

# Fat intake during childhood: metabolic responses and effects on growth<sup>1-3</sup>

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**ABSTRACT** Lipids are considered the most important energy source in the infant diet and are necessary for normal growth and physical activity. Human milk, in which most of the energy is present as fat, provides a relatively high cholesterol intake. Formula provides a much lower cholesterol intake. Infants fed human milk have higher total and LDL-cholesterol concentrations in plasma than do formula-fed infants ( $P < 0.05$ ), whereas plasma HDL- and LDL-cholesterol concentrations are lower in formula-fed infants if a formula high in linoleate is fed ( $P < 0.05$ ). Infants adapt to the high cholesterol content of human milk through a decrease in cholesterol synthesis; in contrast, the addition of cholesterol to formula does not suppress synthesis. Measurements of serum lipoproteins and LDL-receptor activity suggest that it is the fatty acid content, rather than the cholesterol content, of the diet that regulates cholesterol homeostasis. We studied the effect of total energy, source of energy, and fat on growth indexes of children <6 y of age in Latin America with use of food balance data. With respect to availability of animal fat, a negative relation was evident for being underweight (percentage weight-for-age <2 SDs of the World Health Organization–National Center for Health Statistics standards) and for having a low birth weight; the latter was also negatively related to energy. Wasting (percentage weight-for-height <2 SDs) was not related to dietary factors. These results suggest that diets that provide <22% of energy from fat and that are low in animal fats may restrict growth. The coexistence of early stunting with adult obesity in Latin America creates a dilemma for public nutrition intervention programs. *Am J Clin Nutr* 2000;72(suppl):1354S–60S.

**KEY WORDS** Fat energy ratio, monounsaturated fatty acids, polyunsaturated fatty acids, HDL cholesterol, LDL cholesterol, LDL receptor, food energy, Latin America, triacylglycerols, children, total cholesterol, food balance data, formula feeding, breast-feeding, growth

## INTRODUCTION

We discuss 2 distinct aspects of fat intake during childhood: 1) the effect of controlled, selected fat intake during infancy on lipoprotein and cholesterol metabolism and 2) the effect of fat intake on growth of children in Latin America, as assessed by using both cross-country comparisons of fat intake based on national food balance information and aggregate data of growth based on anthropometric information.

## CLINICAL STUDIES OF CONTROLLED LIPID SUPPLY OF THE INFANT DIET

Lipids have traditionally been considered the most important energy source in the infant diet and are necessary for normal growth and physical activity. Lipids provide approximately one-half (45–55%) of the energy in human milk and a similar proportion is found in most artificial infant formulas. Lipids constitute the major energy stores in the body. The energy content of adipose tissue on a wet weight basis is 7–8 fold higher than that of tissue containing glycogen or protein, considering that the latter substrates are in a hydrated state. Dietary lipids provide essential fatty acids and facilitate the absorption of lipid-soluble vitamins. Fats generally slow gastric emptying and intestinal motility, which may affect infant satiety and thereby gross intake.

Over the past decades, interest has focused on the role of lipids in central nervous system development and the role of fatty acids and cholesterol in lipoprotein metabolism throughout the life cycle. Lipids serve as structural components of all tissues and are indispensable for cell and plasma membrane synthesis. The brain, retina, and other neural tissues are particularly rich in long-chain polyunsaturated fatty acids (PUFAs). Some long-chain PUFAs serve as precursors for eicosanoid production (prostaglandins, prostacyclins, thromboxanes, and leukotrienes). These autocrine and paracrine mediators are powerful regulators of numerous cell and tissue functions (eg, thrombocyte aggregation, inflammatory reactions and leukocyte functions, vasoconstriction and vasodilatation, blood pressure, bronchial constriction, and uterine contractility). Dietary lipids affect cholesterol metabolism at an early age and may be associated with cardiovascular morbidity and mortality in later life. Lipid supply and metabolism have also been shown to affect neural development and function (1, 2).

Human milk is the preferred mode of infant feeding. Present recommendations suggest that term infants be exclusively breast-fed for the first 6 mo of life. Present approaches to evaluate the adequacy of formula feeding are based on the capacity of formula to support growth and development in a manner comparable with

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**TABLE 1**  
Demographic and anthropometric characteristics of the study groups<sup>1</sup>

	High monounsaturated group (n = 10 M, 10 F)	High polyunsaturated group (n = 11 M, 11 F)	Human milk group (n = 9 M, 16 F)
Weight (kg)			
Birth	3.44 ± 0.48 [20]	3.60 ± 0.39 [22]	3.59 ± 0.45 [25]
12 mo	9.68 ± 0.95 [19]	10.11 ± 1.30 [20]	9.66 ± 0.81 [23]
Length (cm)			
Birth	50.9 ± 5.6 [20]	50.8 ± 1.5 [22]	51.6 ± 2.3 [25]
12 mo	75.7 ± 2.5 [19]	76.0 ± 2.8 [20]	75.9 ± 3.1 [23]
Head circumference (cm)			
Birth	34.5 ± 1.1 [20]	34.8 ± 1.3 [22]	35.2 ± 1.6 [25]
12 mo	45.9 ± 1.2 [19]	46.4 ± 1.2 [20]	47.1 ± 1.4 [23]

