Preweaning Diet Programs Postweaning Plasma Thyroxine Concentrations in Baboons[1] (44024)

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Abstract. **We tested the hypothesis that breast- and formula-feeding of infant baboons affect postweaning plasma thyroid hormone concentrations and that differences in thyroid hormone concentrations are associated with long-term effects of infant diet on lipoprotein concentrations and cholesterol metabolism. Newborn baboons were breast-fed (n = 12) or fed formulas with a high polyunsaturated/saturated (P/S) fat ratio (n = 11) or with a low P/S ratio (n = 12) similar to baboon breast milk. Baboons were weaned at 14 weeks of age to a high cholesterol, saturated fat diet. Plasma thyroid hormone concentrations were measured in this group of baboons until about 223 weeks of age. Thyroid hormones were also measured at 400 weeks in a second group of adult baboons (n = 80) that as infants were either breast-fed or fed formulas with varying levels of cholesterol. Baboons breast-fed as infants averaged 11% higher ($P < 0.03$) thyroxine (T_4) concentrations from 34 to 400 weeks of age compared with those fed formulas. From 70 to 400 weeks of age breast-fed baboons had 10% lower T_3/T_4 ratios ($P < 0.03$). Breast- versus formula-feeding did not affect postweaning T_3 and fT_3 concentrations. Postweaning thyroid hormone concentrations were not significantly affected by the P/S ratio or the cholesterol level of the infant formulas. The rank correlation of the means of the sire progeny groups for T_4 and HDL-C concentrations was statistically significant ($r_s = -0.83$; $P < 0.05$). Partial correlations of T_4 concentrations with body weight, feed intake, or measures of cholesterol metabolism were not significant. T_4 concentrations were significantly correlated with T_3 concentrations ($r = 0.42$; $P < 0.02$), and T_3 concentrations were correlated with bile acid synthesis rate ($r = 0.47$; $P < 0.01$), acyl-CoA cholesterol acyltransferase ($r = 0.66$; $P < 0.001$), and plasma HDL_1-C levels ($r = -0.49$; $P < 0.007$).**

These effects suggest that altered thyroid hormone homeostasis may partially mediate the long-term differences in cholesterol metabolism caused by breast- versus formula-feeding. [P.S.E.B.M. 1996, Vol 212]

Some investigators speculate that thyroid hormones in milk have important functions in infant development or attenuate the effects of neonatal hypothyroidism (1–3). Breast-feeding compared with formula feeding increased thyroid hormone concentrations measured in pre-term babies and in some studies of euthyroid infants (4–6), but statistically significant differences in thyroid hormone concentrations due to infant diet were not observed in several other studies with normal or hypothyroid full-term babies (7–9). We recently reported that at 14 weeks of age, prior to weaning, breast-fed baboon infants had 20%–40% lower T_3 and fT_3 concentrations than did those fed formulas (10).

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In addition to the dietary differences in thyroid hormone homeostasis during the preweaning period in baboons and humans, one study indicates a link between breast-feeding and subsequent thyroid hormone concentrations. Women at 60–71 years of age who were breast-fed as infants and weaned after 1 year of age had 10%–15% higher fT_4 concentrations compared with those weaned before 1 year or bottle-fed (11).

This report describes the postweaning effects of breast- and formula-feeding on plasma thyroid hormone levels in two experiments that originally were designed to test the hypothesis that infant diet affects cholesterol metabolism later in life (12, 13). We also present the associations among thyroid hormones, body weight, food intake, and measures of cholesterol metabolism.

