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Pediatric Nutrition

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Pediatric Nutrition

Volume Editors

R. Reifen, Rehovot
A. Lerner, Haifa
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Contents

VII **Preface**

1 **Recommended Dietary Allowances: Changing Concepts**
Udall, J.N., Jr.: Suskind R.M. (New Orleans, La.)

12 **Muscle Function and Malnutrition**
Thomson, A.: Jeejeebhoy, K.N. (Toronto)

22 **New Fuels for Enteral and Parenteral Nutrition**
Friel, C.M.; Babineau, T.J.; Blackburn, G.L. (Boston, Mass.)

40 **Hyperlipidemia in Childhood**
Kaluski, D.N. (Jerusalem); Kaluski, E. (Zrifin); Deckelbaum, R.J. (New York, N.Y.)

50 **Food Protein Hypersensitivity: Management and Strategies**
Freier, S.; Branski, D. (Jerusalem); Walker-Smith, J.A. (London)

64 **Carbohydrates in Infant Nutrition**
Reif, S. (Tel-Aviv); Lebenthal, E. (Jerusalem)

80 **Nucleotides in Infant Nutrition: Effects on Immune Function**
Kuchan, M.; Winship, T.; Masor, M. (Columbus, Ohio)

95 **Dietary Fiber in Childhood**
Stark, A.H.; Madar, Z. (Rehovot)

110 **Osteoporosis: An Emerging Problem in Pediatrics**
Ish-Shalom, S.: Rozen, G.S.; Lerner, A. (Haifa)

122 **Vitamin A in Pediatric Nutrition**
Reifen, R. (Rehovot); Wasantwisut, E. (Bangkok)

136 Nutritional Management of the Immunocompromised Pediatric Patient
Heyman, M.B.; So, A.L. (San Francisco, Calif.)

154 Metabolic and Nutritional Support of the Critically Ill Child
Kallas, H.J.; Dimand, R. (Sacramento, Calif.)

182 Nutritional Management of Cystic Fibrosis
Wilschanski, M. (Jerusalem); Pencharz, P.B.; Durie, P.R. (Toronto)

210 Nutrition in Pediatric Inflammatory Bowel Disease
Simpser, E.; Daum, F. (New York, N.Y.); Dinari, G. (Tel-Aviv)

227 Short Bowel Syndrome
Jeejeebhoy, K.N. (Toronto)

240 Is Obesity an Imbalance in Energy Expenditure and Energy Intake? Is Leptin the Answer?
Figueroa-Colon, R. (Birmingham, Ala.)

254 Author Index

255 Subject Index

Preface

Nutrition can be considered one of the most important factors influencing physiological processes in health and disease. In the past decades it has become clear that nutrition in early life can influence health outcome. Studies showing a relation between intrauterine and early postnatal undernutrition and the development of cardiovascular disease, diabetes mellitus and hypertension during adulthood are still the center of scientific interest. Epidemiological studies also focus on the influence of nutritional habits during childhood and adolescence on the development of health problems later in life including abnormalities in fat and bone metabolism (Ish-Shalom et al.) and the gastrointestinal tract.

In the meantime our knowledge on nutritional requirements and the role of different nutrients in growth and development has rapidly been increasing. New research tools, like stable isotope studies, have made it possible to investigate in vivo normal metabolic processes and the consequences of congenital and acquired disorders on these processes in different age groups. These new insights are of paramount importance especially in infancy and childhood, when most of the requirements for energy and essential nutrients are necessary for growth. Based on recent scientific data formulae are developed for oral and enteral use, in which the composition of macro- and micronutrients are fine-tuned for nutritional intervention in a range of inherited and acquired disorders. Undoubtedly scientific work in the near future will keep changing our opinions.

In this book, new insights into the clinical and therapeutic potential of the interaction between immunological dysfunction and wasting and malnutrition is described (Heyman et al.). The nutritional problems arising in specific diseases like cystic fibrosis (Wilshanski et al.), inflammatory bowel disease (Simpser et al.) and short bowel syndrome (Jeejeebhoy) are discussed. A broad updated comprehensive review of the new fuels to the gut (Frie et al.) and the

possible role of nucleotides in infant formulae are presented (Kuchan et al.), as well as the attitude towards hyperlipidemia (Kaluski et al.) and osteoporosis. Nutritional support of the critically ill patient (Kallas and Dimand) and the nutritional aspects of obesity including the possible role leptin plays in the scene (Figueroa-Colon) are also discussed.

This book, written by the leading experts in nutrition, provides an update on different nutritional issues, important for today and tomorrow, based on the best evidence available now and directed towards practical and clinical application into the second millennium.

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Recommended Dietary Allowances: Changing Concepts

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Introduction

Recommended dietary allowances (RDAs) have been prepared by the Food and Nutrition Board since 1941 to provide 'standards to serve as a goal for good nutrition' [1]. In principle, the RDAs are based on studies of controlled diets, nutrient balance data, biochemical measurements, intake data of breast-fed infants, epidemiological studies and in some instances animal experimentation (table 1). Because of the wide use of the RDAs, it is important to understand their appropriate applications and limitations. Three points are of particular importance [1].

(1) The recommended allowances for nutrients are the amounts intended to be consumed as part of a normal diet. If the RDAs are met through diets composed of a variety of foods derived from diverse food groups rather than by supplementation or fortification, such diets will likely be adequate in all other nutrients for which RDAs are not currently established.

(2) RDAs are neither minimal requirements nor necessarily optimal levels of intake. Rather, the RDAs are safe and adequate levels, reflecting the state of knowledge concerning a nutrient, its bioavailability and variations among the US population.

(3) Although the RDAs are most appropriately applied to groups, a comparison of individual intakes averaged over a sufficient length of time allows an estimate to be made concerning the probable risk of deficiency for a given individual.

In this article the currently recommended nutrients, limitations of the RDAs and concepts which may be considered as the RDAs are refined and updated, and each will be discussed.

Table 1. Types of evidence on which the RDA is based

1	Studies of subjects maintained on diets containing low or deficient levels of a nutrient followed by correction of the deficit with measured amounts of the nutrient
2	Nutrient balance studies that measure nutrient status in relation to intake
3	Biochemical measurements of tissue saturation or adequacy of molecular function in relation to nutrient intake
4	Nutrient intakes from the food supply of fully breast-fed infants and of apparently healthy people
5	Epidemiological observations of nutrient status in populations in relation to intake
6	Extrapolation of data from animal experiments

Modified from the Food and Nutrition Board [1; p 1] with permission.

Recommended Nutrients

The level of intake of nutrients in food is set on the basis of scientific knowledge as judged by the Food and Nutrition Board with the assumption that the level is adequate to meet the nutrient needs of practically all healthy persons. RDAs are set for energy, carbohydrates, lipids, protein, fat- and water-soluble vitamins, and selected minerals and trace elements.

There are over 100 known elements. Of these, as noted in table 2, eleven elements, termed the major elements, account for 99.7% of the body weight of humans [2]. The remainder of the body weight is accounted for by approximately 25 trace elements, each of which contributes less than 0.01% to the body weight. Of these trace minerals, a mammalian nutrition requirement has been established for iron, iodine, zinc, copper, chromium, selenium, molybdenum, manganese, cobalt, nickel, vanadium, silicon, arsenic, boron and fluoride [2]. Unconfirmed reports suggest that lead, cadmium and tin may also be required in trace quantities, and it is quite possible that a nutritional requirement for additional trace elements will be elucidated in the future. While it is reasonable to assume that the trace elements required by humans are similar to those required by other mammalian species, human nutritional requirements are accepted only for iron, iodine, zinc, copper, chromium, selenium, molybdenum, manganese, and cobalt as vitamin B_{12}. Because of its beneficial effects in the prevention of dental caries, fluoride is also included in this list [2].

Infants are at an increased nutritional risk because the requirement for protein, calories and most nutrients, when expressed per kilogram body weight per day, is increased early in life. The protein intake for infants should be 2.2 g/kg body weight/day and for adults 0.8 g/kg body weight/day (table 3).

Table 2. Elements with a role in human physiology

Major elements	Trace elements	
	recognized	probable
Carbon (C)	Iron (Fe)	Nickel (Ni)
Hydrogen (H)	Iodine (I)	Vanadium (V)
Nitrogen (N)	Zinc (Zn)	Silicon (Si)
Oxygen (O)	Copper (Cu)	Arsenic (As)
Sodium (Na)	Chromium (Cr)	Boron (B)
Potassium (K)	Selenium (Se)	
Phosphorus (P)	Molybdenum (Mo)	
Sulfur (S)	Manganese (Mn)	
Chloride (Cl^2)	Cobalt (Co)	
Calcium (Ca)	Fluoride (F)	
Magnesium (Mg)		

Modified from Krebs and Hambridge [2; table 7-1, p 91] with permission.

Table 3. RDAs for protein and energy

	Age years	Weight kg	Height cm	Protein g/kg body weight	Energy kcal
Infants	0–0.5	6	60	2.2	kg × 115
	0.5–1	9	71	2.0	kg × 105
Children	1–3	13	90	1.8	kg × 100
	4–6	20	112	1.5	kg × 85
	7–10	20	132	1.2	kg × 85
Boys	11–14	45	157	1.0	kg × 60
	15–18	66	176	0.9	kg × 45
Girls	11–14	46	157	1.0	kg × 50
	15–18	55	163	0.8	kg × 40
Adult male	23–50	70	178	0.8	kg × 33–44
Adult female	23–50	55	153	0.8	kg × 29–44

Modified from the Food and Nutrition Board [1; table 3.5, p 33, and summary table, p 285] with permission.

Table 4. RDAs for fat-soluble vitamins (per kg body weight/day)

	Age years	A μg RE	D μg	E mg α-TE	K μg
Infants	0–0.5	62.5	1.25	0.50	0.83
	0.5–1	42.0	1.11	0.44	1.11
Children	1–3	31.0	0.77	0.46	1.15
	4–6	25.0	0.50	0.35	1.00
	7–10	25.0	0.36	0.25	1.07
Boys	11–14	22.0	0.22	0.22	1.00
	15–18	15.0	0.15	0.15	0.98
Girls	11–14	17.5	0.22	0.17	0.98
	15–18	14.5	0.18	0.15	1.00
Adult male	23–50	12.5	0.06	0.13	1.01
Adult female	23–50	12.5	0.08	0.13	1.03

Modified from the Food and Nutrition Board [1; summary table, p 285] with permission.

Not only is the quantity of protein required for health important, but also the quality of the protein ingested. Using nitrogen balance and growth as criteria, and most recently with the aid of studies of blood amino acid levels, the requirements of essential amino acids for children and adults have been estimated. Such estimates show wide variations among individuals and between laboratories, but on careful analysis of published data, it is possible to arrive at values that are reasonably concordant and certainly relevant to utilization of dietary proteins of varying amino acid composition [3]. Estimates of the needs for essential amino acids suggest that additional quantities of essential amino acids are required during infancy compared to later in development [4].

Energy requirements for infants are 115 kcal/kg/day, whereas for adults they are 29–44 kcal/kg/day (table 3). Once protein needs are met, energy requirements should be provided by carbohydrates and lipids. Young infants should receive 3% of their caloric intake in the form of essential fatty acids [5]. Infants and especially premature infants are at an increased risk for essential fatty acid deficiency if essential fatty acid requirements are not met. Studies performed 20 years ago have shown that premature infants receiving intravenous nutrients and no essential fatty acids are prone to develop biochemical evidence of essential fatty acid deficiency within 2 weeks of birth [6]. As noted in tables 4 and 5, the requirements for fat-soluble and water-soluble vitamins

Table 5. RDAs for water-soluble vitamins (per kg body weight/day)

	Age years	Thiamin mg	Riboflavin mg	Niacin mg NE[a]	B_6 mg	Folate µg	B_{12} µg	C mg
Infants	0–0.5	0.05	0.07	0.83	0.05	4.17	0.05	5.00
	0.5–1	0.04	0.06	0.67	0.07	3.89	0.06	3.89
Children	1–3	0.05	0.06	0.69	0.08	3.85	0.05	3.08
	4–6	0.05	0.06	0.60	0.06	3.75	0.05	2.25
	7–10	0.04	0.04	0.46	0.05	3.57	0.03	1.61
Boys	11–14	0.03	0.03	0.38	0.04	3.33	0.04	1.11
	15–18	0.02	0.03	0.36	0.03	3.03	0.03	0.91
Girls	11–14	0.02	0.03	0.33	0.03	3.26	0.04	1.09
	15–18	0.02	0.02	0.27	0.03	3.27	0.04	1.09
Adult male	23–50	0.02	0.02	0.24	0.30	2.53	0.03	0.76
Adult female	23–50	0.02	0.02	0.24	0.30	2.85	0.03	0.95

Modified from the Food and Nutrition Board [1; summary, table, p 285] with permission.
[a] 1 NE (niacin equivalent) is equal to 1 mg niacin or 60 mg dietary tryptophan.

when expressed per kilogram body weight per day are also increased for infants and children compared to adults. This is also true for selected minerals (table 6).

There are conditions that may require an adjustment in the application of the RDAs, such as climate, strenuous physical activity, metabolic dysfunction, chronic disease, injury, prematurity and drug therapy [1].

Limitations of RDAs

Hegsted [7] has noted that standards are often inappropriately used, and that many people assume that the RDAs and similar standards are nutrient requirements, the minimal amount of a nutrient required to maintain health. The RDA committee states specifically that the 'RDA should not be confused with requirements' [1]. People are different and there is a range of requirements to accommodate these differences. The extent of this variation is not known, but it is clear that 50% of the population requires more than the average intake of a given nutrient and 50% requires less than the average. Thus, the 'recommended intake' must be established above the average requirement and be adequate for all or nearly all of the group. However, this may not be

Table 6. RDAs for selected minerals (per kg body weight/day)

	Age years	Ca mg	P mg	Mg mg	Fe mg	Zn mg	I μg	Se μg
Infants	0–0.5	67	50	6.7	1.00	0.83	6.7	1.67
	0.5–1	67	56	6.7	1.10	1.10	5.56	1.67
Children	1–3	62	62	6.2	0.77	0.77	5.38	1.54
	4–6	40	40	6.0	0.50	0.50	4.50	1.00
	7–10	29	29	6.1	0.36	0.36	4.29	1.07
Boys	11–14	27	27	6.0	0.27	0.33	3.33	0.89
	15–18	18	18	6.1	0.18	0.28	2.27	0.76
Girls	11–14	26	26	6.1	0.33	0.26	3.26	0.98
	15–18	22	22	5.5	0.27	0.22	2.73	0.91
Adult male	23–50	10	10	4.3	0.13	0.20	1.90	0.89
Adult female	23–50	13	13	4.4	0.24	0.19	2.38	0.87

Modified from the Food and Nutrition Board [1; summary table, p 285] with permission.

nutritionally advantageous for all individuals. For example, an individual who requires a level of energy intake at the 10th percentile but ingests at a level of the 90th percentile is destined to be obese.

How should optimal intake be defined? Should this level of intake lead to 'optimal health' and freedom from disease or 'optimal function'? If so how are 'optimal health' and 'optimal function' determined? Does the concept of optimal health take into account individual variation related to gender, age and the many aspects of genetic endowment? Furthermore, what may be optimal intake for one individual is not necessarily the optimal intake for another. These questions remain unanswered.

Other shortcomings of the RDAs are the uncertainties in our knowledge base. It is not possible to set RDAs for all nutrients. For instance, as mentioned earlier, lead, cadmium and tin may be required. There are no recommendations for these trace minerals. In addition, appropriate dietary amounts of fiber have not been included in the current RDAs. Fiber has important health benefits for children and adults. It has been recommended by others that children over 2 years of age should have an intake of dietary fiber equal to their 'age plus five'. Thus, fiber intake would increase from 8 g/day at age 3, to 25 g/day by age 20 [8].

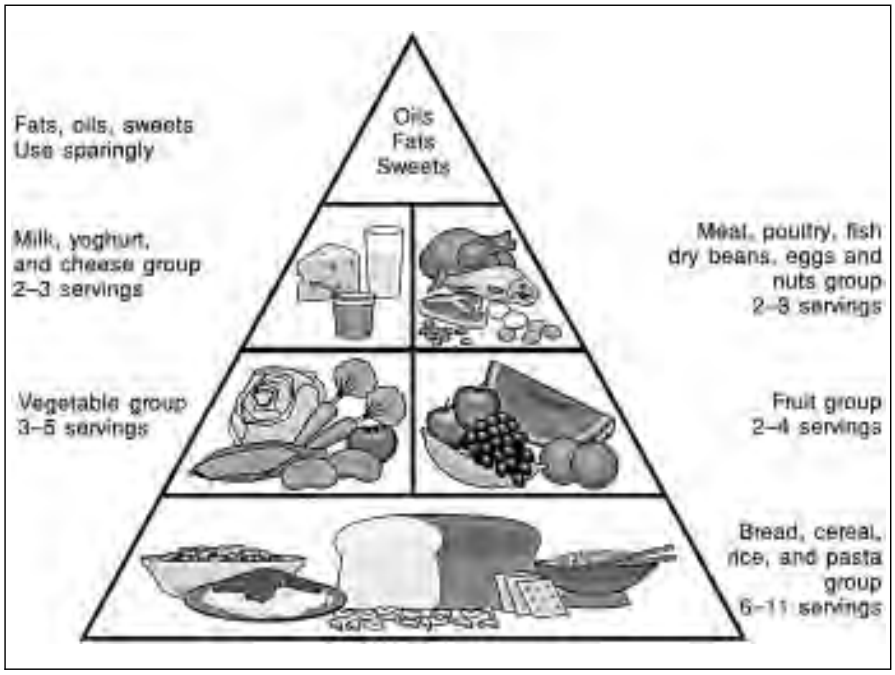

Fig. 1. Food guide pyramid: a guide to daily food choices. From the US Department of Agriculture and the US Department of Health and Human Services with permission.

Changing Concepts

Despite progress in the field of dietary recommendations, the following issues still need to be addressed or verified. Do the recommendations that today are almost universally accepted actually prevent disease? Are the recommendations for one nutrient compatible with the recommendations for other nutrients? Is it necessary to adhere to all dietary recommendations or just some of them, in that following some recommendations usually involves following others? Should nutrient allowances be consolidated with dietary guidelines for health and disease prevention? These questions should be answered.

A food guide pyramid developed by the US Department of Agriculture has been proposed to help older children and adults in the US follow dietary guidelines (fig. 1). Unlike earlier food guides, the new food guide specifies foods for a total diet; that is, it addresses both concerns about adequacy and moderation. The food guide recommends increased intakes of the vegetable, fruit, and grain groups with special emphasis on dark-green leafy vegetables,

Table 7. Nutritional goals set by the WHO

Macronutrients	Limits, %	
	lower	upper
Total fat	15	30
Saturated fat	0	10
Polyunsaturated fat	3	7
Total carbohydrate	55	75
Complex carbohydrate	50	70
Protein	10	15

Modified from the WHO [21; table 14, p 116] with permission.

legumes, and whole-grain products. These foods are important sources of several vitamins and minerals, complex carbohydrates, and dietary fiber, and they are generally low in fat. Analyses of expected nutrient levels provided by the food guide diet patterns indicate that the nutrient contribution of whole-grain products is particularly important for diets at lower calorie levels. In these diets, it is recommended that at least half the number of servings in the grain group be supplied by whole-grain products. In all diets, it is recommended that several servings of whole-grain products be included each day. The pyramid graphic has been especially helpful in emphasizing to the public the importance of increased consumption of vegetables, fruits and grain products for a healthful diet [9].

Some investigators have studied the impact of adherence to dietary recommendations and subsequent rates of total mortality and mortality from specific causes. Farchi et al. [10] studied diet and the prospective risk factors related to cancer and cardiovascular disease in two rural Italian cohorts. A dietary survey was first performed in these two cohorts in 1965. It involved 1,538 men aged 45–65 years. A 20-year follow-up evaluation was conducted on every participant. The investigators noted that conformity with the WHO recommended level of intakes for carbohydrates, lipid and protein (table 7) was associated with a lower relative risk for total mortality (0.84) and cancer mortality (0.73), but an increased risk for coronary heart disease mortality (1.34; 1.0 being the usual risk). The investigators found that diet-associated differences in mortality persisted after adjustment for confounding by age, smoking habit and physical activity. They concluded that when recommended levels of intake of macronutrients are ingested there is an associated lower total mortality. However, the decreased risk is

not equally appropriate for specific causes of death, such as cancer and coronary heart disease [10].

Restriction of caloric intake increases longevity, slows the rate of functional decline, and reduces the incidence of age-related disease in a variety of species [11–13]. The mechanism of action of caloric restriction remains unknown; however, cellular functions may be altered in such a way that destructive byproducts of metabolism are reduced and defense or repair systems are enhanced by this nutritional manipulation. It has also been suggested that the anti-aging effects of caloric restriction are believed to relate, at least in part, to changes in energy metabolism. Lane et al. [14] noted that many studies of caloric restriction in rodents and lower animals indicate that caloric restriction retarded the aging processes, as evidenced by increased longevity, reduced pathology and maintained physiological function in a more youthful state. The investigators found that core (rectal) body temperature decreased progressively with age from 2 to 30 years in rhesus monkeys fed ad libitum and was reduced by approximately 0.5 ºC in age-matched monkeys subjected to 6 years of a 30% reduction in caloric intake. A short-term (1 month) 30% caloric restriction of 2.5-year-old monkeys lowered subcutaneous body temperature by 1 ºC. Indirect calorimetry showed that 24-hour energy expenditure was reduced by approximately 24% during the short-term caloric restriction. The temporal association between reduced body temperature and energy expenditure suggested to the authors that reductions in body temperature caused an energy conservation mechanism during caloric restriction. These results are consistent with findings in rodent studies in which the aging rate was retarded by caloric restriction. The authors concluded 'that restriction of caloric intake may exert beneficial effects in primates analogous to those observed in rodents' [14].

In another study, Trichopoulou et al. [15] assessed the influence of a specific dietary pattern on overall survival in 182 elderly residents living in three Greek villages. Data were collected as part of an international cross-cultural study of food habits in later life. The diet was assessed with a validated semi-quantitative questionnaire on food intake. A 1-unit increase in diet score, devised a priori on the basis of eight component characteristics of the traditional common diet in the Mediterranean region, was associated with a significant 17% reduction in overall mortality (95% confidence interval 1–31%). The authors suggested that a diet meeting currently understood health criteria does predict survival among elderly people [15].

Recently, a fascinating study of diet and health was conducted with 4 adult males and 4 adult females who were locked in a 3.15-acre biosphere space containing an ecosystem that was energetically open (sunlight, electric power, and heat) but materially closed, with air, water, and organic material being recycled [16]. The 8 subjects were sealed inside, living on food crops

grown within. Their diet, low in calories (average 1,780 kcal/day), low in fat (10% of calories), and nutrient-dense, conforms to that which in numerous animal experiments has promoted health, retarded aging, and extended maximum life span. The nutritional scientist among the group reported medical data on the 8 subjects, comparing data obtained prior to the subjects being enclosed in the biosphere with data 6 months after closure. Significant changes included: (i) weight from 74 to 62 kg (men) and from 61 to 54 kg (women); (ii) mean systolic/diastolic blood pressure from 109/74 to 89/58 mm Hg; (iii) total serum cholesterol, from 191 ± 11 to 123 ± 9 mg/dl (mean $\pm$ SD; 36% mean reduction), and high density lipoprotein cholesterol from 62 ± 8 to 38 ± 5 mg/dl (risk ratio unchanged); (iv) triglyceride from 139 to 96 mg/dl (men) and from 78 to 114 mg/dl (women); (v) fasting glucose from 92 to 74 mg/dl, and (vi) leukocyte count from 6.7 to 4.7×10^9 cells/l. The authors conclude that drastic reductions in cholesterol and blood pressure may be instituted in normal individuals in Western countries by application of a carefully chosen diet and that a low-calorie nutrient-dense regime shows physiologic features in humans similar to those in other animal species [16].

Finally, Finch and Pike [17] used the Gompertz mortality rate model and estimated that the potential increase in human longevity depends on the slowing of age-related acceleration in mortality. If the degree of mortality rate slowing achieved in animals by dietary restriction is applied to humans, the researchers estimated that, using their model, the median human life expectancy would approach 120 years.

We have much to learn concerning the optimal intake of nutrients for population groups, subpopulations and individuals [18–21]. Hopefully, the recommended dietary allowances will continue to be refined with thought to enhancing the quality and longevity of human life.

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Muscle Function and Malnutrition

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Introduction

It has long been recognised that malnutrition is associated with a deterioration in skeletal muscle function and that this is one of the mechanisms by which suboptimal nutritional status leads to increased morbidity and mortality. Klidgian et al. [1] showed that skeletal muscle function as measured by hand grip strength was more accurate in predicting postoperative complications than a range of other biochemical and nutritional parameters (calculated arm muscle area, weight loss and serum albumin). Further work using age- and sex-adjusted grip strength measurements showed that patients presenting electively for abdominal surgery were almost five times more likely to develop postoperative complications if their preoperative grip strength was below the 85th percentile [2]. These observations and the need to develop more objective methods to assess muscle function have focused attention on changes in skeletal muscle 'energetics' (objective measures of muscle function and the associated biochemical changes within muscle) accompanying malnutrition. Such changes have profound clinical implications in that there is now compelling evidence to suggest that during periods of suboptimal nutritional intake muscle function begins to alter well before any change (or observable change) in body composition. In addition there is also increasing evidence that skeletal muscle function and the associated changes in cellular energetics constitute a more sensitive determinant of morbidity in nutrition-related disease and a more accurate predictor of nutrition-related surgical complications.

Changes in Skeletal Muscle Function Associated with Malnutrition

In 1981 it was shown that skeletal muscle in malnourished individuals exhibited greater fatigue (as defined by a greater rate of reduction in the force of contraction with repeated tetanic contractions) than the muscle tissue of normal controls [3, 4].

Lopes et al. [5], in a systematic study of skeletal muscle function in a group of malnourished patients and normal controls, showed a number of other nutrition-related changes in muscle function. In normal controls increasing the rate of electrical stimulation of the adductor pollicis muscle from 10 to 100 Hz raised the force of contraction of this muscle. In the malnourished, however, this increase did not occur suggesting a reduction in energy production in malnutrition. In addition in the same series of experiments it was shown that the rate of skeletal muscle relaxation was decreased in the malnourished patients again suggesting that energy production and ATP hydrolysis were impaired (muscle relaxation as well as contraction requires energy; see below). Subsequently it was shown that obese patients who received hypocaloric diets for 2 weeks developed similar changes in muscle function to those described above and that these changes were reversible with refeeding [6] suggesting that they occur before any measurable change in body composition and thus constitute a more sensitive index of declining nutritional status. In addition it has also been shown that these changes are not influenced by non-nutritional factors such as uraemia, steroids, chronic obstructive lung disease, sepsis or surgery [7–9] and that they cannot be attributed to disuse atrophy which is associated with *faster* relaxation after stimulation-induced contraction compared with normally innervated muscle [10]. Importantly, malnutrition has been associated with similar alterations in diaphragmatic function [8, 11], an observation clearly of clinical significance. Such changes in muscle function demonstrable in both animals and humans and occurring at an early stage in the development of suboptimal nutritional status not surprisingly have stimulated interest in the changes in muscle energetics which accompany them. In order to understand fully the changes in the energetics occurring in muscle from malnourished animals and humans, it is first necessary to understand the energetics of normal skeletal muscle.

Skeletal Muscle Energetics

When a muscle contracts calcium is released from the sarcoplasmic reticulum and binds to troponin which in turn causes tropomyosin to move in such a way as to expose the myosin filaments to actin filaments and a contraction

is initiated; further energy is then required to produce actual contraction. In order for contraction to cease and for the link between the actin and myosin filaments to be broken, the tropomyosin must resume its original position and this requires Ca^{2+} to be pumped back into the sarcoplasmic reticulum; the latter process as with muscle contraction requires energy and hence ATP. Both contraction and relaxation therefore are energy-dependent. And it thus follows that factors affecting the function and energetics of muscle affect both contraction and relaxation.

The ATP used in muscle contraction and relaxation is converted to ADP and inorganic phosphate as follows:

$$ATP + H_2O \Leftrightarrow ADP + Pi + H^+ \quad (1)$$

This reaction is catalysed by ATPase and occurs in the cytoplasm. As with all reactions, the hydrolysis of ATP has a 'free energy of hydrolysis' (delta G) which is dependent on the standard free energy of ATP hydrolysis (delta Go) and the relative concentrations of the reactants and products:

$$\text{Delta G} = \text{delta Go} + 2.58 \ln[\text{ADP}][\text{Pi}]/[\text{ATP}] \quad (2)$$

In order for the reaction to occur the delta G must be negative, and the more negative it is, the greater the forward flux with which the reaction proceeds. Because there is a constant need for ATP it is necessary that it be regenerated from ADP and this is accomplished by phosphocreatine (PCr) donating a phosphate group in the reaction below:

$$PCr + ADP + H^+ \Leftrightarrow ATP + Cr \quad (3)$$

This reaction is catalysed by creatine phosphokinase and occurs in the cytoplasm and mitochondria. It constitutes a means by which ATP can be regenerated relatively quickly (a process that can be saturated leading to deterioration of muscle function and the accummulation of lactate). PCr can thus be thought of as a buffer to guard against ATP depletion during periods of increased metabolic demand. The PCr itself, however, must be regenerated, and this is also accomplished by the creatine phosphokinase reaction using phosphate groups from mitochondrial ATP (fig. 1).

ADP produced by the hydrolysis of ATP enters the mitochondria in increased amounts during heightened metabolic demand and its level is related linearly to the level of oxidative phosphorylation. In a series of groundbreaking experiments Chance et al. [13, 14] showed that under physiological conditions the ADP so produced also bore an approximately linear relationship to the ratio of intracellular PCr and inorganic phosphate (Pi) in skeletal muscle and thus pioneered a method by which the level of oxidative phosphorylation occurring in muscle could be measured indirectly by determining the relative levels of these two metabolites.

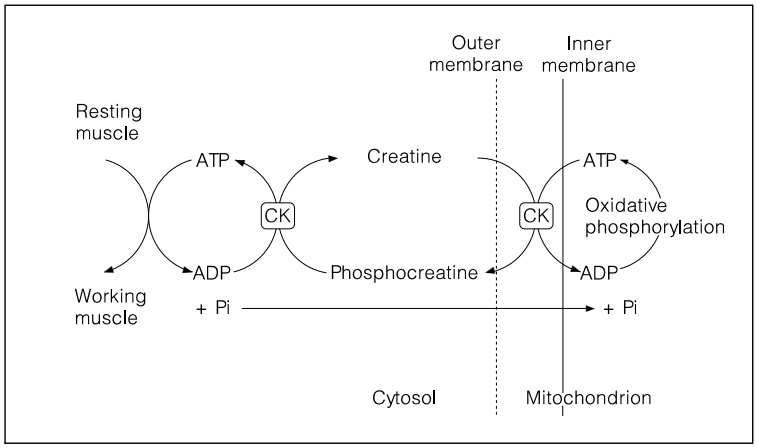

Fig. 1. Biochemical reactions involved in muscle energetics. As resting muscle begins to contract, reactions involving adenosine triphosphate (ATP), adenosine diphosphate (ADP), phosphocreatine and creatine occur in the cytosol and mitochondria. The initial decrease in ATP levels triggers phosphocreatine to rephosphosphorylate ADP to form more ATP resulting in lowered phosphocreatine values. ADP values increase stimulating oxygen consumption in the mitochondria. Oxidative phosphorylation occurs synthesizing ATP. Phosphocreatine levels are replenished as ATP is transported from the mitochondria into the cytosol. The process can occur until ADP levels reach a plateau and levels of lactate and H^+ ions build up, leading to muscle fatigue. CK = Creatine phosphokinase. Reproduced with kind permission from Zelin [12].

Oxidative Phosphorylation and Malnutrition

The fact that the regeneration of ATP is dependent on oxidative phosphorylation which is an energy-dependent process occurring in the mitochondria and that muscle function is dependent on the continued availability of ATP, suggests that impaired oxidative phosphorylation in the malnourished state may be important in the pathogenesis of the above changes in muscle function. Consistent with this was the observation by Russell et al. [6] that the skeletal muscle biopsies of hypocalorically fed obese patients developed morphological changes (on electron microscopy) in the mitochondria of their skeletal muscles. In addition it was subsequently shown that malnutrition was associated with a reduction in mitochondrial enzymes involved in the glycolytic and tricarboxylic acid pathways (phosphofructokinase and succinate dehydrogenase) [5, 6]. These observations further pointed to the importance of the changes in skeletal muscle energetics associated with malnutrition and led to an examination of the alteration in malnutrition of high-energy phosphates

as indirect measures of mitochondrial oxidative phosphorylation and hence nutritional status.

The Role of Nuclear Magnetic Resonance Spectroscopy in Studying Altered Energetics of Skeletal Muscle

Although direct measurement of high-energy phosphates (by biochemical analysis of muscle) and creatine can be performed to study muscle energetics in animals, because it is invasive its role in humans is limited and, in addition, it cannot provide a continuous measure of metabolites in a dynamic setting.

Nuclear magnetic resonance (NMR) spectroscopy (NMRS) has to a large extent overcome many of these limitations and has now been used extensively to study the energetics of skeletal muscle in both humans and animals. Isotopes, which have an uneven number of protons in their nucleus have their polarity altered if subjected to a magnetic field and the differing speed and manner of relaxation following cessation of this magnetic field between different molecules containing the isotope of interest can be used to differentiate and quantitate each of these molecules. In the case of muscle energetics many of the substrates of interest contain phosphate (PCr, ATP and Pi) and the relative concentrations of these can be determined using ^{31}P NMR (fig. 2). The values so derived have been shown to bear a close relationship with values determined using biochemical assays. Much of the subsequent discussion is based on work done using both direct measurement of muscle metabolites and NMR.

Changes in Muscle Energetics Associated with Malnutrition in Rats and Humans

The ATP, PCr and total creatine of muscle can be determined readily either biochemically or using NMRS. The Pi can be determined using NMRS and the pH can be calculated from the frequency difference between the PCr and Pi peaks in the ^{31}P NMRS spectra. In addition NMRS can determine the relative amounts of α-, β- and γ-ATP which has important implications as it is β-ATP which is hydrolysed during muscle contraction. The [ADP] cannot be determined directly or using NMR as its concentration is so low relative to the other metabolites. However, it is possible to determine the ADP concentration indirectly using the values of the other metabolites and the equilibrium constant, Kck, of the creatine phosphokinase reaction:

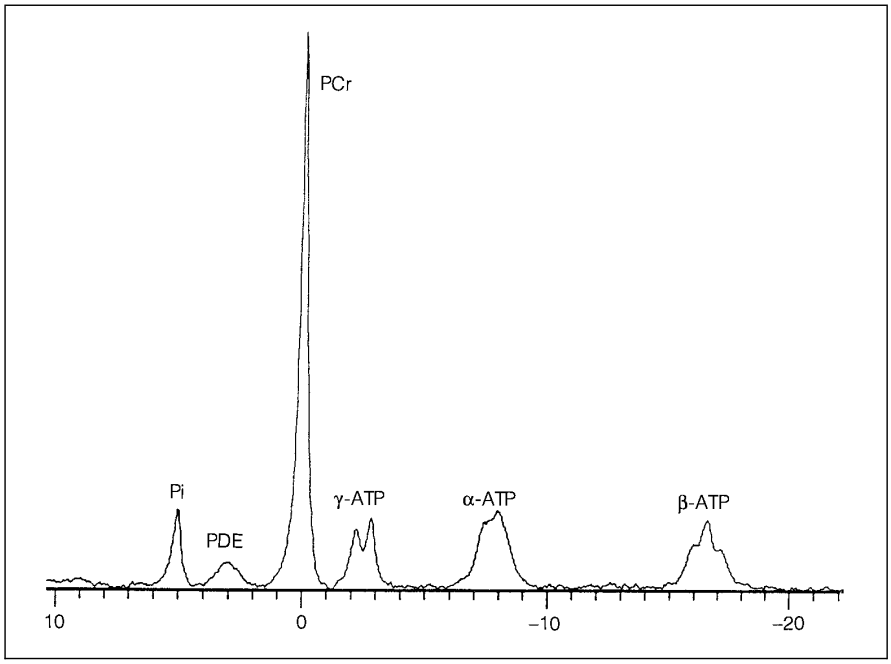

Fig. 2. Typical in vivo ^{31}P nuclear magnetic resonance spectrum of human calf muscle obtained using a surface coil. Shown is the Marquaratt-Levenberg least squares best fit of the Fourier transformation of the raw data. Peak assignments are as follows: inorganic phosphate (Pi); phosphodiesters (PDE); phosphocreatine (PCr); γ-, α- and β-adenosine triphosphate (ATP). The horizontal axis represents a standardised frequency with the PCr peak made to be zero. The relative values of these metabolites can be obtained by integrating the curves pertaining to each.

$$[ADP] = [ATP][Cr]/[PCr][H^+]Kck \quad (4)$$

The free energy of ATP hydrolysis can then be calculated by substituting for [ADP] in equation 2 above:

$$\text{Delta } G = \text{delta Go} + 2.58 \ln[Cr][Pi]/[PCr][H^+]Kck \quad (5)$$

In this way the free energy of ATP hydrolysis of skeletal muscle of malnourished animals and humans can be compared with that of normal controls.