<sup>1</sup> $\bar{x} \pm SD$ ; n in brackets. The high monounsaturated group received an oleic acid–enriched diet; the high polyunsaturated group received a linoleic acid–enriched diet. Data from reference 15.

human milk. This includes the need to compare the biochemical, metabolic, and functional responses of breast-fed infants with those of infants given defined formula diets. Human milk provides 50% of energy as fat, mostly saturated and monounsaturated fatty acids (3). To provide fat in infant formula, various vegetable oils (corn, soy, safflower, olive, or sunflower) are used. The use of vegetable oils in the infant diet is based on availability, nutritional properties, and relative costs. The oleic acid or linoleic acid content of the formula depends on the oil source. The need to include linoleic acid, the parent n–6 essential fatty acid (EFA), has been recognized for >30 y (4). The n–6 PUFAs are abundant in commonly used vegetable oils whereas n–3 PUFAs are relatively low, except in soy and canola oils. More recently, the need to provide  $\alpha$ -linolenic acid as a source of the n–3 EFAs important in retinal and nervous system development was recognized (5). A possible need for long-chain fatty acids, with carbon lengths of >18, is being studied. Presently, most formulas are designed to provide a fatty acid composition similar to that of mature human milk from omnivorous women, although the fatty acid composition of human milk, including the EFA and long-chain PUFA content, varies according to the maternal diet.

Formula-fed infants receive a fat energy ratio (FER) similar to that of human milk, but have a much lower cholesterol intake (0.06–0.16 mmol/d, or 25–60 mg/d) than do infants receiving human milk (0.26–0.39 mmol/d, or 100–150 mg/d) (3). Cholesterol is not routinely added to formula except in experimental products used in clinical research. The beneficial effects of cholesterol supplementation of artificial formula have not been established (6, 7).

Interest in the effect of high cholesterol feeding in early life arose after Reiser et al (8) proposed that high cholesterol feeding in early life may serve to regulate cholesterol and lipoprotein metabolism in later life. Animal data in support of this hypothesis are limited, but the idea of a possible metabolic imprinting served to trigger several retrospective and prospective studies comparing cholesterol and lipoprotein metabolism in breast-fed and formula-fed infants. Studies in suckling rats suggested that the presence of cholesterol in the early diet may serve to define a metabolic pattern for lipoproteins and plasma cholesterol that could be of benefit later in life, a hypothesis attributed to the work of Reiser et al (8). Differential diets in infant baboons in studies by Mott and McGill (9) provided evidence to the contrary in terms of benefit. These investigators noted that increased atherosclerotic lesions associated with increased concentrations of plasma total cholesterol were related to increased dietary cholesterol in early life. Nevertheless, the observation of modified responses of adult cholesterol production rates, bile cholesterol saturation indexes, and

bile acid turnover depending on whether the baboons were fed breast milk or formulas served to attract further interest.

Short-term human studies have been confounded in part by diversity in solid food weaning regimens, as well as by the varied fatty acid composition of components of the early diet. The fatty acid composition of the diet is now known to affect circulating lipoprotein cholesterol species (10–13). Mean plasma total cholesterol concentrations by the age of 4 mo in breast-fed infants reached  $\geq 4.65$  mmol/L (180 mg/dL), whereas concentrations in formula-fed infants tended to remain <3.88 mmol/L (150 mg/dL) (14). In a study by Carlson et al (13), infants who received predominantly a linoleic acid–enriched oil blend had a mean cholesterol concentration of  $\approx 2.84$  mmol/L (110 mg/dL). A separate group of infants who received predominantly oleic acid had a mean cholesterol concentration of 3.44 mmol/L (133 mg/dL); moreover, infants fed breast milk and oleic acid–enriched formula had relatively higher concentrations of HDL cholesterol and apolipoproteins A-I and A-II than did the infants fed the predominantly linoleic acid–enriched diet. The ratio of (LDL + VLDL) to HDL was lowest for infants who received the oleic acid–enriched formula. Using a similar oleic acid–predominant formula, Darmady et al (10) reported a mean value of 3.85 mmol/L (149 mg/dL) in infants aged 4 mo, compared with 5.07 mmol/L (196 mg/dL) in a parallel breast-fed group. Most of those infants then received an uncontrolled mixed diet and cow milk, with no evident differences in plasma cholesterol concentrations at 12 mo, independent of the type of early feeding.

In a previously published study, we assessed the effect of feeding a controlled lipid diet on plasma cholesterol lipoprotein fractions in infants (15). In this prospective, randomized study, we fed matched populations of white, normally growing infants a controlled diet from birth to 12 mo, followed by an ad libitum diet from 12 to 24 mo. We compared an oleic acid–predominant diet with a linoleic acid–predominant diets (both low in cholesterol) and with human milk (oleic acid–predominant and high in cholesterol). Study subjects were enrolled from a population of 69 healthy infants from highly motivated families followed in a single private practice office in Dallas. Anthropometric characteristics of the subjects are shown in **Table 1**.