Materials and Methods

Newborn infant baboons derived from three sire breeding groups were randomly assigned at birth to breast-feeding or to one of two formulas that had a high polyunsaturated/saturated (P/S) fatty acid ratio (P/S = 1.69) or low P/S ratio (P/S = 0.33). The high P/S formula was commercially available Similac (Ross Laboratories, Columbus OH) and the low P/S formula was formulated by Ross Laboratories with a fatty acid composition similar to baboon milk (P/S = 0.49). The formulas with different fatty acid compositions were designed to test the hypothesis that programming effects of breast milk and formula on cholesterol metabolism are mediated by differences in fatty acid composition. The compositions of baboon milk and the formulas are described in detail elsewhere (14). A total of 35 infants were obtained, each from a different dam. There were 19 females and 16 males, and the three sire breeding groups provided 9, 12, and 14 offspring, respectively. At 15 weeks of age, the infant baboons were weaned gradually to a solid chow. Animals that did not wean immediately to the chow were adapted by mixing small amounts of high P/S formula with the chow until they were completely weaned from their mothers or formulas by 25 weeks of age. The postweaning diet was comprised of about 40% of energy from fat, a P/S ratio of 0.35, and 0.41 mg cholesterol/kJ (13), and fed *ad libitum* in gang cages once a day. Blood was drawn under ketamine immobilization (10 mg/kg body wt) and transferred to tubes on ice. The collection tubes contained, per milliliter of blood, 1 mg Na_2EDTA and 250 KIU of aprotinin in 10 μl of 0.2 *M* potassium phosphate buffer, pH 7.4. Plasma was recovered by centrifugation at 1500 *g* for 15 min at 4°C. We also measured thyroid hormones from EDTA plasma stored at −70°C which was obtained at 400 weeks from a second group of baboons. These adult baboons (n = 80) were either breast-fed or fed formulas with 2, 30, or 60 mg/dl cholesterol as infants and were weaned to diets either high or low in cholesterol with 40% of energy from saturated (P/S ratio = 0.37) or unsaturated fat (P/S ratio = 2.1). We measured feed intake during a 5-day period at an average age of 390 weeks of age. The experimental design and composition of the diets are described elsewhere (12). The animal procedures were approved by the Institutional Animal Research Committee. The Southwest Foundation for Biomedical Research and the University of Texas Health Science Center are accredited by the American Association for the Accreditation of Laboratory Animal Care.

Plasma total T_3 and T_4, and free T_3 and T_4 concentrations were measured in Group 1 at 25, 34, 52, 70, 88, and 97 weeks with commercial RIA kits as described previously (10). Total T_3 and T_4 were measured at average ages of 149 and 223 weeks of age in Group 1 and at an average of 400 weeks of age in Group 2. All assays were performed with kits from Diagnostic Products (Los Angeles, CA), except the T_3 measurements at 400 weeks were made with a kit from Amersham Corp. (Arlington Heights, IL).

The data were analyzed by analysis of variance (ANOVA) after logarithmic transformation. For analysis of data from Group 1, the statistical model included the main effects of preweaning diet group, sire, and sex, and all two-factor interactions. For Group 2, the statistical model also included the type of dietary fat and cholesterol level in adulthood. We combined the results of analyses of Group 1 and 2. The difference between the averages for the breast- and formula-fed groups and the standard error of the difference were estimated for each experiment. A weighted average of the two experiments was computed using as weights the inverse of the estimated variances. The statistical significance was assessed using a normal distribution. Underlying relationships among variables were identified from partial correlation coefficients adjusted for the effects of infant diet, sire, and sex. Also, in Group 2 in which the 80 baboons were progeny of six sires, we estimated associations among variables by rank correlations among sire progeny group means.

Results

After 25 weeks, T_4 concentrations were higher among breast-fed baboons compared with those fed formulas. The difference in T_4 concentrations was greatest at 34 weeks (33%), decreased to 21% at 52 weeks, and from 34 to 400 weeks averaged 11% higher ($P < 0.03$) among the breast-fed group than in the combined formula groups (Table I) (Fig. 1). T_4 concentrations of the high and low P/S formula groups were not significantly different at any postweaning age (Table I) or among the animals in Group 2 fed formulas with varying levels of cholesterol. At 25 weeks of age, total T_3 concentrations of baboons previously breast-fed

Table I. Plasma T_4 Concentrations by Preweaning Diet Group

Preweaning diet group	Age (weeks)								
	14[a]	25	34	52	85[b]	149	223		400
Breast-fed (n = 12)	114.7 ± 10.9	83.8 ± 5.34	118.5 ± 11.0	119.3 ± 10.2	95.3 ± 5.43	76.8 ± 6.44	78.9 ± 5.71	Breast-fed (n = 22)	83.6 ± 3.68
High P:S formula (n = 11)	120.6 ± 13.1	97.6 ± 8.11	85.2 ± 10.3	104.3 ± 11.6	86.1 ± 6.41	68.2 ± 7.48	75.4 ± 7.12	Formula 2[c] (n = 20)	82.1 ± 4.05
								Formula 30 (n = 20)	76.8 ± 3.56
Low P:S formula (n = 12)	116.8 ± 10.9	87.9 ± 5.37	94.0 ± 8.33	92.1 ± 7.54	91.0 ± 4.97	69.5 ± 5.60	73.3 ± 5.09	Formula 60 (n = 18)	78.2 ± 4.09
Significance (P value)									
Breast versus formulas	NS[d]	NS	<0.03	<0.08	NS	NS	NS	Breast versus formulas	NS
High versus low P:S formula	NS	NS	NS	NS	NS	NS	NS	Level of formula cholesterol	NS

Note. Values are expressed as mean ± SEM (n*M*).
[a] Preweaning values (14 weeks) derived from Ref. 10.
[b] Mean of three measurements, 70, 88, and 97 weeks of age.
[c] Formulas with 2, 30, or 60 mg cholesterol/dL.
[d] NS, not significant; $P > 0.1$.

