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COW'S MILK AND LINEAR GROWTH IN INDUSTRIALIZED AND DEVELOPING COUNTRIES

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■ **Abstract** The strongest evidence that cow's milk stimulates linear growth comes from observational and intervention studies in developing countries that show considerable effects. Additionally, many observational studies from well-nourished populations also show an association between milk intake and growth. These results suggest that milk has a growth-stimulating effect even in situations where the nutrient intake is adequate. This effect is supported by studies that show milk intake stimulates circulating insulin-like growth factor (IGF)-I, which suggests that at least part of the growth-stimulating effects of milk occur through the stimulation of IGFs. Given that the biological purpose of milk is to support the newborn during a period of high growth velocity, such an effect seems plausible. Adding cow's milk to the diet of stunted children is likely to improve linear growth and thereby reduce morbidity. In well-nourished children, the long-term consequences of an increased consumption of cow's milk, which may lead to higher levels of IGF-I in circulation or an increase in the velocity of linear growth, are likely to be both positive and negative. Based on emerging data that suggest both growth and diet during early life program the IGF axis, the association between milk intake and later health is likely to be complex.

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INTRODUCTION

Milk is the first food consumed by mammals. Given that milk supports the growth of nursing infants, the question arises as to whether sustained consumption of milk likewise enhances growth throughout childhood. As increasing numbers of human populations are continuing to consume cow's milk as a part of the diet after weaning and during childhood (230), with some even continuing into adulthood, it is of public health importance to understand the health implications of cow's milk consumption on growth.

The "milk hypothesis," put forward by Bogin, proposes that a greater consumption of milk during infancy and childhood will result in taller adult stature (26). Milk might have a positive impact on linear growth via a number of its elements (Table 1). Milk provides an important supply of energy, depending on the fat content, 266 kJ/100 g of whole milk, and 151 kJ/100 g of skim milk. It also has a high protein content, 3.5 g/100 g, and contains many micronutrients and bioactive factors that may have growth-promoting abilities. It is plausible that these constituents, in addition to supplying the nutrients required for growth, may also directly stimulate growth. According to the milk hypothesis by Bogin, it is not the energy supplied by milk that results in increased growth in height, but rather it is a "height factor," which is likely another nutrient, or combination of nutrients, in

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TABLE 1 Composition of whole cow's milk (150)

Nutrient	Units	Value per 100 g
Energy	kJ	266
Carbohydrate	g	4.4
Protein	g	3.5
Fat	g	3.5
Water	g	87.9
Minerals		
Sodium, Na	mg	48
Potassium, K	mg	144
Calcium, Ca	mg	115
Magnesium, Mg	mg	11
Phosphorus, P	mg	93
Iron, Fe	mg	0.046
Copper, Cu	mg	0.010
Zinc, Zn	mg	0.43
Iodine, I	μg	5.61
Manganese, Mn	mg	0.010
Chromium, Cr	μm	0.052
Selenium, Se	μg	1.4
Nickel, Ni	μg	2.0
Vitamins		
Vitamin A	RE	30
Retinol	μg	27
β-carotene	μg	16
Vitamin D	μg	0.10
Vitamin E	α-TE	0.089
α-tocopherol	mg	0.089
Thiamin	mg	0.039
Riboflavin	mg	0.17
Niacin	mg	0.86
Vitamin B_6	mg	0.047
Pantothenic acid	mg	0.34
Biotine	μg	1.4
Folate	μg	9.0
Vitamin B_{12}	μg	0.45
Vitamin C	mg	1.2

milk. Although a number of milk nutrients are liable to contribute in explicit ways to the growth process in general, research in humans so far has focused chiefly on a few constituents as predominantly important to bone growth.

The consumption of cow's milk is a relatively recent phenomenon in human history, as it dates back only to the beginning of animal domestication. In some populations, its introduction into the diet of children is very recent, having occurred only

within the last 50 years (27). Because milk contains numerous growth-enhancing components (52, 172), its consumption beyond the traditional weaning age has the potential to have positive and negative effects on health. This chapter focuses on the association between the consumption of cow's milk and linear growth, with an additional brief examination of its potential effects on health.

This review is organized according to the conceptual framework illustrated in Figure 1, and the bracketed letters in this paragraph correspond to this illustration as well as to the main section headings used in the text below. The main focus is on the relationship between the consumption of cow's milk and linear growth [A]. As it is likely that the effect of cow's milk is mediated through physiological actions of insulin-like growth factors (IGFs), studies on how cow's milk is associated with serum levels of IGFs are also reviewed [B]. Additionally, a short section on IGFs and growth is included [C]. Although it is unknown which components in milk are responsible for stimulating the IGFs, it is currently speculated that bioactive peptides, milk IGF-I, amino acids, or milk minerals are involved. Therefore, these components and their potential mechanisms of action are discussed [D]. Although a detailed discussion of the effects of cow's milk intake on health is beyond the scope of this review, we have included a short discussion on how the intake of cow's

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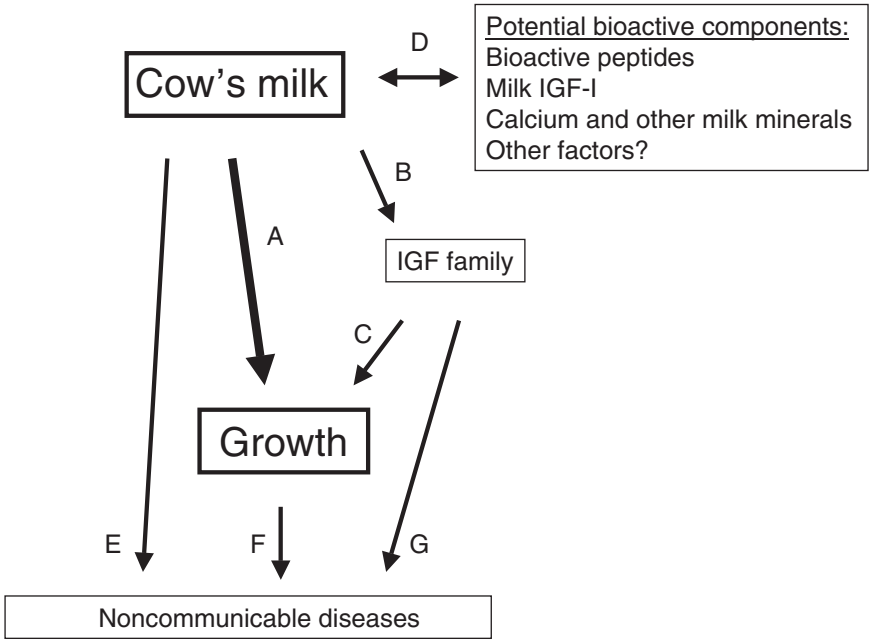

Figure 1 Conceptual framework for the association between the consumption of cow's milk, linear growth and the risk of developing noncommunicable diseases. The letters refer to separate sections in the review. IGF, insulin-like growth factor.

milk [E], linear growth [F], and blood concentrations of IGFs [G] are positively and negatively associated with the risk of developing several noncommunicable diseases.

Many studies and reviews have examined the effect of animal protein on growth, primarily focusing on the situation in developing countries (3, 5). Among populations consuming nutrient-deficient diets, animal protein foods supply important nutrients, such as high-quality protein, calcium, zinc, and other milk minerals, which are important for linear growth. We have not reviewed studies on the effect of meat on linear growth, but we have included some studies in which the effects of milk and meat have been compared.

The regulation of linear growth is not fully understood. It seems as though adult height, at least to some degree, is programmed before puberty (175). Evidence suggests that the first two years of life may be an especially critical period (25, 41). Therefore, nutrition during this period may be a more important determinant of height than is nutrition at older ages (183). In addition, there are also endocrinological reasons for making a distinction between infant and childhood growth. Although the regulation of infant growth is not fully understood, it is known that growth hormone (GH) is less important during this period in comparison with later in childhood, when linear growth is primarily regulated by GH. Karlberg (112) modeled childhood growth by decomposing the normal linear growth curve into three additive and partly superimposed components of infancy, childhood, and puberty (the ICP growth model). In this model, GH plays a more active role beginning at approximately 9 months of age (Figure 2). Additionally, more recent results show that the GH-IGF axis can be programmed during early life, a finding that provides support for the concept that adult height, at least to some degree, is programmed during the first years of life.

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COW'S MILK AND LINEAR GROWTH [A]

A large number of studies on the association between the consumption of cow's milk and linear growth have been conducted in developing and industrialized countries, where the general nutritional status of the population varies widely. In populations with poor nutritional status, the addition of milk to the diet likely supplies nutrients that are important for growth and are deficient in the typical diet. In well-nourished populations, an effect of milk on growth is less likely to occur because of a correction of nutrient deficiencies, but rather as the result of some modification of growth-regulating factors.