The 2 formula-fed groups, which consisted of infants <4 d of age whose mothers opted not to breast-feed, were randomly assigned to 1 of 2 low-cholesterol formulas that provided 40–42% total fat. The high mono group (n = 22) received an oleic acid–enriched diet (modified Wyeth SMA; Wyeth, St David's, PA) whereas the high poly group (n = 22) received a linoleic acid–enriched diet that provided 38–40% total fat as PUFAs

**TABLE 2**Fatty acid composition of plasma triacylglycerols at age 12 mo in the 3 study groups<sup>1</sup>

	High monounsaturated group (n = 17)	High polyunsaturated group (n = 15)	Human milk group (n = 16)
	% by wt		
Palmitic acid (16:0)	19.7 ± 2.3	20.6 ± 3.1	22.1 ± 2.3
Stearic acid (18:0)	4.3 ± 1.0	3.2 ± 0.8	4.2 ± 1.2
Oleic acid (18:1n-9)	50.7 ± 3.3	29.5 ± 3.8	46.3 ± 3.0
Linoleic acid (18:2n-6)	18.6 ± 1.7	39.1 ± 6.9	19.8 ± 1.6

<sup>1</sup> $\bar{x} \pm$  SD. Data from reference 15.

(Wyeth SMA). The 2 formulas, depending on volume of intake, provided each infant 0.04–0.06 mmol (15–25 mg) cholesterol/d. After weaning, the 2 formula groups received a selection of pre-defined solid foods and supplemental oil provided by the investigators (California Fats & Oils, Richmond, CA) to maintain a daily fatty acid intake resembling that of the initially assigned infant formula but with a lower total fat content (35% of total energy). The calculated mean intake for this study was published previously (15).

A third group fed breast milk (human milk group;  $n = 25$ ) was weaned at a mean age of 6.2 mo (range: 4–8.5 mo) and received from weaning to the age of 12 mo a mixed diet resembling human milk in its cholesterol (0.39–0.52 mmol/d or 150–200 mg/d, ie,  $\approx$ 1 egg yolk equivalent) and oleic acid content. This was accomplished by adding egg yolk (Gerber, Fremont, MI) and the same Wyeth SMA formula otherwise prescribed for the high mono group to the diet. The selected solid foods and oil supplements given to all infants after weaning were designed to maintain the relative fatty acid and cholesterol intakes of the assigned diet group. Postweaning, all infants received, as a function of increasing age, 460–502 kJ·kg<sup>-1</sup>·d<sup>-1</sup> (110–120 kcal·kg<sup>-1</sup>·d<sup>-1</sup>) and 2.5–3.0 g protein·kg<sup>-1</sup>·d<sup>-1</sup>, which was customary for this population. The diets provided vitamins and minerals to meet or exceed the US recommended dietary allowances according to age. As a result of weaning, the percentage of energy delivered as fat decreased in all groups from 50% (to age 4 mo) to 35% (from ages 4–12 mo).

The extent of compliance in each infant group was validated by periodically determining plasma triacylglycerol fatty acid composition. Compliance was stressed in verbal and written instruction booklets, by providing 24-h telephone access to the investigator team, through home deliveries of infant food to individual families, by sending motivation letters, and by sending quarterly newsletters to every family. In addition, compliance

was enhanced by interacting frequently with the private practice office from which the study cohorts were derived.

Venous blood samples collected at 4, 9, 12, and 24 mo of age (as close to 2 h after a feeding as possible) were assayed by standard methods for enzymatic quantitation of total cholesterol (16) and triacylglycerols (17) in plasma. VLDL cholesterol was measured as the corrected difference between total cholesterol and the cholesterol content of the infranant fraction with a density of 1.109 obtained after plasma centrifugation. HDL cholesterol was derived after heparin-manganese precipitation and LDL cholesterol was estimated as the difference between total cholesterol and (VLDL + HDL) cholesterol (18, 19). Total plasma lipids were obtained by solvent extraction and plasma triacylglycerols were isolated by thin-layer chromatography (20, 21). The fatty acid composition of triacylglycerols was determined by capillary column gas-liquid chromatography after boron trifluoride hydrolysis-methylation (22).

Anthropometric measures at each time interval were made independently by 2 trained team members using standardized methods with a precision of  $\pm 0.2$  cm for length,  $\pm 0.1$  cm for head circumference, and  $\pm 3$  g for body weight. Characteristics of study groups and results of growth are summarized in Table 1. Detailed food records provided at monthly intervals by each study family were examined by computer-assisted dietary analysis; the respective manufacturers provided food-composition data.

Significant results from this study are summarized here. As evidenced by the relative plasma triacylglycerol fatty acid composition of each of the 3 cohorts at 12 mo (Table 2), long-term compliance with these controlled diet interventions was achieved. The mean relative oleic acid content was higher in the high mono group than in the high poly group, whereas the mean relative linoleic acid content was higher in the high poly group. The human milk cohort more closely resembled the high mono group, in accord with the similar 18:1 composition of the diets fed.

Plasma cholesterol and triacylglycerol concentrations in each cohort are shown in Table 3. Consecutive 4-, 9-, and 12-mo blood samples were available for repeated-measures analysis of variance (ANOVA) in the 3 diet groups. The human milk group was significantly different from both the high mono and the high poly groups at 4 mo and significantly different from the high poly group at 9 mo. At all time intervals, the high poly group had lower cholesterol concentrations than did the human milk group. Additionally, cholesterol concentrations of the high poly group were lower than those in the high mono and human milk groups at 12 mo. Triacylglycerol concentrations in the high poly group were lower than in the high mono group at 4 mo, but because these concentrations were highly variable, few conclusions can be drawn from these data.