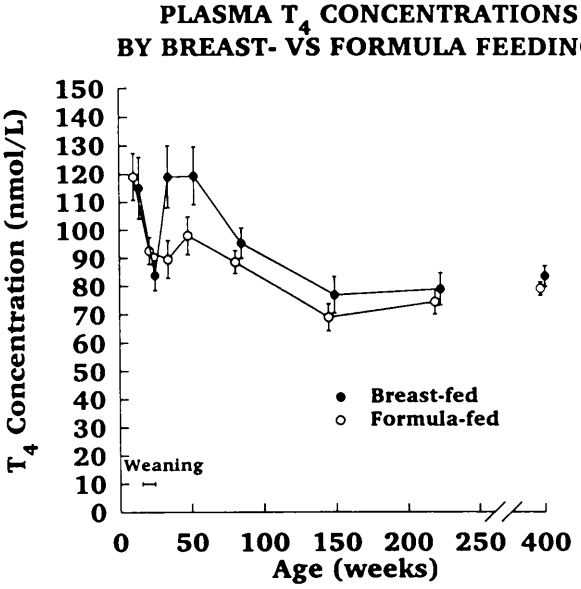

Figure 1. Thyroxine (T_4) concentrations by breast- versus formula-feeding from 14 weeks to 400 weeks of age. Vertical bars, ±1 SEM. Data at each time point for breast- and formula-fed animals are offset for clarity. Effects of breast- versus formula-feeding from 34 to 400 weeks were significant ($P < 0.03$).

were lower than in those fed formulas ($P < 0.06$), (Table II) similar to the differences observed before weaning at 14 weeks (10) (Table II). After 25 weeks of age we did not observe significant differences between breast- and formula-fed infants in T_3 or fT_3 concentrations (Table II and III). Occasionally, T_3 and fT_3 concentrations differed between the low and high P/S formula groups, but these differences were not consistently observed at other ages (Table II and III). Higher T_4 concentrations among breast-fed baboons compared with those fed formulas resulted in a 10% lower T_3/T_4 ratio among breast-fed baboons from 70 to 400 weeks (Fig. 2) ($P < 0.03$). In contrast, at 14 weeks the T_3/T_4 ratio of breast-fed baboons was 22% lower ($P < 0.02$) than for those fed formulas (Fig. 2) due to lower T_3 levels. At 25 weeks, fT_4 concentration was lower among breast-fed than among formula-fed baboons ($P < 0.01$), but from 34 to 97 weeks no consistent differences in fT_4 concentrations (Table IV) were observed among any of the infant diet groups.

In Group 2, the current level of dietary cholesterol (high or low) and the type of fat (saturated or unsaturated) had no significant effects on thyroid hormone concentrations. The mean T_4 concentration of adult baboons fed an unsaturated fat diet with or without cholesterol for more than 7 years was 81.1 n*M*, and in those fed identical diets except enriched in saturated fat the T_4 concentration was 79.2 n*M* ($P > 0.6$).

The correlations between pre- and postweaning thyroid hormone concentrations were not significant (results not shown). However, the T_3/T_4 ratio at 14 weeks was positively associated with the ratio after 34 weeks in Group 1 either with or without adjustment for the effects of infant diet. The correlation of the T_3/T_4 ratio at 14 weeks with the ratio at 52 weeks was 0.29 ($P = 0.11$), and with an average ratio from 70 to 223 weeks, 0.50 ($P < 0.003$).

Male and female baboons had similar thyroid hormone concentrations at all ages (results not shown), except at 25 weeks females had higher serum T_4 concentrations than males (99.1 vs 77.7 n*M*; $P < 0.006$) and higher fT_4 levels (21.1 vs 15.0 n*M*; $P < 0.02$). No consistent differences in thyroid hormone concentrations were observed among the sire progeny groups in either Group 1 or Group 2 (results not shown).