In populations with marginal or poor nutritional status, increased intake of animal foods has been shown to stimulate weight gain and linear growth in infancy, childhood, and adolescence (4, 136, 179, 217, 224). A potential explanation is that animal foods provide micronutrients and high-quality protein. In most populations, however, the intake of dietary protein is already sufficient to cover physiological requirements. Even if the protein intake derives mainly from vegetable foods,

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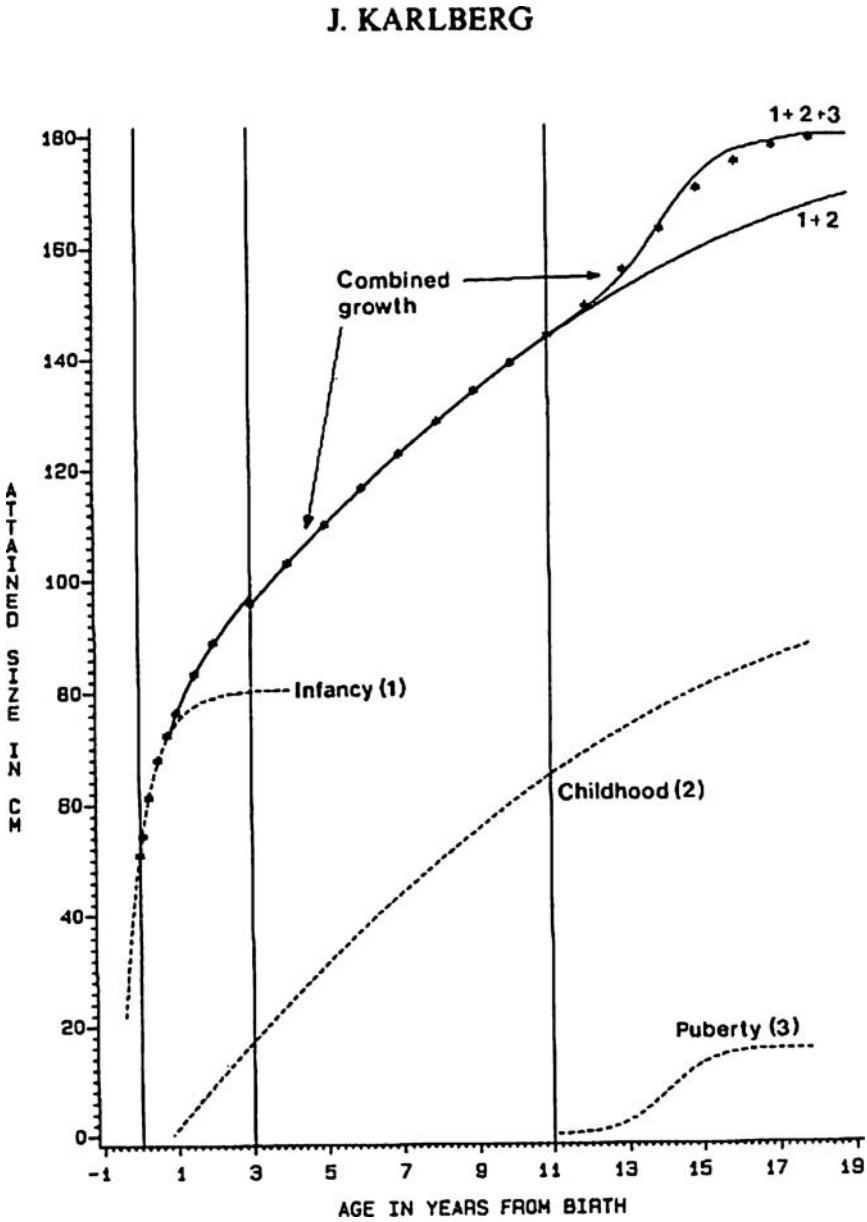

Figure 2 The Infancy, Childhood and Puberty Model of linear growth developed by Karlberg (112). The model divides growth into three separate components. Printed with permission from Stat Med.

the quality of the protein intake is often reasonable, especially if it comes from a mixture of cereals, pulses, and vegetables. Therefore, it is likely that characteristics of animal foods other than protein are also important for growth.

It is unclear whether a positive association between intake of animal protein and linear growth also exists in industrialized countries, where protein intake typically is high. Some studies indicate that protein intake and protein quality may also have a regulatory effect on growth in populations with protein intakes above the basic requirements.

Generally, the protein intake of children in industrialized countries is considerably above basic physiological requirements. During the period of complementary feeding, when infants shift from a diet based on breast milk or formula to a diet based on family foods, there is a dramatic increase in protein intake. For example, during weaning a breast-fed infant goes from having a protein intake of approximately 1 g/kg body weight (5% of energy from protein) to an intake of 3–4 g/kg body weight when eating the family diet, which typically provides 15% of its energy from protein (183). This amount is 3–4 times greater than the physiological requirements of the average infant.

In this section on cow's milk intake and linear growth, we discuss studies separately for each of the age groups: infants, preschool children, and school-age children. Within the headings for preschool children and school-age children, we have divided the studies into intervention studies and observational studies.

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Breast-Fed and Formula-Fed Infants

There is global consensus that breast milk is optimal for infants, and the World Health Organization recommends exclusive breast-feeding for the first six months of life. Unmodified cow's milk is generally not recommended for human infants in the first year of life, although in some countries, e.g., Denmark and Sweden, cow's milk can be gradually introduced from the age of 9–10 months.

Infants fed formula based on cow's milk grow at a faster rate than do breast-fed infants, especially during the latter half of infancy (1, 44, 46, 47, 82, 144, 156). Although the difference is most evident for weight, some studies also find a significant difference in linear growth (48, 144). There is no difference in growth in head circumference. As these studies are not randomized, and as there are many differences between breast- and formula-fed infants and their families, it is difficult to identify the reasons for the differences in linear growth. It has been suggested that there is a down-regulation of energy intake by breast-fed infants, or differences in complementary feeding between breast-fed and weaned infants, either due to self-selection or because breast-feeding mothers provide different complementary foods (33, 45–48, 82, 89, 156, 227). Additionally, it may also be explained by differences in protein quality or amount, as there is a higher protein content in formula than in breast milk (82).

In a study comparing growth among 4- to 6-month-old infants fed formulas with different contents of protein, it was found that a high protein intake was

associated with higher growth velocity in weight and length (14). In another study of 5- to 10-month-old Danish infants, who all had protein intakes well above the basic requirements, we found a positive association between the intake of protein and weight gain and a trend for a positive association between protein intake and length gain (156). Breast-fed infants received significantly less unmodified cow's milk than did those who were not breast-fed.

A decreased protein intake from formula during weaning results in markers of protein metabolism and growth that are more similar to those of breast-fed infants than are markers when conventional follow-up formulas are used (12, 13, 130). We speculate that the reason infants fed formula have a higher linear growth velocity than do breast-fed infants is because they receive more of the growth-stimulating factors from cow's milk, which may not be present, or are present to a lesser degree, in human milk. Evidence to date suggests that there are no adverse consequences associated with the lower linear growth velocity in breast-fed infants. In fact, a few studies show that breast-fed infants are taller as adults (139, 218).

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Preschool Children

In this section, studies only including preschool children are discussed separately because growth velocity is still high in this period, especially during the first years, and an effect of cow's milk might be more pronounced during this period.

INTERVENTION STUDIES A longitudinal intervention study in Guatemala did not identify an effect of protein supplementation on growth. Preschool children were provided either with a good-quality protein supplement of *atole,* which was a mixture of dry skim milk and cereal, or with *fresco,* which contained only energy and no protein. Results from this intervention showed that energy intake was the important predictor of increases in linear height (and weight) (140). However, it is not clear whether the effects of the *atole* on height were due only to its energy content, because the dried skim milk and cereal in this supplement probably provided greater amounts of milk proteins and some micronutrients in comparison with *fresco* (3).

OBSERVATIONAL STUDIES Although randomized controlled trials are the most reliable investigations of an association between milk and linear growth, some observational studies have linked milk consumption to height. In an analysis of Demographic and Health Survey data on children from 12 to 36 months of age from seven countries in Central and South America, Ruel analyzed the association between height and intake of milk, meat, and egg/fish/poultry products (188). Milk intake was found to be significantly associated with higher height-for-age Z-scores in all seven countries, whereas meat and egg/fish/poultry intakes were only associated with height in one of the countries.

In a study of Mexican preschool children, Allen et al. did not identify a significant association between each child's average intake of energy, protein, or other

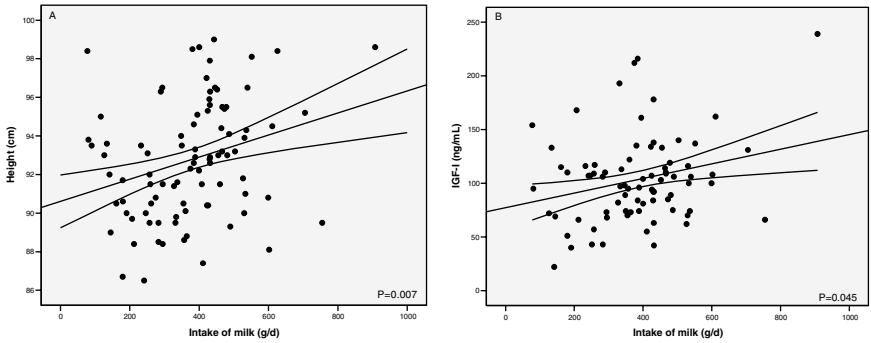

Figure 3 Height (*A*) and serum IGF-I levels (*B*) according to milk intake in 2.5-year-old children (n = 90). Fitted regression lines with 95% confidence intervals from analyses that controlled for sex and body weight are shown. Created from (95).