**TABLE 3**Plasma concentrations of total cholesterol and triacylglycerols as a function of diet and time<sup>1</sup>

Age	Plasma total cholesterol			Plasma triacylglycerols		
	High monounsaturated group	High polyunsaturated group	Human milk group	High monounsaturated group	High polyunsaturated group	Human milk group
	mmol/L					
4 mo	3.52 ± 0.78 [19] <sup>a</sup>	3.49 ± 0.49 [21] <sup>b</sup>	4.24 ± 0.85 [23] <sup>a,b</sup>	1.91 ± 0.76 [19] <sup>b</sup>	1.10 ± 0.68 [21] <sup>b</sup>	1.42 ± 1.05 [23]
9 mo	3.80 ± 0.47 [20]	3.59 ± 0.52 [19] <sup>c</sup>	4.09 ± 0.62 [22] <sup>c</sup>	1.15 ± 0.56 [20]	1.29 ± 0.89 [19]	1.21 ± 0.65 [22]
12 mo	4.03 ± 0.80 [17] <sup>c</sup>	3.31 ± 0.52 [16] <sup>d,e</sup>	4.03 ± 0.78 [23] <sup>d</sup>	1.85 ± 1.06 [17]	1.19 ± 0.72 [16]	1.70 ± 1.22 [23]

<sup>1</sup> $\bar{x} \pm$  SD;  $n$  in brackets. Groups with the same superscript letter are significantly different,  $P < 0.05$  (repeated-measures adjusted ANOVA). Data from reference 15.



TABLE 4

Plasma concentrations of HDL cholesterol and LDL cholesterol as a function of diet and time<sup>f</sup>

Age	HDL cholesterol			LDL cholesterol		
	High monounsaturated group	High polyunsaturated group	Human milk group	High monounsaturated group	High polyunsaturated group	Human milk group
	mmol/L					
4 mo	1.29 ± 0.31 [16]	1.19 ± 0.26 [19]	1.29 ± 0.34 [19]	1.86 ± 0.57 [16] <sup>f,h</sup>	1.99 ± 0.36 [19] <sup>e</sup>	2.59 ± 0.88 [23] <sup>f,s</sup>
9 mo	1.11 ± 0.26 [20]	1.01 ± 0.26 [18]	1.16 ± 0.57 [22]	2.28 ± 0.52 [20]	2.17 ± 0.64 [18]	2.53 ± 0.62 [22]
12 mo	1.14 ± 0.26 [16] <sup>a</sup>	0.91 ± 0.21 [16] <sup>a</sup>	1.09 ± 0.28 [23]	2.53 ± 0.62 [16] <sup>h,j</sup>	2.04 ± 0.41 [16] <sup>j</sup>	2.48 ± 0.21 [23]

<sup>f</sup> $\bar{x} \pm$  SD; *n* in brackets. Groups with the same superscript letter are significantly different,  $P < 0.05$  (repeated-measures adjusted ANOVA). Data from reference 15.

Data for the HDL- and LDL-cholesterol fractions are shown in **Table 4**. Differences in plasma LDL-cholesterol concentrations were evident at 4 mo between the human milk group and each of the other 2 cohorts. These differences were no longer significant beyond 4 mo. The high poly group maintained the lowest LDL-cholesterol values for the 12-mo controlled diet period, but values rose significantly to parallel the other 2 groups at the 24-mo follow-up. HDL-cholesterol concentrations fell as the study proceeded; at 12 mo, the high poly group had significantly lower values than did the high mono group. The overall time effect across diet groups indicated an overall lowering of plasma HDL-cholesterol concentrations at 9 and 12 mo relative to 4 mo.

Twenty-two of the original study infants returned for lipid analyses at the age of 24 mo. At this time, after the infants had been consuming diets ad libitum, there were no significant differences in concentrations of total cholesterol or in lipoprotein cholesterol fractions across diet groups. At 24 mo, total cholesterol and LDL-cholesterol concentrations in the high poly group rose to approximate the values observed in the other 2 groups.

Our study showed significant effects of exclusive breast-feeding on lipoprotein cholesterol concentrations at 4 mo. At the ages of 9 and 12 mo, while cholesterol and fatty acid intakes were maintained to mimic human milk, concentrations of HDL and LDL cholesterol in the human milk group were not significantly different from those of the high mono group (which consumed a low-cholesterol diet). The high poly group (which also consumed a low-cholesterol diet) had lower total and LDL-cholesterol concentrations throughout the study. Thus, our data suggest that fatty acid intake plays a predominant role in determining total and LDL-cholesterol concentrations. We cannot fully discard the role of high dietary cholesterol associated with exclusive breast-feeding during the first 4 mo of life because at this time the human milk group had significantly higher total and LDL-cholesterol concentrations than did the high mono group.