Using the above techniques, it has been shown that hypocalorically fed and fasting rats exhibit a number of reversible changes in skeletal muscle energetics (lower PCr/Pi ratios, lower free energy of ATP hydrolysis and higher free ADP), changes consistent with a fall in mitochondrial oxidative potential [17]. In addition it has been shown that the changes in energetics associated with

muscle contraction (reduced PCr/Pi and PCr/ATP) were slower to normalize in the skeletal muscle of malnourished rats as compared with normal rats [18].

With respect to humans, using NMRS, Gupta et al. [19] showed similar changes in the skeletal muscle of malnourished children compared with children of normal nutritional status. The fact that skeletal muscle from patients with mitochondrial myopathy exhibit similar changes in muscle energetics as those outlined above and that these changes were shown using NMRS [20] further corroborates that the changes in energetics observed in malnourished states are consistent with a decline in mitochondrial function and that NMRS is a valid method for their delineation.

As most of the energy of ATP hydrolysis is used to maintain the Na^+-K^+ gradient across the cell membrane [21], ionic fluxes into and out of the cell can also be used to study the effects of malnutrition on cellular energetics. Malnutrition is associated with a fall in muscle membrane potential, total body potassium and intracellular potassium [22, 23]. Upon refeeding the reduction in total body potassium resolves before the restoration of total body nitrogen (the traditional marker of body cell mass) [24, 25]. These observations together with the fact that the deficit in potassium cannot be corrected by exogenous administration suggest that the deficit in potassium is due to reduced efficiency in cellular energetics rather than a fall in lean body mass and further corroborate the hypothesis that cellular energetics are more sensitive as markers of changes in nutritional status than body cell mass.

Clinical Studies

The clinical significance of alterations in muscle function associated with even mild degrees of malnutrition was highlighted by Christie and Hill [26] who examined a group of 19 malnourished patients with inflammatory bowel disease who were given short courses of intravenous nutrition. They demonstrated that there was rapid physiological improvement in the first 2 weeks of all measures of skeletal muscle function (respiratory muscle function, forced expiratory volume over 1 s, peak expiratory flow rate, hand grip strength and changes in force of contraction with increasing frequency of supramaximal ulnar nerve stimulation). In contrast the change in total body protein (as measured by adjusting the total body nitrogen measured by in vivo neutron activation analysis) and serum levels of protein took several weeks to improve. Another study from the same group with 102 patients showed that a low body weight preoperatively was only significant in terms of predicting postoperative morbidity and mortality if accompanied by a reduction in skeletal muscle function [27].

Further evidence to support the prognostic significance of muscle function in the context of malnutrition is that a change in limb muscle strength, although not body composition, protein biochemistry, muscle power and respiratory muscle strength of patients with cystic fibrosis has been shown to correlate with growth in this group of patients [28]. The failure of respiratory muscle function to reflect growth was attributed to respiratory function being affected by ongoing progression of pulmonary disease as well as overall nutritional status.

In a recent study involving elderly women randomly allocated to receive either of two isocaloric diets one of which was low in protein and the other of normal protein content, Castenada et al. [29] demonstrated that the most striking difference between the 2 groups was a change in muscle function (as measured by EMG) and that other nutritional parameters were affected relatively little even after 63 days of the study. This study further serves to demonstrate the sensitivity of muscle function to changes in dietary intake. The possible clinical implications of the study in the nutritionally compromised or challenged patients is clear and it may be that a diet relatively high in protein may be beneficial in terms of preventing nutrition-related morbidity.

From the above it is clear that in contrast to the more traditional measures of nutritional status which have focused on static measures of body composition, nutrition-related changes in muscle function reflect recent *change* in physiological function and as such add a new dimension to the assessment of nutritional status. The evidence to date suggests that muscle function constitutes a more sensitive and clinically significant measure of nutritional status than other currently used nutritional markers and the failure of measures of body composition to predict accurately postoperative morbidity or mortality is thus not surprising.

Conclusion

The changes in muscle function and energetics associated with malnutrition are both significant and clinically relevant in that they provide a measure not only of nutritional status but also of recent change in nutritional status. The further delineation of these changes and the mechanisms which underlie them using noninvasive techniques such as NMRS is as ongoing area of interest and promise.

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New Fuels for Enteral and Parenteral Nutrition

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Introduction

Over the last several decades nutrition support has become increasingly important in the care of the critically ill patient. During periods of illness, the body rapidly mobilizes peripheral protein from skeletal muscle in order to support the more vital visceral lean tissue. Over the short term this redistribution is crucial, as the body attempts to produce the proteins essential for immediate survival. However, this process is not 100% efficient and a considerable amount of nitrogen is lost to catabolism. With the loss of approximately 50% of lean tissue, death is eminent. Therefore, metabolic and nutrition support has become a crucial component when caring for the critically ill. By providing protein, calories and the necessary essential micro- and macronutrients we can retard the rapid nitrogen loss, allowing more time for the body to heal and for other supportive interventions to work.

As our nutritional knowledge has become more sophisticated there is increasing evidence that certain nutrients, when given in relatively large quantities, may have beneficial effects that directly influence the disease process. By manipulating these nutritional components, it may be possible to have a positive therapeutic effect. This would change the role of nutrition from one of support to one that potentially has pharmacologic consequences. This chapter focuses on new fuels that have this potential. Unfortunately, most of the data are still experimental. There is some limited human clinical data, but this is primarily in adults. Nevertheless, the principles of this chapter should apply to pediatrics. Clearly, however, more clinical work would be necessary in the pediatric population before these nutrients are routinely used.

Glutamine

Glutamine is a 5-carbon amino acid. Unlike most amino acids, it contains two nitrogen groups, one in the usual amine position and the second as an amide group. Glutamine is the most abundant amino acid in blood [1] as well as in the intracellular cytosol, particularly in skeletal muscle. As such, it is an excellent transport vehicle for nitrogen and carbon to various organs [1]. Since glutamine is a common substrate in many processes, its metabolic fate is quite varied. This makes glutamine an extremely versatile nutrient. It is the preferred oxidative fuel for many rapidly dividing cells, especially enterocytes and lymphocytes [1], and is essential for the renal production of ammonium. As a carrier of nitrogen it provides a nontoxic vehicle to shuttle nitrogenous waste from the periphery to the liver, where it is converted into urea. Its breakdown products are essential precursors to the production of nucleic acids and its carbon skeleton can even be used in fatty acid synthesis. However, despite its central role in nitrogen metabolism, it is classified as a nonessential amino acid since the body is capable of its de novo production. As such, glutamine is not a standard ingredient in total parenteral nutrition (TPN) and is only a minor component in most standard enteral formulas.

Under normal conditions, the concentration of glutamine in the bloodstream is quite high. A steady state is maintained since cellular release of glutamine is equal to systemic uptake. In the postabsorptive state the small intestine is the principal consumer of glutamine while the skeletal muscle is the principal producer. In rats, the glutamine turnover rate greatly exceeds the bodily stores and oral intake, indicating that de novo production of glutamine is necessary.

Under certain catabolic stresses (e.g. surgery), the serum level of glutamine dramatically decreases [2] as does the intracellular stores within skeletal muscle [1]. This indicates a greater peripheral utilization of glutamine during catabolic stress, since, despite increased efflux from skeletal muscle, serum levels of glutamine decrease [1]. Under these conditions, there is increased de novo synthesis in order to compensate for the increased utilization. Nevertheless, the decreased serum and intracellular levels has led to the concern that during periods of catabolic stress a glutamine deficiency exists that may be clinically harmful. If this is true, glutamine should be considered a 'conditionally essential' amino acid requiring exogenous supplementation during periods of catabolic stress [1].

The role of glutamine is particularly important with regard to the function of the gastrointestinal tract. Historically, the gut was considered unimportant during periods of critical illness. Since most patients with critical illness develop anorexia and an ileus, enteral feeding was usually not attempted. Furthermore,

with the introduction of TPN, enteral nurition was even more neglected, as was the function of the gut. However, as patients continued to die of multisystem organ failure (MSOF) and 'sepsis'-like picture, with no clear infectious source, attention was refocused on the gastrointestinal tract.

It is known that the gut displays a crucial barrier function, protecting the host from intraluminal bacteria and their byproducts. The mucosal barrier consists of nonimmunological factors such as gastric acid, proteolytic enzymes, mucus and motility, as well as immunological factors including secretory IgA and gut-associated lymphoid tissue. In critical illness, it is now presumed that the mechanical and physiologic barriers of the gut are compromised, allowing for translocation of bacteria and toxins, which may incite the syndrome of MSOF. By preserving the functional and mechanical integrity of the gut, it may be possible to prevent this phenomenon, thereby limiting the events leading to MSOF and death.

It is this hypothesis regarding MSOF that has lead to the intense interest in glutamine. Souba et al. [2] demonstrated that postoperatively gut utilization of glutamine increases significantly. This effect may be mediated via glucocorticoids and glucagon, since separate infusions of these compounds also result in increased glutamine utilization by the gut [2]. The small bowel is the primary consumer of glutamine after operative stress. Interestingly, the efflux of glutamine from the skeletal muscle is not sufficient to provide for the increased gut utilization. Therefore, during operative stress, the lung also appears to be a significant producer of glutamine [3]. Souba and Austgen [3] refer to this complex relationship as the 'interorgan pathway of glutamine metabolism'. One of the byproducts of glutamine metabolism, alanine, is immediately shuttled to the liver where it is converted to glucose via gluconeogenic pathways. The net effect of this interorgan exchange is that peripheral glutamine (e.g. from skeletal muscle, lung) provides fuel for the enterocytes and the byproduct of this metabolism, alanine, is then converted to glucose via hepatic gluconeogenesis for use by cells which are obligate glucose users.

During sepsis and endotoxemia the interorgan flow of glutamine is somewhat altered [3]. Using a rat model, Souba and Augsten [3] demonstrated that there is still a significant decrease in both blood and skeletal muscle glutamine, indicating increased peripheral utilization. However, gut glutamine uptake is diminished in endotoxemic rats. Furthermore, the lung does not release as much glutamine. Although not proven, it is presumed that the liver and lymphocytes are the principal consumers of glutamine after endotoxin challenge. It is precisely under these conditions that glutamine may be considered conditionally essential. It is possible that during the severe stress of sepsis the body is incapable of producing sufficient glutamine to keep up with demand. If this is true, then glutamine may be shuttled away

from the gut, as is seen in the endotoxemic rat, since, in this circumstance, the gut is a relatively less important organ. Under these conditions the gut may become 'semistarved', resulting in mechanical and physiologic dysfunction, translocation, MSOF, and, ultimately, death. By providing exogenous glutamine it may be possible to interrupt such a process by supplying the gut with the necessary fuel to maintain its mechanical and functional integrity.

In rat models, there is significant gut atrophy with the use of standard TPN [1]. Most of this effect seems to be due to a lack of enteral feeding, since rats orally fed the TPN solution had substantially less gut atrophy [4]. Nevertheless, this loss of gut mass may lead to impaired immunologic function. In a series of experiments, Alverdy et al. [5] demonstrated a significant decrease in biliary levels of S-IgA when rats were given a standard TPN formula vs. rats fed a standard oral chow. This effect was reversed by using a glutamine-enhanced TPN formula [6]. Furthermore, bacteria were cultured from the mesenteric lymph nodes in 58% of the rats fed standard TPN vs. only 8 and 0% of rats receiving glutamine-enriched TPN and standard chow, respectively, suggesting that glutamine-enriched TPN may prevent translocation. Since all these data are from normal, nonstressed rats, the clinical significance remains uncertain. Nevertheless, these experimental data do suggest that the addition of glutamine to standard TPN may improve the immunologic function of the gut and prevent bacterial translocation.

Using a model of radiation enteritis Souba et al. [7] further demonstrated that a glutamine-enriched diet before radiation improved small bowel morphology, decreased weight loss and resulted in less translocation (less positive bacterial cultures in mesenteric lymph nodes) compared with an elemental diet. In subsequent studies, Souba et al. [8] also demonstrated that glutamine as a sole nutrient after radiation resulted in improved gut morphology, less translocation, less episodes of bowel perforation and decreased mortality when compared with glycine. Interestingly, these effects were not observed using a glutamine-enriched TPN formula in a similar rat model [9], indicating that the route of administration may be critical [5].

A similar study by Fox et al. [10] using a methotrexate-induced enterocolitis model also showed beneficial effects when a glutamine-enriched enteral diet was given before insult. Using this model, they demonstrated improved gut morphology, less weight loss, improved mortality and less episodes of bacteremia with the use of a glutamine-enriched diet. All these data suggest that glutamine, especially when given orally, may accelerate small-bowel healing and improve the immunologic response of the small bowel after serious small-bowel injury. Whether this translates into improved morbidity and mortality in critically ill patients has yet to be determined.

A human clinical study was conducted by Ziegler et al. [11] on bone marrow transplant patients. In this study patients receiving glutamine-enriched TPN had better nitrogen balance, less clinical infection and a shorter hospital stay when compared to standard TPN. Currently there is a prospective, randomized trial using glutamine-enriched TPN in postoperative patients. Although the numbers are still quite small, there is a decrease in morbidity in patients receiving the glutamine-enhanced TPN [12]. Final results are still pending.

Currently, glutamine is not provided in standard TPN. This is due to its chemical instability in an aqueous solution. However, in Europe a dipeptide formulation containing glutamine is being investigated [13]. This formulation is stable in aqueous solution and the glutamine is readily bioavailable. Clinical studies using the dipeptide version of glutamine in TPN have showed improved nitrogen balance in postoperative patients [13].

In summary, glutamine is an important amino acid for rapidly dividing cells such as enterocytes and lymphocytes. There is growing evidence that during catabolic stress glutamine is conditionally essential and may require exogenous administration via either the parenteral or enteral route. However, since glutamine is also a preferred fuel for tumor cells, its indiscriminate use is not yet recommended.

Arginine

Arginine, also an amino acid, has a pivotal role in the biosynthesis of other amino acids and is a central component of the urea cycle. Although considered nonessential for normal growth, arginine, like glutamine, may be 'conditionally essential' under circumstances of injury, stress [14] and rapid growth. Both in vivo and in vitro studies suggest its presence is necessary for optimal growth [15]. Assuming that recovering from injury and stress is akin to rapid growth, exogenous supplementation of arginine may be beneficial in patients recovering from major illness [14].

During periods of high nitrogen turnover and high ammonia production, a large supply of arginine may be necessary to detoxify ammonia. In some animal models, hyperammonemia develops in animals fed an arginine-free diet [16]. Although of unclear clinical significance, during periods of severe illness, when urea production rises secondary to increased protein breakdown, there is an increased demand for arginine which may exceed endogenous production. Under such circumstances, an exogenous supply of arginine may prove beneficial.

Arginine is a potent secretagogue for many hormones, including growth hormone, prolactin, insulin, glucagon and catecholamines [17]. Most of these

hormones are stimulated by large doses of either intravenous or oral arginine, suggesting that amino acids may not simply be the building blocks of biochemical end products, but may also have inherent profound biological effects. In fact, many of the beneficial effects of arginine may be secondary to the stimulation of these various hormones. This is particularly true for the pituitary hormones, prolactin and growth hormone, since many of the beneficial effects of arginine are absent in hypophysectomized rats [17].

Arginine has been shown to have beneficial effects on wound healing. When subjected to minor surgical trauma, rats fed an arginine-free diet had considerable less weight gain postoperatively [14]. In addition, the wounds of the arginine-deficient rats had less collagen deposition and a decreased breaking strength when compared with rats fed arginine. In a separate experiment, the wound strength was further enhanced by additional arginine when compared with rats fed normal chow. Similar effects were found using arginine-supplemented TPN [18]. In normal humans subjected to minor surgical trauma, there was increased collagen and protein deposition in the wounds of patients fed an arginine-supplemented diet compared with controls [19]. Interestingly, these patients also had significantly higher levels of insulin-like growth factor-1, which may be the mechanism for enhanced collagen deposition. Finally, these patients also demonstrated enhanced T-lymphocyte function which can also enhance wound healing.

Although the exact mechanism for the improved wound healing has not been elucidated, there is speculation that it may be secondary to secretagogue effects on growth hormone. This is supported by an elegant experiment in which the pituitary axis was ablated in one group of rats. The rodents were supplemented with the necessary hormones and then given an arginine-supplemented diet. A second group of rats was also given an arginine-supplemented diet. After minor surgical trauma, the hypophysectomized rats had more weight loss and less wound collagen deposition when compared with the normal rats supplemented with arginine [17], suggesting that the secretion of pituitary hormones may be critical to the improved wound healing demonstrated with arginine.

Arginine also appears to be a potent stimulator of the cellular immune system. This was first noted when arginine supplementation seemed to blunt the normal thymic involution associated with injury [20]. Subsequent studies demonstrated that the maintenance of thymic weight was secondary to increased amounts of lymphocytes [19]. Barbul et al. [20] also demonstrated that arginine supplementation resulted in increased blastogenesis of lymphocytes to various mitogens. Arginine also results in a greater rejection of allogenic skin grafts in rodents, which is mediated via cellular immunity. Most interestingly, arginine supplementation in genetically athymic nude mice resulted in greater

lymphocyte proliferation to mitogens and a markedly increased delayed type sensitivity response [21], but not an increased rejection of allogenic skin grafts. Nevertheless, this elegant experiment demonstrated that the arginine supplementation can effect T-cell maturation independent of the thymus. Barbul et al. [20] have since demonstrated that arginine supplementation in healthy human subjects also increases blastogenesis of circulating lymphocytes to mitogens. Daly et al. [22] showed similar results in postoperative cancer patients fed an arginine-supplemented diet. The exact mechanism by which arginine enhances T-cell function has not been elucidated. However, as with wound healing, it seems that an intact pituitary axis is essential [17]. This suggests that arginine may not have a direct effect, but that it may stimulate other hormones which have the described effects.

Whether enhanced cellular immunity results in improved clinical outcome has not been determined. However, there are multiple animal models of sepsis that suggest arginine supplementation may improve survival [23]. Using an animal burn model, Gance et al. [24] have demonstrated improved cellular immunity when guinea pigs were supplemented with up to 2% arginine compared with controls. The arginine-supplemented animals also had significantly improved survival. Interestingly, animals given a 4% arginine diet did worse, suggesting that there may be a narrow therapeutic range. In a second set of experiments, arginine supplementation did not improve the survival of guinea pigs subjected to peritonitis [24]. In fact, animals given 6% arginine did considerably worse, indicating that high doses of arginine may be harmful. However, later experiments using rats with peritonitis again demonstrated improved outcome. In this set of experiments rats supplemented with a 2% arginine diet had significantly improved survival after cecal ligation and puncture [25]. Importantly, this improved survival was eliminated if the rats were given an inhibitor of nitric oxide (NO) production prior to injury, suggesting that NO production may be the crucial step leading to improved survival (see below).

Recently, arginine was shown to be the substrate for the production of NO. In vitro studies suggest that arginine's proliferative effect on lymphocytes may be mediated by the production of NO [26]. The blastogenic effects of arginine were eliminated with an NO inhibitor, whereas exogenously supplied NO (from sodium nitroprusside) restored the proliferative effects. NO may also be crucial for optimal macrophage function, which may explain the experimental findings of Gianotti et al. [25], who demonstrated that the survival benefits of supplemental arginine were eliminated when an NO inhibitor was given to septic rats.

In summary, arginine seems to have many beneficial effects, especially with regard to immune function. The animal data are compelling. However,

there has been very little work in the critically ill. Therefore, its exact role in clinical practice has not been defined and needs further study before it is recommended as a pharmacologic additive to nutrition programs.

Branched-Chain Amino Acids

The branched-chain amino acids (BCAAs) are valine, leucine and isoleucine. Unlike most amino acids, which are metabolized in the liver, the BCAAs are metabolized primarily in the periphery, where they are initially transaminated in muscle to their respective keto acids. After a meal, the plasma levels of the BCAAs increase to a greater extent since the liver does not clear the BCAAs, as it does with other amino acids. The peripheral metabolism of the BCAAs provides a nitrogen source for the production of alanine and glutamine as well as providing a potential energy source for muscle.

Much of the interest in BCAAs has focused on their role in the treatment of hepatic encephalopathy. Early work by Fischer et al. [27] demonstrated an altered amino acid profile in patients with cirrhosis and hepatic encephalopathy. These patients had high levels of aromatic amino acids (AAAs) and low levels of BCAAs. During hepatic encephalopathy, the ratio of BCAAs/AAAs is decreased from a normal ratio of 3.5 to approximately 1.25 [27]. This is presumably secondary to the decreased utilization of the AAAs, due to liver dysfunction, and the increased peripheral utilization of the BCAAs. Fischer et al. [27] postulated that since these amino acids use the same active transport mechanism to cross the blood brain barrier a significant alteration in the plasma concentrations could result in a similar alteration in the brain CSF. High levels of central AAAs could result in the production of 'false neurotransmitters', resulting in encephalopathy. Therefore, normalization of the plasma AAA/BCAA ratio might help alleviate the symptoms and sequalae of hepatic encephalopathy.

It was this 'false neurotransmitter' hypothesis which lead to much of the early work of Fischer et al. [27]. In a classic set of experiments using dogs with end-to-side portacaval shunts [27], they demonstrated that the amino acid profile of the dogs could be normalized using a BCAA-enhanced TPN formula. Furthermore, these dogs had improved survival and less evidence of encephalopathy than dogs given standard TPN or control dogs given hypertonic dextrose alone. Subsequently, Fischer et al. [28] administered BCAA-enhanced TPN to 11 patients with hepatic encephalopathy. They again demonstrated improvement in the amino acid profile and improvement in neurological symptoms. This and subsequent early work were largely anecdotal and uncontrolled. Many of the observed improvements may have been secondary to better nutritional support.

Nevertheless, this work clearly demonstrated that encephalopathic patients could tolerate large protein supplementation and was the impetus for multiple controlled, prospective trials using BCAA-enhanced TPN.

There have been a number of randomized, prospective clinical trials using BCAA-enhanced TPN for the treatment of hepatic encephalopathy. A major flaw in most of these studies is that the control groups generally received no protein. Therefore, it is possible that the improvement in encephalopathy may be due to better nutritional support. Nevertheless, these trials suggest that BCAAs may help ameliorate the symptoms of hepatic encephalopathy.

One of the earliest studies is from Rossi-Fanelli et al. [29]. This study of 40 patients compared the use of pure BCAAs vs. standard neomycin treatment. Although not clinically significant, the recovery from encephalopathy was slightly improved with the BCAA treatment. The authors concluded that the use of BCAAs was at least as effective as neomycin in the treatment of hepatic encephalopathy. Just as importantly, this study again demonstrated that these patients can tolerate high protein loads if BCAAs are used, thus allowing for better nutritional support in these critically ill patients. Interestingly, this study demonstrated an improvement in the BCAA/AAA ratio with the use of BCAAs. However, within 8 h after the infusion was stopped, the ratio rapidly returned to pretreatment levels and did not correlate with the return of encephalopathy, suggesting that simply correcting the ratio is probably not the sole mechanism of clinical improvement.

Subsequent studies using neomycin as the control [30] yielded similar results. Cerra et al. [30] suggested that the use of a BCAA formula resulted in significant improvement in encephalopathy while maintaining nitrogen balance and enhancing survival. In contrast, a study from Wahren et al. [31] demonstrated no improvement in clinical encephalopathy using 40 g of BCAAs compared with placebo. Most of the other studies showing positive results used approximately 1 g of BCAAs/kg, suggesting that 40 g may be insufficient to demonstrate clinical improvement.

The use of oral BCAAs was first studied by Eriksson et al. [32]. They studied a small group of patients with chronic, low-grade encephalopathy. One group of patients were given an addiltional 30 g of oral BCAAs daily while the others were given placebo. While there was no significant improvement in encephalopathy, there were also no side effects with the administration of more protein. Horst et al. [33] subsequently demonstrated that oral BCAAs were extremely well tolerated in patients prone to encephalopathy. In their study, Horst et al. [33] demonstrated that nitrogen balance could be achieved if patients were given 80 g of protein/day. When a significant portion was BCAAs, only 1 of 17 patients developed encephalopathy. In contrast, if regular protein was used 7 of 20 patients developed encephalopathy.

Controversy still exists over the exact etiology of hepatic encephalopathy and the relative efficacy of BCAAs in its treatment. Nevertheless, the data suggest that, at worst, the use of BCAAs is just as effective as neomycin or lactulose combined with protein restriction in the treatment of hepatic encephalopathy. However, by using a BCAA-enhanced formulation, the patient also receives adequate protein for nutritional support and is more likely to remain in nitrogen balance. Therefore, although BCAAs may not be indicated for the routine treatment of hepatic encephalopathy at this time, any patient suffering from hepatic encephalopathy who requires nutritional support should receive a BCAA-enhanced formulation. This is certainly true for hospitalized patients with acute decompensation, but probably also applies to outpatient cirrhotics who are prone to encephalopathy.

Glycine

Glycine is structurally the simplest amino acid. Until recently, glycine was considered nutritionally innocuous, used primarily as a control in many experiments. However, over the last several years there has been increasing interest in glycine, focused primarily on the preservation of transplanted organs, since the addition of glycine to preservation solutions has been shown to help prevent reperfusion injury in rat liver transplant models [34].

Investigators are now examining whether administration of intravenous or enteral glycine might prevent reperfusion injury after septic, low-flow states. Much of this work is being pursued by Zhong et al. [35]. Using a rat reperfusion model, they have demonstrated less liver parenchymal death when rats were given glycine as compared with controls [35]. Additional studies have shown markedly improved survival when rats given a glycine-enhanced diet were challenged with endotoxin [36]. When these rats were subjected to a double hit model (hepatic reperfusion and endotoxin challenge) all the control rats died, whereas 83% of the glycine-fed rats survived. Using a rat reperfusion model of the intestinal tract, Calvano et al. [37] demonstrated that rats enterally fed a glycine-enhanced diet prior to injury had less intestinal injury, less bacterial translocation and less associated lung damage. More importantly, the rats fed a glycine-enhanced diet had improved survival [37]. Although the exact mechanism remains unknown, Zhong et al. [35] postulate that glycine prevents the accumulation of intracellular calcium by activating a glycine-sensitive chloride channel. This prevents the Kupffer cells from producing toxic metabolites which lead to organ damage and death.

Nucleotides

Nucleotides are crucial to many biological processes. These molecules are primarily found in DNA and RNA, but are also contained in ATP and other essential molecules. The liver is capable of the de novo synthesis of nucleotides. However, as with other nutrients, there is concern that during periods of metabolic stress the body may be incapable of providing sufficient endogenous nucleotides and that exogenous administration may be beneficial.

Much of the early work on nucleotides has been pioneered by Van Buren and colleagues who demonstrated improved T-cell function with nucleotide supplementation. Using a rat model, Pizzini et al. [38] also demonstrated that adding nucleotides to the diet could reverse starvation-induced immunosuppression. Additional studies demonstrated that mice fed a nucleotide-free diet had significantly increased mortality and decreased macrophage function when challenged with intravenous *Staphylococcus aureus* as compared with rats fed a diet consiting of RNA or uracil [39]. The interest of Van Buren et al. [40] in nucleotides stemmed largely from observations that renal transplant patients receiving TPN, which is nucleotide-free, had less episodes of rejection and required less immunosuppressive medication. These observations were supported using rat allograft models, in which animals given a nucleotide-free diet had less episodes of rejection compared with animals given a nucleotide-enriched diet [41].

Currently, nucleotides are provided in some enteral formulas. These formulas have demonstrated some improvement in clinical outcomes. Unfortunately, these formulas contain other nutritional supplements, making it difficult to attribute the benefits directly to nucleotide supplementation.

Lipids

ω-3 Fatty Acids

Lipids are an excellent source of nutrition. In addition to providing calories, lipids are essential for cellular membranes, the absorption of fat-soluble vitamins and the production of many hormones. Until recently, lipid was primarily considered an efficient source of calories. All types of lipid were considered equivalent, since they were primarily seen as providing calories. Therefore, until recently, lipid was administered almost exclusively as long-chained triglycerides (LCTs) comprised mostly of ω-6 fatty acids. However, there is now abundant evidence that lipids are intimately involved in the inflammatory response and that the type of lipid used in nutritional support may be crucial.

The body is capable of synthesizing most types of lipid. There are two essential fatty acids that must be provided in the diet. These are linoleic and linolenic acid. These represent the parent compounds for the ω-6 and ω-3 lipids, respectively. Using the same elongating and desaturating enzymes, these essential fatty acids can be converted into a series of metabolites. In the ω-6 family, these metabolites include arachidonic acid (AA) and the eicosanoids, including prostaglandins, leukotrienes and thromboxanes of the '2' and '4' series. Vegetable oils are rich in ω-6 fatty acids and are the source for all parenteral and the majority of the enteral fat found in commercially available products within the United States. Conversely, the metabolites of the ω-3 family include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are commonly found in fish oils. EPA and DHA can be converted into prostaglandins, leukotrienes and thromboxanes of the '3' and '5' series, which are generally less inflammatory than their '2' and '4' counterparts derived from ω-6 fatty acids [42].

Most North American diets contain an abundance of ω-6 fats and very little ω-3 fats. This is reflected in the composition of cellular membranes, which can contain twenty times as much ω-6 as ω-3 fatty acids [43]. However, the composition of the cellular membrane can be changed with the addition of fish oil in the diet. This has been demonstrated in both animal [44] and human experiments [43, 45], and is true for a number of cell types, including macrophages, monocytes, neutrophils and platelets. With the administration of supplemental fish oil to normal human subjects the ratio of ω-6 to ω-3 can be substantially changed [43]. These changes often take several weeks, but have been demonstrated in as little as 7 days [45], especially if given in a continuous fashion.

As noted earlier, AA is an ω-6 metabolite. AA can be converted to prostaglandins or thromboxanes via the cyclooxygenase pathway, or to leukotrienes via the lipoxygenase pathway [46]. These eicosanoids have very short half-lives and tend to work in an autocrine or paracrine fashion, but may also exhibit some endocrine function. Their effects are varied and include vasoconstriction and platelet aggregation (thromboxand A_2) and chemotaxis (leukotriene B_4, LTB_4). In addition, LTB_4 has been shown to be a potent stimulus for the production of inflammatory cytokines, including interleukin-1 (IL-1). Prostaglandin E_2 (PGE_2) also has proinflammatory properties [42]. However, it also seems to be a potent regulator of the immune and inflammatory response [46]. In higher concentrations PGE_2 has immunosuppressive effects, especially on lymphocyte function [46], and inhibits the production of tumor necrosis factor (TNF) and interleukins [42]. In this regard, PGE_2 seems to function as a feedback mechanism which downregulates the inflammatory response. However, the immunosuppressive effects of PGE_2 may be the mechanism for

the relative immunosuppression associated with severe hemorrhage and trauma [42]. In general, the metabolites of AA incite a state that is 'proinflammatory'. Presumably these effects are beneficial in acute, moderate illness. However, in chronic or severe illness these inflammatory effects may, in fact, be detrimental, and may lead to severe complications, including adult respiratory distress syndrome and MSOF.

Interest in ω-3 fatty acids has focused on the inflammatory response. The ω-3 fatty acids utilize the same enzyme pathways as the ω-6 fatty acids and therefore act as competitive inhibitors. As a result, when taking a diet rich in fish oils there is less production of AA and its metabolites [45] and more utilization of the ω-3 fatty acids, EPA and DHA. This is reflected in the membrane composition and the plasma free fatty acid levels.

There are a number of human studies which suggest that a diet enriched in ω-3 fatty acids may reduce cytokine production. Endres et al. [43] gave healthy human volunteers a fish oil diet over 6 weeks. Using stimulated peripheral blood mononuclear cells, they demonstrated a significant decrease in the production of the IL-1 and TNF to endotoxin challenge. In addition, there was a decrease in the chemotactic response of neutrophils. These observations were still present 10 weeks after the diet was discontinued, but absent after 20 weeks. In addition there have been numerous clinical trial using dietary fish oils in the treatment of chronic inflammatory states, including rheumatoid arthritis, psoriasis and Crohn's disease [47]. Most of these studies have reported mild to moderate clinical improvement and less relapses with the use of dietary ω-3 fish oils, suggesting that dietary fish oils may blunt the chronic inflammatory state.

In animal models of infection, pretreatment with dietary ω-3 has shown beneficial results. Mascioli et al. [48] demonstrated increased survival with guinea pigs subjected to endotoxin after receiving a diet enriched with ω-3 fats. Pomposelli et al. [49] showed less lactic acidosis in guinea pigs challenged with endotoxin when pretreated with parenteral ω-3 fatty acids. Finally, Ertel et al. [50] recently demonstrated that mice fed ω-3 fat did not demonstrate the same immunosuppressive effects after hemorrhagic shock that is observed with control rats. In an earlier study, Ertel et al. had shown similar results when pretreating mice with a cyclooxygenase inhibitor, suggesting that a reduction in PGE_2 may have been the mechanism in both sets of experiments.

Important clinical data regarding ω-3 fatty acids has recently been published by Daly et al. [51]. In a randomized, prospective clinical trial, postoperative cancer patients were enterally fed a commercially available product supplemented with arginine, RNA and ω-3 fatty acids. There was improved in vitro lymphocyte mitogenesis in the study group when compared with controls. More importantly, there was a significant improvement in infectious

and wound complications, which translated into a shorter length of stay. In a similar study of intensive care patients, Bower et al. [52] found that infectious complications and length of stay were again decreased with the same experimental formula. Although this enteral formula contains many immunostimulatory ingredients, some of its benefits are presumed to be due to ω-3 fatty acids and their metabolites.

The effects of dietary lipid are varied and complex. The ω-6 fatty acids result in the production of AA and its metabolites. These tend to be 'proinflammatory' and, in the case of PGE_2, immunosuppressive. Many of these effects may be beneficial in the acute setting. However, in severe injury of sepsis this 'proinflammatory' state may be too strong, resulting in end organ damage and life-threatening immunosuppression. This has led some investigators to recommend medications which block the production of prostaglandins and leukotrienes in cases of severe sepsis and trauma. Others have argued that blocking their production could also eliminate beneficial effects and may actually worsen outcome. ω-3 fatty acids are particularly intriguing because they do not block the production of the eicosanoids. In contrast, they alter their metabolism and may simply blunt the inflammatory response by producing metabolites with less inflammatory properties. Therefore, the beneficial effects of the eicosanoids may be preserved while reducing some of their toxicity. Preliminary results suggest that ω-3 fatty acids do, in fact, blunt the inflammatory state, especially in chronic inflammation. Their use in critical illness also appears promising, but additional studies are necessary in order to carefully identify the subset of patients who will most benefit from their use.

Medium-Chain Triglycerides

Medium-chain triglycerides (MCTs) range from 6 to 12 carbons (mostly 8–10). They are not typically found in vegetable oils and, as such, are not standard components of parenteral fat. Some specialty enteral formulas contain MCTs, but most standard enteral formulas use only LCTs.

The potential efficacy of MCTs is primarily due to their metabolism. Unlike LCTs, MCTs are rapidly hydrolyzed to free fatty acids which are directly absorbed into the portal circulation. They do not require chylomicron formation and are not cleared via the lymphatics. Their intraluminal absorption is direct and rapid, nearly equaling that of glucose [53]. For this reason MCTs are particularly useful in diseases of fat malabsorption, such as pancreatic insufficiency and wasting diseases, such as HIV-associated diarrhea.