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nutrients during the previous 12 months and length at 30 months (4). However, positive associations were found between the intake of specific foods and linear growth. The typical diet of taller children contained more animal products—especially milk and meat—and fewer maize tortillas than did the diet of shorter children (4).

Few observational studies of well-nourished children have investigated the association between milk intake and height. In our observational study of 90 healthy and well-nourished 2.5-year-old Danish children, the protein intake was close to what has been found in other studies of the same age group. The tenth, fiftieth, and ninetieth percentiles of daily protein intakes were 2.4, 2.9, and 4.0 g per kg of body weight, respectively. Sixty-three percent of the protein intake came from animal foods. The mean intake of milk was 385 mL/day. In multiple linear regressions with adjustment for sex and weight, height was positively associated with intakes of animal protein and milk (Figure 3*A*), but not with those of vegetable protein or meat (95). The effect on IGF-I is discussed in a section below.

School-Age Children

The school-age period includes both the prepubertal period, with a relatively low growth velocity, and puberty, when growth velocity varies considerably and includes the peak height velocity. Because most studies include a wide age range and because the age of peak height velocity varies considerably, it has not been possible to divide the studies into prepubertal and pubertal studies. This section also includes some studies with a wide age range, including both preschool and school-age children.

INTERVENTION STUDIES In the early 1900s, a number of studies explored the effects of milk and milk products on height. In the famous Boyd Orr study conducted in Scotland at the beginning of the previous century, the effect of milk given

to schoolchildren was examined (164). In a very simple and elegant experiment, Boyd Orr compared the effects of supplementing the diet of children at school with (*a*) whole milk, (*b*) skimmed milk, or (*c*) biscuits that contained the same amount of energy as the other supplements. In addition, a control group did not receive any supplementation. The intervention was conducted in three age groups of children: 5–6, 8–9, and 13–14 years.

Irrespective of the age group, compared with those in the control group, children who received either whole or skim milk grew 20% more in height during seven months. Children who received the biscuits did not grow any differently from those in the control group (Figure 4). In a follow-up study on these children, Leighton & Clark (126) found that those who continued to receive milk supplements for a second year continued to grow at the faster rate, and those children who stopped receiving milk supplements after a year returned to the slower growth rate. Because information was not provided, it is not possible to evaluate the degree to which the children participating in the study were poorly nourished at the onset of the study. However, because this study was conducted in the 1920s, it is plausible that some degree of malnutrition was present.

More remarkable results than those of the Boyd Orr study were found with a similar supplementation program in New Guinea. It was conducted among 7- to 13-year-old Bundi children who had a very-low-protein diet and the majority of

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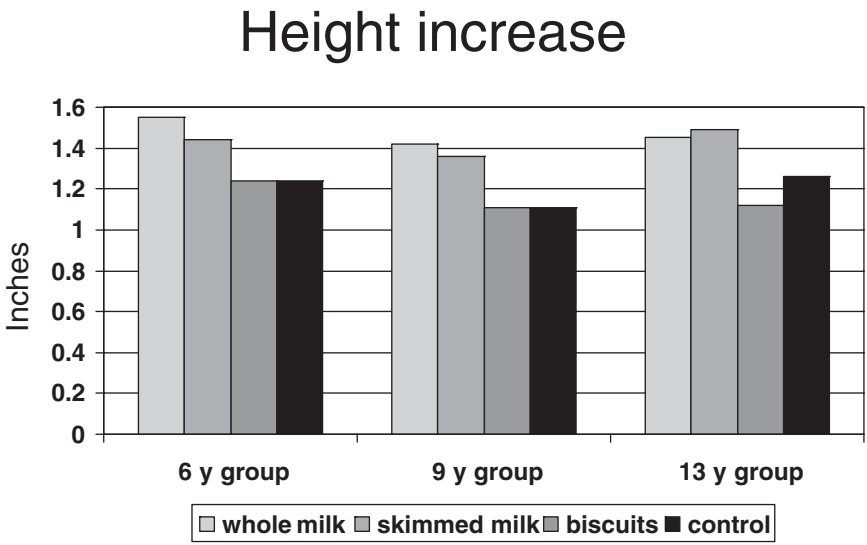

Figure 4 Height increases during a seven-month period in the classical Boyd Orr study from 1928. The effects of four different interventions given together with the school lunch were examined. Children were given whole milk, skimmed milk, biscuits that contained the same energy as the other diets, or they did not receive any supplements. Created from (164).

whom were below the third percentile in height at the beginning of the study (210). The Bundi have a reliable supply of food throughout the year from their staple root crops of taro and sweet potatoes, although the diet is usually low in protein. Although this study was not designed to test the effects of milk on growth per se, Lampl et al. (117) compared the linear growth velocity of a control group that received only their normal school diet with three groups of children supplemented with (*a*) skim milk powder, (*b*) margarine with an equivalent amount of energy as the milk powder, or (*c*) extra servings of taro root and sweet potatoes over a 13-week period. The linear growth velocity nearly doubled among the children receiving the skim milk supplement in comparison with children in the other groups (117, 134).

In a study in 1925, forty-seven 6- to 14-year-old children living in the California State School for the Deaf and Blind were repeatedly examined for physical indices of growth (152). During an 18-week period, as a supplement to lunch, 13 children were given one half-pint of milk each per day, 13 children were given one orange each, and 10 were given four pulled figs each. Eleven children were used as controls. After 14 weeks, children in the milk group had the greatest increases in both standing and sitting height in comparison with the other groups. In the milk group, 61% of the children showed increases in sitting height compared with only 30% of the orange group, 30% of the fig group, and 36% of the control group. Unfortunately, the children were not divided into age groups in this study. The reason the difference between the supplemented groups was more pronounced in sitting height may be that during pubescence the growth velocity is higher in the trunk than in the legs, in contrast to prepubertal growth, when the highest growth velocity is seen in the legs.

In 1945, a three-year study in Alabama was initiated to determine the effect of the daily supplementation of either whole or nonfat dried milk on the growth of a selected group of children with chronic nutritive and growth failure (53, 54, 200, 201). The 82 children with nutritive and growth failure chosen to receive the supplements were paired with a child who was not given milk. Pairings were made on the basis of similarities of sex, growth pattern, nutritional status, and social and economical level. Of the 82 children given milk supplements, 41, ranging in age from 4 to 15 years, received an amount equivalent in protein to 5.7 liters of milk per week for 20 months. The other 41 children, ranging in age from 1 to 10 years, received an amount equivalent in protein to 2.8 liters of milk per week for 40 months. During the milk period, a significantly greater number of children in the intervention group improved in their height scores as compared with the number in the control group showing similar changes. The children receiving the milk supplements gained an average of 1.23 cm above the gain made in the control group during the supplementation period.

In a more recent controlled supplementation study, Baker et al. (16) randomized 520 7- to 8-year-old British schoolchildren classified as "disadvantaged" to receive 190 mL of free milk daily for $21^1/_2$ months or to a control group. The mean difference in height gain at the end of the intervention period was 2.9 mm

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($P < 0.05$) in favor of the children provided with the free milk. A recent study from Beijing (55) indicated a significant and positive effect of a school milk intervention on growth in height among approximately 700 Chinese 10- to 12-year-old girls with low baseline intakes of calcium and milk. Supplemented subjects were given 330 mL of calcium-fortified milk five days/week, and they grew significantly, but modestly (0.7 cm), more than the unsupplemented group over two years. Similarly, in a two-year intervention study of 2677 6- to 9-year-old children in Malaysia, Chen found that the implementation of a school milk program providing 250 mL of milk twice weekly significantly reduced the percentage of stunted children from 16.3% to 8.3% (37, 38).

Not all intervention studies conducted in school-age children, however, have shown an effect on growth. In studies of schoolchildren in the United Kingdom in the 1970s and 1980s, Rona & Chinn reported no consistent associations between supplying milk in the schools and rates of growth in three samples of 5- to 10-year-old children, even when stratified by poverty status and ethnic background (185).

A study published in 1923 by Chaney was conducted in children who were 7% or more underweight and from homes in California with good economic conditions. Results from this study indicated that not all undernourished children are best treated by the feeding of supplementary lunches of milk and crackers, which were normal in the United States at that time (35). She found that schoolchildren given an orange daily, instead of milk, showed, on average, better growth during the two 8-week periods of observation than did the milk-fed children. Both of these groups showed considerably better growth than did the control group, which did not receive a supplementary lunch. The main criterion of growth used in this study was gain in weight, although standing and sitting heights were also measured but were not reported. Since the children came from homes with good economic conditions, the total quantity and the variety of food supplied were probably adequate. Apparently, these families served plenty of milk at home, although exact information on this point was not reported.

Furthermore, in a Kenyan study, Grillenberger et al. (73) found that among a sample of 554 schoolchildren with a mean age of seven years, those who were given milk daily for two years did not grow significantly more than those given meat or fat with energy contents similar to the milk supplement. Only those children with a baseline height-for-age Z score below the median grew significantly more (1.3 cm) than those in the control group without a supplement. Among these children, however, milk did not produce greater gains in height than did the supplements of nondairy animal foods.