T_3 concentrations were correlated with bile acid synthesis rate ($r = 0.47$; $P < 0.01$), acyl-CoA cholesterol acyltransferase ($r = 0.66$; $P < 0.001$), and plasma HDL_1-C levels ($r = -0.49$; $P < 0.007$). These variables were significantly different during the postwean-

Table II. Plasma T_3 Concentrations by Preweaning Diet Group

Preweaning diet group	Age (weeks)								
	14[a]	25	34	52	85[b]	149	223		400
Breast-fed (n = 12)	2.21 ± 0.185	1.40 ± 0.195	2.11 ± 0.446	1.82 ± 0.244	1.58 ± 0.0846	0.960 ± 0.145	0.923 ± 0.0754	Breast-fed (n = 22)	1.54 ± 0.0533
High P:S formula (n = 11)	3.27 ± 0.310	2.12 ± 0.384	1.04 ± 0.287	1.64 ± 0.286	1.57 ± 0.110	1.047 ± 0.206	1.18 ± 0.126	Formula 2[c] (n = 20)	1.62 ± 0.0627
								Formula 30 (n = 20)	1.49 ± 0.0543
Low P:S formula (n = 12)	2.81 ± 0.230	1.88 ± 0.252	1.96 ± 0.397	1.47 ± 0.188	1.74 ± 0.0891	0.994 ± 0.143	0.964 ± 0.0756	Formula 60 (n = 18)	1.61 ± 0.0663
Significance (P value)									
Breast versus formulas	<0.003	0.06	NS[d]	NS	NS	NS	NS	Breast versus formulas	NS
High versus low P:S formula	NS	NS	<0.07	NS	NS	NS	NS	Level of formula cholesterol	NS

Note. Values are expressed as mean ± SEM (n*M*).
[a] Preweaning values (14 weeks) derived from Ref. 10.
[b] Mean of three measurements, 70, 88, and 97 weeks of age.
[c] Formulas with 2, 30, or 60 mg cholesterol/dl.
[d] NS, not significant, $P > 0.1$.

Table III. Plasma fT_3 Concentrations by Preweaning Diet Group

Preweaning diet group	Age (weeks)				
	14[a]	25	34	52	85[b]
Breast-fed (n = 12)	4.57 ± 0.380	3.02 ± 0.538	5.87 ± 1.34	4.22 ± 0.822	4.35 ± 0.321
High P:S formula (n = 11)	7.50 ± 0.687	3.96 ± 0.921	2.79 ± 0.836	3.36 ± 0.854	4.05 ± 0.390
Low P:S formula (n = 12)	7.08 ± 0.674	4.55 ± 0.776	4.81 ± 1.08	2.56 ± 0.479	4.50 ± 0.318
Significance (P value)					
Breast versus formulas	<0.0001	NS[c]	NS	NS	NS
High versus low P:S formula	NS	NS	NS	NS	NS

Note. Values are expressed as mean ± SEM (p*M*).
[a] Preweaning values (14 weeks) derived from Ref. 10.
[b] Mean of three measurements, 70, 88, and 97 weeks of age.
[c] NS, not significant; $P > 0.1$

ing period between breast- and formula-fed baboons (13). Although partial correlations of T_4 lipoprotein concentrations with measures of cholesterol metabolism were not statistically significant, rank correlations among the means of the six baboon sire progeny families (Group 2) for T_4 and lipid measures were observed. The sire progeny rank correlation of T_4 with total HDL-C was -0.83 ($P < 0.05$) and with HDL_2-C was -0.71. T_4 was not significantly correlated with body weight or food intake.

Birth weight in Group 1 was positively associated with fT_3 ($r = +0.39$; $P < 0.02$) and with fT_4 ($r = +0.37$; $P < 0.03$) concentrations measured from 70 to 97 weeks.

Discussion

Long-Term Effects. This experiment was undertaken to explore possible programming of thyroid hormone homeostasis by infant diet and the relationships of thyroid hormones to measures of cholesterol metabolism affected by breast- versus formula-feeding (13). Breast-fed baboons maintained consistently higher plasma T_4 concentrations from 34 weeks to adulthood than those fed formulas. This long-term effect of infant diet on T_4 levels is similar to the report that plasma fT_4 concentrations were about 10% higher among older women who were breast-fed compared with those bottle-fed as infants (11). The increase in T_4 concentrations of baboons at 34 and 52 weeks of age (equivalent to 2- to 3-year-old humans) is consistent with the report of a significant positive correlation of age at weaning with T_4 concentrations in 1- to 2-year-old children who were breast-fed for at least 60 days compared with those breast-fed a shorter time (6). However, in that study no statistically significant effects of infant diet on T_3 and T_4 concentrations were detected from 2–7 years of age (15). The power to detect differences was greater in the experiment reported by Phillips *et*