To address potential mechanisms for these effects, we also evaluated LDL-receptor activity in lymphocytes obtained from these infants at 12 mo. We studied 43 infants whose families consented to having the extra blood sampled and whose lipid profiles were comparable to those of the total group. Lymphocyte LDL-receptor activity was assessed by studying the recovery of the proliferative response to mitogen stimuli after blocking endogenous cholesterol synthesis by preincubation with hydroxymethylglutaryl-CoA reductase inhibitors (23). The recovery of proliferation is dependent on the LDL-cholesterol-mediated uptake. The method uses peripheral blood mononuclear cells isolated from 10 mL of anticoagulated blood, which are then cultured in lipoprotein-depleted medium and stimulated with phytohemag-

glutinin (0.5 mg/L) as a mitogen. Lovastatin (0.5  $\mu$ mol/L) is used to block endogenous cholesterol synthesis. Exogenous cholesterol is provided as LDL in graded concentrations and mevalonate (the product of the hydroxymethylglutaryl-CoA reductase reaction) is used as a positive control. [<sup>3</sup>H]Thymidine incorporation serves to assess lymphocyte proliferation. Percentage inhibition is calculated by comparing the phytohemagglutinin-stimulated proliferation of cells with and without lovastatin. The LDL concentration needed to restore lymphocyte proliferation by 50% is defined as the LDL<sub>50</sub>. Normal control LDL<sub>50</sub> ranges from a mean of 1.5 to 1.8 mg/L, whereas patients with heterozygous forms of familial hypercholesterolemia have mean values close to 4 mg/L and those with homozygous forms have values > 30 mg/L.

At 12 mo, the human milk group had a mean LDL<sub>50</sub> of 2.4 mg/L, which was higher than the mean of 1.7 mg/L found in the high poly group. The high mono group had an intermediate mean value of 2.1 mg/L. The nonparametric analysis of these results showed that a significantly ( $P < 0.03$ ) higher proportion (6/13) of subjects in the high poly group had low LDL<sub>50</sub> values whereas only one (1/13) had a high LDL<sub>50</sub> value. Conversely, only one (1/13) of the children given human milk had a low LDL<sub>50</sub> value, whereas a high proportion (6/13) had high LDL<sub>50</sub> values (24). The high poly diet increased the LDL-receptor activity of the lymphocytes and was associated with lower plasma LDL-cholesterol concentrations. The human milk group had the lowest LDL-receptor activity (highest LDL<sub>50</sub>); that is, the lymphocytes required higher concentrations of LDL cholesterol in the media to reverse the lovastatin-induced suppression of proliferation.

A separate set of collaborative studies conducted in Cincinnati and Houston evaluated the potential mechanisms underlying the metabolic adaptation of infants to high- and low-cholesterol diets (25, 26). These authors fed deuterated water to enrich red blood cell membrane free cholesterol with deuterium. The rate of incorporation of deuterium into cholesterol, measured by using combustion chamber isotope ratio mass spectrometry, served to assess cholesterol synthesis. Fractional synthetic rates (FSRs) were derived from kinetic analysis of the enrichment over time by using deuterium enrichment of body water at 24 and 48 h as an index of pool size. The comparison of the FSRs of 4-mo-old infants fed human milk (high-cholesterol diet) or formulas based on cow milk (low-cholesterol diet) and soy protein (low-cholesterol diet) with and without added cholesterol (no-cholesterol diet) showed that infants adjust to low-cholesterol feeding with increased cholesterol synthesis; conversely, a reduced FSR was observed in infants fed human milk (25). The addition of cholesterol to soy milk lowered the FSR by  $\approx 10\%$  ( $P < 0.03$ ). Infants fed cow milk formula had nonsignificantly lower cholesterol FSRs than did infants fed soy milk formula to which cholesterol had been added to equal the

**TABLE 5**  
Availability of total energy, fat, and protein as derived from national food balance sheets for Latin American countries (mean values)<sup>1</sup>

Country	Energy	FER	Total fat	Animal fat	Animal fat	Protein
	<i>kJ/d</i>	<i>% of energy</i>	<i>g/d</i>	<i>g/d</i>	<i>% of total fat</i>	<i>g/d</i>
Argentina	12342	31	103	67	65	97
Bolivia	8942	23	51	27	53	52
Brazil	11673	26	82	34	41	64
Chile	10627	23	65	33	51	70
Colombia	11004	21	62	29	47	59
Costa Rica	12008	24	78	31	40	69
Ecuador	10627	32	90	26	29	52
El Salvador	10586	21	58	18	31	62
Guatemala	9540	17	42	11	26	57
Haiti	3096	13	26	6	23	41
Honduras	9665	24	61	19	31	56
Jamaica	10795	22	64	25	39	64
Mexico	13347	27	94	39	41	80
Nicaragua	9581	20	52	16	31	55
Panama	9372	26	65	32	49	59
Paraguay	10962	32	92	45	49	68
Peru	7866	16	34	15	44	50
Uruguay	11213	32	96	75	78	83
Venezuela	10837	26	75	24	32	65

<sup>1</sup>FER, fat energy ratio. Data from reference 28.

cholesterol content of cow milk, suggesting a minor effect of soy components on FSR. Soy isoflavone urinary excretion was negatively associated with cholesterol FSR in infants receiving soy formula. A significant negative correlation was observed between FSR and plasma LDL-cholesterol concentration.