Similarly, using data collected annually from 1972 to 1976 in 28 areas of England and Scotland, Cook et al. (42) investigated the effect of the availability of free school milk on height gains in one year among a very large sample of 6- to 7-year-old schoolchildren. Children with access to free milk did not grow significantly more in height than did those without such access. Further, the number of glasses of milk consumed did not predict height gain for children from any

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social class. Of 16 sex-, country-, and year-specific analyses of children only from the manual laborer social classes, 13 showed no significant evidence of greater height gains in children who had access to milk.

More recently, a number of intervention studies have investigated the effect of dairy product consumption on variation in different aspects of bone biology, which also report differences in height between supplementation and control groups. In a randomized intervention trial, 83 healthy, well-nourished 12-year-old girls who had a low habitual milk intake of approximately 150 mL/d were assigned to receive either one pint (568 mL) of milk or no supplementary milk for 18 months (30). In contrast to results from calcium supplement studies, which typically do not find effects on bone size, Cadogan et al. (30) found an increase in both bone mineral content and bone size among the girls who received milk. Girls in the intervention group had a 6% increase in height and the girls in the control group had a 5% increase in height during the 18 months. There was a 0.7 cm difference in height between the two groups, but it was not statistically significant.

In a study using a milk-based mineral mixture as supplement in Swiss 6- to 9-year-old girls, Bonjour et al. also found an effect on both bone mineral content and bone size (28). A group of 108 girls were supplemented with 850 mg calcium from milk and compared with a placebo group to whom similar amounts of energy, protein, lipids, and carbohydrates were given. After 48 weeks, there were no differences in height gain (28). However, in the girls with a habitual calcium intake below the median, there was a tendency toward a higher increase in height among the supplemented girls compared with those in the placebo group ($P = 0.08$). Furthermore, although no significant difference in height gain was observed one year after the end of the supplementation, 3.5 years after the end of the supplementation, the difference (1.4 cm) in the mean gain of standing height was marginally significant ($P = 0.06$). Additionally, in the bones of the lumbar spine (L2–L4), there was a greater, and highly significant, increase in size among those in the supplement group compared with those in the placebo group (29). However, because sitting height was not measured, it was not possible to determine whether the difference reported in the longitudinal growth was restricted to the axial skeleton.

In a 12-month randomized controlled study, 48 girls from Utah, aged 9 to 13 years, were randomized to a dairy or a control group. The diet of those in the dairy group was supplemented with dairy products to at least 1200 mg calcium/d. Dairy products included milk, cheese, and yogurt (32). The girls in the control group continued to eat their usual diet. Even though girls in the dairy group had significantly greater increases in bone mineral density both in the bones of the lumbar spine and the total body, heights were similar at the start and end of the study compared with the control group. Additionally, the percentage of height gain was not different between the groups.

Likewise, in a three-year study with two years of supplementation and one year of follow-up, New Zealand girls aged 15 to 18 years were able to increase significantly their bone mineral density when their diets were supplemented with dairy

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product foods to a mean calcium intake of 1000 mg/d. No significant differences in height were observed between the two groups (142).

The effect of milk interventions on bone size and bone turnover may indicate a special effect of some milk components on bone metabolism. Intervention studies conducted in Japanese men (213) and women (8, 232) showed that milk whey protein, especially its basic protein fraction, was able to promote bone formation and inhibit bone resorption.

OBSERVATIONAL STUDIES Results from several observational studies indicate that children who do not drink milk tend to be shorter than those who do drink milk. In a recent study, Black et al. (24) found that in a sample of 250 three- to ten-year-old children from New Zealand, the 50 children who avoided drinking cow's milk were significantly shorter (age-adjusted Z-score -0.65, $P < 0.01$) than the 200 matched children from the same town who drank milk. However, a large number of the milk avoiders seemingly had allergies and/or asthma. Additionally, children with lactose intolerance (202) and children with an allergy to milk are shorter than the population average in most (99, 100, 167, 212), but not all (192), studies. Although it seems likely that the reason these children are shorter is a lack of growth stimulation from milk, it cannot be excluded that atopic diseases or lactose intolerance have other effects that impair the absorption of nutrients from the gastrointestinal mucosa.

Data on growth of traditional living pastoralists, whose diet is based on animal milk, and agriculturalists, who grow rice and grains and whose diet is usually devoid of milk and milk products, have been reviewed by Takahashi (206). Both Central Asian (peoples of the Gobi, Takola Makan, and Kavil deserts) and East African (the Masai, Samburu, and Datoga) pastoralists were taller than the agriculturalists. Other observational evidence suggests that the relatively tall stature of the Turkana pastoralists of Kenya may be ascribed to their high protein intake, as they have a diet based for the most part on animal foods such as dairy products (128, 129). Additionally, in a global review of height in connection to ecological factors, Takahashi found that populations with the largest attained heights were those that had diets based mostly on dairy products, although he did not control for nutrient intake or overall diet (205).

In a large cohort of 12,829 U.S. children, aged 9 to 14 years, who were followed from 1996 to 1999, there was significantly greater growth in height during one year for boys (0.058 cm per daily serving of milk, reported at the time of the earlier height measurement; $P = 0.008$) and girls (0.043 cm per serving; $P = 0.004$) who drank more than three servings of milk per day compared with those who drank fewer servings (23).

Much larger effects were observed in a longitudinal study of 92 Japanese children aged 9 years (161). Those who consumed large amounts of cow's milk (>500 mL/d) gained 2.5 cm more in height over three years than did those who consumed less milk (<500 mL/d), even though increases in body weight did not differ significantly. In a cross-sectional study of 545 male and 615 female students

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aged 12–18 years from two schools in Bangkok, Thailand, Jirapinyo et al. reported that milk intake contributed positively to adolescent height in females (102).

To investigate the association between milk consumption and height among American children, an analysis and follow-up of the NHANES 1999–2002 study was undertaken (228). Two hypotheses were tested: (*a*) if the reported frequency of childhood milk consumption was positively related to adult height and (*b*) if height of children from 5 to 18 years of age was predicted by the reported frequency of milk consumption and/or milk intake from 24-hour dietary recalls. Milk consumption at ages 5 to 12 and 13 to 17 years was positively associated with adult height after controlling for sex, education, and ethnicity. Cross-sectional analyses revealed that milk consumption had no effect on the height of 5- to 11-year-olds after controlling for age, birth weight, energy intake, and ethnicity. In contrast, milk consumption frequency and milk intake (measured as grams of milk, or protein or calcium from milk) were significant predictors of the height of 12- to 18-year-olds, along with age, sex, household income, and ethnicity. Thus, in this study, the concurrent effect of milk intake on linear growth was larger in pubertal children than in prepubertal children.

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Secular Trend in Adult Height

Since the nineteenth century, there have been clearly documented secular trends of increases in adult height in most European countries (17, 18, 25, 79, 208). During the most recent decades, adult stature has increased steadily (41). We compiled data on conscripts from 11 European countries from 1960–1990 (190). The largest increases in height were observed among conscripts in southern Europe, but these countries also had the shortest conscripts to begin with. In the Scandinavian countries and the Netherlands, the increases in height appeared to have leveled off during the 1980s, whereas the trend toward increasing adult height continued in the middle and southern European countries (190). This pattern was confirmed in an update of the conscript data, including the period up to 2004 (120). A secular trend of increasing adult height has also been seen in other countries, such as the United States (175).

It has been suggested that the considerable increase in animal protein consumption may explain some of the marked increases in adult stature observed during the past decades (66). In the Netherlands, where conscripts are the tallest, the average consumption of dairy products is among the highest in the world (66). Results from numerous studies in children also support this idea. A study in 10-year-old French children showed that even though total protein intakes remained constant from 1978 to 1995, the ratio of animal to vegetable protein increased. This increase was mainly a consequence of declines in vegetable protein consumption, and declines in the percentage of energy from protein in the diet. Over this same period, children became taller (182). As in western countries, secular trends of increases in height and weight of Japanese children between 1950 and 1990 are matched by a parallel increase in animal protein intake (207). This is supported by an analysis

of regional differences in height and corresponding milk consumption in school lunch programs in Japan. These results suggest that milk intake was a major determinant of the secular increase in height in Japan (204, 206). Furthermore, the increase in height of 5-year-old Japanese children from the end of World War II onward was accompanied by a steep increase in the ratio of animal to vegetable protein in the diet, from 0.66 in 1952 to 1.53 in 1994 (153).

Conclusions

Most of the studies reviewed involved the addition of milk or milk components to diet in free-living individuals. It should be noted that for several studies it was difficult to determine the nutritional status of the population because the baseline diet was not described. Overall, published results on the association between cow's milk intake and height strongly suggest that the intake of cow's milk has a stimulating effect on linear growth, although not all studies showed an effect. Several studies have compared the consumption of cow's milk with supplements of other nutrient-rich foods, such as meat, and found that cow's milk has a special growth-enhancing effect. It appears that cow's milk may have the strongest effects in children with existing undernutrition, as several intervention studies have identified an effect of cow's milk consumption on linear growth. In well-nourished populations, there are several observational studies showing clear positive association between the consumption of cow's milk and linear growth in children. However, among the intervention studies from well-nourished populations, the association is not as clear.