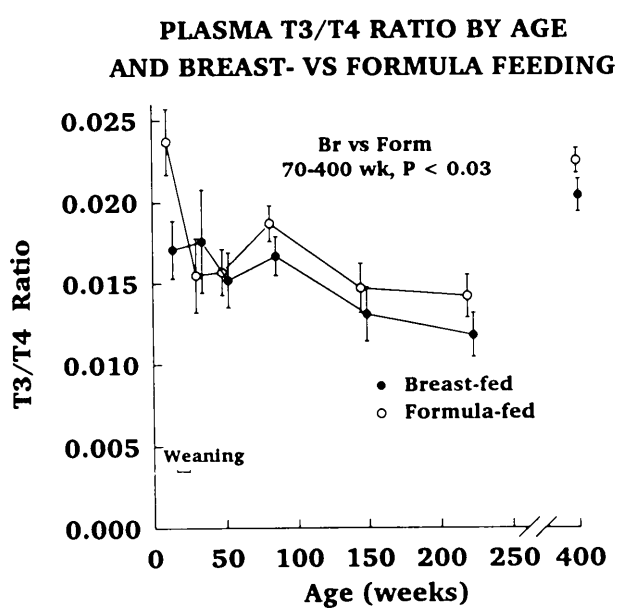

Figure 2. T_3/T_4 ratio by breast- versus formula-feeding from 14 weeks to 400 weeks of age. Vertical bars, ±1 SEM. Data at each time point for breast- and formula-fed animals are offset for clarity. Effects of breast- versus formula-feeding from 70 to 400 weeks were significant ($P < 0.03$).

al. (11) compared with the study of Strbak *et al.* (15) because of larger numbers of subjects. If the biological and methodological variation in T_4 determinations in humans are similar to those observed in baboons, large numbers of subjects and/or measurements may be required to detect a long-term effect of early diet. We estimate that for baboons, five repeated measures in two groups of 80 animals each are necessary to detect a 10% difference in plasma T_4 concentrations with a power of 0.8 (two-tailed test, significant level, 0.05).

Differences in thyroid hormone concentrations in the preweaning period can permanently affect thyroid function. T_4 administration to newborn rats causes hypothyroidism in the adult (16–18), an apparent permanent suppression of TSH secretion. An extreme manipulation of perinatal thyroid hormone levels with the drug propylthiouracil, an inhibitor of thyroid hormone synthesis and deiodination of T_4 to T_3, causes hypothyroidism and a permanent elevation of serum TSH concentration and increased thyroid gland weight (19). These experiments resulting in permanent effects on thyroid hormone concentrations suggest that lower preweaning T_3 and fT_3 concentrations among breast-fed baboons compared with those fed formulas (10) (Table I and II) may program the higher T_4 concentrations after weaning (Fig. 1).

Several studies of breast- and formula-fed human infants during the early preweaning period report significantly higher thyroid hormone concentrations among breast-fed infants (4–6). However, by 42 weeks T_3 concentrations decreased among breast-fed infants compared with those already weaned (6), which is consistent with the lower T_3 concentrations we observed among breast- versus formula-fed baboons at 14 weeks (10). Whether differences in thyroid hormone concentrations in infancy mediate the effects of early diet on subsequent T_4 levels is not known. Although our results show a difference in thyroid hormone concentrations of breast- and formula-fed groups in both the pre- and postweaning periods, we did not observe significant partial correlations between pre- and postweaning T_3 and T_4 concentrations. Nevertheless, the preweaning T_3/T_4 ratio at 14 weeks was positively associated with the ratio after 34 weeks.

Phillips *et al.* (11) reported a negative association of birth weight with plasma fT_4 concentrations measured in elderly women. We observed a positive correlation of birth weight with both fT_3 and fT_4 concentrations measured at 70–97 weeks. These results suggest that fetal growth rate may also influence the set-point of thyroid function in later life. The inconsistency in the relationships for humans and baboons may be due to age or species differences or other factors. The mechanism of these relationships with birth weight is unknown.