Further studies by the same group investigated whether the addition of cholesterol to formula (0.34 mmol/L, or 13.3 mg/dL) at a concentration mimicking human milk or to an oleic acid-predominant formula (cholesterol content: 0.09 mmol/L, or 3.3 mg/dL) influenced endogenous cholesterol synthesis. Groups of 4-mo-old infants were compared with a breast-fed control group (breast-milk cholesterol content: 0.31 mmol/L, or 12.0 mg/dL) (26). The results of this study confirmed a lower cholesterol FSR in breast-fed infants than in the formula-fed groups. The addition of cholesterol to regular formula elevated total and LDL cholesterol but did not suppress the high FSR observed when the low-cholesterol formula was fed. These findings suggest that factors in human milk other than cholesterol may be responsible for the regulation of cholesterol synthesis. The form of cholesterol may be important: human milk cholesterol is incorporated into a membrane matrix encompassing the fat globule, rather than being present as the crystalline pure cholesterol form provided by the authors. This envelope contains phospholipids, long-chain PUFAs, glycolipids, and multiple other specialized membrane glycoproteins (3).

These results suggest that infants adapt to a low-cholesterol diet such as provided by a lipid-modified cow milk or soy-protein-based formula through an increase in endogenous cholesterol synthesis. Infants fed human milk receive cholesterol and a unique lipid mix that suppresses endogenous cholesterol synthesis. Infants with a high serum LDL-cholesterol concentration will down-regulate cholesterol synthesis. The addition of cholesterol to a cow milk or soy formula does not suppress the rate of cholesterol synthesis at 4 mo, suggesting that other factors present in human milk may be responsible for this regulatory effect. Measurements of serum lipoprotein concentrations and LDL-receptor activity in human lymphocytes suggest that it is the

PUFA content rather than the cholesterol content of the diet that regulates cholesterol homeostasis. The pathways for the regulation of endogenous cholesterol synthesis in infants appear to be regulated similarly as in adults, that is, by LDL-receptor activity. This similarity also includes the dominance of fatty acid composition over cholesterol in the diet as the main factor responsible for establishing the steady state LDL-cholesterol concentration that suppresses endogenous cholesterol synthesis (27).

#### EFFECTS OF DIETARY FAT ON THE GROWTH OF LATIN AMERICAN CHILDREN

Dietary patterns in the Latin American region are changing drastically as a result of rapid urbanization and economic growth, with an accompanying increase in global trade, which includes food commodities. These changes affect all segments of the population but particularly the low-socioeconomic groups, who now have an increased selection of foods from both local production and foreign sources. Some of the new food products are viewed as status symbols and as opportunity to share products with a global presence. There are few national up-to-date dietary surveys that provide a clear picture of food consumption. Most of the data come from analysis of family expenditure, which in many cases includes food purchases. The only data that are systematically collected by the United Nations system in virtually all countries is the food balance information. This balance data includes the total of the food produced in the country added to the food imported. The food exported and that used as animal feed is subtracted from the total, and the balance is taken to represent the total food available for indigenous consumption. This amount is then divided by the population to provide the mean food available to each individual. This approach assumes that all individuals receive an equal portion of the food and that the production of foods for self-consumption is not significant (28).

Shown in **Table 5** are the fat-related components derived from food balance sheets published by the latest Food and

**TABLE 6**Percentage of Latin American children <6 y of age with abnormal growth on the basis of anthropometric measurements (mean values)<sup>1</sup>

Country	Underweight (weight-for-age $\leq 2$ SDs)	Stunted (height-for-age $\leq 2$ SDs)	Wasted (weight-for-height $\leq 2$ SDs)	Low birth weight ( $\leq 2500$ g)
	%			
Argentina	1.9	4.7	1.1	6.5
Bolivia	15.7	28.3	4.4	12.0
Brazil	7.0	15.4	2.0	11.0
Chile	0.9	2.6	0.3	5.8
Colombia	10.1	16.6	2.9	10.0
Costa Rica	2.3	9.2	—	6.0
Ecuador	16.5	34.0	1.7	15.1
El Salvador	11.2	22.8	1.3	16.0
Guatemala	33.5	57.9	1.4	14.0
Haiti	33.9	40.6	4.2	15.0
Honduras	19.3	39.4	1.5	10.6
Jamaica	7.2	8.7	3.4	12.0
Mexico	19.0	35.1	5.5	12.0
Nicaragua	11.9	23.7	1.9	10.0
Panama	6.1	9.9	2.7	10.0
Paraguay	3.7	16.6	0.3	7.6
Peru	10.8	36.5	1.4	12.0
Uruguay	1.7	7.4	1.5	6.9
Venezuela	10.2	6.4	1.3	10.4

<sup>1</sup>Data from reference 29. Underweight, stunted, and wasted were defined on the basis of a 2-SD deviance from the median value of the respective growth index in the World Health Organization–National Center for Health Statistics standards.