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COW'S MILK AND INSULIN-LIKE GROWTH FACTORS [B]

The IGF Family of Growth Factors

The IGF family of growth factors consists of the three ligands, insulin, IGF-I, and IGF-II. Each ligand has a similar peptide as well as tertiary structure. Insulin is generally regarded primarily as being involved in the maintenance of metabolic homeostasis. The IGFs are also thought to act as hormones regulating metabolism and to function as regulators of cellular proliferation (mitogenesis) as well as having other tissue-specific functions (122). However, insulin, IGF-I, and IGF-II all have metabolic as well as mitogenic actions in the regulation of cellular proliferation (106). Circulating IGF-I is bound to one of six IGF binding proteins (IGFBP-1 to -6) (19). IGF-I forms binary complexes with all the binding proteins, but forms a ternary complex solely with IGFBP-3, which consists of IGF-I, IGFBP-3, and an acid-labile subunit (ALS). This complex, in which more than 95% of circulating IGF-I is bound, is not available to the tissues. The molar ratio of IGF-I to IGFBP-3 may reflect free, biologically active IGF-I in circulation (106).

Cow's Milk and IGF-I

The synthesis of IGF-I is regulated mainly by growth hormone and by nutrition. Therefore, it is likely that nutritional regulation of IGF-I is more important during infancy, when IGF-I concentrations are low (107), rather than later in childhood and in adulthood. Concentrations of IGF-I appear to be influenced by energy, protein, and certain micronutrients (158), as shown in both animal and human studies. Dietary depletion has a pronounced negative effect on IGF-I concentrations in children (84) and in adults (40, 97, 98). Additionally, during the rehabilitation of malnourished children with low concentrations of IGF-I, there is a fast increase in IGF-I levels (197).

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INTERVENTION STUDIES WITH CHILDREN AND ADOLESCENTS Some studies suggest that milk consumption increases the circulating concentrations of IGF-I, but intervention studies in children and adolescents show conflicting results. In 12-year-old girls, supplementation with one pint of milk (568 mL) for 18 months tended to increase serum concentrations of IGF-I in comparison with a control group. The effect was significant only after adjustment for pubertal status (30). The authors speculate that this could partly be due to the increased intakes of protein, but they could not exclude an effect of other nutrients in the milk or an effect of an increased energy intake, as there was a trend toward increased energy intake ($P = 0.065$) in the intervention group. Interestingly, the effect on circulating IGF-I appeared slowly, and reached significance only after 18 months.

In a one-week intervention study of 24 prepubertal eight-year-old boys, we examined the effect of milk intake on IGF-I (92). The boys were asked to consume either 1.5 liters of skimmed milk daily or the same amount of animal protein as low-fat meat. They were free to choose the rest of their diet. The high intake of milk increased concentrations of IGF-I by 19% ($P = 0.001$) (Figure 5*A*) and the IGF-I/IGFBP-3 ratio by 13% ($P < 0.001$). There were no increases in the meat group. Thus, a high intake of milk, and not a high intake of meat, increased the concentrations of s-IGF-I and s-IGF-I/s-IGFBP-3 significantly. The increase in protein intake in this short intervention was very high, from 2.3 to 4.0 g/kg/d, but the level of protein intake during the intervention (expressed as gram per kg body weight per day) was close to the level seen in a large proportion of infants and young children during the complementary feeding period. During this period, the average intake is typically around 3–4 g/kg body weight, with some children having a considerably higher intake (183).

INTERVENTION STUDIES WITH ADULTS Intervention studies conducted in adults have also yielded conflicting results. A randomized intervention study was conducted in 204 healthy and elderly men and women, who habitually consumed fewer than 1.5 servings of dairy foods per day. Among those who were randomized to consume three servings per day of nonfat or 1% fat milk for 12 weeks, there was a significant 10% increase in serum IGF-I concentrations in comparison

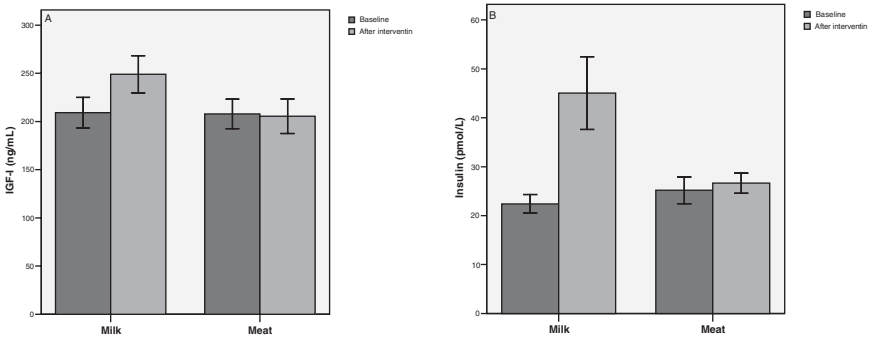

Figure 5 Fasting concentrations of serum IGF-I in ng/mL (*A*) and insulin in pmol/L (*B*) at baseline (*dark bars*) and after seven days (*light bars*) of intervention with 53 grams of animal protein as either skim milk or lean meat in 24 eight-year-old boys. In the milk group, IGF-I increased by 19%, from 209 to 249 ng/mL ($P = 0.001$), and insulin by 105%, from 22 to 45 pmol/L ($P = 0.007$). There were no significant increases in the meat group. Created from (92, 94).

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with the control group, which consumed no milk (81). In a six-month, randomized, placebo-controlled trial, 80 elderly patients with a recent osteoporotic hip fracture received either a 20 g/d protein supplement, composed of 90% milk protein, or an isocaloric placebo. A significant increase of circulating IGF-I was found in the milk group compared with the placebo group (191). However, in another study, supplementation with either four glasses of milk per day or a placebo did not change IGF-I concentrations in older women (203). In all three studies, the protein intake increased significantly in the intervention groups compared with other groups.

OBSERVATIONAL STUDIES WITH CHILDREN AND ADOLESCENTS Most of the observational studies of determinants of IGF-I concentrations have been conducted in middle-aged and elderly men, although some have included women and/or younger adults. Studies examining the association between diet and circulating IGF-I in children are more scarce. A recently published study from the United Kingdom using data on 521 children from the Avon Longitudinal Study of Parents and Children investigated associations between diet and IGF-I and IGFBP-3 levels in 7- to 8-year-old children. Complete information on dietary intake, IGF levels, and all confounding variables was available for all children (181). Both total and animal, but not vegetable, protein correlated strongly with both IGF-I and IGF-I/IGFBP-3. Despite positive associations between animal protein consumption and IGF-I, no associations with intakes of meat and other major sources of animal protein were found. However, in a previous analysis of the same cohort study (180), a positive association was found between intake of dairy products and IGF-I. Dairy products were the major source of protein in this population, accounting for almost one fourth of the total protein intake.

In a cross-sectional study of 90 healthy, 2.5-year-old Danish children, we examined the associations between protein intake, IGF-I concentrations, and height (95). The mean intake of milk was 385 mL/day and the mean intake of meat was 37 g/day. In multiple linear regressions with adjustment for sex and weight, IGF-I was positively associated with intakes of animal protein and milk (Figure 3*B*) but not with intakes of vegetable protein or meat. These data show that milk intake was positively associated with IGF-I concentrations in this group of well-nourished Danish children with a normal protein intake far above the physiological requirements. The effect was quite strong: An increase in milk intake from 200 to 600 mL/d corresponded to a 30% increase in circulating IGF-I. Although it is an observational study, it suggests that some milk compounds have a stimulating effect on IGF-I and thereby on growth.

In another observational study of 105 healthy ten-year-old Danish children, we found that the mean daily protein intake was 2.3 g/kg. In analyses controlling for sex, protein intake was positively associated with height but not with IGF-I (93). However, in the same study (93), the mean daily protein intake at nine months of age was 2.7 g/kg, and protein intake was positively associated with both length and IGF-I in analyses that controlled for sex. Additionally, positive associations (tracking) of length/height, IGF-I, and protein energy percentage in the diet were observed between infancy and late childhood. Furthermore, protein intake in infancy was positively associated with height in late childhood, suggesting that early protein intake—also above physiological requirements—may stimulate linear growth. In this study, there were no associations between milk intake and IGF-I at either nine months or ten years of age.

OBSERVATIONAL STUDIES WITH ADULTS Several observational studies have examined the association between milk intake and circulating IGF-I in adults. Some observational studies imply that milk may stimulate circulating concentrations of IGF-I, but other studies show conflicting results.

In more than 1000 women in the Nurses' Health Study, a positive association between protein intake and circulating IGF-I concentrations was found, and it was largely attributable to milk intake (91). Ma et al. (132) found that age- and smoking-adjusted concentrations of IGF-I, IGFBP-3, and the molar ratio of IGF-I/IGFBP-3 were higher in 40- to 84-year-old men in the highest tertile of milk intake (5–6 glasses/week to $\geq$2 glasses/day) than in the lowest tertile (never/rarely). There were no differences among tertiles of meat, poultry, or fish intake (132). Recently, Giovannucci et al. (71) found that in well-nourished elderly men, the major sources of animal protein, including milk, fish, and poultry, but not red meat, were associated with higher IGF-I concentrations.