Enteral MCTs are transported directly to the liver via the portal circulation, where most are rapidly metabolized. Given the short carbon chain, MCTs

are poor substrates for lipid production and are mostly metabolized. MCTs can enter the mitochondria in a carnitine independent manner and is converted to acetyl-coA. These subunits can be further metabolized into CO_2 via the Krebs cycle or converted to ketones, which are then utilized by peripheral tissues. Since MCTs are ketogenic, they are contraindicated in patients who are acidotic or prone to ketosis [53]. Unlike LCTs, MCTs are rapidly cleared in the bloodstream and not used as a structural fat [54]. Nearly all of the administered fat, therefore, is efficiently used as fuel. This is true for both enterally and parenterally administered MCTs.

In addition to its efficient properties as a fuel source, animal studies suggest that MCTs do not impair the reticuloendothelial system (RES), a problem associated with the rapid administration of LCTs [55]. Using a rat model of trauma and sepsis, Hamawy et al. [56] demonstrated that rats fed LCTs had altered RES function and more episodes of bacteremia than those fed a diet consisting of an MCT/LCT mixture [56]. It is hypothesized that during the prolonged and rapid administration of LCT, the RES is overloaded as it sequesters LCT. This may lead to decreased phagocytic function and increased immunosuppression. MCTs, which are rapidly metabolized and cleared from the bloodstream, are not sequestered in the RES and do not produce RES dysfunction. This is supported by human studies which demonstrated a significant decline in RES function (as measured using a ^{99}Tc-sulfur colloid scan) after the rapid administration of LCTs. This decline in function was not demonstrated when an MCT/LCT mixture was administered in a similar fashion [57]. However, MCTs do not provide the essential fatty acids and, therefore, cannot be the sole lipid source.

Conclusion

These new fuels provide an exciting way to further delineate the role of nutrition. There is a considerable amount of experimental data which suggest that all of these fuels, when given in pharmacologic dosages, may provide direct therapeutic benefits. As with all new therapies, the next step is to clearly identify which patient populations are most likely to benefit from these nutritional interventions. In the future, it may be possible to specifically design a nutritional program for different disease processes which not only provides the necessary nutritional support, but also acts as a primary pharmacologic intervention.

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Hyperlipidemia in Childhood

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Atherosclerotic coronary heart disease (CHD) is a slowly progressive pathologic process that begins early in life but rarely produces symptoms until middle age. Often the disease goes undetected until the time of the first heart attack, which is often fatal.

Between 30 and 40% of today's children will eventually die of heart disease [1]. Some will die prematurely of accelerated atherosclerosis caused by medical conditions that begin in childhood and adolescence, such as disorders of lipid metabolism, hypertension and diabetes mellitus [2]. Modern therapy has greatly improved the outlook for patients inflicted with CHD. Still, a major breakthrough in our battle against this number one killer depends on progress in preventive measures.

Relationship between Lipoprotein Levels and CHD

Evidence supporting a causal relationship between blood cholesterol levels and CHD comes from a wealth of congruent results from genetic, experimental pathologic, epidemiologic, and intervention studies. At the same time it is clear that an elevated blood cholesterol level is not the only cause of CHD. Hypertension, cigarette smoking, diabetes mellitus, obesity, and physical inactivity along with other risk factors such as age, sex, and family history are important contributing causes.

The phenotypic classification of the dyslipoproteinemias was first proposed by Fredrickson et al. [3] in 1967. Application of Fredrickson's classification has served as an essential tool for the clinician in both the diagnosis

and therapy of the dyslipoproteinemias, and has stimulated investigation of molecular pathophysiology in this field [4].

Cholesterol is carried in blood in several protein-lipid combinations known as lipoproteins and most blood cholesterol in humans is carried by low-density lipoproteins (LDL-C). Some is also present in high-density lipoproteins (HDL-C) and in very low-density lipoproteins (VLDL). LDL-C and HDL-C mainly transport cholesterol, while VLDL is the major carrier of triglycerides. Chylomicrons, occurring in nonfasting subjects, carry mostly triglycerides of dietary origin. Phospholipids, together with apolipoproteins, are essential components of lipoproteins that help solubilize, transport, and deliver triglycerides and cholesterol to various tissues.

Impressive progress has been made in understanding the structure and expression of the genes that code for apolipoproteins, the chromosomal localization of these genes, the kinetics and regulation of lipoprotein assembly and secretion, and the lipoprotein transport gene abnormalities underlying CHD susceptibility. However, since the general analysis of polygenic traits such as atherosclerosis is not possible directly in humans, our understanding of the genetics of atherosclerosis is derived largely from analysis of various relatively rare genetic abnormalities and from genetic studies of 'candidate genes'.

Genetic abnormalities in the metabolic pathways of one or more lipoproteins may produce an increase in the levels of cholesterol, triglycerides, or both. A critical factor raising cholesterol levels in many individuals is the habitual dietary intake of excessive amounts of saturated fatty acid, cholesterol, and total energy [5]. The significance of raised plasma cholesterol (more specifically raised LDL-C) and of reduced HDL-C as major CHD risk factors is generally accepted.

Some patients develop premature CHD with apparently normal LDL-C. The reevaluation in recent years of the importance of dyslipidemia in CHD has revealed a range of commonly occurring abnormal lipoprotein phenotypes which may be as atherogenic as hypercholesterolemia [6]. These include reduced levels of HDL-C, increased lipoprotein (a), as well as hypertriglyceridemia. High levels of oxidized LDL-C or other oxidative products are emerging as candidate risk factors [7].

Lipoprotein (a) is an LDL subfraction containing a large side chain homologous to plasminogen. As an inhibitor of intrinsic fibronolytic activity lipoprotein (a) enhances thrombogenicity. Patients with lipoprotein (a) exceeding 30 mg/dl have an approximately threefold prevalence of CHD.

Secondary hyperlipidemia must be excluded in all children and adolescents with high LDL-C levels. Conditions associated with secondary hyperlipidemia are pregnancy, endocrine and metabolic disorders, storage diseases, chronic renal diseases, obstructive liver diseases, certain drugs, alcoholism, obesity,

anorexia nervosa, progeria, collagen diseases, dysgammaglobulinemia, and Klinefelter syndrome. If the hyperlipidemia is secondary, the primary disorder should be treated, if possible.

Rationale for Intervention in Childhood

A strong body of evidence indicates that the atherosclerotic process begins during childhood years. With the rare exception of familial hypercholesterolemia (FH), the atherosclerotic pathology observed in young children (≤ 10 years) is limited to endothelial dysfunction and fatty streaks. Although these are regarded as the precursors of more advanced occlusive forms of atherosclerotic lesions seen in the adults diagnosed with CHD, these early stages of atheroclerosis are reversible [8, 9]. The extent of the atherosclerotic process correlates with the levels of LDL-C and VLDL-C [10], and are inversely related to HDL-C [11].

In children as in adults from different countries, the average serum cholesterol levels reflect the saturated fat intake [12].

'Imprinting' should be considered as another reason for intervention in early childhood. That is, it may be easier to introduce healthful nutritional habits in childhood, rather than try to modify them at a later stage in life. Healthful diet early in life may also contribute to optimal lipoprotein regulation and homeostasis.

In summary, there is a wide spectrum of compelling genetic, pathological, epidemiological, and behavioral data to consider intervention strategies for lowering cholesterol in both healthy children and in those diagnosed with elevated serum cholesterol [13].

Limitations and Accuracy of Screening Tests

Total cholesterol (TC) as well as HDL-C can be measured directly from a nonfasting venous or capillary blood sample. Due to physiologic variability and measurement error, the result may not reflect the actual mean levels. Stress, concurrent illness and seasonal variation may change the levels of TC up to 11%.

Laboratory tests are subject to random errors due to variability in the sampling mode, handling, and methodology. Moreover, systematic errors may overestimate or underestimate cholesterol values. It is estimated that the average bias of the measurement of TC obtained from capillary blood is $+4$ to $+7\%$ compared to venous samples. Regression to the mean should be taken into account when abnormally high levels of TC are measured.

Consequently, a single measurement of TC can vary as much as 14% from one's personal average. Hence, if a precise level is warranted, it is recommended that an average of two separate samples be calculated from samples drawn on two different days. If the gap between the two measurements exceeds 16%, a third sample should be drawn.

Screening Children According to Family History

Family aggregation of CHD and hypercholesterolemia may serve as an indicator of children who are at risk for heart disease as adults.

Several studies have shown that the childhood rank order of cholesterol is maintained over time (known as tracking), although not as consistently as the rank order of height and weight is maintained [14, 15]. Thus, children whose cholesterol levels are observed to be high tend to have high levels as adults. However, many will have levels that are not as high as would have been predicted from their childhood levels [16].

In some families, elevated levels are inherited in a specific manner, that is, under the influence of a single major gene. Such cases are known as monogenic disorders. The most severe monogenic disorder is FH. One of two children born to a parent with FH has hypercholesterolemia, and 90% of those affected have CHD by age 65. However, FH is believed to account for only about 4% of premature CHD (diagnosed before 55 years of age) [17].

The most commonly recognized genetic condition that predisposes to premature CHD (accounting for about 11%) is the monogenic disorder known as familial combined hyperlipidemia (FCH). It is characterized by hypercholesterolemia, hypertriglyceridemia, or both. The phenotypic expression of FCH as hyperlipidemia is often delayed to the third decade, particularly if one starts with affected adults and tests their offspring. But recently it was shown that in lipid specialty clinics, where children are referred for suspected hyperlipidemia or a family history of early CHD, FCH was the most common familial disorder [18].

Both of the above-mentioned monogenic lipid disorders do not explain even a majority of premature CHD. Polygenic disorders resulting from the expression of a number of genes, each with a small but additive effect, combined with environmental contributions may explain the rest.

Also, family aggregation of lipoprotein levels is the result, in part, of a shared environment including nutritional habits, smoking, exercise, alcohol and drug use [19].

The impact of early screening may have some unfavorable aspects. 'Labeling' a normal child as dyslipidemic and turning him into a patient because

of some striking manifestations of CHD in one of his parents may contribute to unjustified anxiety. Issues of insurability, insurance cost and employability are also of concern.

Population Strategies in Children

The population approach aims to lower the average levels of blood cholesterol among all children and adolescents through population-wide changes in nutrient intake and eating patterns, emphasizing the role of 'heart healthy' nutrition.

This strategy is currently recommended for all children over the age of 2 years in the United States [20] and Europe [21]. Prior to that age nutritional intake of fat and cholesterol should not be limited in order to promote growth and development. The policy is endorsed by the National Cholesterol Education Program (NCEP) Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction [15], consistent with recommendations made by the American Heart Association [22], the United States Department of Agriculture [23], the National Cancer Institute [24], the National Research Council [25], the European Atherosclerosis Society and the International Task Force for Prevention of Coronary Artery Disease [20].

The major objectives are to limit saturated fat intake since this is the major nutritional determinant of high blood cholesterol levels, followed by dietary cholesterol [26]. Although recent evidence suggests that fat intake exceeding 30% of total energy can still be associated with lowering blood cholesterol levels as long as saturated fat intake is kept low [27], it is advised to keep the total fat intake below 30%. This reflects the concern that higher fat intake is likely associated with an increased risk of obesity in both children and adults.

The following recommendations have been issued [19]: (1) nutritional adequacy should be achieved by eating a wide variety of foods, and (2) energy (calories) should be adequate to support normal growth and development and to reach or maintain desirable body weight. The following distribution of nutrient intake is recommended: (1) saturated fatty acids should be $<10\%$ of total calories; (2) total fat should be on average no more than 30% of total calories, and (3) dietary cholesterol should be 100 mg/1,000 kcal or a total of <300 mg/day.

In the past years the effects of other fatty acids and fats have been brought to light. The intake of polyunsaturated fatty acids is associated with a decrease in both serum LDL-C and HDL-C levels, while consumption of monounsaturated fatty acids decreases serum LDL-C and has no or a positive effect of

HDL-C. Fish oil intake is associated with a decrease in serum triglyceride levels, while trans fatty acids are determinants of serum cholesterol levels. The role of antioxidants (vitamins, phytochemicals, etc.) are under extensive research. Only with consolidation and refinement of results will an updated nutritional guideline be justified.

A number of studies have confirmed the safety of the above-recommended diet and the lack of adverse effects on growth and development of children [28, 29].

This diet may not be as difficult to introduce as is generally perceived. Basch et al. [30] recently suggested that by simply changing from whole milk (4% fat) to 1% fat milk in free-living children, approximately 75% of children can achieve the recommended guidelines.

The population approach warrants coordinated implementation from various directions: school systems should provide healthful food and lifestyle guidance; government and food industry should cooperate in insuring that food labeling is of sufficient quality and is easy to understand thereby allowing the public to make sensible food choices in terms of designing their diet. The media have a major responsibility in promoting the public diet and lifestyle attitudes [19].

Strategies in Hypercholesterolemic Children

Current guidelines in the United States [19] and Europe [20] suggest cholesterol screening of children with a family history (in a parent or grandparent) of high blood cholesterol (≥ 240 mg/dl) and/or documented cardiovascular or cerebrovascular disease, or sudden cardiac death at age 55 years or less. The NCEP also recommends that children whose family history is unobtainable, or those with other risk factors (i.e. smoking, hypertension, HDL-C < 35 mg/dl, obesity, diabetes mellitus, and physical inactivity) may be screened to identify individuals that will benefit from nutritional consultation [19].

The stratification of hypercholesterolemia in children and adolescents is based upon LDL-C percentile and is similar both in the United States [19] and Europe [20] (table 1). Since there is only mild variation in cholesterol percentiles between ages 2 and 19 years, the percentile cutoff points in table 1 [19] can be applied to all children and adolescents. At puberty total serum cholesterol decreases slightly in both males and females due to HDL-C reduction. These variations in cholesterol profiles do not warrant different approaches to hyperlipidemia in adolescents.

The algorithm provided by the NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents [19] should be followed.

Table 1. Classification of total and LDL-cholesterol levels in children and adolescents (ages 2–19 years) [19]

Category	Total cholesterol mg/dl	LDL-C mg/dl	Percentile
Acceptable	<170	<110	<75th
Borderline	170–199	110–129	75–95th
High	>200	>130	>95th

Children found to have acceptable LDL-C levels (<75%) should follow the general guidelines for the pediatric population at large. Those with borderline levels of LDL-C (75th–95th percentile) should also follow the recommended diet, but other risk factor interventions should be implemented (e.g. weight loss, physical activity). For those found to have a high LDL-C, a comprehensive clinical evaluation is warranted and should include: screening the rest of the family; defining the type of hyperlipidemia, and detecting other risk factors for CHD. The therapeutic goal is to reduce LDL-C to <130 mg/dl and ideally <110 mg/dl. The recommended American Heart Association step-1 diet (essentially identical to the population diet) should be the first step of intervention along with other risk factor modifications. If after 3–6 months on the step-1 diet, the therapeutic goal has not been obtained, the step-2 diet (see below) should be implemented.

The step-1 and step-2 diets differ by the reduction in maximum saturated fat intake from 10% in step 1 to 7% in step 2. While the step-1 diet can be safely implemented by families without nutritional counseling, the NCEP recommends that implementation of the step-2 diet should not be done without professional nutritional counseling [19].

A decrease in total fat intake is generally associated with slight decreases in HDL-C levels (an undesired effect), and recent data suggest that increasing the intake of simple carbohydrates (monosaccharides and disaccharides) in children leads to further falls of HDL-C. This decrease in HDL-C is not observed with the intake of complex carbohydrates (starch, etc.) [31]. Further studies are required in order to elucidate these findings.

Foods high in fiber are considered as a component of a cholesterol-lowering diet, since an increased fiber intake has been associated with modest reductions of TC and LDL-C in adults. Since these effects have not been confirmed in children, fiber supplements are not recommended.

Guidelines for introducing drug therapy for hypercholesterolemic children are conservative. The NCEP Pediatric Panel [19] and the International Task

Force for Prevention of Coronary Artery Disease [20] recommend that drug therapy be considered in children 10 years and older only after a trial of diet therapy and other risk factor modification (for 6 months to 1 year) in the following situations: (1) children with LDL-C levels of >190 mg/dl after appropriate dietary interventions, and (2) LDL-C remains >160 mg/dl and (a) there is a positive family history of premature cardiovascular disease or (b) two or more other coronary vascular disease risk factors are present in the child or adolescent after vigorous attempts have been made to control these risk factors (e.g. smoking, obesity, HDL-C <35 mg/dl, hypertension, and diabetes).

Drug therapy is initiated after the age of 10 years because early lesions of atherosclerosis develop at this age. A more radical approach, however, may be applied to children at a younger age with extreme hypercholesterolemia and an unfavorable clinical profile. The minimal goal of drug therapy is to achieve an LDL-C level of <130 mg/dl. Presently, only bile acid sequestrants and nicotinic acid are recommended for use in children [19]. While long-term safety trials on the effects of HMG-CoA reductase inhibitors are in progress in adolescents and children with severe hypercholesterolemia, their long-term safety has not yet been established, and therefore, they are not recommended.

Conclusions

A population approach and selective screening constitute the mainstay of atherosclerosis prevention in children. Drug therapy is reserved for extreme cases of hypercholesterolemia with prognostically unfavorable clinical profiles.

The lack of understanding of the natural history of atherosclerosis and the effects of drug therapy in childhood, as well as the lack of data on the safety and cost-effectiveness of such interventions preclude at this time a more widespread use of cholesterol-reducing agents.

As with adults, we still are unable to stratify risk reliably and predict the evolution of CHD accurately. Future developments in molecular biology and genetics supported by clinical experience and epidemiological data will enable us to fingerprint the hyperlipidemic patient beyond cholesterol, and consequently make screening a much more effective tool.

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Food Protein Hypersensitivity: Management and Strategies

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Introduction

Interest in food hypersensitivities presumably caused by immune aberrations has been increasing over the last three decades [1, 2], and the diagnosis has been promoted from one of doubtful existence to a place of respectability. In spite of the fact that several drugs, such as disodium cromoglycate and prostaglandin synthetase inhibitors, have been shown to be efficacious in a limited number of patients in the treatment of food protein hypersensitivity [3, 4], the results of pharmacotherapy have been disappointing and the mainstay of treatment remains dietary elimination. Despite the fact that no significant progress has been achieved in new modes of treatment, personal experience suggests that there is decreased morbidity. Emaciated infants, due to malabsorption following undiagnosed protein hypersensitivity, have become a rarity. This is probably due to the following factors. The rising incidence of breast-feeding in many populations has delayed the exposure of infants to the potentially harmful antigens [5]. The use of adapted formulae has mitigated the severity of the adverse reactions to cow's milk protein, though it has not reduced their incidence [6]. Greater awareness of the diagnosis and proficiency of pediatricians in the use of alternatives to milk-based formulae and hypoallergenic foods have also contributed in improving the management of this condition. The rapid strides that are being made in understanding the pathogenesis of this condition hold out hopes for the future.

Definition

In this article the term food hypersensitivity refers to untoward reactions induced by articles of diet and mediated by, presumably, immune-mediated mechanisms. It does not include intolerance generated by enzymatic defects such as lactose intolerance or other chemical phenomena. The term 'food allergy' is reserved for those immune reactions which are IgE-mediated. It is common practice, however, particularly in Europe, to employ the term 'food allergy' to include all immune reactions to food, whatever the mechanism.

Epidemiology

Food protein hypersensitivity is frequent in infancy and at this age is commonly a transient phenomenon. We have never seen hypersensitivity phenomena in the first 3 weeks of life, presumably because the intestine is not equipped with the immune mechanisms required for staging an adverse response. The condition commonly presents at weaning and, therefore, breast-feeding may delay or totally prevent its appearance. In infants who are artificially fed from birth, the onset may already be at 3–5 weeks. New cases continue to appear particularly during the first 2 years of life but may continue to present at any time of life. As the criteria for diagnosis vary from one study to another, so do the estimates for its incidence. A recent study found it to be 2.8%. The principal symptoms were gastrointestinal in 50%, dermatological in 30% and respiratory in 19% [7].

Antigenic Proteins

In the first few months of life the allergens are those of the infant foods. In those infants who are not breast-fed, cow's milk proteins are the most common offenders. Of these β-lactoglobulin is probably the main culprit [8]. Adapted formulae contain about one half the amount of protein than does unadulterated cow's milk, thus reducing the antigenic load. Although this has not reduced the incidence of cow's milk protein hypersensitivity, it may have mitigated the severity of the adverse reaction [6].

In patients with cow's milk protein hypersensitivity soy-based formulae are frequently employed. However, 7–35% of patients so treated may subsequently develop hypersensitivity to the soy protein [9, 10]. We, therefore, recommend treating these patients with protein hydrolysate formulae. At all ages, but particularly in infants under 3 months of age and in infants with hypersen-

sitivity enteritis, protein hydrolysates are the preferred milk substitute. Even these, however, are not without risk. These hydrolysates may still contain antigenic material and hypersensitivity phenomena have been described [11–13]. Infants over 3 months of age are not always willing to accept the taste of hydrolysate formulae and soy formulations may have to be used. The so-called 'partial' hydrolysates, which are on sale in Europe, are not indicated in the treatment of protein hypersensitivity as some 50% of infants fed these formulae react adversely to them [14].

Hypersensitivity to mother's milk is unknown, but infants may react to proteins ingested by the mother and secreted into her milk [15]. Here, too, the commonest offender is cow's milk protein and this has been reported to produce rhinitis, atopic dermatitis, colic, gastroduodenitis and colitis in breast-fed infants.

It is a common misconception that goat's milk is a good substitute for infants sensitive to cow's milk protein. Goat's milk protein largely cross-reacts with cow's milk and should not be used in infants with cow's milk protein hypersensitivity. Eggs, bananas and peanuts are also common causes of hypersensitivity, whereas meat and poultry are relatively hypoallergenic foods.

Secondary Food Protein Hypersensitivity

Secondary food protein hypersensitivity is the name given to hypersensitivity arising immediately after an attack of acute infectious gastroenteritis. It is commoner in infants under 3 months of age given a high antigenic load on realimentation [16].

Genetics

Infantile food protein hypersensitivity has a genetic basis. The incidence of food protein hypersensitivity in families with 1 affected infant is 12% as opposed to 1.3% in a control group [7]. Furthermore, there is an increased incidence of food protein hypersensitivity in families with an atopic background. However, so far no genetic markers have been identified [17].

Pathogenesis

While the pathogenesis of food protein hypersensitivity is not fully understood, a discussion of this topic must include a number of phenomena which,

acting in concert, determine whether the body will stage an untoward reaction to a foreign protein or whether it will tolerate it. The transition from a reacting to a non-reacting intestine is a process of maturation which requires consideration of the subjects of antigen uptake, the humeral immune response, IgE-mediated reactions, tolerance, the production of cytokines and prostaglandins and the cellular immune response.

The natural history of infantile food protein hypersensitivity is that the neonatal intestine is not capable of reacting to foreign proteins. Thus newborns, subjected to the frequently unjustified habit of having their breast-feeds supplemented with formula on the neonatal ward, will stage no adverse reactions even if they subsequently do so. Infants given formula feeds from birth may have adverse reactions from the 3rd week onwards. Sucklings often have their first reaction when weaned onto formula. The intensity of the reaction usually diminishes thereafter and frequently disappears by the age of 2 years and often long before. It seems likely that food protein hypersensitivity is, in the first 2 years of life, a condition due to the administration of foreign protein at a time of life when Nature has equipped it with the mechanisms for absorbing maternal proteins only.

Late-onset food protein hypersensitivity is more likely to be due to an atopic background and a case can be made for distinguishing between these two types of food protein hypersensitivity.

Antigen Uptake

In order for the body to stage an immune response, foreign antigen must enter the epithelial layer of the intestine. It has been shown that antigen uptake is greater in the premature neonate than in the mature one. The process of antigen uptake continues, however, during the whole adult life of the individual and is a requisite for the process of antigen recognition and the production of specific antibodies. There may be separate pathways for soluble and particulate antigens. It is believed that soluble antigens are absorbed by enterocytes along the gastrointestinal tract [18]. Particulate antigens are taken up by M cells overlying Peyer's patches [19]. These cells are designed to facilitate antigen uptake. They have few microvilli and no lysozomes, features which indicate that the antigen is not meant to be digested by the cell. Thence, the antigens pass to the adjacent antigen presenting cells. Here they are broken down to peptides which are complexed with the HLA class-II molecules and presented to T cells for antigen recognition.

Humeral Immune Response

The appearance of serum immunoglobulin (Ig) G antibodies is a physiological phenomenon not accompanied by clinical manifestations [20]. IgG antibodies play no role at mucosal surfaces except in the case of local inflammation. IgG4 antibodies are an exception as they are reaginic antibodies and participate in immediate allergic reactions.

Secretory IgA is absent at birth. Plasma cells first appear in the lamina propria in the 2nd week of life; however, IgM-producing cells predominate until the infant is 6 weeks old. Thereafter, IgA-producing cells increase until they constitute 85% of the plasma cell population [21].

Secretory IgA plays an important role in modulating the intestinal immune response. IgA is produced by the lamina propria plasma cells in a dimeric form (i.e. two identical IgA molecules are joined by a J [joining] chain peptide). The dimeric IgA moves towards the basolateral membrane of the enterocyte where it is internalized by receptor-mediated endocytosis. The receptor is a secretory component which attaches itself to the dimeric IgA, thus completing the assembly of secretory IgA. This immunoglobulin traverses the enterocyte and is discharged into the intestinal lumen. Secretory IgA is resistent to tryptic digestion. Thus, it is ideally suited to function within the gastrointestinal tract. Secretory IgA complexes food proteins at the mucosal level [22, 23].

IgE-Mediated Reactions

Immediate allergy is one of the mechanisms of the immune response of the intestine. The probable mechanism is as follows. The ingested allergen combines with specific IgE antibodies attached to mucosal mast cells. This results in degranulation of the mast cells with release of histamine and other mediators of inflammation. These proinflammatory mediators cause vasodilatation with loss of water and electrolytes into the lumen of the intestine resulting in a decrease in intravascular water and then diarrhea [23].

Immune Tolerance

The development of tolerance to food is an important aspect of the normal intestinal immune response, and in the absence of tolerance, food protein hypersensitivity occurs. In principle, the introduction of antigens orally usually prevents the subsequent development of the clinical systemic immune reactions [24]. The balance of the two helper T-cell populations, T_{H1} and T_{H2}, is an

important factor in the modulation of the body's reaction to foreign protein. Cytokines secreted by these two cell types have opposite effects in the experimental animal. T_{H2} cells secrete interleukin-4 which induces B cells to secrete IgE. T_{H2} cells also induce the proliferation of mast cells, which are an important constituent of the immediate-type allergic response. T_{H1} cells secrete transforming growth factor-β and interferon-γ, factors that depress the immune response and promote tolerance [25–27]. We have shown that, at least in the experimental animal, hypersecretion of prostanoids is part of the intestinal immune response [28].

Clinical Features

In the breast-fed baby, a typical onset is at the time of weaning onto formula. An immediate-type response is manifested by the onset of *vomiting*, within 0.5 h of the feed. The vomiting recurs several times and ultimately becomes bile stained.

Chronic vomiting is not typical of food protein hypersensitivity and in the first year of life is more likely to be due to gastroesophageal reflux or to infectious, metabolic or structural abberations. In an infant who presents with vomiting in the first year of life, a change of diet is justified in order to exclude food protein hypersensitivity. If the onset is after the introduction of gluten into the diet, it must be remembered that celiac disease, too, may present with chronic vomiting.

Diarrhea is a common manifestation of food protein hypersensitivity. The stools may be watery, fatty or contain mucus and blood.

Malabsorption may be manifested as diarrhea or failure to thrive or both. Since malabsorption may be present without diarrhea, infantile food protein hypersensitivity should be suspected in any formula-fed infant who fails to gain weight. The corollary of this statement is a good rule: any infant on formula who is not gaining weight in the absence of any obvious cause should be considered to have food protein hypersensitivity until proven otherwise.

Blood loss may be occult or overt. The blood may be fresh signifying colitis or there may be malena due probably to protein-induced duodenitis [29, 30]. Blood loss may result in *iron deficiency anemia*.

Constipation is an unusual manifestation of food protein hypersensitivity [31].

Dermatological manifestations include *urticaria* and *angioedema. Atopic dermatitis* is manifested by chronic erythema, scaling, papules and vesicles. It should be distinguished from seborrheic dermatitis.

Uncommon Clinical Manifestations

Rarely, the presenting feature of food protein hypersensitivity may be the presence of unexplained metabolic acidosis [Freier S, personal observation]. Proteinuria, which resolves with the discontinuation of cow's milk in the diet has also been described.

A number of unusual findings in the gastrointestinal tract have also been reported. Protein-losing enteropathy is probably commoner than is suspected [32]. The occasional presence of constipation as the dominant feature has already been mentioned [31]. An extreme form of this is a transient intestinal pseudo-obstruction [Freier S, personal observation]. Food protein hypersensitivity-induced colitis should be suspected if bloody diarrhea is present. Indeed, it has been claimed that most cases of colitis under the age 2 years are manifestations of food hypersensitivity [33].

Migraine headaches have been described as a neurological manifestation of food protein hypersensitivity [34, 35].

Diagnosis

In spite of a number of tests and epiphenomena of food protein hypersensitivity, the diagnosis is usually based on a clinical suspicion that a particular food is responsible for the patient's symptoms. Thus the presence of unexplained diarrhea, malabsorption, failure to gain weight or vomiting following the ingestion of a new food, chronic rhinitis or any of the other manifestations mentioned above should call for the discontinuation of the suspected offender in the diet. In some centers it is practice to obtain an initial intestinal biopsy before instituting an elimination diet in order to exclude the possibility of giardiasis, celiac disease or other conditions characterized by abnormal gastrointestinal histology. If the diagnosis is correct recovery should follow, but this may be delayed as damage may have been inflicted on the intestinal tract which takes time to recover. Following the period of recovery, the patient is challenged with the food under suspicion. It is our custom to allow a recovery period of at least 2 months before performing the challenge.

In infants two open food challenges are sufficient. If cow's milk hypersensitivity is suspected, lactose intolerance should first be excluded by observing the effect of a lactose challenge or in older children by performing a lactose H_2 breath test. Because of the possibility of a severe reaction, the challenge should only be performed in a setting with facilities for the administration of intravenous fluids. The patient is weighed before the challenge. The suspected antigen is administered in a dose of 2 ml. The dose is doubled every hour. The patient is observed for the appearance of any untoward reaction, such as

shock, vomiting, diarrhea, weight loss, wheezing, generalized rash, diaper rash, circumoral rash or edema. The stool is monitored for the presence of sugar. The patient should be weighed at weekly intervals in order to exclude a late reaction. In older children and adults a double-blind food challenge is more reliable [36]. Before the challenge all drugs containing antihistamines, steroids or nonsteroidal anti-inflammatory agents should be discontinued. The patient should be fasting on the morning of the challenge and be under observation to allow treatment should a severe adverse reaction occur. The food and the placebo are administered in indistinguishable capsules on different days. The patient is observed for potential reactions. The key of the contents is available only to the pharmacist. The test may have to be repeated on several occasions until consistent results are obtained.

Differential Diagnosis

In patients with chronic diarrhea the possibility of a lactase deficiency, or of a chronic infection should be considered. If steatorrhea is present, the possibility of celiac disease or pancreatic insufficiency such as occurs in cystic fibrosis or Shwachman's syndrome has to be excluded. Patients with chronic respiratory complaints such as chronic rhinitis or asthma should be given a trial of a milk-free diet.

Investigations

Investigations in cases of suspected food protein hypersensitivity are specific and nonspecific. Nonspecific investigations are not helpful in making a diagnosis but enable one to obtain parameters of the patient's nutritional status and absorptive capacity. They include a complete blood count, the prothrombin time, serum iron and folate levels, electrolytes and blood gases, serum calcium, phosphorus, liver enzymes, proteins and vitamin A, D and E levels. In severely ill infants, tests for malabsorption such as the xylose tolerance tests, Sudan red test for fat in stool or a 72-hour stool fat collection may be warranted.

More specific investigations include measurement of serum immunoglobulins, in particular total IgE, and serum IgE antibodies to suspected antigens. Skin testing may be useful in children over 1 year old. Positive reactions are of no significance, but a negative reaction means that the food is probably not responsible for producing the patient's symptoms. Histological changes in intestinal biopsies before and after challenge have been used for

making the diagnosis [37]. A few centers consider this to be a routine procedure for diagnosis. Intragastric provocation during endoscopic observation is another test employed in a few centers. The basophil histamine release assay is employed in few laboratories only and has not proven to be a reliable test.

Treatment

The encouragement of breast-feeding is one of the most important prophylactic measures in the prevention of food protein hypersensitivity. As this condition is frequently a transient phenomenon in infancy, breast feeding may prevent the appearance of food protein hypersensitivity or mitigate its severity.

If breast-feeding is not possible, soy or protein hydrolysate formulae should be considered in infants with a family history of food hypersensitivity in order to try to prevent its occurrence. The mother must be instructed, however, only to use established formulae and not to try to make up a home-made preparation without proven nutritional adequacy.

The treatment of established food protein hypersensitivity is dietetic. Various pharmacological agents have been advocated in the course of the years, but none have stood the test of time [3, 4]. In infancy, when the diet is limited to human milk, cow's milk protein or soy bean-based formulae, elimination of the offending protein is relatively easy. If the infant is breast-fed, the mother has to abstain from the potential allergens, which frequently are also cow's milk; if not, only by a process of trial and error can the offending antigen in mother's milk be identified.

In infants, total protein hydrolysate formulae are the preferred treatment. However, infants over 3 months old are not always willing to take them because of their taste. If so, a soy protein formula should be tried. It must be borne in mind that an appreciable number of infants with cow's milk protein hypersensitivity may also develop sensitivity to soy protein.

Hypoallergenic formulae are of two kinds: the extensive hydrolysates, and the elemental formulae.

The protein of extensive hydrolysate formulae is enzymatically digested with pepsin-trypsin. These formulae may be based on cow's milk proteins, either casein or on the whey proteins, on soy protein or on collagen. The fat is of vegetable origin and the carbohydrate is glucose or glucose polymers. A high degree hydrolysates include such products as Nutramigen™, Pregestimil™ and Profylac™. The extensive hydrolysate formulae have proven to be the most important and the most efficacious means of treating food protein hypersensitivity of infants in the first year of life. They are also employed in the treatment of galactosemia and lactose intolerance. All protein hydrolysate

formulae contain peptides that are potentially antigenic and, therefore, one still meets patients that have adverse reactions even to the extensive hydrolysates. Such reactions are rare in our experience, but there have been several reports in the literature [11–13]. One prospective study even claims that the incidence of hypersensitivity to the extensive hydrolysates may be as high as 10% [14]. In Europe trials have been undertaken with so-called 'partial' hydrolysates. Of infants with cow's milk-induced food protein hypersensitivity, some 50% reacted to the partial hydrolysates confirming that partial hydrolysates are not indicated in the treatment of cow's milk-induced food protein hypersensitivity. These preparations have been suggested as a means of prophylaxis of protein hypersensitivity, but their efficacy still has to be evaluated. The elemental formulae are discussed below.

Soy-based formulae: Soy milk has been used as an infant food in China and Japan for centuries. It was introduced in 1929 into the Western world as an alternative for infants with cow's milk protein hypersensitivity. Commercial soy-protein infant formulae are adequate for normal growth and bone mineralization in term infants [12]. However, soy proteins have a lower protein efficiency ratio than do cow's milk proteins. Unadulterated soy protein has antitryptic properties which are of course undesirable. Commercial products are heat treated which destroys the antitryptic properties and reduces the antigenicity of the products. However, even after heat treatment, soy proteins may trigger an adverse intestinal immune response and cause food protein hypersensitivity in some individuals.

The composition of soy formulae includes purified soy protein. The major soy protein is a globulin consisting of β-conglycine and glycine. The fats are vegetable oils. The carbohydrates are glucose or glucose polymers, maltodextrins, sucrose or cornstarch. None of the formulae contain cow's milk protein or lactose [12]. They are usually fortified with *L*-methionine, taurine, iron, vitamins and trace elements. It is advisable for carnitine to be added as well. In addition to the use of soy formulae for the treatment of cow's milk protein hypersensitivity, other indications are lactase deficiency, galactosemia. Soy formulae may also be used as a standard formula for healthy infants. Contraindications to the use of soy formulae are hypersensitivity to soy protein. Soy formulae are also contraindicated as a diet for premature infants, as they are not capable of preventing rickets at this age.

Infants having adverse reactions to the hydrolysate and to the soy formulae, present a challenge to the treating physician. Some of these infants will do well on *elemental formulae* such as Vivonex™, Tolarex™, Neocate™ and L-Emental pediatric™. These formulae contain isolated amino acids, glucose and glucose polymers, essential fatty acids, vitamins, electrolytes and trace elements. They contain no antigenic material. If the patient has severe malab-

sorption as a result of prolonged ingestion of a protein deleterious to the patient, even the absorption of the elemental formula may not supply the patient with an adequate amount of food. In such cases recourse must be had to intravenous alimentation.