Agriculture Organization World Food Survey (28). The proportion of energy from fat, or the FER, and the percentage of animal fat are derived from the primary data (5). Despite the limitations of this approach, we can observe large differences between countries in energy, fat, and percentage animal fat available. To explore the effect of the dietary variables on the growth of children, we also compiled available data from the World Health Organization (WHO) on anthropometric measures of young children from the region, as well as the percentage of children with a birth weight <2500 g (29). The classification of abnormal growth was based on a 2-SD deviance from the median value of the growth indexes derived from the WHO and US National Center for Health Statistics standards. Thus, the mean percentage of children who were underweight (low weight-for-age), stunted (low length-for-age or height-for-age), wasted (low weight-for-length or weight-for-height), or had a low birth weight are presented in **Table 6**.

We then evaluated the effect of diet-related variables obtained from national food balance data on growth indexes of children <6 y of age from 18 countries in Latin America. A simple correlation analysis with a linear model was tested. The correlation matrix is shown in **Table 7**. Underweight prevalence was negatively related to available energy and to the FER but the strongest correlation was with animal fat as a percentage of total fat ( $r = -0.66$ ). For 12 countries with the lowest animal fat intake, the correlation was  $r = -0.83$  ( $P < 0.001$ ), whereas for countries with >45% of total fat from animal sources, the correlation was  $-0.1$  (NS). There was a trend for stunting to be negatively related to energy ( $r = -0.53$ ), FER ( $r = -0.45$ ), and animal fat ( $r = -0.54$ ). For countries with an FER <22%, the correlation with stunting was stronger ( $r = -0.6$ ,  $P < 0.05$ ), whereas for those with an FER >22% there was no correlation ( $r = -0.01$ ). Wasting of children was not related to dietary factors, suggesting that the small percentage of children who were wasted were in

**TABLE 7**Correlation coefficients relating food availability and abnormal growth indexes of Latin American children <6 y of age<sup>1</sup>


Country	Underweight (weight-for-age $\leq 2$ SDs)	Stunted (height-for-age $\leq 2$ SDs)	Wasted (weight-for-height $\leq 2$ SDs)	Low birth weight ( $\leq 2500$ g)
Energy (kJ/d)	-0.497	-0.529	-0.090	-0.643 <sup>2</sup>
Fat energy ratio (% of energy)	-0.446	-0.449	-0.099	-0.331
Energy from fat (kJ/d)	-0.519	-0.544	-0.069	-0.539
Total fat (g/d)	-0.550	-0.520	-0.184	-0.499
Animal fat (g/d)	-0.569	-0.539	-0.196	-0.629 <sup>2</sup>
Animal fat (% of total fat)	-0.657 <sup>2</sup>	-0.438	-0.125	-0.628 <sup>2</sup>
Energy from animal fat (kJ/d)	-0.575	-0.547	-0.084	-0.647 <sup>2</sup>
Protein (g/d)	-0.529	-0.563	-0.203	-0.636 <sup>2</sup>

<sup>1</sup>Data from reference 28. Underweight, stunted, and wasted were defined on the basis of a 2-SD deviance from the median value of the respective growth index in the World Health Organization–National Center for Health Statistics standards.

<sup>2</sup> $P < 0.05$  in univariate linear regression model.

that condition secondary to poor sanitation, infections, or particular dietary factors that do not affect most of the community. The prevalence of low birth weight was negatively related to energy ( $r = -0.64$ ), absolute animal fat intake ( $r = -0.63$ ), percentage animal fat ( $r = -0.63$ ), energy from animal fat ( $r = -0.65$ ), and protein intake ( $r = -0.64$ ). Thus, despite the limitations of national food balance data as putative indexes of food intake and of national aggregated growth data, these results suggest that diets providing <22% of energy from fat and that are low in animal fats (<45% of total fat) restrict fetal and infant growth, as evidenced by significant correlations with the prevalences of low birth weight, underweight, and stunting.

Multistep linear regression analysis of these data sets was also conducted, including the availability of specific food groups (dairy, meats, and oils). The main food determinants of being underweight were availability of dairy, oils, and meats (multiple  $R = 0.81$ ,  $R^2 = 0.66$ ,  $P < 0.0008$ ). The main factors linked to stunting were protein, total fat, total energy, and animal fat (multiple  $R = 0.58$ ,  $R^2 = 0.34$ ,  $P < 0.09$ ). The dietary determinants that best explained having a low birth weight were protein, energy, and total fat availability (multiple  $R = 0.67$ ,  $R^2 = 0.44$ ,  $P < 0.009$ ). The main conclusions from this analysis are that animal food products are important to support the normal growth of children. They provide good-quality protein, essential fats, and micronutrients key for normal growth and development.

The coexistence of early stunting with the recent progressive increase in urban obesity in Latin America creates a dilemma for public nutrition intervention programs. The need to improve growth beyond providing an increased energy supply is suggested by the analysis. The association of improved growth with animal fat and protein suggests that micronutrients (for example, vitamin A, zinc, and iron) or other essential components (essential amino acids or n-6 and n-3 fatty acids) may be limiting the growth of Latin American children. The need to promote an active lifestyle is also stressed by these results. 