Gunnell et al. (74) examined the association of diet with IGF-I and IGFBP-3 in 344 healthy middle-aged men. Milk intake was positively associated with raised levels of IGF-I but not IGFBP-3 or IGF-I/IGFBP-3. Men in the lowest tertile of milk intake ($<^1/_2$ pint/d) had significantly lower values of circulating IGF-I than did those in the middle ($^1/_2$–$^3/_4$ pint/d) and highest (1+ pint/d) tertiles ($P = 0.004$).

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There was a tendency toward a positive association between total dairy intake and circulating levels of IGF-I ($P = 0.09$) (74).

However, in a recently published study from Sweden, an association between intake of milk and circulating IGF-I was not found in 226 healthy middle-aged and elderly men (121). Limitations to this study are that neither IGFBP-3 nor free IGF-I were measured; therefore, the possible dietary influence of bioavailable IGF-I could not be determined. In addition, some observational studies have not found associations between total dairy intake and circulating IGF-I. In a study of British women who were 20 to 70 years of age, serum IGF-I concentrations were 13% lower in the vegan women compared with meat-eaters and vegetarians. There were no significant differences in IGFBP-3 concentrations among the diet groups (6). These data suggest that a plant-based diet without milk is associated with lower circulating levels of total IGF-I. However, there was no evidence to suggest that increasing dairy intake was associated with increasing IGF-I levels among the meat-eaters and vegetarians. Yet, the authors suggest that in this study there may have been insufficient heterogeneity in milk intake among the milk consumers to detect a significant association.

However, Kaklamani et al. (111), who examined the association of dietary intakes with plasma IGF-I and IGFBP-3 levels in 130 healthy Greek subjects between 30 and 84 years of age, found that IGF-I levels were positively associated with intake of red meat and not with the intake of milk and milk products. IGFBP-3 was not associated with any of the food groups examined.

Overall, although positive, negative, and no associations have been reported between the consumption of cow's milk and circulating levels of IGF-I in observational studies, it appears from intervention studies that increased intakes of cow's milk are able to increase the concentration of IGF-I in the circulation.

PROGRAMMING OF THE IGF AXIS An increasing number of studies suggest that the IGF axis can be programmed by early growth. It is possible that milk intake during early life also has a role in this programming. Birth weight, which is an indicator of intrauterine growth, is negatively associated with serum IGF-I levels in childhood. This was shown in a study examining serum IGF-I in two groups of prepubertal children from England and India (70). In this study, it was found that IGF-I levels were positively associated with current height. However, once current height was controlled for in the analyses, it was found that IGF-I was negatively associated with birth weight. Also, in a study of Swedish women, birth weight was inversely associated with IGF-I, when current weight was adjusted for (101). These results suggest that intrauterine undernutrition can reprogram the IGF-I axis.

This finding is in accordance with data from the Avon Longitudinal Study of Parents and Children study, in which weight gain from 0–2 years was positively associated with IGF-I levels at age 5 years. In other words, infants that showed catch-up growth from 0–2 years had higher IGF-I values in analyses controlling for current height (163). In a cohort study from South Wales, downward centile

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crossing at any time in childhood was negatively associated with IGF-I levels in adulthood in analyses that controlled for adult height (21).

Further evidence of the long-term effect of nutrition on the IGF axis comes from the Dutch Famine cohort that was exposed to extreme nutritional deprivation (57). In this small study of postmenopausal women, a linear trend showed that increased exposure to the famine in childhood was associated with higher IGF-I and IGFBP-3 concentrations. The authors speculated that extreme nutritional deprivation resulted in a resetting of homeostatic mechanisms such that there was a permanent overshoot after the famine had ended.

At least three studies have shown that breast-fed infants have lower levels of IGF-I than do formula-fed infants (36, 189, 199). This is in accordance with studies showing that breast-fed infants have a linear growth velocity that is slightly, but significantly, slower than formula-fed infants (48, 144). Despite this difference in IGF-I and growth between breast- and formula-fed infants, other studies have shown that breast-fed infants have both higher IGF-I levels during childhood (138) and are taller as adults (139, 218). Again, these results suggest that postnatal nutrition has a programming effect on the IGF-I axis and growth.

The potential effect of cow's milk in programming the IGF-I axis was shown in the Barry Caerphilly Growth Study (20), which was conducted in the United Kingdom during the 1970s. This intervention study included 951 pregnant mothers and their offspring who were randomized to either a supplement or a control group. The supplemented group was provided with milk tokens throughout pregnancy and subsequently until their children were five years old. The tokens entitled them to additional free milk delivery by the milkman. Measures of IGF-I, IGFBP-3, and the molar ratio of IGF-I to IGFBP-3 were taken in 663 of the offspring at the age of 25 years. Subjects in the intervention group had a significantly lower IGF-I and IGF-I/IGFBP-3 ratio than did the subjects in the control group. Thus, a high milk intake by the mother during pregnancy, combined with a higher milk intake during the first five years of life, resulted in a lower IGF-I concentration as an adult. Therefore, results from this study also suggest that there is a sensitive period during intrauterine or postnatal life when a high milk intake can program the IGF-I axis and result in lower values later in life. However, because this study included milk intake up to the age of 5 years, it is not known when the sensitive period or "window" is.

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Cow's Milk and Insulin

The effect of milk consumption on insulin response is not completely elucidated. In a study using regular or fermented milk products, a discrepancy between the glycemic index (GI) and insulinemic index (II) of these products was found. Despite the overall low GIs (GI = 15–30), high IIs were found (II = 90–98) for both milk and yogurt (165). From this study, it was concluded that the insulinotrophic effect was related to not only the carbohydrate component of milk, but also to some yet unidentified food component. In another study of postprandial glucose

and insulin responses, the addition of even an ordinary amount (200 mL) of milk increased the insulin response (+300%) to a low-GI meal to a level typically seen from a meal of very-high-GI white bread (127).

Furthermore, the hormonal response to a meal was compared in 43 breast-fed and 43 cow's milk formula-fed one-week-old term infants (131). In both breast-fed and bottle-fed infants, plasma-insulin had risen at 55 minutes postprandial. The insulin levels, however, were greater in the formula-fed group at 90 and 150 minutes postprandial.

The effect of milk consumption on insulin seems to influence not only postprandial levels, but also fasting values. In our one-week intervention study with healthy, eight-year-old boys, we gave 12 boys 1.5 liters of skim milk daily; another group of 12 boys were given the same amount of animal protein as lean meat (94). In the milk group, fasting insulin concentrations doubled (Figure 5*B*), whereas there was no increase in insulin in the meat group. This indicates that a short-term intake of a large quantity of milk, but not meat, increased insulin secretion. However, the long-term consequences of this effect, both for growth and glucose-insulin metabolism, are unknown.

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INSULIN-LIKE GROWTH FACTORS AND LINEAR GROWTH [C]

IGF-I Facilitates Skeletal Growth

IGF-I facilitates bone growth by increasing the uptake of amino acids, which are then integrated into new proteins in bone tissue (31). IGF-I is primarily produced in the liver, but it is also produced in osteoblasts. It is the most abundant growth factor in bone. It has a strong anabolic effect on growing bone tissue, as it stimulates the chondrocytes in the epiphyseal plate. IGF-I is also involved in calcium and phosphate metabolism (114). Circulating levels of IGF-I are correlated with bone mass in adults (81), which suggests that IGF-I may play an essential role in bone remodeling.

Circulating IGF-I During Growth

In infancy, IGF-I concentrations decrease from birth to age six months and then subsequently increase in late infancy (109). In childhood, IGF-I concentrations increase slowly (108) and exhibit a steep increase in puberty. Maximal levels of IGF-I are reached at 14.5 years in girls and 15.5 years in boys (108). This difference between the sexes is in accordance with the different timing of peak growth velocities in girls and boys (7). IGF-I concentrations are positively correlated with height velocity only in prepubertal children (108), since in pubertal children, IGF-I concentrations correlate more with pubertal maturation, with the highest concentrations seen in Tanner stage 3–4 in girls and Tanner stage 4 in boys (9). There is a positive association between IGF-I levels and height in children (95) and to

some degree in adults (21). Levels of circulating IGF-I are lower in children who experience growth faltering (21, 211), but, in contrast, children who are born small but then have a high growth velocity throughout childhood have particularly high levels of IGF-I (60).

Insulin as a Growth Factor

In relation to linear growth, insulin secretion may also be of interest. Insulin is a potent mitogen for many cell types in vitro. Abnormal insulin secretion or action, either before or after birth, is often associated with disordered growth, which suggests that insulin may also function as a growth factor in vivo (83). Maternal insulin levels during pregnancy are positively associated with intrauterine growth. Therefore, insulin is associated with the growth of the fetus and may play a role in the regulation of growth after birth (184). However, the importance of insulin as a growth factor during infancy and childhood is not yet understood. Increased height at diagnosis of type 1 diabetes has been frequently reported, and it has been suggested that this is caused by hyperinsulinemia prior to the diagnosis (56).