Mechanisms. There are several possible mechanisms for the infant diet effect on postweaning T_4 concentrations. The thyroid hormones in breast milk may permanently imprint peripheral receptor-mediated uptake of T_4 or the conversion of T_4 to T_3 by tissue 5′-monodeiodinase. Alternatively, breast- versus formula-feeding may imprint the set-point of the hypothalamic-pituitary-thyroid axis. Interactions with other hormones such as corticosteroids may mediate some of the effects of thyroid hormones (20, 21). Interactions could result from glucocorticosteroid intake in breast milk or from corticoid responses to the feeding environment. It is possible that differences in tissue 5′-monodeiodinase activity affect tissue levels of T_3 and therefore have metabolic consequences without affecting circulating T_3 levels. Formula-fed lambs have 10-fold increased brown adipose tissue monodeiodinase activity compared with ewe raised lambs without differences in serum T_3 concentrations (22). If higher tissue deiodinase activities were present in formula-fed baboons, a higher T_4 to T_3 conversion rate could affect metabolism in selected tissues and also decrease plasma T_4 concentrations compared with those breast-fed.

Possible Dietary Mediators. Although, the mechanism by which breast- versus formula-feeding modifies thyroid hormone concentrations is not known, several differences in milk and formula composition may affect plasma thyroid hormone concentrations or their action. Thyroid hormones and numerous other hormones are found in breast milk (3, 23), but not in commercial formulas. Another difference between breast milk and most commercial formulas is

Table IV. Plasma fT_4 Concentrations by Preweaning Diet Group

Preweaning Diet Group	Age (weeks)				
	14[a]	25	34	52	85[b]
Breast-fed (n = 12)	25.1 ± 2.04	15.1 ± 1.39	21.5 ± 2.89	22.7 ± 2.66	20.3 ± 1.20
High P:S formula (n = 11)	24.6 ± 2.26	22.2 ± 2.65	15.2 ± 2.67	18.2 ± 2.78	18.9 ± 1.46
Low P:S formula (n = 12)	23.3 ± 2.21	19.9 ± 1.74	22.5 ± 2.90	17.2 ± 1.93	20.3 ± 1.16
Significance (P value)					
Breast versus formulas	NS[c]	<0.01	NS	<0.09	NS
High versus low P:S formula	NS	NS	<0.09	NS	NS

Note. Values are expressed as mean ± SEM (n*M*).
[a] Preweaning values (14 weeks) derived from Ref. 10.
[b] Mean of three measurements, 70, 88, and 97 weeks of age.
[c] NS, not significant; $P > 0.1$.

the more highly saturated fatty acid composition of breast milk. During the preweaning period, T_3 concentrations among baboons fed the high P/S formula were slightly higher compared with those fed the low P/S formula (10), but there is no evidence of postweaning differences in thyroid hormones between the high and low P/S formula-fed groups (see Table I–IV). We did not observe a significant effect of type of dietary fat fed for more than 7 years on serum thyroid hormone concentrations, nor are we aware of other studies showing that type of dietary fat affects circulating thyroid hormone concentrations. Because certain unsaturated fatty acids are potent inhibitors of *in vitro* binding of T_4 and T_3 to thyroxine binding globulin (24) and of T_3 to its nuclear receptors (25, 26), type of dietary fat may influence the metabolic effects of thyroid hormones. The responses of certain lipogenic enzymes to thyroid hormones also are influenced by type of dietary fat (27).

Physiologic consequences. The consequences of long-term effects of early feeding regimen on T_4 levels appear complex. The significant inverse rank correlation of T_4 with HDL-C is consistent with the higher level of T_4 and lower HDL-C concentration (13) observed in breast-fed baboons. This relationship and the associations of T_3 concentrations with measures of cholesterol metabolism suggest that altered thyroid hormone homeostasis may contribute to the long-term effects of infant diet on cholesterol metabolism (12, 13). Other hormones also may be affected by infant diet and interact with thyroid hormones and cholesterol metabolism. Further studies are necessary to determine if the differences in T_4 concentrations directly mediate the differences in cholesterol and lipoprotein metabolism.

Conclusions. We conclude that breast-feeding compared with formula feeding increases postweaning T_4, which decreases the T_3/T_4 ratio. This programming effect of infant diet on thyroid hormone homeostasis cannot be attributed to the type of dietary fat or level of cholesterol intake during infancy. Variations in T_4 concentrations of the magnitude observed in this study are considered normal by clinical criteria and are not associated with acute symptoms. Nevertheless, the profound effects of thyroid hormones on metabolism suggest that a lifelong difference of 10% in T_4 concentrations could have important physiologic consequences.

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