Follow-Up

Following the institution of an appropriate diet, the physician should ascertain that the growth remains normal. Growth should continue to be charted, as the main criterion of effective treatment is a normal growth curve. Late food protein hypersensitivity reactions may be manifested only by a failure to gain weight.

The patient should be challenged with the putative antigen at regular intervals. It is our custom to do this every 2 months. However, the exact interval is at the discretion of the physician. It is important to establish to what foods the patient is hypersensitive, and to give appropriate instructions to the staff of the Home Care Center, if the patient attends one.

In older children who are on limited diets because of their food hypersensitivities, it is important to ascertain, if need be with the help of a dietician, that the patient receives adequate amounts of protein, calories, calcium, phosphorus, iron, carnitine and trace elements.

When the food challenge no longer evokes a pathological response, the child can return to a normal diet.

Prognosis

The rate of recovery from food protein hypersensitivity reactions varies in different reported series. One reason for this discrepancy is the target organ involved. Gastroenterologists report a recovery rate of 86% at the age of 4 years. In patients attending allergy clinics, only 67% recover by that age. Initial high IgE levels are predictive of slower recovery. Some 42% of children with hypersensitivity to cow's milk protein, develop hypersensitivities to other food proteins, most commonly soy, egg or fruit proteins [38]. Deaths contine to be reported. These may be due to anaphylaxis or to pharyngeal or laryngeal edema causing respiratory obstruction. Nuts appear to be one of the most common allergens responsible for fatalities. This is particularly likely to happen when the patient or his parents are not aware that the allergen in question is present in a specific food eaten. We have seen a case of death in a child hypersensitive to milk, after receiving biscuits marked 'non-dairy' although

subsequent analysis showed them to contain casein. Another dangerous situation is when children sensitive to nuts eat cake containing this ingredient, without it being visible.

The Future

This article was written by pediatric gastroenterologists. It therefore concentrates on that clinical entity seen in their specialty and in the first year of life. Were it written by allergists, it would differ markedly in viewpoint, subject matter, statistics and in the conclusions.

It has been customary, heretofore, to regard infantile food protein hypersensitivity as one nosological entity. It seems to the authors that this classification may have to be revised. It is our contention that in the first year of life we meet two types of food hypersensitivity. One is the reaction of the immature intestine to the insult of being pounded with, for this age, unreasonable amounts of foreign antigen at a time when Nature built an absorptive apparatus specifically designed for having to deal with maternal proteins only. As the intestine matures, the hypersensitivity reactions diminish in intensity and ultimately disappear altogether; often before the age of 1 year and always by the age of 2.

The other type of reaction is atopic and may appear at any age; it often lasts longer.

The above hypothesis has not yet been put to the test: it would be interesting to test its validity by prospective studies and by review of past clinical material.

Treatment by elimination diets has not changed significantly in the last 3 decades. Nonetheless, morbidity seems to be decreasing. This is probably due to an increased awareness by pediatricians, to a higher incidence of breast-feeding and to the reduced antigenic load of modified formulae. Further encouragement and practical tuition in the practice of breast-feeding may improve the morbidity even more.

Future developments must include an intensive study of the mechanism of tolerance in general, and of the part played by cytokines in this process in particular. Many of the cytokine phenomena described so far in hypersensitivity states come from animal studies and studies in atopic dermatitis. Their applicability in infantile food protein hypersensitivity has to be determined. Only then, as a result of the knowledge acquired, will it be possible to modulate the intestinal immune response.

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Carbohydrates in Infant Nutrition

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Introduction

Carbohydrates (CHOs) are the main source of energy in nutrition. There are many concerns related to the use of CHOs, especially in the premature, compromised infant and the growing child with regard to bioavailability, cavities in the teeth, hyperactivity, atherosclerosis, diabetes, etc.

During prematurity and early infancy the concern is related to the availability of enzymes associated with the hydrolysis of disaccharides, and the hydrolysis and absorption of polysaccharides.

The main question evolves around the biologic advantage of having β-galactoside, lactose, as the primary source of CHO during the nursing period. The fact that the enzyme lactase is a rate-limiting enzyme in the small intestinal mucosa and is the first to be affected in small intestinal mucosal injury has raised the need for other possible CHOs as a source of energy in early infancy. Furthermore, the developmental low activity of lactase in prematures has prompted the search for additional CHOs as a source of energy. Indeed, the finding that the enzyme sucrase is abundant and not rate limiting from early life laid the basis for the successful introduction of sucrose to specially designed formulas in infancy.

Another concern was that polysaccharide-like starches cannot be used early in life because of the lack of pancreatic amylase. The finding of high levels of glucoamylase in the mucosa of the small intestine provided a new concept of utilizing short polymers of glucose as an energy source with a low osmolality for prematures and young infants. Furthermore, lactose intolerance

secondary to mucosal injury and diarrhea could be dealt with by using sucrose and short polymers of glucose as an energy source because the enzymes sucrase and glucoamylase are affected to a lesser degree. On the other hand, secondary lactase or disaccharidase deficiencies end up with unabsorbed CHOs in the colon that are hydrolyzed by bacteria to organic acids like acetic, butyric and propionic acids. These acids are the main luminal source of energy to the colonocyte. It is not clear what the importance of these organic acids as an energy source to the colonocyte is, or whether they have deleterious effects on the infants.

In addition to being an energy source, CHOs act as precursors for nucleic acid synthesis. Because they can be synthesized from protein and fat, CHOs are not considered an essential nutrient. However, several structures such as the brain, erythrocytes, the optic lens, and the kidney medulla all utilize glucose for their metabolism [1].

The role of dietary fibers in infant nutrition is discussed by Stark and Madar in this volume.

The Main Dietary Sugars

CHOs can be classified as simple (mono- and disaccharides) and complex (polysaccharides) sugars.

Monosaccharides

These are the simplest sugars. They can come in the form of aldehydes, ketones, pentoses or hexoses. The human diet contains mainly three types of hexose sugars, glucose, fructose and galactose. Glucose is found in fruits, especially grapes, and to a lesser extent in vegetables and legumes. It is commercially produced from the hydrolysis of corn syrup. Fructose is found naturally in fruits, while galactose is usually not freely available in nature.

Disaccharides

Lactose (milk sugar) is composed of glucose and galactose. It is found only in milk (either human or animal) but not in plants. It is the most common source of CHO in regular infant formulas.

Sucrose (cane sugar) is composed of glucose and fructose. It is derived from plants, fruits and vegetables, and is the familiar table sugar which is used as a sweetener because of its sweet taste and solubility.

Maltose is formed by two molecules of glucose linked by a 1,4-glycosidic bond. Most dietary maltose is formed by hydrolysis from starch. It is very soluble but less sweet than sucrose.

Polysaccharides

These can be either homopolysaccharides containing only glucose and form glycogen, amylose, amylopectin, and cellulose, or heteropolysaccharides which are composed of a mixture of different types of monomers. Starch is the main CHO in human nutrition besides sucrose or lactose. Babies consume starch usually in the form of cereal, although small amounts can be found in certain special infant formulas. The two major components of starch are amylose which is composed of a linear chain of glucose units joined by α1,4 linkage, and amylopectin which is composed of linear 1–4 chains and lateral chains joined by α1,6 linkages [2]. It is usually found in plants, cereal grains, seeds, fruit, vegetables and roots. Natural starch comes in the form of crystals. Starch granules are insoluble in water and are heat-sensitive. Commercially, they are modified by substitution which improves stability and cross-linking to preserve their viscosity.

Short Polymers of Glucose

These sugars are very important in the food industry and provide the main contents of formulas when lactose or sucrose are contraindicated [3]. Short polymers of glucose, like corn syrup solids, are available by hydrolysis of starches. In addition to its excellent absorptive capability, it inhibits water and electrolyte secretion by inhibiting cAMP, thus making it an ideal source for infant feeding, particularly when the child has diarrhea [4, 5].

Cellulose

This is a linear polymer of glucose linked by β1,4 bonds without branches. Its source is plants, usually the leaves or stalks. Cellulose is undigestible in the human digestive system and has residue action.

Main Staples Containing Starches

Rice

Rice is consumed in greatest quantities in Asia and Africa where it is the main source of calories. It is usually milled as ordinary white rice with much of its vitamin and mineral content being lost during processing. By boiling or steaming it before polishing, its vitamin and mineral content can be increased. Parboiling also increases the concentration of calcium, potassium, and phosphorus in the final product.

Wheat

This is the main source of CHOs in the Western world. The outer coating of the grain and germ contains the bulk of its minerals and vitamins. As

our knowledge of the physiological importance of fibers in human nutrition increases, a greater proportion of whole wheat will hopefully be milled for the consumer's benefit.

Other Cereals

Cereals that are important but less popular include rye, barely, oat and millet. Only oats have been described as having an anti-lipemic effect [6, 7].

CHO Content in Infant Nutrition

CHOs provide 40–60% of the required calories in the Western world and up to 80% in developing countries. While glucose is the main CHO utilized during fetal life, lactose becomes the major CHO in the initial diet of the healthy newborn. Actually, the period from infancy to childhood is characterized by three phases, each with a different source of dietary CHO. In the initial phase, usually between birth and 4 months of age, the main CHO is lactose derived from human milk or formula in the absence of solids. A transitional phase, starting at around 4 months of life, follows the introduction of other monosaccharides (e.g. fructose) and disaccharides (e.g. sucrose), with fruit and vegetables given together with various polysaccharides (e.g. starches) being added to the infant formula. In the final phase, at around 12 months of age, the shift to solid food is complete and polysaccharides predominate. Human milk as well as milk-base formulas contain around 7 g/100 ml of lactose, while the lactose concentration in cow's milk is only around 5 g/100 ml [8].

The type of CHO in soy formulas is not lactose but sucrose or short polymers of glucose or a mixture of the two. Soy formulas are frequently recommended for infants who have suspected cow's milk protein hypersensitivity or lactose intolerance. It should be emphasized, however, that soy-base formulas are not recommended for routine use, but only when specifically indicated. Ths is because lactose is crucial for calcium absorption, and its absorption is decreased by soy formulas [9]. Because of reports of bone demineralization in preterm infants fed soy formulas, their use in this group of infants has been strongly opposed [10, 11]. Extra calcium is currently added to these formulas and further studies may confirm its potential use. However, a recent study demonstrated that the absorption of calcium in premature infants was more efficient with short polymers of glucose than with lactose [12].

Short polymers of glucose, like corn syrup solids, are composed of 5–10 glucose units joined by an α1,4 linkage. Corn syrup is a generic term for products derived from cornstarch by hydrolysis with acid or enzymes [13].

These products are classified according to their chemical-reducing power relative to glucose, which has a dextrose equivalent (DE) of 100%. The DE of corn syrups ranges from less than 20% to more than 95%. A low DE corn syrup is slightly hydrolyzed, thus it is more starch-like than a corn syrup with a high DE containing large amounts of glucose. Because of the potential malabsorption of the lactose by preterm infants and because of the ability of glucose polymers to decrease osmolarity, short polymers of glucose rather than additional lactose are used in all special formulas for preterm infants [14]. Short polymers of glucose are a frequent additive to infant feeding to boost the caloric content. They are added normally at around 3–4 months of age and can be given even earlier in certain difficult feeding situations or when there is an increased caloric requirement. However, this must be done with care, as imbalance of other nutrients (e.g., proteins) may occur.

Modified Food Starches

Many special formulas (e.g., Nutramigen, Pregestimil) and strained foods contain modified corn or tapioca starches. These formulas may provide approximately 15% of the total calories taken in the form of modified starch which is used to facilitate suspension of insoluble nutrients during feeding. The amount of modified starch added to some commercial infant desserts may amount to as much as 45% of the total solid content. The glucose units of these starches are chemically cross-linked by phosphate and adipate or acetyl-attached groups. Modified food starches also possess certain technical properties such as altered viscosity and 'mouth feel', freeze-thaw stability, gel clarity, and stability in acid products. Animal studies have shown that caloric availability of modified food starches is similar to that of unmodified starches [15].

Digestion and Absorption of CHOs

Most dietary CHOs undergo two main steps: first they have to be digested and then they are absorbed from the intestinal mucosa. The only exceptions are monosaccharides which do not require enzymatic digestion. They can be transported from the bowel lumen through the mucosal barrier into the enterocytes and then to the liver through the portal system. Disaccharides need digestion by disaccharidases which reside in the intestinal mucosa usually located in the upper part of the villi. Starches, on the other hand, first require intraluminal digestion by salivary and to a greater extent by pancreatic amylases.

Absorption of Monosaccharides

Glucose and galactose are both absorbed in the small intestine by the same active transport system. The carrier located in the brush border membrane transfers glucose or galactose via a sodium/glucose cotransporter from the lumen to the cytoplasm of the enterocyte through the cell membrane. This system is driven by the negative gradient of concentration of sodium between the lumen and cytoplasm. This sodium/glucose cotransporter has been cloned and sequenced from the rabbit intestine and termed SGLT1 [16]. The human SGLT1 gene was recently found to be located on chromosome 22, and the entire gene was cloned and sequenced [17, 18].

The mechanism of fructose absorption is distinct from that of glucose and galactose. Fructose is absorbed by facilitated diffusion and is carrier-mediated [19]. This specific carrier, which has a high affinity to fructose, has been termed Glut 5 and has been isolated from the human intestine and cloned [20].

Digestion and Absorption of Disaccharides

Lactose is hydrolyzed by lactase to glucose and galactose before absorption can occur. Lactase is a dimeric enzyme anchored to the upper brush border membrane which protrudes on the luminal surface and is located in the proximal part of the intestine. The active sites have a broad substrate specificity for a variety of β-glycosidase, of which lactose is the only one with significant nutritional importance [21].

Sucrase isomaltase (SI) is a dimeric enzyme consisting of two peptide chains, each with an active site [22]. One is specific for sucrose and maltose and the other is specific for isomaltose and maltose [23]. Although this enzyme is located in the brush border of the intestine, its distribution is less superficial and is thus considered to be less vulnerable to mucosal injury [24]. SI is an α-glucosidase involved in the digestion of sucrose and starch. Sucrase hydrolyzes both the α1,4-glucose linkage of maltose and maltriose and the glucose-fructose linkage of sucrose [25]. Isomaltase is an α-glucosidase and cleaves the α1,6-glucopyransoyl bonds of branched oligosaccharides, the 1,6 linkage of isomaltose, as well as the 1,4 linkage of maltose [26]. The gene encoding SI has been localized to the long arm of chromosome 3 and has been entirely sequenced. A high homology was found between the isomaltase and sucrase portion, indicating that SI probably evolved by partial gene duplication [27].

Trehalase is a disaccharidase with a hydrophobic nature, located more deeply in the mucosa [28]. It is strictly limited to a specific substrate, trehalose, which is a disaccharide made of two glucose moieties with a glycosidic bond

in the 1–1 configuration. Trehalose is found in mushrooms, yeast, wine and honey. The food industry is showing considerable interest in trehalose because it has been found to have a protective effect on food during air drying, a cost-effective alternative to freeze drying.

Digestion and Absorption of Starch

Starches are mainly composed of two types of glucose polymers, amylose and amylopectin. Amylose is a linear polymer of glucose units linked by α1,4-glycosidic bonds, while amylopectin is a branched polymer with side chains of α1,6 bonds [29]. The starch digestion first undergoes luminal digestion which begins in the mouth by salivary α-amylase. This process is very limited in humans due to inactivation of salivary amylase by gastric acid and pepsin during passage in the stomach [30]. The major source of amylase is from the exocrine pancreas and is secreted to the duodenal lumen. However, in small infants and particularly in premature infants, salivary amylase and breast milk amylase replace the nonexistent or low level of pancreatic amylase. Amylase can breakdown starch to maltose, maltotriose, maltotetrose, and maltopentatose. Mucosal digestion is the final digestive process accomplished by hydrolysis of these short glucose polymers into free glucose by maltase glucoamylase or SI located in the brush border membrane. Glucoamylase is a brush border enzyme that acts upon glucose polymers containing relatively few (4–9) glucose units. In contrast to disaccharidases, it is more deeply located with a wider distribution, making it the least vulnerable enzyme, whereas brush border disaccharidases are likely to be diminished during chronic diarrhea because of their predominant localization in the proximal small intestine where the mucosal injury is more severe [31]. Thus, in addition to starch digestion, it has a major role in the digestion of short polymers of glucose, derived from rice or corn which are supplied in many specially designed infant formulas. Finally, it has been proven in several studies that short polymers of glucose, despite their more complex structure, are better absorbed than monosaccharides [32] and that their lower osmolarity makes them the ideal carbohydrate source for the infant with prolonged diarrhea.

Ontogeny of the Absorption of CHOs

The changes in dietary CHOs during development are associated with corresponding changes in the absorption of monosaccharides. By the time weaning takes place, the amount of galactose will decrease with a correspond-

ing increase in glucose and fructose. Glucose and galactose are absorbed by a similar active transport. This mechanism seems to develop fairly early in intrauterine life, although it was reported that younger infants have a delay in the appearance of maximal blood glucose after an oral load of glucose than do older infants. This may either represent a slower rate of absorption or it can result from a different rate of utilization. Despite the relative deficient monosaccharide uptake in children as compared to adults, the transport mechanism does not seem to be the limiting step in CHO absorption. Fructose absorption occurs by facilitated diffusion that is energy-independent. This mechanism is intact around birth, although no data are available as to the timing of its development. On the other hand, premature babies can tolerate only moderate amounts of fructose [33].

Intestinal lactase is detected as early as 12 weeks of gestation, but it accumulates slowly so that only 30% of the specific activity in term infants is present by 28–34 weeks of gestation. The peak level is achieved only around 38–40 weeks of gestation. This makes the preterm infant relatively lactase-deficient. Levels of lactase decline at around 3–4 years of age in most individuals; it diminishes up to trace activity in 70% of the black race [34].

Sucrase activity is present by 10 weeks of gestation and by 28–34 weeks of gestation it reaches 70% of the specific activity of term babies. Sucrase activity persists during the entire lifetime. The developmental pattern of maltase and isomaltase is basically the same as that of sucrase. Glucoamylase is present in the intestine by 28 weeks of gestation and attains 50–100% of the adult level at term. Pancreatic α-amylase has been detected in the fetal pancreas by 22 weeks of gestation. Most studies, however, show that α-amylase activity in the duodenal fluids of infants up to the age of 4 months remains low or absent. In premature infants (i.e., 32–34 weeks of gestation), virtually no α-amylase can be detected in the duodenum during the first month of life.

Despite the lack of α-amylase in the duodenal fluid, most newborns and even premature babies tolerate short polymers of glucose suggesting an alternative pathway of digestion. This route can be achieved by the relatively high level of intestinal glucoamylase. In addition, salivary amylase and human mammary amylase contribute to polysaccharide digestion. The contribution of salivary amylase in starch is disputable, because the contact between starch and salivary amylase is mainly in the oral cavity. In the adult or older child as salivary amylase reaches the stomach, it is rapidly inactivated by gastric acid and pepsin, but the stomachs of small infants and particularly those of premature babies are less acidic.

These ontogenic findings on the digestion of short polymers of glucose provided the ability to use short polymers of glucose that have high caloric density and low osmotic load. These properties make them an ideal supplement

for infants aged 3–4 months and older or even earlier when either additional calories are required for a poor weight-gaining infant or the infant with gastroesophageal reflux when there is a need to thicken the formula.

Malabsorption of CHOs

Mechanism of CHO Malabsorption and Clinical Implications

Malabsorption can be caused by a defect in the digestion such as an enzymatic defect, either luminal or mucosal, or by dysfunction of the mucosa. When malabsorption is secondary to mucosal injury, it usually affects many nutrients and may be associated with structural damage to the absorptive villi or to brush border enzymes. In contrast, congenital enzymatic deficiency usually involves a single enzymatic defect, thus it is specific to a single CHO. As mentioned earlier, most CHOs need to be digested before they can be absorbed across the intestinal barrier. The singular exception is the intraluminal step carried out by amylase which can also be replaced, at least partially, by intestinal glucoamylase.

CHO malabsorption is mostly secondary to mucosal damage either by infections or specific mucosal injury, e.g., celiac, cow's milk allergy, and immune enteropathy. While a primary enzymatic defect is rare, its detection is crucial since it is a persistent condition which requires specific and ongoing nutritional measures.

Knowledge of the pathophysiologic basis of CHO malabsorption is essential for diagnosis as well as for patient management. The unabsorbed CHOs enter the large intestine where they are fermented by luminal bacteria to short chain organic acids which are predominantly acetic, butyric and propionic acids. They can be partially utilized as an energy source by the colonocytes. However, the presence of these small molecules in the large bowel exerts an osmotic load, resulting in a flow of water and electrolytes into the lumen. In this way, CHO malabsorption is a typical example of osmotic diarrhea which is usually ameliorated by fasting. The stool osmolarity is significantly greater than the stool electrolyte sum. The main clinical symptoms are watery, occasionally explosive diarrhea with no mucous or blood. The diarrhea can cause dehydration, electrolyte imbalance, metabolic acidosis, and failure to thrive (FTT). When the diarrhea is prolonged, it may lead to FTT, malnutrition, edema and irritability. The fermentation also enhances gases production, mainly carbon dioxide, hydrogen and methane. They easily diffuse across the colonic mucosa into the blood stream and can be detected in the expired breath. This is the basis for the hydrogen breath test in which the increase in the expired hydrogen over 20 ppm reflects the specific measured CHO

malabsorption. The production of gases is the basis for abdominal distention, cramps, pain, and flatulence which are the main symptoms of CHO malabsorption. In addition, the stool is more acidic and contains reducing substances.

Glucose and Galactose Malabsorption

Glucose and galactose in the small intestine are both absorbed by the same active system as described previously [16]. Any defect in the carrier impairs the absorption of both of these sugars.

Glucose-galactose malabsorption was first described by Linqvist and Meeuwisse [35]. Since both sugars are included in the diet of all infants, severe symptoms of watery diarrhea, which may lead to dehydration and metabolic acidosis, can begin in the first day of life. As might be expected, intestinal biopsies from children with this condition show no histologic abnormality. The genetic inheritance is autosomal recessive. The defect is Na^+-dependent absorption of glucose in the intestine brush border. A single nucleotide base change, from guanine to adenine, was discovered at position 92 of the gene for SGLT1 on chromosome 22. This mutation led to a change in amino acid 28 from asparate to asparagine [36]. The treatment is the elimination of any source of glucose or galactose from the diet, and the source of CHO should be fructose only. The patients tend to tolerate small amounts of CHO later in life. The diagnosis of this form of malabsorption should be made from the presence of unexplainable watery diarrhea appearing in early infancy.

Fructose Intolerance

Malabsorption of fructose is quite common. It now bears greater clinical significance since the consumption of fructose has increased tremendously. This condition will appear only when fructose is introduced to the infant diet, usually around 4–6 months of life. Since it is dose-dependent, it is very common in toddlers and children who drink large amounts of fruit juice. Apple juice, a very popular drink among children, differs from most other fruit juices in that it contains an excess of fructose as compared to glucose. In contrast, equimolar quantities of both sugars are most efficacious for absorption and thus fructose will be absorbed well in the presence of glucose. Therefore, the Committee on Nutrition of the American Academy of Pediatrics warned that there are potential problems associated with the ingestion of excessive amounts of fruit juices by young children. Malabsorption of CHO may exacerbate

gastrointestinal symptoms in children who already have chronic nonspecific diarrhea or can lead to the onset of symptoms in otherwise healthy children [37].

Sorbitol Intolerance

It was suggested that sorbitol intolerance can promote diarrhea in the toddler. Sorbitol, fructose and glucose are the main sugars in apple juice [38]. There are 4 g of sorbitol in 1 liter of apple juice. Furthermore, it was proported to diminish the absorption of fructose.

Lactose Intolerance

The malabsorption of lactose can be classified into four categories.

(1) Ontogenic developmental lactase deficiency occurs in premature infants born between 26 and 34 weeks of gestation. The lactase specific activity is only 30% of that seen in full-term infants.

(2) Congenital lactase deficiency, an extremely rare disorder, has only been reported only in a few cases and is discovered immediately after birth [39]. Inheritance seems to be autosomal recessive. The activities of other disaccharidases are normal and small intestinal mucosal morphology is normal. The symptoms are very similar to those described for glucose-galactose malabsorption when the infant is first given lactose either by breast milk or regular formula. We have not seen a case of congenital lactase deficiency after performing more than 5,000 biopsies. The disorder can be confirmed by intestinal biopsy demonstrating total absence of lactase activity and an otherwise normal appearance of the mucosa. The only treatment is elimination of lactose from the diet.

(3) Secondary lactase deficiency can occur at any age but is more common in young infants and is associated with an insult, usually gastroenteritis, damaging the intestinal mucosa [40]. As mentioned previously, lactase is the most vulnerable enzyme. Thus, it is not surprising to find that it is a common sequence of gastroenteritis, in particular in young infants. In contrast to the congenital form, the mucosal histology will reveal that the intestinal villi will be flattened and injured, and other disaccharidase activities can be expected to be decreased due to mucosal injury. The obvious treatment would be elimination of lactose until the symptoms disappear. The time needed for this elimination depends on the severity and extent of the primary process which is usualy determined clinically.

(4) Lactose intolerance (or 'adult'-type lactase deficiency) is the most common form occurring after childhood. In most mammals, lactase activity reaches maximal levels around birth, and progressively declines after weaning. In the majority of people worldwide, by about 4–6 years of age, the enzymatic activity is 10% of that at birth due to decreased enzyme synthesis. Lactase activity is genetically and ethnically determined and inherited as an autosomal recessive gene. Nevertheless, it has been proposed that in societies with milk-producing animals, the persistence of lactase activity into adulthood has a significant advantage. Thus, there is a autosomal dominant mutation presumably sustained by a regulatory gene. In this mutation, lactase activity persists throughout adult life [41]. The clinical situation is typified by flatulence, abdominal discomfort, bloating and diarrhea which can occur with the consumption of as little as 12 g of lactose (around 1 glass of milk). The diagnosis is based on a positive lactose hydrogen breath test concomitant with suitable clinical symptoms which vanish with the removal of lactose from the diet. As a result, elimination or, in some cases, reduction of lactose intake constitutes the treatment of choice [42]. Today, many available commercial lactase preparations can be added to milk to predigest the lactose; there are also many lactose-free products available on the market.

SI Deficiency

SI is a dimeric enzyme consisting of two peptide chains, each with specific activity for sucrose or isomaltose. The enzyme, like all the other disaccharidases, is anchored to the brush border making it also vulnerable, but to a much lesser extent than lactase because its location is less superficial. Thus, secondary SI deficiency will occur only with severe mucosal injury. Moreover, there is no age-dependent enzyme activity, and its level remains constant throughout life.

The congenital form of SI deficiency (CSID) has recently been the focus of increased research activity. Important new work has included the elucidation of molecular defects associated with the inherited form of sucrose malabsorption and the recent cloning of the human SI gene. The enzyme SI is a heterodimer complex composed of two similar but not identical subunits. Each subunit consists of a single glycosylated polypeptide chain with an apparent molecular weight in the 120- to 160-kD range. The gene encoding the human SI has been localized to the long arm of chromosome 3. An optimal alignment of the two subunits reveals a high degree of homology between the isomaltase and sucrase portions (41% for amino acids and 52% at the DNA level), indicating that SI probably evolved by partial gene duplication [27]. RNA

probes have localized the greatest accumulation of SI mRNA to the nucleus of cells at the crypt-villus junction. The regulation of SI activity is complex, and multiple factors modulate its activity at the level of transcription, translation, glycosylation, and processing. They contain dietary factors, such as protein, CHO and sucrose levels, as well as hormonal factors, such as thyroxin, and corticosteroids [43]. There is a significant phenotype variation in patients with CSID. They all lack sucrase, but some have only traces of isomaltase activity, some have reduced but significant isomaltase activity, and still others show normal activity. The presence of residual isomaltase activity in some patients suggests that CSID is not the consequence of a complete absence of SI gene expression. It apears that this phenotypic variation may be mirrored in genotypic heterogeneity. Although specific mutations have yet to be identified, it emerges that point mutations causing amino acid substitutions may lead to abnormalities of intracellular processing (glycosylation and folding), intracellular transport and homing and insertion of the enzyme into the brush-border membrane. Yet, as many as five different transport-incompetent or functionally altered enzymes have been discovered in patients with CSID. CSID is considered an uncommon autosomal recessively inherited disease, but due to its wide phenotypic variation, it is likely that its prevalence has been underestimated. As a consequence, the clinical presentation of CSID is also variable. The symptoms will appear only with the introduction of sucrose into the diet. Thus, breast-fed babies or infants consuming lactose-containing formulas will not manifest symptoms until they consume juices, solid foods, or medications sweetened by sucrose. Baby cereals usually cause less severe symptoms because of the compensatory mechanism for starch digestion. The symptoms are typical for all other forms of sugar malabsorption and include vomiting, chronic diarrhea, FTT, abdominal pain and irritable bowel. The diagnosis is based on a sucrose breath test and evidence of clinical improvement with the elimination of sucrose from the diet. Confirmation can be achieved by intestinal biopsy showing normal structure with no sucrase activity, and normal activity for other enzymes. Treatment consists of life-long adherence to a strict sucrose-free diet. It is seldom necessary to make the diet starch-free as well, except in infants or in older children in whom the institution of a sucrose-free diet does not lead to prompt disappearance of symptoms. In this case, the starch content of the diet must be reduced, with special attention to foods having a high amylopectin content, such as wheat and potatoes. Enzyme substitution therapy has recently been applied to patients with CSID. It includes either lyophilized baker's yeast (*Saccharomyces cerevisiae*) or liquid yeast sucrase.

Trehalose Intolerance

Trehalose occurs in mushrooms, insects and some worms. Clinical symptoms of trehalose intolerance are very rare and include severe watery diarrhea which is initially suspected to be due to mushroom intoxication. The defect is a deficiency in trehalase [44].

Glucoamylase Deficiency

Glucoamylase is a monomeric polypeptide brush border enzyme. It hydrolyzes mainly the α1,4-glycosidic bond, and its maximal activity occurs on short polymers of glucose, i.e. 4–9 units. Its deep and wide location makes it resistant to intestinal mucosal injury. However, our group [45] has recently described 15 children with glycoamylase deficiency of whom 6 had a secondary glucoamylase deficiency associated with a significant small intestinal mucosal injury together with other disaccharidase deficiencies. The other 9 patients with normal mucosal morphology were defined as having a primary glucoamylase deficiency. They had symptoms of intolerance, such as diarrhea and abdominal distention, which responded to starch elimination and reoccurred after reintroduction of starches to the diet.

In conclusion, CHO are the main energy and nutrition source in infant nutrition. Understanding their metabolic pathway, absorption mechanism and ontogenic pattern are essential for optimal use in the feeding of the normal infant, with special implications for the premature and compromised infant.

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Nucleotides in Infant Nutrition: Effects on Immune Function

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'Since the demonstration by Victor C. Vaughn that nuclein is a prominent and abundant constituent of the phagocyte, and that it is a powerful germicide, and that the germicidal properties of blood serum are due to nuclein which comes from the polynuclear corpuscles, I have been greatly interested in the subject' [1].

Investigators over 75 years ago [1] claimed that large increases in leukocyte counts resulted from the administration of nuclein, which is nucleic acid derived from wheat germ. These observations were based on patient case and animal studies, and science was not sufficiently equipped to address the how and why of these observations. Since the mid 1980s, animal research has suggested that dietary nucleotides are not essential, but that they enhance immune function by an unknown mechanism [2, 3]. Since human milk contains higher concentrations of nucleotides than cow's milk, and cow's milk-based infant formulas were not fortified with nucleotides, investigators began to ask whether nucleotides might be one of the components of human milk that enhances the immune system of breast-fed infants compared to formula-fed infants. Here we review the two key issues related to inclusion of nucleotides in infant formula and their potential for enhancing the infant's immune system: (1) what are the levels of nucleotides in breast milk, and (2) what clinical data support an effect of nucleotides on immune function.

Background

Nucleotides have diverse biologic functions and they participate in numerous physiologically critical processes. Deoxyribonucleotides carry the ge-

netic code as DNA, and ribonucleotides in various forms of RNA comprise the machinery for implementing that code. As components of coenzymes such as NAD, FAD, and coenzyme A, nucleotides play an integral role in intermediary metabolism. Adenosine metabolism not only provides a primary energy source as ATP, but the ratios of ATP, ADP and AMP modulate the activity of many enzymes. Nucleotides serve to activate metabolic intermediates, such as UDP-galactose in the synthesis of lactose and UDP-glucose in the synthesis of glycogen. Nucleotides, such as cyclic AMP, also initiate second messenger cascades. Thus, nucleotides are ubiquitous compounds found in virtually every plant and animal cell and therefore are normal constituents of human milk and the mixed diet. Nucleotides consist of a nitrogenous base [usually adenine (A), cytosine (C), guanine (G), thymine (T), or uracil (U)] and 1–3 phosphate groups covalently bound to a sugar moiety (ribose or deoxyribose). Removal of the phosphate groups results in a nucleoside. A polymer of deoxyribonucleotides is known as DNA, and one consisting of ribonucleotides is referred to as RNA; ribosomal, messenger or transfer.

History of Feeding Nucleotides during Infancy

Commercial term infant formulas have been on the market supplemented with 10.2 mg nucleotides/l since 1983 and with 33 mg nucleotides/l since 1989. Infant formula with 72 mg nucleotides/l has been marketed since 1996. Nucleotides are added to formulas in relatively pure form, either as free monophosphates or their sodium salts. Breast feeding over thousands of years defines a long history of infants consuming relatively high levels of nucleotides compared to those in formula. Leach et al. [4], in a study described below, identified pooled breast milk samples containing up to 50 mg/l of mononucleotides, the form identical to that added to formula. Further, banked human milk and breast milk have been routinely fed to premature infants for decades. Infants who have been weaned to solid foods consume much higher levels of nucleotides than when breast feeding or drinking nucleotide-supplemented formula [5]. IMP and GMP have a 'generally recognized as safe' (GRAS) status as flavor enhancers and have been added to food for decades. Thus, there is a significant history of infants receiving nucleotides, not only as natural components of human milk and food, but also from infant formula and as food additives.

Nucleotide Content of Human Milk

The presence of nucleotides in milk has been appreciated for over 30 years [6–8]. Investigators determined that the nucleotides were present as nucleosides, nucleotide mono-, di- and triphosphates, and nucleotide adducts (nucleotide-containing compounds such as nucleotide sugars or coenzymes). Concentrations were reported to decrease from a range of 131–168 μmol/l (53–58 mg/l) in colostrum [9, 10] to approximately 98 μmol/l (33 mg/l) in 3-month milk [9].[1]

Although investigators appreciated that human milk also contained nucleotides as RNA and DNA [11], no method capable of quantifying all available sources of nucleotides had been published. This prompted Leach et al. [4] to develop a novel enzymatic method which converted all sources of ribonucleotides present in human milk, including RNA, to nucleosides. The total concentration of nucleosides resulting from this method was reported as 'total potentially available nucleosides', or TPAN.

Leach et al. [4] applied the TPAN method to 100 human milk samples collected at 4 stages of lactation (table 1). Each stage of lactation consisted of pooled samples from 5–7 women at each of four European sites. The mean TPAN concentration ranged from 137 μmol/l (48.9 mg/l) in colostrum to 240 μmol/l (87.1 mg/l) in early mature milk, with a grand mean of 189 μmol/l (67.5 mg/l). The range of values from individual pooled samples was 82–402 μmol/l (32–148 mg/l). This agreed closely with data from a pooled sample collected from 11 American women between 2 and 4 months postpartum which had a mean of 215 μmol/l (72 mg/l; correction for recovery not included in Leach et al. [4]). These concentrations were 2–3 times higher than those previously reported, while the concentrations of free nucleotides and nucleotide sugars were similar to those previously reported [9]. RNA accounted for most of the difference between this and previous reports, and nucleosides and nucleotide adducts (NAD, NADH, etc.) accounted for only a small portion of the difference. These observations indicated that twice the amount of nucleotides are potentially available to the infant compared to previous measurements.