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MILK COMPONENTS THAT POTENTIALLY STIMULATE INSULIN-LIKE GROWTH FACTOR AND GROWTH [D]

Based on the data presented in this review, we find it likely that milk has a specific stimulating effect on linear growth. It is not known, however, which components in milk are responsible for such an effect. It is not likely to be the protein quantity. Potential candidates are bioactive peptides, amino acids, cow's milk IGF-I, or milk minerals, including calcium.

Bioactive Peptides

Approximately 80% of the protein in cow's milk is casein, and the remaining 20% is whey. Casein proteins clot in low-pH solutions. Hence, the acidity in the stomach makes casein aggregate into a gel, whereas whey remains soluble. In a study of the effect of lactose-equivalent dietary sources of protein on concentrations of postprandial insulin, the insulin response to a whey meal was more pronounced than that to a milk meal (157). This differential response suggests that soluble milk proteins have some insulinotrophic components. Furthermore, the addition of whey to meals containing rapidly digested and absorbed carbohydrates stimulated insulin release and reduced postprandial blood glucose excursion after a meal in type 2 diabetic subjects (67). Whether the fasting levels of insulin are also more stimulated by whey rather than by casein proteins is unknown. Both whey and casein contain specific proteins and peptides that may have growth-stimulating effects. Additionally, the degradation of milk proteins when they are exposed to the acid in the stomach results in many other peptides that also may have specific effects. Preliminary data from our group's new intervention study, in which

participants were randomized to whey or a casein drink [the same design as that of our previous study with eight-year-old boys (92, 94)], suggest that casein has a stronger IGF-I-stimulating effect than does whey (94a).

Amino Acids

A high milk intake results in high amino acid concentrations in the circulation. Although insulin secretion has been found to be responsive to a number of amino acids (65, 198), it has been suggested that the branched-chain amino acids (BCAAs; leucine, isoleucine, and valine), which are catabolized primarily in the skeletal muscle, have a particularly stimulating effect on insulin secretion (14, 157). In a study comparing infants who received breast milk or one of two formulas with protein contents of either 1.3 or 1.8 g/100 mL, the infants who received the high-protein formula had a significantly higher weight and length gain in comparison with the infants in the other two groups. A positive association between concentrations of C-peptide, which is synthesized in equivalent amounts as insulin, and weight gain was observed in all groups (14). However, in another study comparing infants who were breast-fed or formula-fed with a formula containing 1.6 g protein/100 mL, there were no differences between the groups in the concentration of the BCAAs or C-peptide in the fasting state. Ninety minutes postprandially, though, the formula-fed infants had concentrations of both the BCAAs and C-peptide that were significantly higher than those of the breast-fed infants (225). It was concluded from this finding that a high protein intake from formula resulted in an increased BCAA concentration and an increased secretion of insulin.

However, in our intervention study with eight-year-old boys receiving the same amount of animal protein as either milk or meat for one week, the doubling of the fasting insulin in the milk group compared with no effect in the meat group could not be explained by the BCAAs, since the concentration of the BCAAs increased similarly in both groups (94). Dietary proteins, including milk proteins, as environmental modifiers of type 1 diabetes mellitus are discussed by Lefebvre et al. (125a) in another chapter in this volume.

Cow's Milk IGF-I

Cow's milk contains IGF-I that is structurally identical to human IGF-I (43, 105) and has a concentration of approximately 30 ng/ml (166). Despite this, it is generally thought that IGF-I will not retain bioactivity when delivered orally because of rapid proteolysis in the upper gut (43, 105). This is supported by results from a study in piglets that showed orally administrated IGF-I was poorly absorbed (51). However, in a study on adult rats, it was shown that some IGF antibodies and dietary protein casein may protect the IGF-I from degradation in the gastrointestinal tract (231). A study of suckling rats (171) also showed that milk-borne IGF-I can be absorbed intact and may exert effects on the liver and other peripheral tissues. To our knowledge, no human data are available, but it is probable that the situation will be closer to that in piglets than to that in rats.

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Calcium and Other Minerals in Milk

The effect of milk on growth may be caused by calcium (119) or other minerals (71) such as zinc that are found in milk (158). Milk contains approximately 115 mg calcium/100 g and 93 mg phosphorus/100 g. There are many reasons to think that these nutrients are positively related to bone growth in terms of its density and linear proportions. This is logical since the inorganic bone matrix is composed of hydroxyapatite crystals, which are created from calcium phosphate and calcium hydroxide, and since vitamin D increases blood calcium, which then results in the deposition of calcium crystals in the bone.

Several calcium intervention studies have shown an effect on bone mass during intervention (28, 29, 50, 103, 124, 125, 160), but only one of the studies with nonmilk calcium salts has shown any lasting effect on bone mass two years after the intervention stopped (49). Wastney et al. (226) found no differences in IGF-I concentrations in adolescent girls after putting them on controlled diets with high (47 mmol/d) and low (21 mmol/d) intakes of calcium as calcium citrate malate in a crossover design. This finding suggests that the effect of calcium from milk on IGF-I may differ from the effect of other calcium supplements.

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COW'S MILK AND NONCOMMUNICABLE DISEASE RISK [E]

The consumption of milk has been linked to a number of noncommunicable diseases, including hormonal cancers of the breast, ovaries, and prostate. The results are equivocal because positive, negative, and no associations have been reported. Milk intake has also been shown to potentially protect against colorectal cancer (132, 155), osteoporosis, and the metabolic syndrome (15). There are many hypotheses as to why milk intake may be associated with an increased risk of cancer. It is possible that a high intake of milk reflects an overall high dietary fat intake, which in turn has been associated with a risk of certain cancers. It is also possible that milk products contain contaminants such as pesticides that are potentially carcinogenic, or that milk may contain growth factors, such as IGF-I, which have been shown to promote cancer cell growth. Very few studies have investigated the potential effect of fat-free milk, which is most relevant to the topic of this review as there are no indications that the effect of milk consumption on growth is caused by milk fat. Because saturated fatty acids comprise milk fat, a high intake of milk fat has been associated with an increased risk of cardiovascular disease (11), whereas whey may be protective against cardiovascular disease (64, 137).

Milk Intake and Cancer in Adults

Several case-control studies examining milk consumption by adults and the risk of developing breast cancer have not shown any associations (85, 113, 116, 178, 215). Other studies have shown a positive association (59, 123, 135, 229, 234);

inverse associations have also been reported (63, 86, 96, 176). Cohort studies, regarded as the epidemiological study design least prone to bias, have generally been more focused on the consumption of dietary fat and animal products than on milk consumption per se. Overall, these studies have not shown an association between milk consumption and breast cancer (147, 148, 214, 216).

One exception was a Norwegian study that identified a positive association between whole milk consumption and the incidence of breast cancer (69). Knekt et al. (115) have thoroughly examined dairy product consumption and breast cancer incidence in a Finnish cohort. In a population with a generally high level of milk consumption, they found that greater milk consumption was associated with a reduced incidence rate of breast cancer. In this study, women in the highest tertile of milk consumption had a 50% reduced incidence rate compared with women in the lowest tertile. A recently published review on the consumption of dairy products and breast cancer concluded that the available epidemiologic evidence does not support a strong association between the consumption of milk or other dairy products and the risk of having breast cancer (151).

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Milk Intake in Childhood and Adolescence and Subsequent Cancer

Few studies have examined the relationship between childhood or adolescent milk consumption and subsequent cancer. Of those that have, most show an inverse association between early milk intake and later breast cancer risk. Results from a case-control study with 852 women with breast cancer and 1569 controls free of breast cancer selected from participants in the Nurses' Health Study I and II suggested that there was a possible negative association between diet before puberty and the subsequent risk of breast cancer, since consumption of whole milk at ages 3–5 years was associated with a decreased risk of breast cancer (145).

In a population-based cohort study of 48,844 premenopausal women in Norway, participants were asked to recall their milk consumption during childhood. They were then followed prospectively. Milk consumption as a child was negatively associated with subsequent breast cancer among the youngest (34–39 years) but not among the older (40–49 years) women (88). In a case-control study conducted in Canada, the association between childhood and adult eating practices and the risk of breast cancer was examined in 846 cases and 862 controls. A reduced breast cancer risk was associated with self-reported frequent consumption of whole milk before the age of 13 years (87). In a population-based case-control study with 172 cases and 190 controls between the ages 20 and 54 years in Utah, fat intake from dairy products in adolescence was associated with a lower risk of breast cancer (176). However, consumption of dairy products during adolescence had no apparent influence on breast cancer risk in a case-control study with 1647 cases and 1501 controls from three geographical regions in the United States (174).

Milk Intake and Metabolic Syndrome

Consumption of milk and dairy products has also been suggested to have a protective effect on other noncommunicable diseases, such as the metabolic syndrome. This syndrome consists of an unfavorable lipoprotein profile, hypertension, and abnormal glucose homeostasis or insulin resistance. Some studies have found a protective effect of milk consumption on some or all of these factors (15, 141, 169). A recently published study showed prospectively that dairy consumption lowered the incidence rate of type 2 diabetes mellitus (T2DM) in men (39). The effect was primarily limited to low-fat dairy foods, with each additional serving consumed daily lowering the relative risk by 9%. Even though some studies indicate that milk and dairy products may have a beneficial effect on fat mass and fat distribution in children (159) and adults (149), other studies do not find these associations (76, 118). One study even found that an increased intake of skim milk was associated with increased weight gain in 9- to 14-year-old children (23).