## REFERENCES

1. Uauy R, Birch DG, Birch EE, Tyson JE, Hoffman DR. Effect of dietary omega 3 fatty acids on retinal function of very low birth weight neonates. *Pediatr Res* 1990;28:485-92.
2. Innis SM. Essential fatty acids in growth and development. *Prog Lipid Res* 1991;30:39-103.
3. Jensen RG. The lipids in human milk. *Prog Lipid Res* 1996;35:53-92.
4. Hansen AE, Wiese HF, Boelsche AN, Haggard ME, Adam DJD, Davis H. Role of linoleic acid in infant nutrition: clinical and chemical study of 428 infants fed on milk mixtures varying in kind and amount of fat. *Pediatrics* 1963;31:171-92.
5. Food and Agriculture Organization of the United Nations (FAO), World Health Organization (WHO). Fats and oils in human nutrition. Report of a joint expert consultation. Rome: FAO, 1994.
6. Tsang RC, Lucas A, Uauy R, Zlotkin SH, eds. Nutritional needs of the preterm infant: scientific basis and practical guidelines. New York: Williams and Wilkins, 1993;65-86.
7. Innis SM. Human milk and formula fatty acids. *J Pediatr* 1992;120: S56-61.
8. Reiser RB, O'Brien C, Henderson GR, Morroe RW. Studies on a possible function for cholesterol in milk. *Nutr Rep Int* 1979;19:835-49.
9. Mott GE, Lewis DS, McGill HC. Deferred effects of preweaning nutrition on lipid metabolism, hyperlipidemia in childhood and the development of atherosclerosis. *Ann N Y Acad Sci* 1991;623:70-80.
10. Darmady JM, Fosbrooke AS, Lloyd JK. Prospective study of serum cholesterol levels during the first year of life. *Br Med J* 1972;2:685-8.
11. van Biervliet JP, Vinaimont N, Caster H, et al. Plasma apoprotein and lipid patterns in newborns: influence of nutritional factors. *Acta Paediatr Scand* 1981;70:851-6.
12. Huttunen JK, Saarinen UM, Kostianen E, Siimes MA. Fat composition of the infant diet does not influence subsequent serum lipid levels in man. *Atherosclerosis* 1983;46:87-94.
13. Carlson SE, De Voe PW, Barness LA. Effect of infant diets with different polyunsaturated to saturated fat ratios on circulating high density lipoproteins. *J Pediatr Gastroenterol Nutr* 1982;1:303-9.
14. Fomon SJ, Bartels DJ. Concentration of cholesterol in serum of infants in relation to diet. *J Dis Child* 1960;99:39-47.
15. Mize CE, Uauy R, Kramer R, Benser M, Allen S, Grundy SM. Lipoprotein-cholesterol responses in healthy infants fed defined diets from ages 1 to 12 months: comparison of diets predominant in oleic acid versus linoleic acid, with parallel observations in infants fed a human milk based diet. *J Lipid Res* 1995;36:1178-87.
16. Roeschlau P, Bernt E, Gruber W. Enzymatic determination of total cholesterol in serum. *Z Klin Chem Klin Biochem* 1974;12:226-7.
17. McGowan MW, Artis JD, Strandbergh DR, Zak B. A peroxidase-coupled method for the calorimetric determination of serum triacylglycerols. *Clin Chem* 1983;29:538-42.
18. Warnick GR, Cheung MC, Albers JJ. Comparison of current methods for high-density lipoprotein cholesterol quantification. *Clin Chem* 1979;25:596-604.
19. Myers LH, Phillips NR, Havel RJ. Mathematical evaluation of methods of estimation of the concentration of the major lipid components of human serum lipoproteins. *J Lab Clin Med* 1976;88:491-505.
20. Blich EG, Dyer WJ. A rapid method of total lipid extraction and purification. *Can J Biochem Physiol* 1954;37:911-7.
21. Vittielo F, Zanetta JP. Thin layer chromatography of phospholipids. *J Chromatogr* 1978;166:637-40.
22. Morrison WR, Smith LM. Preparation of fatty acid methyl esters and dimethyl acetals from lipids with boron fluoridemethanol. *J Lipid Res* 1964;5:600-8.
23. Cuthbert JA, East CA, Bilheimer DW, Lipsky PE. Detection of familial hypercholesterolemia by assaying functional low-density lipoprotein receptors on lymphocytes. *N Engl J Med* 1986;314:879-83.
24. Mize CE, Uauy R. Effect of early infancy dietary lipid composition on plasma lipoprotein cholesterol and LDL receptor activity. *Ann N Y Acad Sci* 1991;623:455-6.
25. Cruz ML, Wong WW, Mimouni F, et al. Effect of infant nutrition on cholesterol synthesis rates. *Pediatr Res* 1994;35:135-40.
26. Bayley TM, Alasmi M, Thorkelson T, et al. Influence of formula versus breast milk on cholesterol synthesis rates in four month old infants. *Pediatr Res* 1998;44:60-7.
27. Grundy SM, Denke MA. Dietary influences on serum lipids and lipoproteins. *J Lipid Res* 1990;31:1149-72.
28. Food and Agriculture Organization of the United Nations (FAO), World Health Organization (WHO). Sixth world food and nutrition survey. Rome: FAO, 1996.
29. Administrative Committee on Coordination, Subcommittee on Nutrition (ACC/SCN), United Nations. Third report on the world nutrition situation. Geneva: ACC/SCN, 1997.