Thorell et al. [12] applied a different method and reported similar findings with a mean of 163 μmol nucleotide equivalents/l (54 mg/l) in milk collected between 3 and 24 weeks of lactation (table 1). Concentrations of polymeric nucleotides, free nucleotides and nucleosides fell within the ranges observed

[1] The literature describing nucleotides in mammalian milk report concentrations on a molar basis. However, infant formula manufacturers describe nucleotide content on a mass basis (mg/100 kcal or mg/l) in keeping with the requirements for making nutrient label claims. To clarify this source of confusion, we report human milk concentrations as μmol/l and, where possible, mg nucleotide equivalents/l. In subsequent discussion of formula, mass units will be used.

Table 1. Comparison of human milk nucleotide analyses by Leach et al. [4] and Thorell et al. [12] (μmol/l)

Reference	Stage of milk	Source of nucleotide[1]					Total	
		polymeric (μmol/l)	NT	NS (μmol/l)	adducts (μmol/l)	uric acid (μmol/l)	μmol/l	(mg/l)
Leach et al. [4]	Colostrum[2]	65.0	49.0	10.9	12.1	ND	137	(46.3)
	Transitional	84.1	63.1	14.1	15.7	ND	177	(59.1)
	Early mature	114.1	85.5	19.0	21.4	ND	240	(113.6)
	Late mature	96.0	71.9	16.0	18.0	ND	202	(67.2)
	Mean	89.8	67.4	15.0	16.8		189	(67.5)
Thorell et al. [12]	Early/late mature[3]	68	84.2	10.3	ND	69[4]	163	(54)

ND = Not done.

[1] Values calculated by multiplying the percent composition in table 3 by pooled means from table 2 in Leach et al. [4]. Data were then corrected for % recovery. Polymeric = RNA; NT = nucleotides; NS = nucleosides; adducts = sugar nucleosides, choline nucleosides and NAD, NADP, NADH, etc.

[2] Colostrum = Through day 2 postpartum. Transitional = days 3–10 postpartum; early mature = 1 month postpartum; late mature = 3 months postpartum.

[3] Samples from 14 mothers at 3–24 weeks of lactation.

[4] Not included in total. May or may not have resulted from the catabolism of purine nucleotides.

by Leach et al. [4]. The difference in mean levels can be partially accounted for by nucleotide adducts, which were not measured by Thorell et al. [12]. Thus, different methods applied in independent laboratories confirm higher concentrations of nucleotides in human milk than previously reported.

Digestion and absorption of polymeric forms of nucleotides clearly occur in the adult human [13–16] and animals [17]. Thorell et al. [12] also considered the availability of nucleotides from human milk RNA. They used an intestinal homogenate from a 22-week-old fetus to digest human milk RNA into nucleotides. Nucleotide metabolites appeared in human milk incubated without an exogenous source of enzymes, confirming the presence of ribonuclease activity. Thorell et al. [12] concluded that the nucleotide profile of human milk likely results to some degree from catabolism by inherent ribonuclease, and that even preterm infants are likely to digest RNA.

In summary, recent literature indicates that previous assessments of the nucleotide content of human milk underestimated the total amount of nucleotides available to the infant by as much as half, with RNA accounting for the majority of the underestimation. The free nucleotide concentration of human milk is likely related to enzymatic degradation of RNA. In addition, available

evidence indicates that human milk polymeric nucleotides are bioavailable to neonates.

Nucleotides and the Neonatal Immune System

Several pieces of evidence, including better immunological protection of the breast-fed compared to the formula-fed infant, the nucleotide content of human milk, and T-cell immaturity in the neonate, suggest that dietary nucleotides may impact the neonatal immune system. There are, of course, numerous reports of the protective effect of breast feeding resulting in a decreased incidence of diarrhea, respiratory infection, and otitis media [18, 19]. Clearly some of these protective effects arise from specific immunological factors such as secretory IgA, lymphocytes, and cytokines [20], but there is also the possibility of immune enhancement from nonspecific factors such as nucleotides.

A wealth of animal experiments has shown effects of dietary nucleotides on stimulating immune function. These include: increased graft-versus-host disease; increased rejection of allogenic grafts and improved delayed cutaneous hypersensitivity and alloantigen-induced lymphoproliferation; reversed malnutrition- and starvation-induced immunosuppression; increased resistance to challenge with *Staphylococcus aureus* and *Candida albicans*, and enhanced T-cell maturation and function in animals fed nucleotide-supplemented diets [2, 3]. These studies indicate that dietary nucleotides stimulate the humoral immune response to T-cell-dependent antigens. Consistent with these observations, rodent resistance to challenge with infectious organisms has been increased with intraperitoneal nucleotide injection [21].

The reported nucleotide effects in animals are particularly intriguing because they address a specific neonatal deficiency, an impaired ability to mount antibody responses to antigens thought to be related to T-cell immaturity [22, 23]. The ability of nucleotides to enhance some T-cell-dependent antigen responses in animal models adds to the likelihood that nucleotides would be of particular usefulness as a dietary supplement during infancy. Results of clinical studies testing nucleotides for stimulation of immune function during infancy are consistent with this relationship and are discussed below.

Nucleotides and the Humoral Immune System

The antibody response to vaccines had previously been used to evaluate the responsiveness of the immune system in infants and children with possible

humoral immune dysfunction [24]. Pickering et al. [25] examined the influence of nucleotides on the immune system of normal term infants by measuring the antibody response to routine pediatric vaccination. This strategy took advantage of the complex, integrated nature of the antibody response to a T-dependent antigen. The antibody response involves effective interaction of antigen-presenting cells, T-helper cells, B cells, numerous regulatory lymphocyte populations, a multitude of cytokines, clonal expansion of specific T and B cells, and commitment of portions of these cells to memory cells. The antibody response to a T-dependent antigen can serve as a measure of immune function and also was thought to reflect the response an infant might have to a challenge with an infectious agent involving T-dependent responses.

Healthy, full-term infants were randomly assigned at 10 days of age to a control formula (n = 107) or the same formula supplemented with 72 mg nucleotides/l (n = 101) and followed to 1 year. Infants were immunized with single lots of Hib (*Haemophilus influenza* type b conjugate vaccine, HibTITER®, Lederle Laboratories, Wayne, N.J.), DTP vaccine (diphtheria and tetanus toxoids and pertussis vaccine adsorbed, Tri-Immunol®, Lederle) and OPV vaccine (oral polio virus vaccine, Orimune® Poliovirus, Lederle) in accordance with the schedule recommended by the American Academy of Pediatrics at 2, 4 and 6 months of age. Antibody responses were measured at 6, 7 and 12 months of age through binding of Hib antigen by total anti-Hib Ig [26]; response to tetanus and diphtheria toxoids by ELISA, and to OPV by virus neutralization. Hib and DTP are injected vaccines that provoke T-dependent antigen humoral responses, and OPV, an orally administered live attenuated virus, replicates in the intestine and may serve to indicate the responsiveness of the mucosal immune system.

Addition of nucleotides to formula did not result in a detectable change in response to any of the vaccines at 6 months of age (table 2). However, the response to both Hib and diphtheria toxoid were significantly increased at 7 months in the nucleotide group. The difference between groups in Hib response, but not diphtheria response, persisted at 12 months of age. Hib-specific IgG was tested at 6 and 7 months and was significantly higher in the nucleotide group at 7 months (data not shown). No impact of supplemental nucleotides was observed on antibody response to either OPV or tetanus vaccines. Thus, formula supplemented with 72 mg nucleotides/l enhanced the infant's immune system as indicated by the increased vaccine response to some T-dependent protein antigens.

To determine the effect of duration of breast feeding Pickering et al. [25] compared the response of those breast fed human milk <6 months to those breast fed ≥ 6 months. Those breast fed ≥ 6 months had a significantly higher OPV response at 7 months of age compared to those breast fed <6 months.

Table 2. Geometric mean antibody titer response to diphtheria toxoid, *Haemophilus influenzae* b, tetanus toxoid, and oral poliovirus vaccine

Vaccination	Feeding	6 months	7 months	12 months
Diphtheria IgG	Control	0.28 (0.22–0.36) 85	1.38 (1.16–1.65) 89[b]	0.25 (0.21–0.31) 87
(U/ml)[2]	Nucleotide	0.36 (0.28–0.46) 78	1.77 (1.49–2.10) 85[a]	0.33 (0.27–0.40) 82
Hib-Farr	Control	0.42 (0.34–0.52) 96	4.05 (3.00–5.47) 101[d]	0.76 (0.59–0.99) 94[f]
(μg Ig/ml)[2]	Nucleotide	0.53 (0.41–0.69) 93[A]	7.24 (5.43–9.66) 94[c, A]	1.41 (1.06–1.87) 89[e, A]
	HM < 6 months[4]	0.31 (0.24–0.40) 60[B]	3.57 (2.34–5.44) 60[B]	0.78 (0.56–1.07) 56[B]
	HM ≥ 6 months[4]	0.34 (0.24–0.48) 37	5.43 (3.44–8.57) 39	0.98 (0.65–1.47) 39
Tetanus IgG	Control[3]	0.71 (0.58–0.88) 82	4.12 (3.55–4.78) 91	0.82 (0.70–0.95) 87
(U/ml)[2]	Nucleotide[3]	0.76 (0.61–0.93) 80	4.75 (4.12–5.49) 86	0.93 (0.78–1.11) 83
Polio VN	Control	175 (118–260) 76[B]	177 (103–303) 49	105 (70–159) 65
(U/ml)[2]	Nucleotide	207 (143–299) 81	162 (96–274) 51[B]	121 (81–182) 75
	HM < 6 months	297 (179–493) 47	233 (140–387) 35	126 (72–219) 56
	HM ≥ 6 months*	442 (266–733) 36[A]	508 (279–925) 27[A]	265 (146–482) 33

Statistical comparisons: [a, b] $p < 0.05$; [c, d] $p < 0.006$; [e, f] $p < 0.002$; [A, B] $p < 0.05$ for human milk, formula comparison; * human milk ≥ 6 months greater than human milk < 6 months at the 7-month time point, $p < 0.05$.

[1] From Pickering et al. [25]. Values are geometric mean antibody titer (range) and number.

[2] Method given in Pickering et al. [25].

[3] Control formula contained 22 μmol nucleotides/l (7 mg/l) and nucleotide formula the same with the addition of 215 μmol nucleotides/l (72 mg/l).

[4] Human milk <, ≥6 months, infants fed exclusively human milk for <6 months or at least 6 months.

The duration of breast feeding had no statistically significant impact on the other antibody responses, although response to Hib followed the same trend as the OPV response.

Despite the fact that the human milk-fed group is nonrandomized, it is common practice to include breast-fed infants in statistical comparisons to formula-fed infants. Since the duration of breast feeding appeared to influence vaccine response, these two breast-fed groups were compared to the formula groups. Infants breast fed for ≥6 months had a significantly higher response to OPV at 6 and 7 months compared to both groups of formula-fed infants. The response of those breast fed for <6 months was not different from that of formula-fed infants (table 2). The Hib response of infants breast fed for ≥6 months was similar to that of infants in the nucleotide group, which was significantly higher than both the control group and infants breast fed for <6 months.

In another study, 24 preterm infants were randomly assigned to receive a control or nucleotide-supplemented formula (19 mg/l) for 3 months [27]. Plasma IgM and IgA concentrations of preterm infants at 20–30 days and 3 months of age were significantly higher in the nucleotide group compared to controls. As one would expect, IgG levels were largely reflective of maternally derived transplacental immunoglobulin and were not influenced by nucleotide supplementation. As a higher level of nucelotides increased the antibody response, but not total Ig subclass levels, in term infants [Pickering et al., unpublished data] these data may indicate that premature infants represent a more compromised population relative to the development of the immune system.

Nucleotides and Cellular Immune Effects

Limited data are available on nucleotide effects on lymphocyte numbers, distribution, and activity. Carver et al. [28] tested the impact of nucleotides on natural killer cell (NK) cytotoxicity and interleukin-2 (IL-2) production in healthy, term infants. Breast-fed infants (n = 9) and infants randomly assigned to a control (n = 15) or formula supplemented with 33 mg nucleotides/l (n = 13) were studied from birth to 4 months of age. At 2 months of age, NK activity (measured by release of ^{51}Cr from K562 target cells) was significantly higher in the breast-fed and nucleotide-supplemented groups compared to the controls. In addition, phytohemagglutinin-stimulated IL-2 production was significantly higher in the supplemented group vs. controls, but neither formula group differed from the breast-fed group. While the differences between the formula groups disappeared at 4 months of age, the breast-fed infants continued to have higher NK activity compared to controls.

The nucleotide-mediated changes in NK activity were not corroborated by data from the infants studied by Pickering et al. [unpublished data]. Neither NK activity nor NK number was influenced by nucleotide supplementation (table 3). However, the breast-fed group had significantly higher NK cell numbers, but not NK cell activity, compared to both formula groups at 2, 6, 7 and 12 months of age (table 3). Consistent with this observation, Pelton et al. [29] found no effect of nucleotides on NK number, but higher numbers in breast-fed infants. The disagreement between these latter studies and the study by Carver et al. [28] could be explained by the limited number of subjects enrolled by Carver et al.

Supplementation of a control formula with nucleotides (72 mg/l) did not modify the number of monocytes, granulocytes, total lymphocytes, B cells, T cells, T-helper cells or T-cytotoxic/suppressor cells [Pickering et al., unpub-

Table 3. Lymphocyte subsets in term infants fed control or nucleotide-supplemented formulas or human milk[1]

Measure	Age months	Control (n = 82)	+ Nucs (n = 82)	HM/SWI[2] (n = 77)
NK activity[3]	2	13.0 (1.6)	16.4 (2.1)	11.8 (1.3)
	6	17.5 (2.2)	13.4 (1.7)	12.5 (1.4)
	7	17.9 (1.9)	19.6 (2.1)	17.5 (1.9)
	12	24.9 (2.1)	23.6 (2.0)	24.1 (1.5)
NK number[4]	2	555 (29)[b]	567 (39)[b]	777 (56)[a]
	6	490 (47)[b]	417 (31)[b]	571 (45)[a]
	7	403 (35)[b]	421 (35)[b]	549 (47)[a]
	12	403 (32)[b]	411 (34)[b]	533 (44)[a]
Granulocytes[5]	12	2,366 (154)	2,195 (130)	2,474 (134)
Monocytes[5]	12	429 (25)[b]	460 (28)[a, b]	520 (27)[a]
Lymphocytes[5]	12	4,924 (200)[b]	5,302 (202)[a, b]	5,870 (234)[a]
B cells[6]	12	1,153 (62)[b]	1,315 (71)[a, b]	1,443 (61)[a]
T cells[6]	12	3,305 (141)[b]	3,551 (138)[a, b]	3,867 (175)[a]
T_H cells[6]	12	2,361 (103)	2,632 (104)	2,682 (111)
T_S cells[6]	12	1,222 (59)	1,254 (56)	1,493 (112)

[a, b] Values in same row with unlike superscripts differed ($p < 0.05$).

[1] Data expressed as number of cells/mm^3 whole blood (SEM). Collected from infants studied by Pickering et al. [25].

[2] Human milk (HM)-fed infants were weaned onto Similac with iron not fortified with nucleotides and therefore represent a mixed feeding group.

[3] NK activity determined by release of calcium fluorescent dye from killed K562 cells, effector:target ratio of 50:1. Values are % cytoxicity.

[4] NK number identified as CD3+, CD16/56+ cells.

[5] Monocytes and lymphocytes determined using anti-CD5/CD14 monoclonal antibodies.

[6] B cells = CD19+; T cells = CD3+; T_H or T-helper cells = CD4+; and T_S or T-cytotoxic/suppressor cells = CD8+.

lished data] (table 3). While the nucleotide group was not different from the breast-fed group, the group fed unsupplemented formula was significantly lower than the breast-fed group for each of these cell populations. These observations suggested that long-term feeding of supplemental nucleotides could induce changes in immune cell populations with potential implications for the antibody response. However, it remains unclear whether these modest

general shifts in lymphocyte populations are related to the effect on vaccine response. At the time of the study, cell surface markers for more specific subsets of lymphocytes that could have revealed nucleotide effects more precisely were not available.

Consistent with these data, nucleotide-mediated increases in antibody detected in marasmic preterm infants [27] were not associated with changes in lymphocyte classes. T-helper cells were increased in the nucleotide group at 10 days, but not at the other time points. Nucleotide supplementation did not affect the gradual decrease in circulating T-cytotoxic/suppressor and NK cells and the increase in B cells observed over the duration of the study [30]. The lack of concurrent change in both the cellular and antibody data may reflect differences between circulating cell populations and those local cell populations secreting antibody.

Nucleotides and Morbidity

Brunser et al. [31] performed the largest morbidity study to date on the effect of nucleotides on infectious diarrhea. A total of 392 infants <6 months of age were enrolled from a low-socioeconomic area in Santiago, Chile. These infants were randomly assigned to receive a control formula or the same formula with nucleotides (20 mg/l) for a period of 3 months. The incidence and severity of diarrhea were monitored through weekly home visits by trained field nurses. Infants fed nucleotide-supplemented formula experienced fewer episodes of diarrhea, fewer first episodes, fewer diarrhea days and a higher percentage of subjects having no episodes [31; personal commun.]. There were no differences in the etiology of diarrhea between groups as indicated by a variety of intestinal pathogens such as rotavirus and *Salmonella* spp. Consistent with these data, a reduced incidence of diarrhea was reported in a subset of infants in the Pickering study; 4 of 27 (15%) infants in the nucleotide group vs. 13 of 32 (41%) in the control group.

Supplemental nucleotides have been reported to reduce the incidence of upper respiratory tract infections (URI) and to modify indices of immunological responsiveness in marasmic preterm infants [27]. Thirty-three infants were randomly fed control ($n=16$) or the same formula supplemented with 20 mg nucleotides/l ($n=17$) for 105 days. The nucleotide group had a lower incidence of URI (6 vs. 38%, $p<0.04$). No differences were observed in the incidence of lower respiratory tract infections, otitis media, acute diarrhea, mucocutaneous candidiasis, purulent conjunctivitis or bacterial skin infections. The nucleotide-supplemented group had a lower percentage of CD4 lymphocytes after 105 days (39.7 vs. 42.6%) and a higher proportion of infants with more than two

positive responses to a battery of delayed type hypersensitivity skin tests. These data indicate that nucleotides can reduce morbidity in vulnerable infant populations; however, it is not clear how this relates to the changes in immune cell populations and other immune responses.

Nucleotides and Other Immune Responses

Another interesting aspect of neonatal immunology is the development of allergy vs. tolerance to dietary proteins. Considerable controversy exists as to what types of exposure lead to tolerance rather than allergy [32]. Some have proposed that low doses of allergens induce responses that lead to increased IgE level and allergic response, while high doses of allergens (such as dietary protein) promote a response that induces tolerance [33]. Consistent with this hypothesis, Kaila et al. [34] reported increased levels of anti-cow's milk protein IgG in healthy, non-allergic formula-fed vs. breast-fed infants. They suggested that this dietary specific antigen response indicated development of tolerance.

The limited data available on allergy-related nucleotide effects suggest that nucleotides are, at worst, neutral in this regard and may have a tolerizing effect. Recent animal studies indicate addition of nucleotides to a purified diet upregulated cytokine responses resulting in both decreased total IgE and IgG1:IgG2a ratios [35]. Pickering et al. [25] measured both total and cow's milk protein specific IgE levels at 12 months of age in their study of term infants and found no differences between groups – nucleotides had no effect on this general marker of allergy. Supplemental nucleotides (80 kcal/dl formula supplemented with 11.7 mg nucleotides/l vs. a similar unsupplemented formula) have been found to increase serum IgG antibodies to α-casein at 7 days of age and to β-lactoglobulin at 30 days of age in premature infants ($n = 27$) [36]. The IgG isotype was not determined making it difficult to relate these observations to the animal data of Nagafuchi et al. [35]. Nonetheless, when these data are taken together with the Kaila et al. [34] hypothesis they suggest that supplemental nucleotides favor a tolerizing response to dietary antigens.

Discussion

Taken together, the increased antibody response to T-dependent antigens in full-term infants and the increased total antibody levels in premature infants suggest that dietary nucleotides enhance certain aspects of the immune

system in infants. The literature on the immunological effects of nucleotides in animals supports these observations. Those data demonstrate that dietary nucleotides stimulate the T-dependent antigen response of the immune system [2, 3] and enhance resistance to challenge with infectious organisms [21]. Consistent with the increased antibody response, Jyonouchi et al. [37, 38] have observed reversible suppression of T-cell-dependent humoral immunity and less in vitro T-helper function in mice fed a nucleotide-free diet. Other investigators have speculated that the decreased cell-mediated immunity observed in mice fed a nucleotide-free diet was due in part to impaired T-lymphocyte proliferation [2]. The weight of these data indicates that dietary nucleotides stimulate that portion of the immune system involved in the T-dependent antigen response.

The clinical studies raise the question, 'What is the optimal level of nucleotide fortification necessary to achieve the immunological benefits?' As studies to date have compared milk-based infant formulas with and without fortification, none provide dose-response data. The benefits associated with lower levels of fortification (20–33 mg nucleotides/l) ranging from increased IgM and IgA to decreased incidence of diarrhea have been observed in vulnerable populations [31, 36]. In contrast, only the study by Pickering et al. [25] (72 mg nucleotides/l) provides clear data supporting an immunologic effect of nucleotides in healthy term infants. The data cannot answer the question of optimal level, but only TPAN concentrations similar to that in human milk have been demonstrated to achieve benefits in normal term infants.

A number of mechanisms could explain the nucleotide effects discussed here. A popular hypothesis is that dietary nucleotides improve tissue function by providing a source of nucleotides whenever high metabolic demand exceeds the capacity for de novo synthesis ('supply theory'). This hypothesis proposes that the cellular proliferation associated with both intestinal mucosal repair and lymphocyte clonal expansion during an antibody response [2] represent conditions of high metabolic demand. In support of this view, Uauy [39] estimated that meeting daily nucleotide requirements during infancy entirely from de novo synthesis would require as much as 10% of the daily protein requirement. Also supportive, the earliest observation of nucleotides affecting immune function was the reduced rejection of kidney transplants in adults on total parenteral nutrition. That reduced rejection could have been a suppressed immune response resulting from a nucleotide-free diet. Additionally, it is conceivable that these patients were receiving marginal supplies of amino acids and energy via parenteral nutrition and may have had compromised de novo nucleotide synthetic capability as well.

There may be several mechanisms by which nucleotides may reduce diarrhea, including an increased ability of the intestine to maintain and

repair its mucosal surface, a more responsive immune system, or both. Other possible interactions exist including the observation that infants fed nucleotide-supplemented formula had increased blood flow to the intestine via the superior mesenteric artery [40], potentially enhancing the ability of the intestine to cope with mucosal challenges. Although dietary nucleotides modify numerous physiological responses, a unifying mechanism has not been established.

We believe the mechanism by which dietary nucleotides modify the immune system is likely to be more complex than the supply theory. First of all, nucleotides are efficiently absorbed and excreted with low levels incorporated into peripheral tissues including the spleen [17]. Dietary nucleotides are metabolized primarily by the gut and liver. A recent stable isotope study in mice confirms these observations by indicating that tissue nucleotides derive primarily from de novo synthesis [41]. Thus, one would predict that dietary nucleotides would be unlikely to modify a humoral immune response involving clonal expansion of lymphocytes in peripheral tissues, including lymph nodes. Secondly, if the supply theory were the operative mechanism, one would expect dietary nucleotides to be more likely to modify an intestinal immune response. However, Pickering et al. [25] found no effect of nucleotides on the response to the mucosal vaccine, oral polio virus. These data lead us to speculate that dietary nucleotides act by modifying lymphocytes temporarily residing in the gut-associated lymphoid tissue. These cells result in an augmented, post-homing, local vaccine response in the peripheral lymph nodes. Jyonouchi et al. [42] have provided support for this hypothesis by immunizing mice with a T-dependent antigen and observing increased IFNγ messenger RNA expression in T lymphocytes harvested directly from the local lymph node. Likewise, the same cells rechallenged in culture secreted more IFNγ and IL-5. These are consistent with our speculation, since lymphocytes residing in peripheral lymph nodes are modified by dietary nucleotides, despite literature indicating that they are predominantly catabolized in gut and liver tissue.

In conclusion addition of nucleotides to infant formula, at total breast milk levels, may confer benefits resulting from enhanced immune function as indicated by the increased response to vaccines, increased antibody levels, and reduced morbidity. These far outweigh the known risk from adding an ingredient with such an extensive history as part of the infant's diet. Nevertheless, elucidation of the relevant mechanisms by which nucleotides enhance immune function is a fertile area for research.

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Dietary Fiber in Childhood

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Introduction

Dietary fiber is used to both prevent and treat a variety of chronic diseases including diabetes mellitus, colon cancer, hypercholesterolemia and diverticulosis. Despite the widespread use of dietary fiber, many questions remain unanswered as to how dietary fibers interact with the gastrointesinal (GI) tract and the mechanisms by which fiber consumption leads to physiological effects throughout the body. Dietary fiber is a complex component of food containing numerous organic compounds. Commonly, dietary fiber is defined as 'all polysaccharides and lignin in the diet that are not digested by the endogenous secretions of the human digestive tract' [1]. Plant cell wall material containing cellulose, hemicellulose, pectinic substances and lignin are the major components of dietary fiber. In addition, mucilages, gums, algal polysaccharides and synthetic polysaccharides are also included in the definition of dietary fiber. The specific makeup of individual fiber sources determines their chemical and physical properties which, in turn, determines their fate and physiological effects.

To clarify the concept of dietary fiber, scientists have grouped individual fiber sources by their physical properties. One widely used classification is of water-soluble or gel-forming viscous fibers and water-insoluble fibers. This distinction is convenient because many of the physiological effects of fiber seem to be based on this property. Soluble fibers are highly fermentable and are associated with carbohydrate and lipid metabolism while insoluble fibers contribute to fecal bulk and reduced transit time.

The chemical structure of dietary fiber is the major factor in determining its physical properties. Cellulose, for example, contains tightly packed linear polysaccharides which are water-insoluble and resistant to hydration and swell-

ing. In contrast, pectin is a charged viscous polysaccharide, readily soluble in water, possessing significant ion binding potential. In plant tissues, a unique mixture of soluble and insoluble fibers are produced making it difficult to accurately predict the physiological effects of dietary fiber in the body [2].

Fate of Dietary Fiber in the GI Tract

Small Intestine

Dietary fiber is consumed as part of foods and directly influences the digestion and absorption of nutrients in the intestine. Because dietary fiber is not broken down by digestive enzymes, it remains virtually unchanged in the stomach and small intestine. The fiber forms a matrix as it moves through the GI tract and most fiber varieties have high water-binding capacities. The fiber matrix is sometimes described as a sponge, that can absorb water, ions, and entrap nutrients [3]. Soluble fibers, as a rule, increase the viscosity of the gastric and intestinal contents. Highly viscous chyme delays gastric emptying and decreases the rate of nutrient absorption in the small intestine. Insoluble fibers tend to be inert compounds which increase bulk in the intestine. In contrast to soluble fibers, insoluble fibers are associated with decreased intestinal transit times [4].

Colon

Dietary fiber undergoes few changes as it passes through the small intestine, but in the cecum and colon, most soluble fibers are readily broken down by anaerobic microbial fermentation. The products of fementation include methane, CO_2, H_2, lactate, alcohol and short chain fatty acids (SCFAs). Acetate is the most common SCFA formed, followed by propionate and then butyrate. Exact ratios are dependent on the type of fiber fermented [5]. In humans, fermentation occurs throughout the large intestine. Recently, much interest has arisen concerning the physiological effects of SCFAs. It has been hypothesized that these compounds may play an important role in lowering plasma cholesterol levels and preventing the development of colon cancer. The primary site of propionate uptake is the liver, butyrate in the gut epithelium, and acetate in the peripheral tissues. It has been suggested that propionate may inhibit endogenous hepatic cholesterol synthesis and butyrate has been shown to promote cell differentiation in cultured colonocytes [6]. In addition, butyrate is considered the preferred energy source of the colonic mucosa and plays a role in maintaining a healthy mucosal lining for the large intestine.

Unlike soluble fibers, insoluble fibers tend to resist fermentation and increase fecal mass. Insoluble dietary fibers prevent reabsorption of fecal water

during transport through the large bowel, therefore the moisture content of the feces increases dramatically [7]. This characteristic of fiber will be discussed in more detail in relation to laxation.

Effects of Dietary Fiber on Intestine Morphology

It is well documented that the morphological structure of the intestine can be modified by dietary patterns [8]. Research has been carried out primarily on the intestinal mucosa where significant morphological changes have been observed following dietary fiber supplementation.

With the aid of electron microscopy, Cassidy et al. [9] showed that modifications in the villous structure occur in rats following 6 weeks on 15% fiber diets. There are distinct differences among fiber varieties in regard to their ability to affect intestinal morphology and influence mucosal growth and cell proliferation rates. It is interesting to note that insoluble dietary fibers, such as cellulose have not been associated with changes in small intestine morphology and have been shown to have a relatively small stimulatory effect in the colon.

A comparative study of the effects of the soluble fibers guar, oat bran and pectin on mucosal growth and cell proliferation in rats indicated that of the three fibers, only guar increased small intestine mucosal mass [10]. Oat bran supplementation had a negligible effect on intestinal morphology, but it did appear to inhibit crypt cell replication. Pectin feeding shortened villi length and increased crypt column depth. Increases in epithelial cell migration rates and crypt cell replication were also attributed to pectin intake. Guar gum increased cell migration and cell replication which apparently exceeded exfoliation resulting in increased mucosal mass. The effects of guar on mucosal morphology were confirmed in more recent studies reporting a significantly increased crypt cell production rate in both the small and large intestine [11].

Intestine Length

Morphological modifications induced by dietary fibers include increased gut length. Soluble fibers, such as pectin and guar, have repeatedly been shown to elongate the intestine [11, 12]. In animal studies carried out in our laboratory, pectin feeding significantly increased the length of both the small intestine and colon [13]. In contrast, cellulose increased the length of the colon in rats, but had little effect in the small intestine.

The high viscosity of gut contents due to pectin feeding leads to retention of fat and other nutrients which are normally absorbed in the jejunum and ileum [14].

Reduction of postprandial blood glucose levels following high fiber test meals also have been well documented [15]. If nutrient absorption is impaired or delayed following fiber feeding, increased intestine length may be a compensatory mechanism to enlarge the absorptive area of the intestine and maximize nutrient absorption. Read and Eastwood [16] proposed that a downward shift occurs in absorptive areas of the small intestine following soluble fiber feeding which would create a need for increased ileal length.

Morphometric Measurements

Although much information is available concerning histological and morphological changes in the intestinal mucosa due to fiber feeding, changes in the muscle layer have not been sufficiently documented. Computerized image analysis, a powerful new tool that quantifies morphological data, provides more precise measurements than previous microscopic methods. Using this new technique, Stark et al. [13, 17] demonstrated dramatic changes in the muscularis layers of the ileum and colon following dietary fiber consumption. Morphological changes in the intestine were determined in rats fed a 15% pectin diet for either 4 or 8 weeks. In comparison to control and cellulose-fed rats, pectin feeding significantly increased the relative area of the muscularis fraction of the ileum and both the relative and absolute muscle area in the mid colon.

Schneeman and Richter [18], using a micrometer in a light microscope, reported that the smooth muscle thickness was increased in the ileum of animals fed psyllium husk or oat bran. Earlier studies of Brown et al. [12] also measured greater smooth muscle thickness in the small intestine following an 18% pectin diet.

Increased muscle mass may increase mixing of intestinal contents to maximize contact between nutrients and the absorptive mucosal layer. On the other hand, stronger muscle action may shorten transit time thus limiting absorption.

The case of cellulose is not as clear. Cellulose feeding did not appear to affect ileal morphology in either short- or long-term experiments [13, 17]. A nonsignificant trend toward increased muscle volume was observed in both the mid and distal colon following 8 weeks on a cellulose diet, but at 4 weeks no morphological changes were observed. It is possible that changes in colon muscle mass occur only after long-term cellulose feeding. Schneeman and Richter [18] reported that wheat bran, an insoluble fiber containing cellulose did not increase smooth muscle thickness in the ileum and changes

in the colon were not measured. Cellulose is a bulking agent that has been shown to shorten intestinal transit times and increase fecal volume [19]. Although greater muscle action appears essential for carrying out this task, experimental data do not indicate that this morphological modification occurs.

An increased amount of physical work is necessary to propel a bulking agent, such as cellulose or a highly viscous gel, such as pectin through the length of the intestine. In the case of cellulose, the intestinal load is increased while transit time is decreased. It is possible that the highly viscous nature of a 15% pectin diet is more difficult to propel the length of the intestine than a high cellulose diet. If this is true, then the need for greater functional activity following pectin intake would account for the increase in muscle mass not seen with cellulose feeding.

Morphological changes in the GI tract occur following dietary fiber feeding. The physiological importance of these modifications are unclear. It appears that the structural changes occur to maximize nutrient absorption and allow the intestinal contents to move through the GI tract efficiently, despite an increased load.

Dietary Fiber in Childhood

Dietary fiber consumption in children has not been well documented. Several recent studies suggest that American children, like adults, consume inadequate amounts of dietary fiber to maintain optimal health [20, 21]. Dietary fiber consumption should be increased in order to promote normal laxation, reduce serum cholesterol levels, and potentially prevent obesity. Long-term benefits include decreased risk of coronary heart disease, diet-related cancers and adult-onset diabetes [22]. The health benefits attributed to fiber intake strongly outweigh any potential risks. Children should be encouraged to consume a variety of fruits, vegetables, cereals and legumes.

The role of fiber in the diet during infancy and weaning has not been fully investigated, largely due to the paucity of studies encompassing this young age group. It has been recommended that weaning infants be introduced to a wide range of foods from all the food groups. This will provide good nutritional balance in the child's diet and accustom children to diets containing fiber. Daily fiber consumption should gradually increase to 5 g/day as the child reaches age 2 [23]. The published dietary goals for fiber consumption in children are targeted for those older than 2 years of age. Nonetheless, it appears prudent to begin introducing dietary fiber, in small quantities, into the daily diet of very young children

Dietary Fiber and Laxation

Normal laxation is probably the most important health benefit of dietary fiber consumption in children. Certain varieties of dietary fiber have been shown to increase stool weight and frequency, soften feces, increase fecal bulk, and reduce GI transit times [24]. Constipation, a common childhood disorder, may be prevented or successfully treated by increasing dietary fiber intake in this age group [25].

Although total intestinal transit time is commonly decreased following fiber consumption, gastric emptying is prolonged by the presence of dietary fiber [4]. In the small intestine, transit times vary depending on the variety of fiber eaten, and the foods eaten at a particular meal. Soluble fibers tend to slow mouth-to-cecum transit times [15, 26]. The presence of dietary fiber in the large intestine allows the fecal material to move more rapidly through the colon, shortening transit time. Overall, dietary fiber increases the frequency of bowel movements.

The type of fiber consumed determines its effect on laxation. Insoluble coarsely ground fiber causes a more marked increase in water retention and an increase in stool frequency than does finely ground fiber or soluble fibers [27]. Individual fiber sources have been evaluated as to their effects on GI transit times. Wheat bran, rich in insoluble dietary fiber, has been shown to decrease GI transit time by 30% and significantly increase the frequency of bowel movements per day [24]. The highly fermentable fiber, guar, as it is broken down by colonic bacteria, loses its viscosity and reduces transit time in the large intestine.

Various hypotheses have been suggested as to how dietary fiber affects the composition of fecal material and the frequency of defecation. A likely explanation is the sponge theory mentioned earlier. Eastwood and Morris [3] describe the passage of dietary fiber in the GI tract as a 'water-laden sponge'. The sponge entraps or adsorbs water, ions, and nutrients, altering intestinal contents and changing the rate of peristalsis. The presence of fiber also affects the microfloral activity of the colon. The end result being decreased intestinal transit time with increased fecal bulk and water. Stools tend to be softer and larger accompanied by increased frequency of defecation.

Soluble forms of dietary fiber have significantly less impact on stool volume and water content than insoluble fibers. The exception being nonfermentable soluble fibers, such as psyllium, which increase fecal bulk and decrease transit time, and are commonly used to treat constipation. In fermentable fibers increased stool weights are attributed to bacterial activity. The bacteria themselves may actually increase the fecal mass. It is important to note that the interactions between soluble and insoluble fiber may be meaningful because the sponge or matrix formed by insoluble fiber may limit

bacterial interaction with soluble fiber. Products of bacterial fermentation of dietary fiber may also directly induce laxative effects in the intestine. Furthermore, gases and acidity may have effects on motility and distension and give rise to propulsive activity.