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LINEAR GROWTH AND NONCOMMUNICABLE DISEASE RISK [F]

A better understanding of the factors responsible for the secular trend in increasing adult height may help us understand why adult height is strongly associated with the risk of having several noncommunicable diseases. Height is negatively associated with ischemic heart disease, stroke, and colorectal cancer, but positively associated with breast cancer, prostate cancer, and osteoporosis.

Infants exposed to a period of nutritional insufficiency followed by a period of sufficient nutrition will show a compensatory increase in growth. Although such growth is beneficial in the short term, it may have a profound adverse affect on the subsequent long-term life history of an organism (143). The possible long-term cost of accelerated growth in humans, although an issue of potentially major biological and public health importance, has not been fully explored. Therefore, it is possible that increases in linear growth are likely to have both positive and negative effects.

A high growth velocity has traditionally been regarded as beneficial and associated with good health (209), whereas a reduced growth velocity has been associated with adverse health and development outcomes (18). Many studies have found that higher adult stature is associated with better health (193), a lower overall mortality (17, 104, 168, 220), and reduced risk of having certain noncommunicable diseases, such as coronary heart disease (104, 168).

Conversely, other studies have found that tallness in both childhood (75, 162) and adulthood (162, 196) is related to a higher risk of having cancer. A high growth velocity during certain periods of infancy and childhood may result in an increased risk of noncommunicable diseases such as cancer of the breast, ovary, and prostate (146, 162), hypertension (186), coronary heart disease (61), and insulin resistance (194). The relationship between growth velocity and the risk of disease later in life

is not simple: Eriksson et al. (58) found that low growth velocity during infancy was associated with an increased risk of coronary heart disease, whereas after the age of one year, a high growth velocity was associated with a further increase in risk.

Furthermore, an increased height gain in childhood leads to earlier pubertal maturity and thereby a reduction in height in adolescence (80). Age at menarche seems to be related to the consumption of milk (228) and animal protein (22). Thus, the association between milk and height among females may be mediated by the timing of menarche. The interactions among milk intake, age at menarche, and growth in adolescence require further study.

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INSULIN-LIKE GROWTH FACTORS AND NONCOMMUNICABLE DISEASE RISK [G]

IGF-I

Numerous epidemiological and intervention studies have found associations between circulating IGF-I and some noncommunicable diseases, including cancer (173, 195). These include several studies quoted in a systematic review and meta-regression analysis of the published literature until 2002 (177) and a recently published review of epidemiologic evidence for an association between circulating IGF-I and cancer risk (219).

In adults, low concentrations of IGF-I may be associated with increased rates of cardiovascular disease (110), whereas high concentrations of IGF-I are associated with an increased risk of prostate, breast, and colorectal cancer (34, 72, 77, 133). In some of these studies, the association between cancer risk and IGF-I concentrations was strengthened if the analyses were adjusted for IGFBP-3 concentrations (72, 133), suggesting that the effect is caused by the level of free IGF-I. Patients with high IGF-I and low IGFBP-3 concentrations have the greatest cancer risk (90). Evidence from case-control studies suggests that the IGF-I/IGFBP-3 ratio may also be related to the risk of childhood leukemia (170) and lung cancer (233). Another explanation is that IGFBP-3 may have an independent effect through its receptor (133).

IGF-I AND OBESITY Levels of IGF-I may also be associated with obesity. Although there are data indicating that IGF-I stimulates the differentiation of other cells, there is little information about the effects on the differentiation of adipocytes. In a review by Ailhaud et al. (2), it is stated that IGF-I is required for the terminal differentiation of preadipocytes into adipocytes. Additionally, the capacity of children's serum to stimulate differentiation of preadipocytes into adipocytes is correlated with the concentrations of IGF-I and IGFBP-3 (78, 223). Since the concentration of IGF-I in serum can be influenced by dietary changes, it is possible that IGF-I is one of the factors involved in the interaction between nutritional intake and fat

cell formation (221, 223). This idea is supported by some observations of high IGF-I concentrations in obese children (62, 187, 222) and by the observation that an increased IGF-I concentration is reversible upon weight reduction (222). However, others have reported that obese children have normal concentrations of IGF-I (10). In physiological concentrations, IGF-I suppresses the secretion of growth hormone (154), which also may contribute to the development of obesity because growth hormone is related to lean body mass. The regulation and effects of IGF-I may differ between children and adults since IGF-I is typically decreased in obese adults (68).

Insulin

It is unknown whether a high level of fasting insulin in healthy, normal-weight children with high velocities of growth is negative or positive. In adults, a high level of fasting insulin is a marker of insulin resistance and for the early development of T2DM. Because insulin also is a growth factor, its actions are more complex in growing children. Therefore, a high level of fasting insulin might thus be an indicator of high velocity of linear growth. It is similarly unknown whether our finding of a stimulating effect of a high intake of milk for one week on fasting insulin (94) is a transitional phenomenon or whether the same is valid over a longer period with a high intake of milk.

Although studies consistently have shown that insulin resistance is associated with an increased risk of the development of T2DM and cardiovascular disease in adults, it remains unknown whether insulin resistance per se or the concomitant hyperinsulinemia represent the primary abnormality. Thus, experimental induced hyperinsulinemia causes insulin resistance in humans and animals, and the widespread belief that hyperinsulinemia represents an attempt of the pancreatic beta cell to compensate for insulin resistance has therefore been challenged. Linking our finding of increased fasting plasma insulin levels after milk intake compared with meat intake in eight-year-old children with the recent observation that a high level of dairy consumption is associated with a 9% decreased risk of developing T2DM in men (39), it may be speculated whether the hyperinsulinemia induced by milk intake in children can provide a way to understand the protective effect of milk on the development of T2DM.

CONCLUSIONS AND IMPLICATIONS

There is considerable evidence that cow's milk stimulates linear growth. As the biological purpose of milk is to support the newborn during a period of high growth velocity, it is plausible that milk consumption can stimulate IGFs and linear growth. Evidence that the intake of cow's milk has a special growth-stimulating effect comes from many types of studies conducted around the world. Primarily, however, the evidence comes from studies conducted in developing countries,

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where several intervention studies have shown an effect of cow's milk on linear growth. Nonetheless, positive associations between the consumption of cow's milk and linear growth have also been identified in observational studies conducted in industrialized countries. We find that the overall evidence is convincing even if many of the studies have important limitations. In the many observational studies, it remains possible that milk consumption is a marker of socioeconomic status and that factors other than milk are causing the increases in linear growth. Furthermore, many of the studies have considerable methodological limitations because a number of studies conducted prior to 1950 were not analyzed using accepted modern methods of statistical evaluation.

There is convincing evidence that milk intake is positively associated with serum IGF-I levels and that at least part of the stimulating effect of milk occurs through a stimulation of the IGFs. It is probable that the growth-stimulating effect occurs in both undernourished and in well-nourished populations where profound nutritional deficiencies are unlikely. Therefore, the traditional concept that growth is optimal if adequate amounts of all nutrients are available may be too simplistic. A hormonal modulation of growth velocity is likely to be responsible for at least some of the growth-promoting effects of milk. The active components in milk may be bioactive peptides, peptides formed in the gastrointestinal tract from the degradation of milk proteins, a combination of certain amino acids, or a combination of proteins and minerals.

Stunting is widespread in developing countries and is associated with increased morbidity and impaired development. One third of children under five years in developing countries are stunted. Adding cow's milk or milk powder to the diet of stunted children is likely to be an effective and relatively inexpensive way of improving linear growth and thus reducing morbidity and improving development. In some populations, however, the incidence of lactase insufficiency is high, which may cause problems if milk and milk products are consumed.

In industrialized countries with well-nourished children, the long-term consequences of an increased linear growth velocity during childhood are likely to be both positive and negative. High levels of circulating IGF-I are associated with a higher risk of developing certain noncommunicable diseases, such as hormonal cancers, but also with a decreased risk of developing cardiovascular disease. Many studies of the association between milk consumption and noncommunicable diseases show positive effects, whereas some also show negative effects. A detailed analysis of the effects of milk on health, which should also be able to distinguish the effect of milk fat, is beyond the scope of this review. Most studies examining the association between milk intake and noncommunicable diseases have focused on milk intake during adulthood. The effect of milk intake during childhood on later health has rarely been examined. Based on the emerging data suggesting that growth and diet during early life can program the IGF axis, the association between milk intake during childhood and later IGF-I levels appears to be quite complex.

Understanding the mechanisms by which milk consumption influences linear growth is important and could improve our understanding of how to prevent and

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treat stunting. If we understand which milk components are responsible for stimulating growth, we may be able to optimize formula feeding of infants, tube feeding, and therapeutic feeding of malnourished children.

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NOTICE:

In the course of preparing this review, the authors consulted Andrea S. Wiley's article "Does Milk Make Children Grow? Relationships Between Milk Consumption and Height in NHANES 1999-2002" [*American Journal of Human Biology*, 17:425–41 (2005)]. While we then cited Dr. Wiley's article in our review, we also unintentionally merged into our text a considerable number of phrases and sentences from Dr. Wiley's paper, without proper attribution. We deeply regret this serious error and apologize to Dr. Wiley.

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