes associated with lipogenesis in adult rats even though the control diet was fed from the age of 30 days; however, this response was not altered by the type of carbohydrate fed during the initial period, and it was not possible to demonstrate any long-term effect of sucrose consumption on serum cholesterol levels. Moreover, there were no differences between prematurely and normally weaned rats in their responses to sucrose, which does not support the idea that dietary adaptations in early life alter the manner in which adult rats respond to dietary stimuli. Other experiments, e.g., from Lemonnier’s laboratory in Paris, could not detect any difference in the aorta cholesterol content of 57-week-old rats fed either sunflower oil or high-cholesterol-containing fat during the early postweaning period. Clinical studies in humans failed also to demonstrate that mode of feeding (breast or formula) during infancy influences subsequent serum concentrations of cholesterol. Surprisingly, in some studies, the plasma cholesterol levels of breast-fed infants were found to be higher later in

7. Fomon SJ, Rogers RR, Ziegler EE, Nelson SE, Thomas LN. Indices of fatness and serum cholesterol at age eight years in relation to feeding and growth during early infancy.
life than were those of infants fed low-cholesterol formulae. Thus I am personally not convinced by the data you present showing some metabolic differences between breast-fed and non-breast-fed infants. In fact, what does "breast-fed" mean exactly? For how long?

Dr. Hahn: I should stress that there is one other paper from an American group which was presented in New York 2 years ago, which again shows that in men 30 years old, those who were breast-fed had lower cholesterol levels than those who were not. However, I completely agree with you that it is very difficult to establish the relationship between early dietary intake and cholesterol levels in later life. I don't know whether we shall ever know whether there is a definite effect in humans, because we really need very long-term experiments to establish this relationship. I have no intention of forcing these ideas of mine on anyone, because I think they have to be proved and not speculated on. Certainly there are genetic factors and environmental factors.

Dr. Rey: Surely in human beings there are critical periods during which the influence of a nutritional factor may be very important and may have significant short-term effects. This is probably true for energy, cholesterol, and perhaps sodium. However, I think that after 6 months or a year the child is able to escape from the environmental factors.

Dr. Boulton: We have mentioned much about diet and the genetics of this, but another factor to be considered is the behavioral component, which we as clinicians and researchers on humans find very difficult to measure because of the lack of hard end points. This came up this morning in relation to appetite, hunger, and chewing, and I think this is the hidden variable that can in fact explain the differences we observe. Humans can be shown to be extremely susceptible to their social environments, and this must be particularly true with regard to food, which plays a central role in relationships with family and friends.

Dr. Hahn: That is perfectly true, I couldn't agree more. I think in humans one cannot really analyze all the factors that play a role. On top of which, of course, the only critical period one can think of in humans, in contrast to the rat, where many other things are developing, is the myelinization of the brain, which continues for 2 years after birth. And so I come back to what I think might be the mechanism by which food in this early period has an effect for the whole of one's life; perhaps it is the question of what kind of food you like after that. Humans have this cortex and need all that myelinization after birth, whereas in the rat the cerebellum isn't developed until 18 days after birth. So in the rat you can really have an effect on the brain in a much simpler way and for a longer relative time than in humans.

Dr. Ballabriga: We studied myelinization and biochemical composition of the brain in newborns who died after having been treated by parenteral nutrition, during which they received large quantities of essential fatty acids by the intravenous route. The brain is very resistant to changes in the fatty acid composition of the diet. The study of the phosphoglycerides and of their fatty acids showed practically no modifications in the brain, while biochemical composition changed immediately in the liver, in the aorta wall, in subcutaneous fat, and in the red cell lipid stroma.