Dietary Fiber and Childhood Obesity

Childhood obesity has increased in the United States by as much as 54% from 1965 to 1980 [28]. The National Research Council reports that 20% or more of American children are obese [29]. The high prevalence of obesity is commonly attributed to the high fat content and calorie-dense foods in the American diet, along with a lack of physical activity. Explanations for the role of dietary fiber in the prevention and treatment of obesity include the reduced caloric density of high fiber foods and the slower rate of food ingestion. It is also thought that dietary fiber may play a role in satiety during and between meals leading to a decrease in overall food consumption [30].

It has been difficult to evaluate the role of dietary fiber in both the prevention and treatment of obesity because of inadequate research methodologies. Most studies lack appropriate control groups, have insufficient sample sizes, and the durations of observations are short. Studies, for the most part, have been carried out in adults, and differences in the nutritional needs of children must be considered when evaluating the data as it applies to pediatric nutrition. To date, there is a total absence of information concerning the association between low-fiber diets and increased risk of obesity in children. Despite these limitations, the available evidence suggests that fiber potentially could play a role in weight control and reduction in children.

In order to prevent the development of obesity, Ali et al. [31] suggest several putative roles of fiber in the diet. These include effects on food intake, changes in digestion and absorption of nutrients, and modification of carbohydrate metabolism. High-fiber foods have a greater bulk than high-fat foods and are less calorie dense per volume. Therefore, if food intake is similar, one might reach satiety with less consumption of calories while eating an equal volume of food. High-fiber foods require more chewing and take longer to eat. This may modify eating behaviors to a certain extent, and allow more time for the body to trigger the satiety response. Additionally, dietary fiber consumption slows gastric emptying which may reduce hunger and prolong the feeling of fullness.

Another explanation of the role of fiber in obesity deals with changes in nutrient digestion and absorption. Inhibition of macro-nutrient digestion would potentially decrease overall caloric intake and be beneficial for both weight loss and prevention of obesity. Although in theory this is an attractive mechanism, little evidence supports this hypothesis. Fecal energy has been

shown to increase following fiber administration [32], but it appears that over time the GI tract compensates for the high-fiber content and maximizes nutrient absorption. A third possible effect of dietary fiber on obesity is its role in carbohydrate metabolism. High-fiber foods produce a flattened postprandial glucose response and moderate insulin levels. This is thought to be advantageous because insulin is considered to be an appetite stimulant.

The therapeutic role of dietary fiber in the treatment of obesity is not definitive. Clinical studies report that fiber supplements, such as methylcellulose and psyllium, have aided or had no effect on body weight reduction. The methodologies used to carry out intervention studies are problematic. Without appropriate control groups, satisfactory conclusions cannot be drawn. Many studies have insufficient sample sizes without statistical power to detect the effect of dietary fiber. Aggregating data for meta-analysis is difficult because many fiber types and doses have been used, participants are heterogeneous and the length of studies is variable. Based on the available evidence, there is a strong indication that dietary fiber could play a useful role in weight reduction, and therefore should be taken into account as a possible treatment for obesity.

For children, fiber administration should be considered as a potential adjuvant therapy for weight loss. In conjunction with other treatments, inclusion of high-fiber foods or fiber supplements in the diet may aid in reducing body weight. In growing children, there is no concensus as to the appropriate therapy for obesity. The safety and efficacy of administering fiber as a treatment needs to be evaluated in a scientifically rigorous manner. This holds true for both fiber supplements and administration of fiber-enriched diets. As the problem of obesity grows in all sectors of the population, safe, innovative methods of prevention and treatment must become integral parts of nutritional recommendations and public health policies.

Safety of High-Fiber Diets for Children

Increasing dietary fiber consumption in children has many clear health benefits, but it is important to raise the issue of potential risks when making dietary recommendations at a population level. Two major concerns arise when considering the scientific data relating to the safety of increased consumption of fiber in childhood. High-fiber diets have the potential for compromised energy intake by reducing absorption of protein, fat and carbohydrate resulting in poor growth, especially in very young children. In addition, high-fiber diets may result in decreased bioavailability of essential vitamins and minerals such as iron, calcium and zinc [33]. Despite these potential risks, deleterious effects

of high-fiber diets are unlikely to occur in highly industrialized countries where children generally consume adequate calories from a variety of foods [34]. In addition, the new American Health Foundation (AHF) recommendation for dietary fiber intake in childhood is within a range thought to provide known health benefits without potential risk to either mineral balance or caloric intake in children 3 years of age and older.

The studies relating to the safety of high levels of dietary fiber consumption have, for the most part, been conducted in adults. Pediatric studies focusing on the potential dangers of high fiber diets have involved populations from countries such as Peru, India, and Iran. Dietary habits are significantly different in developing countries from those in the United States or other industrialized nations. Interpretation of the data must be done with caution, as the relevance is limited.

Several health organizations have set guidelines and made recommendations to establish the level of dietary fiber that will not cause negative physiologic effects and will maximize the health benefits for children. The AHF has recently recommended that the range of dietary fiber intake should be age of child plus 5 g/day to age of child plus 10 g/day for children older than 2 years of age. These levels do not appear to be sufficient to compromise energy intake and should be sufficient to provide the benefits attributed to adequate dietary fiber consumption. The question of bioavailability is more complex and will be addressed below.

In general, pediatricians have been cautious in recommending high-fiber foods for children, but since 1986 the American Academy of Pediatrics (AAP) has advocated the increased intake of complex carbohydrates in youngsters. In 1991, the National Cholesterol Education Program Expert Panel on Cholesterol in Children and Adolescents, in collaboration with the American Heart Association and the AAP recommended a fat-modified 'step-I' diet for all children older than 2 years of age with specific recommendations that carbohydrate sources provide 50–60% of daily calories [35]. Unfortunately, no quantitative level of fiber intake was specified. Despite the lack of specific recommendations for fiber consumption in children, a heightened awareness of the benefits of dietary fiber has led to federally funded projects such as 'Five a Day'. The goal of this large scale American project was to increase the intake of fruits and vegetables to 5 portions a day, well above reported intake levels. The USDA Food Guide Pyramid also uses this approach to recommend fiber-rich foods. Without established guidelines, this method for increasing fiber intake is considered safe with little potential risks involved.

Recent recommendations of the AHF and others have clearly established the importance of dietary fiber as a nutrient in pediatric nutrition and allow for more specific dietary interventions to increase fiber intake.

Dietary Fiber and Micronutrient Bioavailability

A major concern regarding the safety of high-fiber diets is the effect of dietary fiber on the bioavailability of vitamins and minerals. This remains one of the few possible adverse effects of increasing dietary fiber consumption. This is especially relevant in young children where only small quantities of food are consumed and variety may be limited.

Bioavailability is defined as the ratio of the amount of a vitamin or mineral absorbed and utilized compared to the total ingested. The presence of dietary fiber in the GI tract may impair or interfere with micronutrient absorption which could potentially lead to nutritional deficiencies. Dietary fiber can bind ions in vitro and it has been proposed that minerals form chelates with fiber [36]. Although this is a potential problem theoretically, interactions among minerals and fiber are dependent on specific chemical conditions that may or may not be present in the intestine. It has been very difficult to predict the bioavailability of micronutrients in the presence of fiber in the GI tract.

Minerals

Iron, zinc and calcium are the most widely studied minerals in relation to their interactions with dietary fiber. It appears that the variety of fiber consumed determines the effect on bioavailability. Wheat bran has been the fiber source most commonly used in experiments. Several studies have reported a deleterious effect of high-fiber diets on iron and zinc absorption in both animals and humans [37, 38]. Other dietary fiber sources, such as guar gum, lignin and psyllium, have also been shown to negatively affect iron absorption. In contrast, many studies do not confirm that dietary fibers inhibit iron or zinc absorption. These discrepancies may be because fibers often occur together with phytate, a well-documented inhibitor of iron and zinc absorption in humans and rats [39]. It appears that much of the concern around high-fiber diets is due to the presence of phytate. The safety issue of high-fiber diets and mineral bioavailiability may be misleading. At the present time, investigators are asking how much phytate is safe for US children, who generally consume adequate levels of vitamins and minerals.

Research has also indicated that wheat fiber reduces calcium absorption in both animals and humans [40, 41]. The factor or factors in cereal brans that are responsible for this effect have not been identified conclusively, but it is thought that phytates may also play a role in inhibiting calcium absorption.

In conclusion, there are no strong data to support the concept that dietary fibers inhibit mineral absorption through a chelating mechanism. Most likely, it is not fibers that decrease mineral bioavailability, but the phytate associated with some dietary fibers that impair mineral absorption.

Vitamins

Some foods contain inhibitors which decrease the bioavailability of specific vitamins by reducing their solubility or inhibiting their release. Proteinase inhibitors present in some raw fruit and vegetables can affect vitamin absorption, as can substances that reduce bile acid reabsorption [39]. However, limited work has been carried out on the effects of dietary fibers on vitamin bioavailability; vitamins E and D have received the most attention.

The effects of several different types of dietary fibers on vitamin E status were investigated by Kahlon et al. [42]. Coarse wheat bran was found to lower hepatic α-tocopherol bioavailability in rats. Some studies have shown that a high-fiber diet can lead to enhanced elimination of vitamin D. This may be of particular importance in children fed vegetarian or macrobiotic diets where the vitamin-D status is often compromised [43]. The effects of fiber on vitamin A is unclear. Serum vitamin-A and thiamin levels were significantly lower in rats fed a high-fiber diet compared to those fed a low-fiber diet [44]. Other investigators have not concluded that vitamin-A bioavailability is compromised in rats that consume high levels of dietary fiber [45].

Despite studies that show an adverse effect of dietary fiber on micronutrient availability, many researchers firmly believe that there is no convincing scientific evidence that dietary fiber, even when consumed in large amounts, has any adverse effects on nutrition in humans [46]. Deficiencies have not developed in long-term vegetarian adults who consumed more than 50 g of dietary fiber/day [47]. McClung et al. [48] looking specifically at pediatric nutrition also concluded that dietary fiber can be used safely in healthy children without concern for deleterious effects on growth rate, trace mineral, or fat-soluble vitamin status. It has been estimated that in healthy American children consuming adequate levels of nutrients, a doubling of current fiber consumption would have no adverse effects on serum vitamin and mineral levels [49].

Recommendations for Dietary Fiber Intake in Children

Recently, several major American health organizations have made recommendations for dietary fiber consumption in children. In infants, it is widely accepted that dietary fiber is probably not needed in the first year of life. However, the many beneficial effects of fiber suggest that it may be integrated into the diet at an early age. Presently, a diet rich in fruits and vegetables along with whole grains and legumes can be introduced into the daily diet over the first year of life. By the age of 2, diets should contain at least 5 g/day of water-soluble and insoluble fiber [23]. It is also recommended to introduce new foods gradually over time and to consider the relative allergenicity of certain food products.

The AAP Committee on Nutrition recommends a dietary fiber intake of 0.5 g/kg body weight [50]. This recommendation can be problematic because a child's weight in kilograms is not commonly available in the United States. Furthermore, it does not apply for heavier adolescents, where body weight may be in excess of 70 kg. The AAP does set an upper limit of 35 g/day in these cases.

The AHF recommends that a reasonable goal for minimal intake of dietary fiber for children and young adults 3–20 years of age be the equal to age plus 5 g of dietary fiber per day (age plus 5). This recommendation suggests that 3-year-old children consume no less than 8 g/day of dietary fiber and a 20-year-old consume 25 g/day of dietary fiber. The age plus 5 level of fiber intake for children is similar to the AAP recommendation (0.5 g/kg body weight) up to the age of 10 years; however, it is lower for older adolescents. In addition, the age plus 5 recommendation is consistent with current guidelines for adult dietary fiber intake (25–35 g/day) made by the National Cancer Institute and others [51, 52]. Overall, the AHF recommendation as a guide for the general population seems most practical.

It is the general consensus that the recommendations for dietary fiber intake (age plus 5 to age plus 10 g/day) represent levels that are both safe and tolerable for most children based on current knowledge. In addition, revising recommendations based on age represents a physiological approach to the gradual integration of fiber into the diets of all children [34].

In May 1994, a conference on Dietary Fiber in Childhood was held. A summary of the recommendations made is as follows [53]: (1) fiber has important health benefits in childhood; (2) children currently consume suboptimal amounts of dietary fiber; (3) increasing dietary fiber intake in childhood can be accomplished by increasing the consumption of a variety of fruits, vegetables, cereal and other grain products; (4) the potential health benefits of increased dietary fiber in childhood outweigh the potential risk, especially in highly industrialized countries, such as the United States, and (5) children older than 2 years of age should increase their intake of dietary fiber to an amount equal to or greater than their age plus 5 g. Thus fiber intake would increase from 8 g/day at age 3 years to 25 g/day by age 20 years.

In conclusion, dietary fiber has important health benefits in childhood, especially in promoting normal laxation. Developing healthy eating habits at an early age will help to minimize risks of developing chronic diseases in adulthood, including reducing the risk of certain malignancies, cardiovascular disease, diabetes, and obesity. Children currently consume inadequate amounts of dietary fiber for heath promotion and disease prevention. Therefore, increasing dietary fiber consumption to meet recommended levels should be an integral part of the overall strategy in pediatric nutrition.

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Osteoporosis: An Emerging Problem in Pediatrics

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Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bony tissue, leading to enhanced bone fragility and a consequently increased fracture risk [1]. Osteoporosis is manifested primarily in postmenopausal woman but it has its roots in the pediatric and adolescent periods. Impaired bone mineral accretion during childhood and adolescence is now recognized as a major risk factor for adult osteoporosis. The increasing awareness and understanding of the complexity of the normal process of bone mineralization during growth and the possibility of prevention make this major health problem an important subject for the multidisciplinary health caregiver dealing with the growing child.

Since peak bone mass is one of the major determinants of bone health and its nearly maximal value is achieved during the second decade of life, normal bone accretion during this period is important to understand. Bone is a specialized connective tissue that provides mechanical support for locomotion, protects vital internal organs and serves a crucial metabolic function as a reservoir for calcium and phosphate ions which are essential to life. The bone undergoes a complex process of remodeling, involving a number of cellular events, resulting in coordinated resorption and formation of new bone. Bone remodeling is regulated by systemic hormones and by local factors which affect cells of the osteoclast and osteoblast lineage and exert their effects on the replication of undifferentiated cells, the recruitment of cells and their functional differentiation. The major determinants affecting bone mineralization are endocrine, hereditary and nutritional factors.

Table 1. Hormones regulating bone remodeling

Polypeptide hormones	Steroid hormones	Thyroid hormones
Parathyroid hormone	1,25-Dihydroxyvitamin D_3	Thyroxine
Calcitonin	Glucocorticoids	Triiodothyronine
Growth hormone	Sex steroids	
Insulin		

Table 2. Skeletal growth factors

Fibroblast growth factors
Insulin-like growth factors
Transforming growth factor-β family including bone morphogenic proteins
Platelet-derived growth factors
Cytokines of the interleukin, tumor necrosis and colony-stimulating factors families

Endocrine Factors

The end product of remodeling is the maintenance of mineralized bone matrix and the major organic component of this matrix is collagen. Bone metabolism is regulated by polypeptide, corticosteroid and thyroid hormones (table 1) as well as local factors (table 2), which are represented by selected cytokines of the interleukin (IL), tumor necrosis factor (TNF) and colony-stimulating factor (CSF) families [2].

Bone remodeling occurs in small cellular entities called basic multicellular units (BMUs). This process is more active near the marrow cavity and occurs in cycles. The turnover rate of trabecular bone is six times more rapid than the turnover of the lamellar bone; therefore, the trabecular bone is the first to be affected during various metabolic events (prolonged malnutrition, glucocorticoid treatment and hyperthyroidism).

Hormonal Regulation of Bone Remodeling

Polypeptide Hormones

The parathyroid hormone (PTH) regulates the levels of calcium and phosphate in the blood by modulating the activity of specific cells in bone and kidney. This action serves to stimulate the release of calcium and phosphate from bone, enhances reabsorption of calcium from glomerular filtrate and

induces renal synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$), thereby increasing intestinal absorption of calcium and phosphate. Continuous increase in serum PTH stimulates bone resorption. In contrast, intermittent administration results in stimulation of bone collagen synthesis and bone formation [3, 4].

The calcitonin is primarily secreted by thyroidal C cells and is an inhibitor of osteoclastic bone resorption. The secretion of this hormone is stimulated by increase in serum calcium level.

Insulin is an important systemic modulator of skeletal growth, which stimulates bone matrix synthesis and cartilage formation [5]. Insulin is necessary for the normal bone mineralization. Individuals with untreated diabetes mellitus have impaired skeletal growth and decreased bone mineral density.

Growth hormone (GH) increases insulin growth factor-1 (IGF-1) production by the liver, which is responsible for the anabolic action on the musculoskeletal system. It increases calcium absorption in the gastrointestinal tract, by an increase in $1,25(OH)_2D_3$ production. GH causes a small stimulation of IGF-1 production by skeletal cells and indirectly stimulates bone formation. This hormone is necessary for maintenance of normal bone mass. Patients with GH deficiency have decreased bone mass that is restored by GH therapy [6].

Vitamin D ($1,25(OH)_2D_3$), a hormone synthesized primarily in the kidney, stimulates calcium absorption in the gastrointestinal tract and is necessary for normal bone mineralization. $1,25(OH)_2D_3$ stimulates bone resorption and has an indirect stimulatory effect on bone formation [7].

Glucocorticoids (GCs) have a marked effect on bone mineral metabolism. They decrease intestinal calcium absorption, inducing a permanent increase in PTH, which in turn induces an increase in bone resorption. GCs affect the function of osteoblasts, and decrease type I collagen synthesis [8]. GCs inhibit IGF-1 synthesis in osteoblasts, IGF-2 receptor number and the expression of IGF-binding proteins [9]. These effects result in inhibition of skeletal growth, decrease in bone mass and osteoporosis.

Thyroid hormones are necessary for normal linear growth, acting on cartilage formation, possibly in conjunction with IGF-1, but they do not stimulate bone matrix synthesis or bone cell replication. They do, however, stimulate bone resorption [10]. Hyperthroidism may increase the risk of osteoporosis [11].

Sex Steroids

Estrogens and androgens are important in skeletal maturation. Estrogen deficiency following menopause is associated with bone loss, probably via estrogen-induced decrease in the synthesis of cytokines such as IL-1 and IL-6 which stimulate bone resorption. The effect of estrogen levels is just as pronounced when concerning bone accretion. In adolescent girls, low estrogen

levels and amenorrhea (primary or secondary) are associated with lower bone density [12]. It is not certain to what extent this deficiency in bone mass can be corrected later on, since there is evidence of little bone accretion after the age of 16 in girls [13, 14].

Factors Affecting Peak Bone Mass

The factors that determine peak bone mass (PBM) can be categorized as fixed (i.e. genetic disposition, sex, general health state) and those that can be influenced (i.e. nutrition, physical activity, smoking, drug treatment). In this section we will briefly review these factors.

Heredity

A well-established fact is the existing race and sex difference in bone density and bone turnover. Blacks have a higher bone density (and lower bone turnover) than whites, and whites have a higher bone mass than Asians. Men of all races have a higher bone mass than women [15]. Recent research has revealed a more specific genetic determinant, thus explaining variations in bone density in twin studies. This genetic effect was attributed to the vitamin D receptor (VDR) gene polymorphism. Some researchers associated the genotype termed BB to lower bone density and early onset of osteoporosis [16]; others concluded that the BB VDR genotype is not a good predictor of risk for developing osteoporosis [17, 18].

Nutritional Status

Calcium and PBM

A normal range of circulating forms of calcium is necessary for maintaining many physiological functions. Regulation of calcium homeostasis is achieved by the combined action of three hormones: PTH, calcitonin and vitamin D. A unique trait of calcium is in its distribution in the body, since all forms of plasma calcium constitute only 1% of total body calcium and 99% are in the bone. When daily calcium requirements are not met from exogenous sources (diet), the necessary calcium is mobilized by increased bone resorption.

Difficulty in meeting dietary requirements of calcium is very common for two reasons: calcium content of most foods is very low, and foods containing high amounts of calcium – such as milk and dairy products – often prove

offensive to individuals sensitive to lactose or cow milk proteins. The absorption of calcium can range from 15 to 70% depending on physiological condition, age, and other dietary components of food affecting calcium bioavailability.

The pubertal growth spurt that occurs in adolescence, increases dietary needs considerably compared with those of childhood years. Meeting nutritional needs is more problematic in adolescent girls than in boys, since they tend to go on low calorie diets, making it virtually impossible to provide the necessary amounts of zinc, iron, calcium, magnesium and phosphate [19].

Whereas most of the mentioned nutritional deficiencies may be corrected later on in life, lack of calcium during the growth spurt may prevent the achievement of maximal PBM. Low PBM in adult life increases the risk of osteoporosis.

Epidemiologic studies have shown an association between calcium intake and bone density. On the other hand, no such association was found in other studies. Kanis [20] examined these discrepancies and concluded that important influencing factors such as other dietary components and physical activity were not accurately recorded and more specific research was necessary in order to evaluate the exact contribution of calcium intake to PBM.

Sentipal et al. [21] found that calcium intake and maturational stage were good predictors of bone mineral density. Estrogen levels and calcium intake are major factors in the determination of bone mass, thus supporting the hypothesis that better calcium intake during adolescence may optimize, within genetic boundaries, PBM. Studying the risk factors for osteoporosis in the Mediterranean area, the MEDOS research [22] concluded that women with low calcium intake, low body weight, and excessive amounts of fiber in diet had lower bone density.

Some clinical trials have tried to determine the correlation between calcium intake and bone density. Matkovic [23] demonstrated a more pronounced increase in bone mass over a period of 18 months in a calcium-supplemented group (1,640 mg Ca/day) versus control group (750 mg Ca/day), but the differences were not statistically significant, possibly due to type II error. Slemenda et al. [24] demonstrated increased bone mass in children receiving calcium supplementation, but since the participants in the group were at various stages of development it was not possible to determine whether the calcium or the natural bone accumulation due to growth was responsible for the difference. Johnston et al. [25] conducted a 3-year, double-blind, placebo-controlled trial of the effect of calcium supplementation (1,000 mg/day) on bone mineral density in 70 pairs of identical twins. Again, the age and development stage varied (6–14 years), and benefit of supplementation was demonstrated only in the prepubertal group. Lee et al. [26] investigated the acquisition of bone

mass and height in 87 Chinese children, 7 years old, with an initial calcium intake of about 550 mg/day. After receiving 300 mg Ca or placebo daily for 18 months, the results confirmed a positive effect on vertebral bone mass, but no effect on femural-neck bone mass or height.

Calcium Requirements for Optimal Skeletal Growth

Dietary recommendation for calcium intake in healthy adolescent girls ranges from 400 to 1,500 mg Ca/day [27, 28]. One possible way to determine calcium needs is by performing calcium balance studies. In young individuals, calcium balance must be positive to insure bone formation. How positive the calcium balance should be in order to achieve maximal PBM is unknown [29].

Peacock [30] analyzed the results of 487 calcium balance studies performed over the last 40 years and concluded that most of the children and adolescents had insufficient calcium intake to ensure maximal bone mass achievement, when taking into account absorption rate in relation to their intake and obligatory losses. Passive calcium absorption is influenced by dietary intake, and active absorption by vitamin D status and possibly by the vitamin D gene receptor allele combination [31]. In general, absorption data in children and adolescents indicate that efficiency is not much greater than in adults. On the other hand, obligatory calcium losses occur even in severe hypocalcemic state:

(1) Urinary calcium excretion is the major route of obligatory calcium loss. Prepubertal kidney calcium excretion is about 80 mg/day, and increases with age. Body weight, not dietary calcium level, is the main determinant for urinary calcium excretion.

(2) Endogenous fecal calcium loss ranges from 76 to 260 mg/day in healthy adults. Fecal calcium excretion is inversely correlated with calcium intake and absorption conditions: fiber content of diet, pH, transit time, etc.

(3) Dermal calcium loss is underdocumented, but must be taken into consideration, especially in hot, humid climates. Average loss for adults is 60 mg/day.

Maximal calcium accretion per day in adolescents seems to be 375 mg. In order to achieve this goal, 550 mg calcium must be absorbed, and when accounting for all possible losses and average absorption rate, one may set daily calcium requirements at 1,800 mg. This figure is far from being realistic when the average daily intake for adolescent girls in USA is 900 mg [30].

Calcium Sources in Food

According to food tables, content of calcium in foods varies widely in different surroundings (soil, water, etc.). Many food products are also fortified with calcium. For these reasons our recommendations for rich sources of calcium in food are general and not in the form of a table.

Table 3. Calcium absorption

Enhancers	Inhibitors
Acidic pH: Vitamin C Lactose in food Soon after meals	High phosphor diet High animal protein diet High fiber diet High phytic and oxalic acids
Active receptor absorption inspired by vitamin D	Alcohol Caffeine Low calorie diet Fat malabsorption Prolonged diarrhea (Old age)
Medication Penicillin, chloramphenicol	*Medication* Cholestyramine Antacids Peristaltic stimulators

High available calcium content can be found in milk and dairy products such as yogurt and cheese. Other good sources of calcium are sardines (with bones), green leafy vegetables like celery and cabbage, green beans, nuts and sesame seeds. One must bear in mind that the caloric content of nuts and seeds is high, and the high fiber content in the whole form of sesame seeds can impair calcium absorption. A diet containing approximately 1,000 mg calcium should consist of at least three portions of milk and dairy products daily. For detailed information of calcium absorption, see table 3.

Other Nutritional Considerations

When discussing the effect of nutritional status on bone health, a few other factors must be considered, besides calcium intake, especially if children and adolescents are concerned.

Caloric intake and body weight – Adolescents (and even younger) tend to keep very low caloric intake in order to maintain a slim figure. It is very important for three reasons: (1) Most low calorie diets ($<$1,200 cal/day) do not meet the RDA for calcium intake [19]. (2) Many researchers found a strong correlation between body weight and bone density [32–34]. Our initial clinical findings support these conclusions. (3) Low calorie diets have higher protein content, which may increase calcium loss in urine [19]. These facts should be kept in mind when dealing with young patients, since there is little hope of improving low bone density in later years.

Magnesium intake – Magnesium deficiency, severe or even moderate, may decrease PTH secretion. When combined with a low calcium intake for long periods, this fact may decrease bone density. Many more nutritional factors may affect bone metabolism and development, but since their deficiencies are rare, or their role in bone metabolism is not yet understood, we chose to merely cite them. Ascorbic acid, copper and silicon are involved in collagen formation, vitamin K is involved in the formation of bone osteocalcin, phosphorus is a part of the bone calcium phosphate crystals and boron is believed to be necessary for realization of growth potential.

Calcium Intake in Israeli Adolescent Girls

A comprehensive nutritional survey of adolescent girls in Israel shows that average calcium intake at the age of 14.5 years is 1,260 mg/day. 20.4% of Jewish girls and 19.8% of Arab girls consume <800 mg Ca/day. 97% of girls on low calorie diets ($<1,200$ cal/day) consume <800 mg Ca/day. In girls on low calcium intake, 95% of the girls do not reach RDA for phosphate, 85% for magnesium, 90% for iron and 100% for zinc. Data also showed that girls with BMI <17.9 have not attained puberty by the age of 14.5 years [19].

Environmental Factors

Physical activity – When suited to age and physical ability and aimed for bone building, physical exercise has a marked positive effect on bone mass accumulation [35–37]. On the other hand, none or little physical activity, or exaggerated physical stress, as in some competitive sport training programs, can lead to wounds and when combined with inappropriate nutrition is very damaging to bone mass.

Smoking at all ages is considered a risk factor for osteoporosis and has been proven to be deleterious to bone [38].

Drug therapy – When considering drug therapy for children, bone health must be a consideration. The most harmful drugs for bone are GCs [39] and anticonvulsants; the latter act via enhanced cytochrome P_{450} which induces increased metabolic breakdown of vitamin D in the liver [40, 41]. If these drugs are a must, patients should be advised to take measures that will minimize damage, such as calcium supplements.

Malabsorption – A variety of childhood diseases can lead to prolonged diarrhea or malabsorption: milk intolerance, celiac disease, Crohn's disease, cystic fibrosis, carbohydrate intolerance (lactose, sucrose, etc.). In all such cases, special attention must be given to provide appropriate nutrition, by nutritional counseling, to prevent growth impairment and irreversible damage.

Table 4. Causes of juvenile osteoporosis

Primary
Calcium deficiency
Idiopathic juvenile osteoporosis
Osteogenesis imperfecta
Secondary
Endocrine
Cushing syndrome
Glucocorticoid therapy
Diabetes mellitus
Hyperthyroidism
Hyperparathyroidism
Hypogonadism
Turner's syndrome
Gastrointestinal
Inflammatory bowel disease
Cystic fibrosis
Celiac disease
Biliary atresia
Hepatitis
Malabsorption
Inborn errors of metabolism
Glycogen storage disease, type 1
Hematologic
Thalassemia major
Acute lymphoblastic leukemia
Congenital neutropenia
Miscellaneous
Idiopathic scoliosis
Pseudoglioma syndrome

Nutritional deficiencies, malabsorptive conditions, endocrinopathies, immobilization, genetic syndromes and metabolic diseases should increase the pediatrician's awareness for secondary osteoporosis. Table 4 summarizes the diseases associated with osteoporosis.

Idiopathic Juvenile Osteoporosis

After the different etiologies of osteoporosis are ruled out there is a form with particular features including potential reversibility at the time of puberty, referred to as idiopathic juvenile osteoporosis (IJO). The main presenting symptoms are: back pain, difficulty in walking, long bone fractures, progressive kyphosis and failure to thrive. Both sexes are affected and the mean age of presentation is 7.0 years, ranging from 1 to 13 years.

On radiography, metaphyseal compression fractures in the lower limbs, often bilateral and symmetrical, are frequent. Many times, increased density, indicating 'stress' fractures, is apparent. In the vertebrae, symmetrical biconcavity can be seen. The mechanism of bone loss is unclear. Some bone histomorphometric studies have found osteoblast failure and decreased bone formation while others reported increased bone resorption [1, 42]. Recently, the defective osteoblast function theory was not supported since on $1,25(OH)_2D_3$ stimulation test, a normal osteoblast function was shown [42]. Collagen biochemistry did not show quantitative abnormality in patients with IJO. Most recently, however, qualitative abnormality of type I collagen associated with a reduction in total secreted collagen was found in a minority of these patients [1, 43].

Vitamin D metabolites are normal in IJO despite some rare cases with reported abnormal circulating concentration. Total body calcium is significantly reduced in these children. The bone mineral density, particularly of the spine, is generally low [1, 44]. Spontaneous improvement after adolescence is the rule. This is the reason why it is difficult to assess therapy effectiveness. Many therapeutic regimens were tried, including sex hormones, increased calcium intake, vitamin D, calcitonin and bisphosphonates [45–47].

Conclusion

Osteoporosis is one of the major causes of morbidity and mortality in adulthood. High bone mass at skeletal maturity, PBM, is considered the best protection against age-related bone loss and osteoporotic fractures. Health care in children and adolescents should focus on appropriate calcium intake, especially in compromised groups: patients on GC therapy, patients with lactase deficiency, patients with inflammatory bowel diseases and adolescents that are committed to weight-watching diets. Additional prospective longitudinal studies are needed for the establishment of threshold values of various nutrients (calcium, magnesium, etc.) and lifestyle factors for optimization of PBM during childhood and adolescence.

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Vitamin A in Pediatric Nutrition

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Introduction

Vitamin A was the first 'fat-soluble' vitamin to be recognized. The historical development of our knowledge of this vitamin extends to 1500 BC. Night blindness, for example, a condition associated with an impairment of vision in dim light, is caused by lack of dietary vitamin A; the description of this condition has been found in ancient Chinese, Egyptian and Greek literature. During the last two decades, our knowledge of the roles and functions of vitamin A have broadened considerably from the concept of this vitamin being essential in the visual process to examination of its role in regulating gene expression and controlling cell differentiation and growth.

Vitamin A occurs physiologically as the alcohol (retinol), the aldehyde (retinyl aldehyde), the acid (retinoic acid), and the ester (retinyl ester). The term 'vitamin A' refers to these naturally occurring compounds as well as to carotenoids, the provitamin A. The term 'retinoids' includes both natural occurring forms of vitamin A and its many synthetic analogs with or without vitamin A activity [1].

Vitamin A is necessary for normal differentiation of epithelial tissues, visual process and reproduction. These functions are mediated by the different forms of the molecule. Retinol and retinal are both capable of maintaining normal vision and reproductive functions. Whereas retinoic acid can substitute either of these vitamin-A forms for normal growth and development, it is not active in vision and reproduction. The role of vitamin A in the promotion of growth and differentiation of epithelial tissues makes it an important nutrient during development in the neonatal period and during infancy and childhood.

Despite the increasing major advances in our knowledge of the metabolism, chemistry sources, and biological function of the vitamin, its deficiency,

mostly among children and women, remains one of the principal public health problems in the world today.

This chapter focuses on the role of vitamin A and the effect of vitamin-A deficiency in the nutritional management of the infant and the preschool child.

Food Sources

Retinol, or preformed vitamin A, can be found in animal sources such as liver, organ meat, whole egg, whole fish, milk and milk products. Livers of marine fish or mammals are the richest sources of preformed vitamin A. Dark-green leafy vegetables (e.g. amaranth, spinach) and yellow/orange fruits and vegetables (carrot, ripe mango, ripe papaya) provide vitamin A in the form of carotenoids, among which β-carotene has the highest biological activity [2]. The richest sources of carotenoids are red palm oil and carrot oil [3]. In addition, several indigenous foods have been shown to contain high provitamin A carotenoids, for example, the buriti fruit (*Mauritia vinifera*) in north and central Brazil, the gac fruit (*Momordica cochinensis*) in northern Vietnam, the botla benda (*Abutilon indicum*) in India, and the ivy gourd (*Coccinia arandis* L. Voist) in Thailand [4]. The biological activity of vitamin A from both animal and plant sources is expressed as retinol equivalent (RE). In foods, 1 μg RE equals 1 μg of *all-trans* retinol or 6 μg of *all-trans* β-carotene or 12 μg of other provitamin A carotenoids, based on the assumption that the absorption and bioconversion of provitamin A carotenoids to retinol occur at a weight ratio of 6:1 for β-carotene and 12:1 for other carotenoids [2]. Recently, there is a growing body of evidence indicating that these ratios are arbitrary under different dietary and physiological conditions [5]. The bioavailability of dietary carotenoids appears to be affected by factors such as the chemical structure of carotenoids, the amount of carotene in a meal, the matrix of embedded carotenoids in natural form versus those altered by food preparation and processing, dietary components such as fat, chlorophyll and non-provitamin A carotenoids, nutrient status of vitamin A, vitamin E, protein and zinc; host factors such as a genetic defect in the cleavage enzyme, age, gastrointestinal infections and parasites; and finally, the interaction of the aforementioned factors [5].

Metabolism

Dietary retinyl esters are dispersed and emulsified in the stomach; their hydrolysis occurs in the intestinal lumen by pancreatic and other enzymes and solubilization of retinol derived from retinyl ester hydrolysis with bile salts in

mixed micelles [6]. Retinol is taken up by the enteral mucosal cells, where it is largely re-esterified with long-chain fatty acids. The retinyl esters are then incorporated, together with other lipoproteins and apolipoproteins, to chylomicron particles. The chylomicrons are secreted by the enteral mucosal cells into the intestinal lacteals and enter the plasma compartments through the intestinal lymphatics via the thoracic duct. The chylomicron remnant and the retinyl esters are almost completely removed from the circulation by the liver. As much as 90% of the total body reserve of vitamin A is stored in the liver in adults of most animal species. Preterm infants are born with low liver reserves of vitamin A [7]. Vitamin A is also stored to some extent in the neonate's lung, mostly near term; this seems to be independent of liver storage in animal studies.

Vitamin A is transported in plasma as retinol bound to a specific carrier protein, retinol-binding protein (RBP). RBP is synthesized in the liver and secreted to the plasma as the retinol-RBP complex. In plasma, the retinol-RBP complex interacts with another protein, transthyretin, and circulates as a 1:1 molar RBP-transthyretin complex. The absorption of retinol (rate 70–90%) is more efficient than that of carotenoids (rate 20–50%). With increasing amounts of dietary carotenoids ingested, absorption can decrease to levels as low as 10%. Absorption efficiency of both retinol and carotenoids is dependent on a sufficient amount and the quality of dietary lipids [8]. The cellular uptake of vitamin A is dependent upon a specific membrane receptor that recognizes RBP. RBP is returned to the circulation, and is partly eliminated by the kidney and partly reused for vitamin-A delivery. Cellular RBP (CRBP) plays a role in the transfer of retinol from the plasma membrane to specific binding sites for retinol within the nucleus. The cellular retinoid acid-binding protein (CRABP) has a single site for one molecule of *all-trans* retinoic acid. CRABP is involved in the interaction of retinoic acid within the cell nucleus (retinoic acid is derived from oxidation of retinol in the cell).

Vitamin A is excreted in the form of oxidation products, and some of it is retained by reabsorption of the metabolite ester β-glucuronide in the gut. During pregnancy, vitamin A is transferred from the mother to the fetus particularly in late gestation in most animal species. The transplacental transport of maternal retinol-RBP complex appears to be the predominant source of vitamin A of the fetus in early gestation. In late gestation, RBP synthesized by the fetal liver appears to be involved in extracting vitamin A from the placental circulation. Swallowing amniotic fluid containing vitamin A [9] and transfer of maternal lipoproteins containing retinyl esters [10] are other possible sources of vitamin A for the fetus. Fetal plasma vitamin-A concentrations appear to be maintained within a normal range despite variations in the maternal vitamin-A status and intake; the precise regulatory mechanisms by

which this homeostasis is achieved remains unclear. The vitamin-A content of human milk is variable and is influenced by several factors such as age, activity, socioeconomic status and fat content of the milk. The amount of vitamin A in breast milk is related to the maternal dietary intake, particularly at low concentrations of intake [11]. The vitamin-A content of mothers giving birth prematurely differs in composition from that of mothers delivering at term gestation. The vitamin-A concentration of preterm milk is lower than that of term milk in early lactation, but it becomes higher than that of term milk at about the second week of lactation. More than 90% of the vitamin A in human milk is in the form of retinyl esters contained in the core of the milk fat globules. The composition of retinyl esters is dependent on the fatty-acid composition of the milk lipids. Less than 10% of the vitamin A in human milk is present as free retinol. The efficiency of utilization of vitamin A in the preterm neonate-fed human milk depends largely on the ability of the infant's gastrointestinal tract to process retinyl esters.

Pancreatic lipase is markedly lower at birth and in the postnatal period; likewise, the intraluminal bile-acid concentrations and the bile-acid pool size are smaller in newborn infants. The bioavailability of vitamin A in human milk is higher, probably due to the presence of a bile-salt stimulated lipase in human milk, which enhances hydrolysis of retinyl esters.

Requirements

The nutritional requirements for vitamin A in all healthy individuals in a population vary, according to extensive studies conducted by the Joint FAO/WHO Expert Consultation Group [12], the National Research Council in the United States (NRC) [13] and the Society of the European Community (SCF) [14]. Thus, it has been established that the requirements amounted to about 1,200 RE daily to provide plasma vitamin-A concentrations >300 μg/l in all subjects. Great interindividual differences in susceptibility to vitamin-A deprivation and the amount needed to correct known signs were also observed in depletion/repletion studies. According to the SCF, affluent populations which generally have higher plasma retinol values develop deficiency signs when reducing vitamin intakes to plasma levels, at which persons from poorer communities can maintain health. Exceptions are children in whom vitamin A cannot be absorbed and utilized properly, for example in fat malabsorption, zinc deficiency, chronic nephritis, Crohn's disease and in alcohol-induced liver disease. For preterm infants with a birthweight $<1{,}000$ g, an intake of 450 RE/kg/day, and for infants weighing between 1,000 and 2,000 g, an intake of 200–450 RE/kg/day have been recommended [15].

Vitamin A Toxicity

The clinical manifestations of acute intoxication include symptoms and signs of increased intracranial pressure. Bone and joint pains and mucocutaneous lesions, hepatomegaly, hypercalcemia and hematologic changes as well as blurred vision are observed. Toxicity usually results from abusively high intakes of vitamin-A supplementation, and rarely from the consumption of liver from animals or fish. In children, the range of long-term (usually months) consumption that can produce hypervitaminosis A ranges from 3,600 to 15,000 μg RE/day, depending on body size and weight.

Functions

Retinoids play a major role in vision and are involved in cell growth, reproduction, the immune system and the integrity of epithelial cells. Retinoids are also employed in clinical and pathological conditions.

Visual Cycle. The visual cycle is the system in which the role of vitamin A is thoroughly understood. The specific role of vitamin A in the physiological mechanism of vision has been elucidated by George Wald, who won the Nobel Prize in 1967 for the discovery of the role of vitamin A in vision. It has been firmly established that the vitamin is required for vision in the dark and also for color perception. The active form of vitamin A for this function is the aldehyde (retinal) derived from retinyl esters and retinol. Other senses are also affected by vitamin-A status, and taste preference is altered in vitamin-A deficiency [16].

Cell Differentiation. Another major function of vitamin A is its role in cell differentiation [17]. If vitamin A is deficient, differentiation is altered so as to lead to keratinization of squamous cells which replaces normal epithelium, a process known as squamous metaplasia. During this process, mucous membranes change from a single layer of mucin-secreting and ciliated epithelium to multiple layers of deciliated nonsecretory epithelial cells, with overlying keratin resembling that of the skin. The exact role of vitamin A in this process is not entirely clear. However, the epithelia is affected in a different manner in various tissues in states of vitamin A deficiency. Interestingly, in epithelial cells of the intestinal mucosa where there are keratinizing cells, there is a decline in the number of mucous secreting cells. In other tissues, such as the epidermis where there are no mucous secreting cells, one finds keratinization. Gastrointestinal, respiratory and urogenital tracts and the skin are all lined with epithelial cells. The epithelial lining is the first stage of the mechanism protecting against infection, and it has been suggested that keratinization leads

to bacterial colonization and infection. Indeed, the levels of circulating vitamin A are usually found to be depressed in children with active infectious diseases [18]. It is not clear whether this is a result of increased demands due to infection, whether there is an overall decreased food intake during the disease affecting vitamin-A levels as well, or a redistribution of vitamin A in tissues occurs during infection. This last possibility has underlaid the rationale justifying the administration of vitamin-A supplements to children with severe measles irrespective of their prior vitamin-A status [19]. The synergism between vitamin-A deficiency and infections is responsible for the excessive morbidity and mortality in children in the developing world, mostly in diseases affecting the respiratory and gastrointestinal tracts. It has been shown that children, even with mild vitamin-A deficiency, are at an increased risk of respiratory disease and diarrhea.

Immune Function. Vitamin A may be required for optimal maintenance and functioning of the immune system. It is associated with increased susceptibility to infectious disease in both human population and experimental models. The immunopotentiating effects of vitamin A have been supported by animal studies. Studies in rats, mice and chicks have demonstrated lower antibody response to tetanus toxoid, rotavirus, diphtheria, pertussis, *Escherichia coli* and bacterial polysaccharide antigens in vitamin-A-deficient animals as compared to nondeficient animals [20]. In a recent study in 3- to 6-year-old Indonesian children, both primary and secondary IgG responses to tetanus toxoid were enhanced by vitamin-A supplementation. As to cell-mediated immunity, reduction of delayed hypersensitivity has been reported in vitamin-A deficiency, as well as delayed proliferation of T lymphocytes. Significantly depressed levels of splenic NK cell activity and interferon titers have been observed in animals [21]. Peripheral blood mononuclear cells have low NK cell activity in children with acute measles. Decreased humoral immunity in vitamin-A deficiency may be related to impaired T-helper cells.

Reproduction. Vitamin-A deficiency in experimental animals appears to result in both desquamation of germinal cells in seminiferous tubules in males and in resorption of fetuses in females. In males, the deficiency causes changes in accessory organs, such as the prostate and seminal vesicles. In addition to this somatic role of vitamin A in epithelial cell maintenance, it seems to have a specific coenzymatic role in the biosynthesis of testosterone.

Interaction of Vitamin A with Other Nutrients

Despite the fact that the biochemical mechanism is still unclear, vitamin-A supplementation enhances the recovery from iron-deficiency anemia [22].

Zinc deficiency appears to be accompanied by a depression of serum retinol levels. The hepatic concentrations of RBP in zinc-deficient animals have been shown to be less than 60% of control animals, and repletion of zinc-deficient animals restored serum levels of retinol. In a study conducted in the Philippines [23] in vitamin-A-deficient preschool children, zinc supplementation of 100 mg zinc sulfate per week without concomitant intake of vitamin A has been shown to improve the children's vitamin-A status considerably. The exact mechanism by which zinc influences the status of vitamin A is not clear. Zinc plays an important role in protein synthesis; its deficiency may therefore limit the synthesis of RBP and transthyretin (TTR) as well as of the enzymes involved in vitamin-A metabolism, such as retinyl ester hydrolase and alcohol dehydrogenase. Phenomena occurring due to vitamin-A deficiency, such as impaired growth and development, taste acuity, dark adaptation and cell-mediated immunity, are also known to occur as a result of zinc deficiency [24]. An interaction has also been recently determined between growth hormone (GH) levels and vitamin A levels in GH-deficient children, suggesting a direct effect of vitamin A on integrated concentration of GH and insulin growth factor-3 [25].

Therapeutic Potential of Vitamin A

Apart from vitamin A deficiency and conditions such as night blindness and xerophthalmia, which have been discussed previously, vitamin A has been reported as beneficial in a number of conditions, including skin disorders, bronchopulmonary dysplasia and infectious disease. In acne vulgaris, a condition known to respond to a topical application of *all-trans* retinoic acid (tretinoin) retinoic acid seems to increase the cellular turnover in the stratum corneum, making the epidermis very thin [26]. The formation of comedones (keratinous plugs) is thus prevented.

Bronchopulmonary Dysplasia (*BPD*). BPD is a life-threatening disease in neonates resulting from oxygen toxicity and artificial ventilation. Premature infants commonly have low vitamin-A stores, and it has been suggested that low vitamin-A status interferes with the ability of the lung tissue to repair the tissue injury associated with the disorder [27]. Plasma retinol values in babies with BPD have been reported to be lower than in those premature babies without BPD. High doses of vitamin A reduced the incidence of BPD from 85% in controls to 45% in the treated group [28].

Infectious Diseases. Vitamin-A deficiency is associated with increased susceptibility to infections, especially of the respiratory and digestive tracts [29], due to a combined effect of immune status and disintegration of mechanical

barriers to infections caused by the loss of epithelial cilia and by mucus secretion redistribution. A dose of 200,000 IU of vitamin A as retinyl palmitate in oil, administered 1–3 times annually, has been shown to reduce mortality by 30–50% or more in preschool children with infectious disease.

Cancer. The tissues that are dependent on vitamin A for normal differentiation include epithelia in the bronchus, trachea, stomach, intestine, kidney, urinary bladder, testes, uterus, breast, prostate, pancreatic duct and skin. Since malignant transformation is fundamentally a process of loss of cellular differentiation, and since vitamin A promotes this process, the vitamin has aroused interest in recent years as a chemopreventive agent. Fujmaki vitamin-A-deficient rats developed cancer. It is now established that a high proportion of patients with acute promyelocytic leukemia undergo complete remission when first treated with *all-trans* retinoic acid [for extensive reviews, see 30].

Assessment of Vitamin-A Status

Inadequate vitamin-A status reflects the outcome of a continuous process, beginning with a low dietary intake, leading to depletion of tissue storage; this is followed by impaired mechanisms of transport to meeting tissue demands for various functions, thereafter resulting in compromised physiological roles, up to a point where clinical signs or xerophthalmia erupt and end in blindness. Clinical manifestation of xerophthalmia and serum concentrations <0.35 μmol/l reflect severe deficiency, whereas subclinical or marginal deficiency is more difficult to diagnose. Since accumulating evidence indicates that children with a marginal state of deficiency showed an increased risk of morbidity and mortality, there is an increasing demand for reliable and practical community methods to assess the early occurrence of vitamin-A deficiency. This part of the chapter will focus on the indicators for assessment of 'subclinical' vitamin-A status, including biochemical, functional and ecological indicators. Both functional and ecological indicators are best used to screen the problem, which should be verified by biochemical indicators.

Biochemical Indicators

Body Reserves. The most accurate measurement of vitamin-A status is to determine total body stores of vitamin A. The proposed method of isotope dilution [31], however, requires the use of a stable isotope and sophisticated instrumentation (high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrophotometry) and is therefore not applicable in field conditions. The technique is more suitable for use as a reference standard to validate other methodologies. However, the attempts to determine body

stores have resulted in the development of the relative dose response (RDR) [32] and the modified RDR (MRDR) [33] as indirect assessment of liver vitamin-A content which accounts for 90% of body reserves. Both tests are based on the same biological features, the fact that apo-RBP continues to build up in the liver during depletion and that administration of retinol (R) or its analog of 3,4-didehydroretinol (DR) leads to the release of holo-RBP into the circulation. RDR requires two blood draws, and an increase of over 20% in serum retinol 5 h after dosing reflects inadequate liver reserves (<0.07 μmol/g). On the other hand, MRDR requires a single blood draw and a DR/R ratio of 0.06 or above is considered abnormal. These dose-response tests are increasingly being used in field surveys, where serum retinol alone may not be adequate. The constraints are that both tests require a 5-hour wait in the field as well as the laboratory analysis via HPLC, in addition to the fact that DR is not yet available commercially [34].

Serum Retinol. The circulating level of retinol is under homeostatic control and reflects only very high or very low body stores. Therefore, serum retinol is best used for populations in the form of frequency-distribution curves to characterize vitamin-A status of a population as well as evaluating response to an intervention program. Earlier, serum values of <0.35 and <0.70 μmol/l were used to describe deficient and low vitamin-A status, respectively. However, in the recent WHO consultation [34], deficiency was redefined to cover the condition in which tissue levels of vitamin A are depleted to the point of functional disturbances, even though no clinical signs are evident. Based on this change, the cut-off value of ≤ 0.70 μmol/l has been retained to indicate 'low' status and the prevalence levels in preschool children indicating an important public health problem have been proposed as follows: >2 to $<10\%$ mild, >10 to $<20\%$ moderate and $>20\%$ severe. Interpretation of serum values should take into consideration the confounders such as the lowering effect of the acute and chronic underlying infection as well as the presence of malnutrition. In addition, serum levels tend to increase from birth and reach adult values at puberty [34].

Breast-Milk Vitamin A. Milk concentration of vitamin A provides information on vitamin-A status of both mother and infant and has been proposed to be used as an indicator for individuals as well as populations. Sample collection is rather noninvasive and generally acceptable across cultures. A study in Indonesia showed a close correlation between milk vitamin-A concentration and positive RDR tests in 6-month-old infants [35]. Most of the vitamin A in breast milk is in the milk fat and is subject to diurnal and within-feed variation. The problem can be solved by expressing the concentration per gram of milk fat. The average breast milk vitamin-A concentrations in populations with adequate status range from 1.75 to 2.45 μmol/l, while in deficient populations, the average values are <1.4 μmol/l [34].

Functional Indicators. Impaired dark adaptation, night blindness or impaired vision in dim light is an early functional manifestation of vitamin-A deficiency. A history of night blindness (XN) obtained through an interview is a useful tool to assess a community problem, especially when a local term exists for the symptom [36]. In certain circumstances, the use of nonleading questions in relation to the local term can improve the reliability of the interview. The target population includes preschool children, pregnant and lactating women. A minimum prevalence of 1% in preschool children is required to define a public health problem in the community. Other objective assessment procedures currently being developed include pupillary and visual thresholds [37] and vision restoration time (VRT) [38].

Impression Cytology. During an early stage of vitamin A deficiency, the integrity of epithelial tissue is compromised so that the epithelial cells are flattened and enlarged while there is a marked reduction or absence of mucin-secreting cells (goblet cells). Impression cytology evaluates the morphology of cells obtained from the surface of the bulbar conjunctiva on a piece of filter paper. Presently, there are two procedures for handling specimens: conjunctival impression cytology (CIC) and impression cytology with transfer (ICT) [38]. Confounders of impression cytology include inflammatory ocular diseases, such as trachoma and conjunctivitis, which result in abnormal readings. Since impression cytology is likely to reflect the long-term effect of vitamin-A deficiency, it should be combined with other indicators of acute status, such as serum retinol or dose-response tests.

Ecological Indicators. A set of indirect indicators termed 'ecological' provide supportive information in addition to the aforementioned biochemical and functional parameters. They are helpful in identifying the population and area at risk and in planning and monitoring the progress of intervention programs. These indicators include, for example, breast-feeding pattern; prevalence of stunting, wasting and low birthweight; availability of seasonal vitamin-A-rich foods in the market and household; consumption pattern including semiquantitative/qualitative assessment of consumption frequency of vitamin-A-rich foods and so forth.

Magnitude of Vitamin-A Deficiency and Intervention Programs

Vitamin-A deficiency is undoubtedly the leading cause of childhood blindness in developing countries. Even at a subclinical level, it contributes significantly to increased childhood morbidity and mortality [39]. A recent attempt by the WHO to compile and update country data revealed that vitamin-A deficiency is a significant public health problem in 60 countries and is likely

to be a problem in at least 13 additional countries. The global estimate of preschool children clinically affected was 2.8–3 million, and at least 254 million children are severely or moderately subclinically deficient. The major factors contributing to vitamin-A deficiency are inadequate dietary intake including breast feeding and weaning diet in addition to high frequency of infections such as diarrhea, respiratory diseases, measles and associated conditions as well as HIV infection. Other risk factors include pediatric age group, increased demand during pregnancy and lactation, poor socioeconomic status, protein-energy malnutrition, seasonal pattern and location where vitamin-A deficiency tends to cluster [39]. Vitamin-A supplements are used to treat individuals with acute xerophthalmia or those at a high risk of developing clinical deficiency, such as children with severe PEM or infectious diseases. In addition, periodic high-dose vitamin-A distribution is effective in the prevention and control of xerophthalmia in areas where vitamin-A deficiency is a significant public health problem. For the treatment of xerophthalmia, the latest WHO recommendations [40] indicate that immediately upon diagnosis, the following age-specific doses be given: <6 months 50,000 IU; 6–12 months 100,000 IU and >12 months 200,000 IU. These same doses should be repeated the next day and at least 2 weeks later. For the prophylactic purpose, similar age-specific doses should be administered universally or targeted to high-risk children every 4–6 months. Pregnant women as well as women of reproductive age should receive frequent small doses not exceeding 10,000 IU daily. To ensure wide coverage and cost-effectiveness as well as sustainability, vitamin-A distribution should be integrated into existing primary health care systems such as immunization programs, diarrhea control activities, maternal and child health care services.

To ensure adequate vitamin A status in the population, long-term and comprehensive measures should be implemented, such as nutrition education, food fortification and promotion of consumption of vitamin-A-rich foods. In industrialized countries, food fortification offers a direct, effective and sustainable strategy to improve micronutrient nutrition. However, in developing-country settings, implementation of food fortification proves to be a major challenge. A nationwide fortification program requires, for example, the appropriate selection of food vehicles, a technically feasible process, affordable expenses, stability of fortificant, sound monitoring and quality control system, legislative support and community acceptability. Success stories of vitamin-A-fortified sugar and monosodium glutamate have been documented [39]. Other alternative vehicles include rice, wheat flour, milk products, edible oils, tea, salt biscuits and edible sponges [41]. Dietary intervention is regarded as the ultimate long-term approach to control vitamin-A deficiency. Although food high in preformed vitamin A or retinol is readily available and able to replete the stores, it is regarded as expensive and is sporadically consumed by

the vulnerable population. The communities in Asia and Africa where serious problems of vitamin-A deficiency were reported rely on plant sources which account for more than 80% of the total vitamin A intake [42]. Besides horticultural interventions, improving the quality of local food sources in the context of biological activity of vitamin A is, therefore, one essential prerequisite to implementing the food-based program. This improvement can be achieved by understanding the seasonal availability of local food sources, consumption pattern, food preparation and preservation which preserve vitamin-A activity and finally, a practical consumption recommendation which combines animal and plant sources to improve the vitamin-A status of the target population [4]. An integration of animal sources on a periodical basis helps ensure a good repletion of body stores to the point where plant sources can play their role in the daily maintenance of vitamin-A nutriture. To translate this knowledge into practice, an effective nutrition education or communication is required.

Conclusion

Knowledge about the important role vitamin A plays in pediatric nutrition has been briefly reviewed here. In the past two decades, scientific evidence leading to better understanding of vitamin A functions and health significance have been remarkable. Advances in understanding the mechanism by which vitamin A influences genetic expression and consequent cellular differentiation and metabolism has been made. The public health arena has also caught the attention not only of epidemiologists and health scientists, but also of policy-makers and country-leaders. Consequently, a recent call has been made in several international forums such as the World Food Summit, 1992 International Conference on Nutrition, the International Vitamin A Consultative Group (IVACG) Meeting and many regional meetings, have called for a global commitment and action to eradicate vitamin-A deficiency as a public health problem by the turn of the second millennium.

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Nutritional Management of the Immunocompromised Pediatric Patient

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Malnutrition and Immunodeficiency

From birth, our bodies are constantly exposed to and coexist with a myriad of microbes. The immune system defends our bodies against most pathogens (e.g. bacteria, viruses, and parasites, etc.). It also recognizes altered-self cells and protects us against malignancies. Derangements of the immune system (either humoral, cellular or both) predispose an individual to greater risk of developing infectious, autoimmune, and/or neoplastic diseases. Since children, particularly infants, already have an immature immune system, defects in immunologic function (either primary or acquired) put them in a more vulnerable position.

Malnutrition is recognized as a factor predisposing patients to the development of immunologic dysfunction [1–3]. So-called 'nutrition thymectomy' – lymphoid tissue atrophy with lymphocyte depletion – has been observed in patients with wasting syndromes or suffering from starvation [4]. Severe undernutrition is associated with involution of the thymus and a decrease in corticomedullary differentiation and delayed hypersensitivity reactions. Undernourished patients are at increased risk of contracting infections. The two polar types of protein-energy malnutrition (PEM), kwashiorkor and marasmus, are the classical models which illustrate the intimate relationship of nutrition and immunity. Patients with either of these disorders have impaired cellular and humoral immunity. Cell-mediated immunity is especially influenced by PEM. Reduction in tonsil size is a useful indicator of lymphoid atrophy in PEM. Undernourished patients often have a decline of T-cell numbers (CD4+ > CD8+) and T-cell proliferation. Opsonic function is also depressed

Table 1. Micronutrient deficiencies and immune dysfunction

Vitamins	
A	Disruption of epithelial cell barrier, impaired antibody responses to challenge with protein antigens, changes in lymphocyte subpopulations, altered T- and B-cell function
Thiamine	None known
Riboflavin	None known
Niacin	None known
Pyridoxine	Impaired T- and B-cell immunity due to reduced DNA and protein synthesis; lymphoid tissue atrophy and thymic epithelial dysfunction
Folate	Decreased lymphocyte response to antigens
Cyanocobalamin	Possibly predisposes to impaired neutrophil function
Biotin	Impaired B- and T-cell immune responses
Pantothenic acid	Diminished secretion of immunoglobulins by B cells
C	Reduced phagocyte function
D	None known
E	CD4+ cell deficiency; decreased antibody production and cell-mediated immune response (especially if associated with selenium deficiency)
K	None known
Minerals/trace elements	
Iron	Thymic atrophy, impaired humoral and cell-mediated immunity
Zinc	Thymic atrophy, impaired humoral and cell-mediated immunity
Magnesium	Thymic hyperplasia, impaired humoral and cellular immune responsiveness
Selenium	Impaired T-cell function; defective intracellular killing by leukocytes
Copper	Impaired T-cell function, decreased phagocytosis
Manganese	None known
Iodine	None known

because of reduced production and possible consumption of complement components C3 and factor B. Both secretory IgA production and phagocytic function are also decreased in undernourished patients. Death from infections is common in children with PEM. Interestingly, the immunologic dysfunctions in burn patients have been found to be similar to patients with PEM [5]. When a high protein diet was administered to these patients, immunologic abnormalities resolved and mortality rate was diminished [5].

With the advancement of clinical nutrition research, appreciation of the important interactive role between specific nutrients and immunologic function has increased. Micronutrients that modulate immunologic function have been identified and studied [6]. Either deficiency or excess of a single specific nutrient can downregulate the immune response (table 1). Deficiencies of certain vita-

mins effect immunity [7]. For instance, pyridoxine deficiency depresses DNA and protein synthesis, resulting in impaired humoral and cellular immunity. Pantothenic acid deficiency inhibits the stimulation of B cells to secrete immunoglobulins. Folate acid deficiency decreases lymphocyte response to antigens. Vitamin C deficiency has little effect on lymphocytes, but it can adversely affect phagocytic function. Deficiencies of vitamin A and vitamin E not only lead to decreased host resistance to infections, but also depress immune responses to mitogens [8, 9]. Trace elements, which constitute less than 0.01% of the total body weight, are essential to metabolic processes and immunologic function, because they are part of enzyme and cofactor systems [10]. Zinc and iron are particularly important because deficiency of either zinc or iron can lead to thymic atrophy and impaired cellular and humoral immunity. Selenium has also been demonstrated to enhance immune response and has an interactive role with vitamin E and glutathione as an antioxidant.

Of the amino acids, arginine has been demonstrated to enhance immunocompetence in patients whose cellular immunity was impaired by metabolic stress of illness or surgery. In a prospective study of cancer patients undergoing operations, supplementation of arginine in the enteral feeding augmented the T-cell response to mitogens [11]. Arginine can also increase thymic weight. Glutamine has recently emerged as an important component of nutrition support regimens to maintain immune function and, sometimes in conjunction with dietary fiber, intestinal integrity [12].

Nucleotide-free diets have been shown to decrease delayed hypersensitivity responses and interleukin-2 production. Supplementation of nucleotides to enteral or parenteral formulations may be beneficial to immunocompromised patients [13]. Infants may be particularly prone to nucleotide deficiencies and in preliminary studies appear to have enhancement of immune function with nucleotide-supplemented formula [14].

The interactions of fatty acids and the immune system are complex, with both suppression and enhancement of immune function being reported. Recent studies suggest that excessive polyunsaturated fatty acids (e.g. omega-6) in the diet suppress the immune response [15]. In contrast, fish oil and medium-chain triglycerides may improve survival by reducing the rate of infection [16].

Since single micronutrient deficiency can result in immune dysfunction, it is important to recognize those micronutrients that are essential for immune function when correcting malnutrition in immunocompromised patients (table 1). Of note, although single nutrient deficiency can impair immunologic function, intake of megadoses of micronutrients can also have an adverse effect on the immune system. Thus, maintaining a well-balanced diet with proper amounts of essential micronutrients is important to prevent immune function impairment.

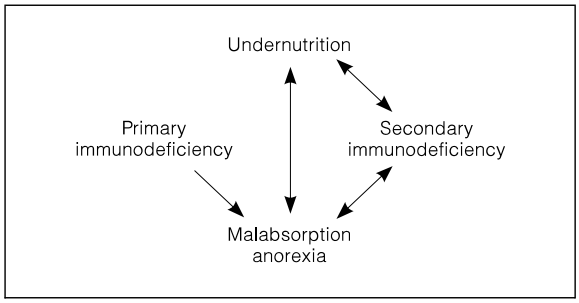

Fig. 1. Interrelationship of immune deficiency and undernutrition.

Since patients who are immunocompromised, whether primary or acquired, have a higher risk of developing infections, they frequently experience anorexia or nutrient loss secondary to vomiting and diarrhea. Fever also increases the resting energy expenditure and thus nutrient requirements. Worsened nutritional status in immunodeficient patients further compromises the immunologic functions. A vicious cycle is therefore established (fig. 1). This article focuses on therapies that will help avoid complications resulting from nutritional deficits in immunocompromised patients.

Primary Immune Deficiency Disorders

Primary immunodeficiency encompasses a heterogeneous group of disorders which result from either or both T- and B-cell defects (table 2). Although primary immunodeficiency disorders, such as common variable immunodeficiency (CVID), can occur sporadically, many primary immunologic disorders are inherited and present in childhood or infancy. Patients with primary immunodeficiency often have recurrent bacterial infections, with sinopulmonary infections as the most common manifestation of their underlying problem [17]. Yet, gastrointestinal (GI) disorders are not uncommon particularly among patients with CVID, severe combined immunodeficiency (SCID), and Wiskott-Aldrich syndrome. Chronic diarrhea and malabsorption are most frequently encountered when nutritional problems develop in these patients. Poor nutritional status presenting early in life inevitably affects the growth and development of children with primary immunodeficiency.

Although secretory IgA is the major player in mucosal humoral immunity, GI manifestations are less common among patients with selective IgA deficiency (the most common primary immunodeficiency) compared with patients

Table 2. Primary immunodeficiency disorders

Defect	GI manifestations
B-cell (antibody) defects	
X-Linked agammaglobulinemia	Diarrhea, protein-losing enteropathy, malabsorption, *Giardia lamblia* infestation
Transient hypogammaglobulinemia of infancy	Diarrhea, malabsorption (resolves by ~1 year of age)
Selective IgA deficiency	Diarrhea, malabsorption, celiac disease, *Giardia lamblia* infestation
T-cell defects	
Congenital thymic aplasia (DiGeorge syndrome)	Hypocalcemia, esophageal atresia, candida esophagitis, diarrhea
Chronic mucocutaneous candidiasis	Candida esophagitis, diarrhea
Combined (B- and T-cell) immunodeficiency	
Common variable immunodeficiency	Diarrhea, malabsorption, protein-losing enteropathy, enterocolitis
Severe combined immunodeficiency (adenosine deaminase deficiency; purine nucleoside phosphorylase deficiency; Nezelof syndrome)	Diarrhea, malabsorption, protein-losing enteropathy
Phagocyte function defects	
Chronic granulomatous disease	Hepatosplenomegaly, diarrhea, malabsorption, gastric outlet obstruction
Leukocyte function associated antigen-1 deficiency	Candida esophagitis, perirectal abscess
Complement disorders	
C2 deficiency	Colitis
C1 esterase inhibitor deficiency (hereditary angioneurotic edema)	Abdominal pain
Other syndromes	
Shwachman syndrome (neutropenia)	Exocrine pancreatic insufficiency, diarrhea, failure to thrive
Glycogen storage disease, type 1B (neutropenia)	Hypoglycemia, oral ulceration, diarrhea (inflammatory bowel disease)
Ataxia-telangiectasia	GI bleeding, abdominal pain, risk of GI malignancy
Wiskott-Aldrich	Diarrhea, GI bleeding
Hyper IgE syndrome	Mucosal lesions (stomatitis)

with CVID [18]. Nevertheless, patients with IgA deficiency who have GI symptoms present with chronic diarrhea and steatorrhea. Patients with IgA deficiency have a higher incidence of celiac disease (1/50) compared with the general population (1/500) [19]. Giardiasis has also been identified as one of the common causes of diarrhea in IgA-deficient patients.

Increased uptake of macromolecules from the GI tract into the circulation has been reported in the setting of hypogammaglobulemia and in some infants with a clinical picture resembling milk- or other protein-induced colitis [20, 21].

GI disorders are quite rare in patients with X-linked agammaglobulemia. GI dysfunction is more frequent in patients with CVID, which is characterized by low serum levels of at least two types of immunoglobulins (IgG, IgM, or IgA). Chronic diarrhea with or without malabsorption occurs in 40–60% of these patients [22–24], some of whom are infected with organisms such as *Giardia lamblia, Cambylobacter*, or *Salmonella*. Identifying the infectious agent and treating the underlying cause of diarrhea can improve nutritional status. However, the majority of cases of diarrhea and malabsorption have no identified etiologies, thereby making directed treatment impossible and supportive therapy often difficult. Correlation between the levels of immunoglobulins and GI disorders has not been found. In contrast, only in patients with abnormal T-cell function has a correlation of the immune and GI dysfunction been found [25]. Intravenous immunoglobulin replacement therapy (IgG) effectively decreases the risk of sinopulmonary infections but has no effect on GI disorders [26]. Sprue-like disorders (villous atrophy with diarrhea and malabsorption) are also frequently observed among patients with CVID [27]. Unlike celiac disease, patients with immunodeficiency syndrome-associated sprue-like disorders do not respond to a gluten-free diet. Furthermore, these patients also have a higher incidence of developing pernicious anemia at an earlier age (20–40 years of age) when compared with those immunocompetent patients (60 years of age) [28]. For some unknown reason, patients with CVID have a higher incidence of developing inflammatory bowel disease, GI malignancies and autoimmune disorders of the GI tract [25, 29, 30]. Intractable diarrhea which progresses into bloody diarrhea is the most common GI manifestation in patients with SCID. The underlying etiology of the intractable diarrhea is unknown. Because of the severity of the GI involvement, patients with SCID always present with failure to thrive during the first year of life. If severe weight loss is present and enteral feeding cannot meet the caloric requirement, total parenteral nutrition should be initiated to sustain life while awaiting bone marrow transplantation. Similarly, bloody diarrhea of unknown etiology is also the most common GI presentation in Wiskott-Aldrich syndrome [31].

Since most patients with primary immunodeficiency do not present with GI disorders, as long as patients remain asymptomatic no special diet or

dietary counseling is required. If patients present with diarrhea of unknown etiology, tests for possible villus atrophy, including a small intestinal biopsy, are beneficial and help to rule out celiac disease. If celiac disease is the cause, diarrhea should cease once a gluten-free diet is implemented. Patients might also benefit from an elemental diet because protein intolerance has been reported in patients with primary immunodeficiency [32]. For instance, the etiology of bloody diarrhea in a patient with Wiskott-Aldrich syndrome has been postulated to be related to protein intolerance. Some of these patients respond well to a restricted diet during infancy and can advance to a regular diet later in life. Small intestinal bacterial overgrowth can be a significant problem in some of these patients and can lead to further intestinal injury and malabsorption [33]. For older patients who develop pernicious anemia, vitamin B_{12} malabsorption is a major concern. Laboratory values of vitamin B_{12}, hemoglobin, and hematocrit measurements should be monitored regularly. Vitamin B_{12} supplementation should be implemented if needed.

In summary, since malnutrition is known to compromise immunity and result in an increased risk of infections, careful dietary monitoring in patients with GI disorders can help to improve the quality of life and growth potential in immunodeficient pediatric patients.

Secondary Imunodeficiency Disorders

A secondary immunodeficiency condition is more commonly encountered by clinicians than primary immunodeficiency disorders. Patients are frequently rendered immunodeficient because of the medical treatment involved. Oncologic therapies and immunosuppressive medications notoriously suppress the immune system to achieve therapeutic goals. In addition, immunodeficiency could be acquired by contracting viruses or overwhelming bacterial infections which disable the immune system. Human immunodeficiency virus (HIV) is the proto-typical example. In fact, with the increasing number of HIV-infected patients, HIV has become the most common cause of secondary or acquired immunodeficiency in children.

Drug-Induced Immunodeficiency

Immunosuppressive Drugs

Immunosuppressive drugs have been the standard treatments for childhood malignancies (e.g., leukemia and lymphoma), autoimmune diseases, chronic inflammatory conditions (e.g., inflammatory bowel disease and colla-

Table 3. Nutritional influences of immunosuppressive medications

Antineoplastic medications	
5-Fluorouracil	Thiamine antagonist, directly damages small intestinal mucosa
Methotrexate	Folate antagonist
Cyclophosphamide	Directly injures small intestinal mucosa
Procarbazine	Neurotoxicity (pyridoxine deficit)
Cis-Platin	Nephrotoxicity: excessive magnesium losses
Doxorubicin	Cardiotoxicity resembling vitamin-E deficiency
Anti-inflammatory medications	
Methotrexate	Folate antagonist
Sulfasalazine	Folate deficiency
Colchicine	Small intestinal injury, malabsorption
Corticosteroids	Catabolic, sodium retention, diabetogenic, growth suppression, osteoporosis
Immunosuppressive medications	
Azathioprine (6-mercaptopurine)	Hepatotoxicity, pancreatitis
Mycophenalate mofitil	GI toxicity (abdominal pain, diarrhea, GI bleeding)
Cyclosporin A	Nephrotoxic (mineral losses)
Tacrolimus (FK506)	Nephrotoxic (mineral losses)

gen vascular diseases), and post-transplantation (treatment or prevention of rejection or graft verus host disease; table 3). Most immunosuppressive agents are cytotoxic to bone marrow cells and to B and T lymphocytes. They inhibit cellular proliferation and suppress immune responses. One of the major side effects of chemotherapy is rendering the patients immunodeficient. During periods of intensive immunosuppressive treatment, patients are susceptible to develop infections because of the low lymphocyte count and impaired immune function. Complications such as fever or diarrhea secondary to infections are particularly common and often lead to nutrient loss. In addition, during treatment many patients have GI complaints such as nausea, vomiting and anorexia, thereby decreasing oral intake. To complicate the nutritional problems further, because of excessive production of proinflammatory cytokines, many patients have already experienced weight loss or even protein calorie malnutrition prior to the diagnosis of neoplastic disease. Hence, poor oral intake and nutrient loss due to nausea and vomiting further exacerbate the problems of malnutrition and weight loss.

To meet the nutrient requirements during immunosuppressive therapy, a high protein and carbohydrate diet is strongly recommended. A high protein and carbohydrate diet boosts the caloric intake and helps reduce the amount

of food that has to be consumed. Diets containing such foods as dairy products, eggs, meat/fish, and legumes have a potentially increased protein content, while breads, cereals, mayonnaise and fruits are rich in carbohydrates. Milk or cream can be used to replace water in cooking. Nutritional supplements (e.g., Pediasure®, Magnacal®, and Ensure-Plus®) may be utilized and encouraged as additional sources of calories and protein. Beverages high in protein and calories are preferred. To obtain all required nutrients, patients should try to eat a well-balanced diet containing food from all food groups. Moreover, most patients have poor appetite and experience satiety quickly during the immunosuppressive treatment. Thus, instead of having three meals a day, they should try to eat small frequent meals and multiple snacks. It is very important to follow a schedule and eat meals at definite times. To limit the feeling of fullness, drinking should be 30–60 min after or before meals but not during the meals. Because fatty foods cause delayed gastric emptying, fatty and greasy food should be limited in the diet. Food that cause a bitter taste and nausea feelings should be avoided. Since many patients develop mouth sores, patients should maintain good oral hygiene and brush and floss their teeth before and after meals. Topical anesthetics on these lesions may decrease anorexia. Light exercise, if tolerated, has also been shown to stimulate appetite. Some patients also experience taste change. In this case, red meat or foods that give a bitter taste should be avoided. Adding seasonings, dressing, or lemon juice to the food can enhance the flavors and stimulate appetite.

Constipation and diarrhea are also common problems encountered. Consuming adequate liquid is crucial to prevent dehydration due to diarrhea and help relieve constipation. A high fiber diet including brans should be consumed to counteract constipation, while greasy foods, certain carbohydrates (especially juices/drinks with high fructose corn syrup solids) and other foods that cause diarrhea should be avoided when attempting to treat diarrhea.

The overall goal of nutritional support is to optimize the nutritional status in patients who are receiving immunosuppressive therapies. This is particularly true for patients with neoplastic disease, because nutritional status is a major factor in predicting treatment outcome and survival rate. Malnutrition has been shown to be a poor prognostic factor in the outcome of children with acute lymphoblastic leukemia [34, 35]. Hence, regular nutritional assessment and follow-up are critical in managing patients receiving immunosuppressive therapies.

Corticosteroids

Corticosteroids are used as nonspecific anti-inflammatory agents to treat a variety of disorders of the immune system including disorders of autoimmunity, inflammatory responses, and other diseases of unknown etiology in which the

immune system appears to be disinhibited, unregulated, or over stimulated. However, in addition to suppression of the immune response, corticosteroids have many systemic side effects. Nutrition-related effects include changes in body composition due to catabolism, impaired linear growth, blood pressure elevation due to sodium retention, inhibition of bone mineralization, and altered glucose metabolism with variations in blood glucose levels. Hence, patients who are taking corticosteroids should be advised to focus particular attention on their diet in order to manage these possible side effects. A high protein diet is preferred to counteract corticosteroid-induced muscle breakdown. Since many patients on steroids experience weight gain and changes in body composition (moon facies, buffalo humps), patients should limit sugar and carbohydrate-rich foods in the diet to maintain a healthy weight. Reduced salt intake can help minimize fluid retention, swelling, and high blood pressure. High blood glucose and cholesterol levels are also common side effects of steroids, and the levels of blood glucose and cholesterol should be monitored. Calcium intake should be monitored and supplemented to the recommended daily allowance, although osteoporosis due to corticosteroids does not generally respond to oral calcium.

Human Immunodeficiency Virus

HIV is a retrovirus that infects helper T cells and monocytes of the immune system. Since helper T cells orchestrate B-cell differentiation and maturation and T-cell proliferation via the production of cytokines, the destruction of helper T cells cripples both humoral and cell-mediated immunity and results in progressive generalized immunodeficiency. Almost all HIV-infected children eventually develop the acquired immunodeficiency syndrome (AIDS). The incubation period for primary infection (subclinical or flu-like symptoms) is usually 2–4 weeks. Approximately 20% of HIV-infected children develop AIDS within the first year of life and have a more aggressive course of disease. Later the chances of developing AIDS is 8%/year in the majority of HIV-infected children. To date, more than 2 million children have been afflicted since the first case of pediatric AIDS reported in 1982 [36, 37]. In the United States about 82% of pediatric AIDS cases have resulted from perinatal transmission from an HIV-infected mother.

HIV is preferentially harbored in the lymphoid tissues. Since gut-associated lymphoid tissue is the largest lymphoid organ in the body, AIDS patients frequently manifest a broad spectrum of GI diseases. Children with HIV often have decreased weight, weight-for-height, arm muscle circumference, and overall growth compared with uninfected children [38]. Failure to thrive

and malnutrition are common manifestations in children with AIDS [39]. In fact, wasting, which is defined as weight loss of $>10\%$ of the body weight over a 2-month period, is one of the criteria of defining AIDS in an HIV-infected subject, according to criteria established by the Centers for Disease Control [40]. Weight loss is frequently the first manifestation of AIDS, before the marked decline of CD4+ T cells and development of opportunistic infections. Similarly, malnutrition has been hypothesized to be an early manifestation and a prognostic factor for the development of opportunistic infections in HIV-infected patients. Due to the crucial role that nutritional status plays in determining immunocompetence, AIDS patients who have significant weight loss and malnutrition are more susceptible to infectious complications and have a higher mortality rate compared with weight-stable patients. Moreover, HIV-infected patients are prone to have multiple nutrient deficiencies, including decreased levels of vitamins (vitamins A, B_1, B_6, B_{12}, folate, D, E) and minerals (copper, zinc, selenium, calcium, magnesium) [39, 41].

The etiology of malnutrition in HIV patients is multifactorial. Inadequate intake of nutrients, commonly found among HIV-infected children, is one of the common causes. These patients often exhibit anorexia secondary to excessive proinflammatory cytokines or chronic illness. Lesions in the mouth/esophagus commonly encountered in HIV patients can also interfere with oral intake. Furthermore, fatigue with mastication or swallowing and psychosocial problems lead to diminished oral intake. Treating the underlying organic problems and approaching the psychosocial issues may improve oral intake.

Even if HIV-infected children appear to have adequate oral intake, malabsorption might preclude them from receiving optimal calories for their age, weight, and size. Direct effects of the HIV itself on the GI mucosa may lead to malabsorption [42]. GI infection is another cause of malabsorption. Etiologies and organisms leading to GI dysfunction in AIDS are listed in table 4. Opportunistic infections may also involve the pancreas and hepatobiliary systems, resulting in malabsorption of fat-soluble vitamins and other essential elements.

Efforts should be made to uncover the underlying causes of malabsorption or failure to thrive, because once the underlying cause is treated and caloric intake is adequate, growth generally resumes. However, many AIDS patients have AIDS-associated enteropathy where no causative agents have been identified. Patients with AIDS-associated enteropathy have decreased oral intake and increased metabolic requirements resulting in caloric deprivation. AIDS-associated enteropathy is characterized by villus atrophy and maturational defects of the intestinal tract [42]. Additionally, brush border disaccharidase (including β-galactosidase) activities are decreased and lactose intolerance is

Table 4. Gastrointestinal manifestations of AIDS

Oral	Candidiasis	Small intestinal	Giardiasis
	HSV		Cryptosporidiosis
	Human papilloma virus		CMV
	Hairy leukoplakia		*Salmonella*
	Kaposi's sarcoma		*Shigella*
	Lymphoma		Mycobacteria
			Lymphoma
Esophagus	Candidiasis	Colon	CMV
	CMV		*Salmonella*
	HSV		*Shigella*
	Cryptosporidiosis		*Campylobacter*
	Kaposi's sarcoma		*Entamoeba*
	Lymphoma		Lymphoma
Stomach	CMV	Anus/rectum	Kaposi's sarcoma
	Cryptosporidiosis		Lymphoma
	Kaposi's sarcoma		Squamous cell carcinoma
			Papovavirus
Hepatobiliary	Mycobacteria	Pancreas	CMV
	CMV		Mycobacteria
	Cryptococcus, histoplasmosis		Cryptosporidiosis
	Hepatitis B, C, D		
	Cryptosporidiosis		
	Kaposi's sarcoma		
	Microsporidium		

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more frequently found among AIDS patients when compared with the reference populations [42, 43].

Under the conditions of stress such as fever, tissue damage, sepsis, and acute diarrhea, these patients have higher caloric requirements. Hence, caloric requirements should be adjusted according to the clinical status of HIV-infected patients. Measurements of resting metabolic rates in HIV-infected and AIDS adult patients yield conflicting results (table 5). One study of adult AIDS patients showed that clinically stable AIDS patients had normal to decreased metabolic rates compared with normal control subjects [44]. Most studies have shown increased resting energy expenditure in asymptomatic HIV-infected adult patients compared with the uninfected controls. As the HIV-

Table 5. Effects of HIV infection on body composition and energy expenditure

Study	Weight, kg		FFM, kg		REE, kcal/kg		REE, kcal/kg FFM	
	patients	controls	patients	controls	patients	controls	patients	controls
Kotler et al. [44], 1990	57.7	65.4[1]* 72.8[2]*	50.1	56.1[1]* 61.1[2]*	21.2	26.4[1]* 26.4[2]*	28.9	34.0[1]* 37.1[2]*
Hommes et al. [45], 1990	68.2	78.1*	55.7	62.9*	25.8	21.7*	31.6	26.9*
Hommes et al. [46], 1991	66.7	78.1*	55.8	62.9*	25.6	21.7*	30.6	26.9*
Melchior et al. [47], 1991	52.5	59.5*	43.9	46.8*	30.7	24.1*	37.4	29.9*
Singer et al. [48], 1992		67.3			29.2[3]			
Grunfeld et al. [49], 1992	77.4[4] 74.4[5] 75.6[6]	77.4			22.6[4] 25.5[5] 26.3[6]	20.4*		
Melchior et al. [50], 1993	55[4, 5] 50.5[6]	59.9*	46.8[4, 5] 41.8[6]	48.2*	31.0[4, 5] 40.8[6]	25.7*	31.0[4, 5] 49.3[6]	31.5*

FFM = Fat-free body mass; REE = resting energy expenditure.
From Heyman MB: Nutrition and Pediatric AIDS. AAP Nutrition Handbook, 1997, chapt 33.
* $p < 0.05$ vs. patients.
[1] Homosexual control.
[2] Heterosexual control.
[3] 1.23 above predicted value by Harris-Benedict equation.
[4] HIV+.
[5] AIDS.
[6] AIDS-secondary infection.

infected patients develop AIDS, the resting energy expenditure increases further but without any significant weight loss noted until infections and fever develop [49]. AIDS patients also have increased nutritional requirements and an increased rate of tissue catabolism. The pattern of decline of lean body mass in AIDS patients is similar to patients with sepsis [51]. The increased rate of tissue catabolism has been attributed to proinflammatory cytokine production. AIDS patients have elevated levels of interleukin-1β and tumor necrosis factor-α. Increased triglyceride levels observed in AIDS patients might be related to tumor necrosis factor-α which can cause hepatic lipogenesis. Further studies of energy expenditure and metabolism are necessary to characterize the changes that occur in growing and HIV-infected children.

Although malnutrition may be the inevitable consequence of progressive HIV disease, early nutritional intervention may minimize further impairment of immunologic function and reduce the susceptibility to develop infections. Some guidelines regarding nutritional support of HIV-infected children have been proposed [52]. First and most important, all HIV-infected infants and children require a thorough nutritional assessment. In addition to routine medical history inquiring about infections, fever, and GI problems (diarrhea, vomiting, dysphagia), a detailed dietary history including information about feeding habits and appetite should be obtained. Anthropometric measurements particularly including weight, height, muscle circumferences, fat folds, and head circumference (in infants and toddlers) should be performed to document adequate growth. If patients exhibit significant weight loss and failure to thrive, a nutritional team consisting of pediatric gastroenterologists and nutritionists should be consulted. In addition, any underlying infections should be identified and treated in order to improve GI function. The levels of hemoglobin, hematocrit, albumin, minerals, vitamins, iron and zinc should be regularly monitored, because micronutrient deficiencies are frequently found in HIV-infected patients. If growth is adequate in HIV-infected pediatric patients, no nutritional intervention is necessary. Azidothymidine treatment alone has been shown to improve the nutritional status of AIDS patients without nutritional intervention.

In situations where patients exhibit failure to thrive or significant weight loss, nutritional counseling is essential to provide dietary guidance based on the GI function of each individual. Twenty-four-hour recall of diet history and calorie count are necessary to assess the catch-up nutritional requirements. An elemental formula might be beneficial for patients who have diarrhea. In infants with HIV, concentrating the formula to higher calories (e.g., 30 kcal/oz of formula) or adding modular nutrient supplements (e.g., peptides, oligosaccharides, or medium chain triglycerides) may enhance the caloric intake. Since many HIV patients have micronutrient deficiencies, dietary supplementation of vitamins and minerals should be provided at one or two times the recommended daily allowance. Patients should be followed closely to determine whether any alteration of the dietary plan is needed. Nutritional intervention is more efficacious if initiated early. Many patients show clinical improvement after starting on elemental diets and can eventually be switched to more standard formulas and diets. Many AIDS patients with advanced infectious or non-infectious enteropathy cannot tolerate disaccharides because of disaccharidase deficiencies. Hence, restriction of lactose in the diet is sometimes recommended in children with AIDS, in which case it is necessary to provide an alternate source of dietary calcium.

If patients have intractable diarrhea, stools should be sent for investigation of infectious agents. However, many patients have known infectious agents

such as *Cryptosporidium* or *Mycobacterium avian intracellulare* where effective antimicrobial agents are not currently available. If no infectious agents are identified and weight loss persists, stools should be evaluated for reducing substances, pH, fat (by 72-hour fecal fat balance study), and protein (by fecal α_1-antitrypsin determination) to determine the type of malabsorption and nutrient losses. AIDS patients who have far advanced disease are usually too ill to tolerate enteral nutrition, so enteral tube feedings might be necessary to provide adequate nutritional support. The choice of formula depends on the GI functions. In an uncontrolled, retrospective study, enteral tube feedings in children with AIDS improved growth [53]. Since HIV-infected pediatric patients with wasting or failure to thrive have increased morbidity and mortality, aggressive nutritional support has been advocated. Yet, no studies or data thus far have demonstrated the efficacy of aggressive nutritional support to improve the survival of HIV-infected pediatric or adult patients. Percutaneous endoscopic gastrostomy tube placement has been advocated for patients with HIV infection requiring prolonged enteral tube feedings, although these patients may be at risk for increased complications compared with other patients receiving this modality [53, 54]. Parenteral nutrition is the last resort for HIV-infected patients. Because of an increased risk of infectious complications or technical complications following central venous catheter placement, parenteral nutrition is implemented only when enteral feeding has been unsuccessful (usually due to severe GI dysfunction, pancreatitis, or intolerance to tube feedings) [55, 56].

Conclusions

Nutrition has a clear and strong interaction with the immune system. Undernutrition certainly hampers immunologic function. Hence, clinicians who provide medical care for immunocompromised patients, either primary or secondary (including acquired), should be cognizant of the nutritional status of their patients by performing a thorough nutritional assessment. Once nutritional problems are identified, appropriate nutritional diet or intervention designed by a nutritional support team should be implemented. The nutritional support team is desirably staffed by pediatric gastroenterologists and nutritionists who specialize in tailoring the nutritional plan based on the GI function of each individual. The ultimate goal of the nutritional plan is to improve the quality of life by optimizing the nutritional status and immunologic function of immunocompromised patients. Involvement of the patient's family is the key to success because they can participate in dietary surveillance and help ensure that the patient receives optimal nutritional care. All of these aspects

involved in the nutrition support of immunodeficient and immunocompromised pediatric patients require further investigation to determine optimal therapies and their effects on patient outcome, especially quality of life and survival.

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Metabolic and Nutritional Support of the Critically Ill Child

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The metabolic and nutritional support of critically ill children poses unique challenges. The primary goals of such support for the pediatric intensive care unit (PICU) patient must focus on efforts to minimize the deleterious effects of the hypermetabolism and catabolism that follows an acute injury. Secondary goals are to promote positive nitrogen balance and, ultimately, growth. A key difference between children and adults is this requirement for the return of anabolism *and* growth.

Surveys of hospitalized pediatric patients indicate a 20–40% prevalence of protein-energy malnutrition (PEM); in acutely or chronically ill populations, malnutrition prevalence is likely higher. In one recent study of hospitalized children, acute PEM occurred in 24.5%, chronic malnutrition was noted in 27.2%, and 24% of children had a serum albumin of < 3.0 mg/dl [1]. In children with congenital heart disease, acute and chronic malnutrition was diagnosed in 33 and 64%, respectively [2]. A higher mortality risk is associated with primary PEM, especially if concomitant infection exists. Malnourished patients also have increased morbidity and longer hospitalizations. Even mild and moderate malnutrition may increase mortality, as shown in a recent meta-analysis of 28 studies [3].

Although few studies have been conducted specifically in the PICU, it seems reasonable that nutrition is essential for critically ill infants and children as they are especially at risk for PEM. Successful nutritional management requires knowledge of the patient's preexisting nutritional state, prediction of caloric needs as related to the acute stress, and understanding the metabolic requirements associated with the illness. Little data exist in pediatrics to make specific recommendations for particular diseases or to prognosticate outcome

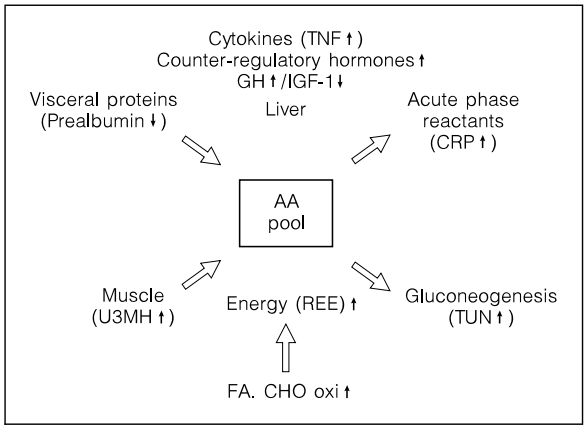

Fig. 1. Metabolic response to acute injury [5]. TFN = Tumor necrosis factor; GH = growth hormone; IGF-1 = insulin-like growth factor-1; AA = amino acid; CRP = C-reactive protein; TUN = total urinary nitrogen; FA, CHO oxi = fatty acid and carbohydrate oxidation; U3MH = urinary 3-methylhistidine; REE = resting energy expenditure.

with metabolic-nutritional support. Nonetheless, the majority of children can be nutritionally supported by various enteral and parenteral techniques.

Metabolic Response to Acute Injury

The physiologic response to acute injury has been characterized in three phases. Acute insults, such as surgery, trauma, infection, or respiratory insufficiency, may trigger a hypermetabolic response. The first phase generally lasts only minutes to hours, causing sympathetic nervous system stimulation, tachycardia, increased body temperature, and relative hypoglycemia. The second phase, often referred to as the 'ebb phase', produces an acute decrease in metabolic rate which may be transient or persistent depending on injury severity and the duration until adequate circulation is restored. Body temperature and insulin levels decrease as levels of catecholamines, glucose, lactate, and free fatty acids increase.

The third phase of acute injury, the 'flow phase', represents a period of hypermetabolism which may persist for days to weeks after resuscitation. This hypermetabolic period can be divided into catabolic and anabolic periods. Initially, body tissue is catabolized to provide substrates for the hypermetabolic response, then anabolic hypermetabolism restores tissue composition and depleted energy-protein reserves. Clinical consequences of the flow phase include

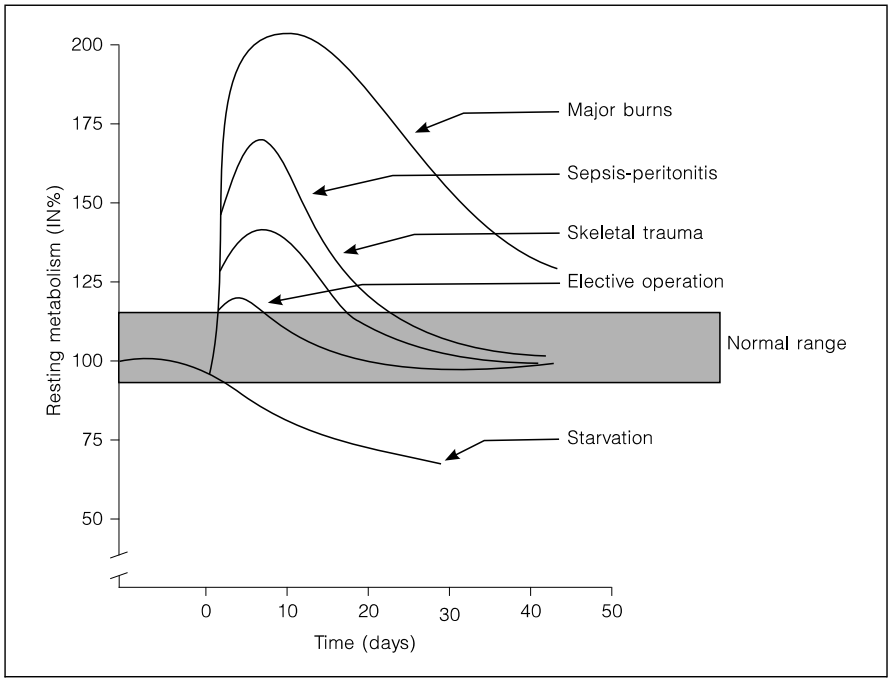

Fig. 2. Changes in resting energy expenditure over time as a function of stress level [71].

increased cardiac output and minute ventilation, impaired intestinal motility and bile excretion, loss of brush border enzymes and mucosal barrier integrity, stress ulceration and bleeding, and a myriad of cellular and humoral responses.

Hypermetabolism after acute injury is an area of active research involving numerous interwoven cascades of neural pathways, endocrine mediators, and inflammatory cell products (fig. 1), and is the subject of recent reviews [4, 5]. The magnitude and duration of the metabolic rate increase is greatly influenced by the level of physiologic stress (fig. 2). Systemic hypermetabolism often begins with the central nervous system's response to somatic injury; blocking trauma or pain-induced neural transmission to the central nervous system can greatly attenuate catecholamine, cortisol, and vasopressin increases. Other mediators of this complex hypermetabolic response include glucagon, insulin, growth hormone (GH), aldosterone, renin, angiotensin, interleukin-1, interleukin-6, tumor necrosis factor, histamine, serotonin, bradykinin, and complement.

The catabolic state is associated with an active inflammatory process, hyperglycemia, glucose intolerance, lipolysis, and a negative nitrogen balance.

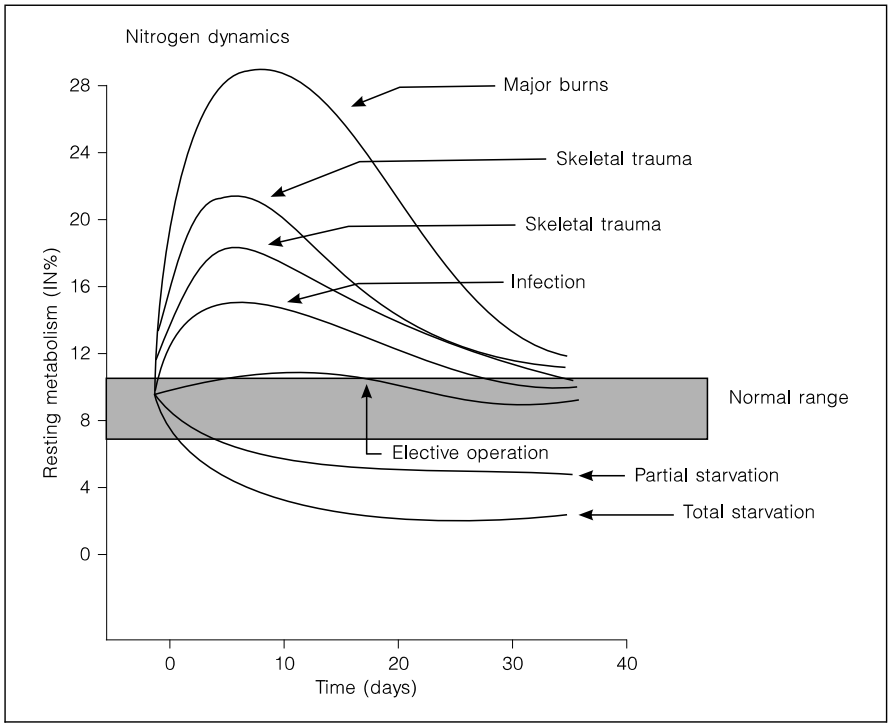

Fig. 3. Nitrogen excretion over time as a function of stress level [71].

Following the release of tumor necrosis factor and other cytokines, levels of catecholamines, glucagon, and cortisol rise and insulin levels fall; this process is often termed the 'counter-regulatory response'. Catecholamines increase metabolic rate, oxygen consumption ($\dot{V}_{O_2}$), and carbon dioxide production ($\dot{V}_{CO_2}$), and also induce triglyceride mobilization, liberate hepatic and skeletal muscle glycogen, and stimulate hepatic gluconeogenesis. Glucagon promotes gluconeogenesis and glycolysis. Cortisol promotes insulin resistance, muscle proteolysis, and hepatic gluconeogenesis. Insulin-like growth factor-1 levels fall, resulting in GH-mediated substrate mobilization. Hepatic protein synthesis changes to production of acute phase reactants (e.g., C-reactive protein), rather than visceral protein synthesis (e.g., prealbumin).

As glycogen and carbohydrate stores are rapidly depleted, gluconeogenesis and ketone body production provide essential cellular energy from stored fat and protein. Substrates for gluconeogenesis are derived primarily from smooth and skeletal muscle breakdown. Catabolism of skeletal muscle and visceral protein is hallmarked by a negative nitrogen balance, increased urinary nitrogen

Table 1. Indirect calorimetry equations and respiratory quotient (RQ) values

$\dot{V}_{O_2} = V_I(F_IO_2) - V_E(F_EO_2)$

$\dot{V}_{CO_2} = V_I(F_ICO_2) - V_E(F_ECO_2)$

Resting energy expenditure (kcal/min) $= (3.9 \cdot \dot{V}_{O_2}) + (1.1 \cdot \dot{V}_{CO_2})$

$$RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

	RQ
Fat oxidation	0.7
Protein oxidation	0.8
Carbohydrate oxidation	1.0
Carbohydrate to fat conversion	8.0

$\dot{V}_{O_2}$ = oxygen consumption (l/min); V_I = volume of inspired gas; F_IO_2 = fraction of oxygen in inspired gas; V_E = volume of expired gas; F_EO_2 = fraction of oxygen in expired gas; $\dot{V}_{CO_2}$ = carbon dioxide production (l/min); F_ICO_2 = fraction of carbon dioxide in inspired gas; F_ECO_2 = fraction of carbon dioxide in expired gas.

losses, and/or 3-methylhistidine excretion in the urine. Adult ICU studies have demonstrated prolonged increases in $\dot{V}_{O_2}$ and negative nitrogen balance in most critically ill patients; the magnitude and duration of these metabolic alterations is dependent on the type of physiologic stress (fig. 2, 3). The metabolic consequences of hypermetabolic catabolism are reviewed elsewhere [6, 7]. Ultimately, in children who recover, anabolism ensues associated with tissue repair and a positive nitrogen balance, followed by a resumption of growth.

Determination of Energy Expenditure and Substrate Utilization

By precisely measuring $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and nitrogen balance, it is possible to determine energy expenditure (EE) and to estimate the relative oxidation of carbohydrate, fat, and protein. Such measurements may be made using an indirect calorimeter, involving the administration and collection of measured volumes and concentrations of respiratory gases. Tables 1 and 2 provide the equations necessary to calculate EE, respiratory quotient (RQ), and substrate utilization. To determine nitrogen balance in critically ill infants and children, accurate total urinary nitrogen measurements are necessary as urinary urea nitrogen yields an inadequate estimate in this population [8]. RQ determinations may be valuable in the diagnosis and management of carbohydrate overfeeding ($RQ > 1.0$), particularly in patients with ventilatory insufficiency.

Table 2. Equations used in the determination of caloric sources (requires nitrogen balance studies)

1	Protein (g) = $6.25 \times$ UN (g) Protein (kcal) = 4.1 kcal/g $\times$ protein (g)
2	Fat (g) = $(1.689 \times V_{O_2}) - (1.689 \times V_{CO_2}) - (1.943 \times UN)$ Fat (kcal) = 9 kcal/g $\times$ fat (g)
3	CHO (g) = $(4.115 \times V_{CO_2}) - (2.909 \times V_{O_2}) - (2.539 \times UN)$ CHO (kcal) = 4.1 kcal/g $\times$ CHO (g)
4	EE (kcal) = $(3.78 \times V_{O_2}) + (1.16 \times V_{CO_2}) + (2.98 \times UN)$

UN = urinary nitrogen in grams; CHO = carbohydrate; V_{O_2} and V_{CO_2} = volume of oxygen and carbon dioxide in liters.

Several studies using indirect calorimetry have documented increased resting EE and $\dot{V}_{O_2}$ in critically ill pediatric patients [9] despite inhibition of somatic growth during acute stress [5]. In children undergoing uncomplicated surgical procedures, a significant increase in $\dot{V}_{O_2}$ is not seen.

Critically ill children metabolize mixed substrates to meet their energy requirements. In one study of 18 heterogeneous PICU patients, approximately 50% of the energy utilized was derived from fat oxidation, 33% from carbohydrates, and 12–15% from protein; resting EE averaged 1.48 times the basal EE [10]. This substrate utilization pattern is similar to data from critically ill adults. Altering substrate administration does not significantly change substrate utilization distribution.

Although calorimetry techniques are available for children, they remain primarily research tools, aiding our understanding of critical illness metabolism. These methods may be difficult or impossible to perform accurately, reproducibly, or practically in the PICU; however, they may be helpful in individual cases. Major limitations in applying indirect calorimetry in children include air leaks related to uncuffed endotracheal tubes and inaccuracies in RQ calculations with inspired oxygen concentration of $>40\%$.

Nutritional Assessment

Assessing the metabolic and nutritional needs of hypermetabolic critically ill children and their response to support is difficult. Nutritional assessment and therapy should be tailored to the specific requirements of a particular child given the circumstances of their illness. Identification of nutritional-

Table 3. Some pediatric conditions frequently requiring increased nutritional support

Increased nutritional losses
AIDS
Chylothorax
Cystic fibrosis
Hepatic failure
Inflammatory bowel disease
Malabsorption
Protein losing enteropathies
Protracted diarrhea
Renal failure
Increased nutritional requirements
Bronchopulmonary dysplasia
Burns
Chronic lung disease
Congenital heart disease
Fever
Infection
Surgery
Decreased nutritional intake
Altered level of consciousness
Anorexia
Chronic neurologic disorders
Malignancy
Nausea/vomiting

metabolic deficiencies and/or excesses, developing a nutrition-oriented therapeutic plan, and evaluating the effectiveness of nutritional interventions are key elements in this endeavor. Numerous pediatric disorders increase malnutrition risk (table 3). Although increasingly sophisticated methods are becoming available to assess children's nutritional status, four methods are commonly and generally applicable: anthropometry, biochemical markers, clinical determinations, and dietary evaluation. However, all of these methods have shortcomings in the PICU patient.

Anthropometric measures, especially when repeated in an individual over time, provide an appraisal of overall health and nutritional status. However, in the acutely ill hypermetabolic PICU patient, anthropometry does not confer enough detailed information regarding the child's nutritional-metabolic status. Furthermore, in patients with edema, ecchymosis, burns, or acute fluid shifts, measurements may not accurately reflect nutritional status.

Biochemical studies can identify specific nutritional deficiencies but may not provide accurate global nutritional assessment in the critically ill. Several

serum proteins may be used as biochemical markers of nutritional status. Shorter half-life proteins (e.g., retinol-binding protein and prealbumin, with half-lives ($t_{1/2}$) of 0.5 and 2 days, respectively) correlate better with acute changes in nutrition-metabolic status, whereas long-lived proteins (e.g., albumin, with $t_{1/2}$ of 20 days) tend to be decreased in chronic malnutrition. Alterations in plasma protein levels do not occur until significant depletion is present. In critically ill patients, several factors lower protein levels, including increased metabolism, decreased protein synthesis, capillary leak with extravascular extravasation, and dilution after fluid resuscitation. In neonates recovering from major surgery, prealbumin has been demonstrated to be a more sensitive indicator of nutritional status than albumin [11]. C-reactive protein (CRP), an acute phase reactant, may also be valuable. CRP has been used to stratify acute metabolic stress: in infants, a declining CRP may indicate recovery from metabolic stress and herald the resumption of somatic growth [12]. Skin tests to assess type-IV hypersensitivity, total lymphocyte count, and cell-mediated immunity are affected by numerous PICU diseases, including cancer, uremia, and hepatic dysfunction. Thus, although studies demonstrate a correlation between patient outcome and nutritional status based on protein markers, skin tests, and/or other nutritional indices, the actual prognostic value of such studies in any individual PICU patient remains unclear.

Although clinical signs of chronic malnutrition are usually easily detected, severe acute malnutrition accompanying the hypermetabolic response may have few or no overt clinical signs. Physical changes in the skin, hair, skeleton, mucus membranes, and eyes as well as aberrant sexual maturation are only seen in the late stages of malnutrition. Early signs of nutritional deficiency may be obscured by the critically ill child's acute illness.

Dietary evaluation plays a vital role in comprehensive nutritional assessment in the PICU. The use of recommended dietary allowances does not apply to acutely or chronically malnourished children. Measurement of total caloric intake, as well as protein, carbohydrate, fat, vitamin, trace element, and mineral intake is essential. Assessing the child's ability to intake nutrition is very important in determining the amount and type of supplementation required. In addition to disease-specific alterations, therapies and medications used in the PICU may have dramatic metabolic effects. Monitoring a patient's progress is essential to determine if the therapeutic goals are being met or if further nutritional plan modifications are required. A detailed description of such an approach can be found elsewhere [13].

Determining Caloric Requirements of Critically Ill Children

In the typical clinical setting where indirect calorimetry is not available, we must rely on one of numerous methods that attempt to predict EE, and

Table 4. Age, weight, height, and recommended daily energy and protein intake for healthy, growing infants and children [13, 72]

Age	Weight kg	Height cm	Energy needs kcal (range)	Protein requirement, g	Fat requirement, g/kg
Infants				2–2.5 g/kg	4–5
0–6 months	6	60	kg × 115 (95–145 kcal/kg)	kg × 2.2	
7–12 months	9	71	kg × 105 (80–135 kcal/kg)	kg × 2.0	
Children				1.5–2 g/kg	3–4
1–3 years	13	90	1,300 (900–1,800)	16	
4–6 years	20	112	1,800 (1,300–2,300)	24	
7–10 years	28	132	2,000 (1,650–3,300)	28	
Males				1–1.5 g/kg	2–3
11–14 years	45	157	2,500 (2,000–3,700)	45	
15–18 years	66	176	3,000 (2,100–3,900)	59	
Females				1–1.5 g/kg	2–3
11–14 years	46	157	2,200 (1,500–3,000)	46	
15–18 years	55	163	2,200 (1,200–3,000)	44	

therefore nutritional requirements, based on age, weight, and/or height (table 4). Normal 'maintenance' calories for healthy growing children are often calculated based on weight alone: 110 kcal/kg for the first 10 kg of body weight, an additional 55 kcal/kg for each kilogram of body weight between 10 and 20 kg, and an additional 25 kcal/kg for each kilogram more than 20 kg body weight. Thus, a 32-kg child would require approximately 1,950 kcal/day (1,100 + 550 + 300 kcal). Caloric requirements are a summation of basal metabolic needs, activity, and growth (table 5). In healthy children, basal metabolic rate accounts for approximately 50% of total EE and acitivity often accounts for 15–50% of total EE. Additionally, daily nitrogen losses in the urine (2 mg nitrogen/basal kcal/day), feces (20% of urinary losses/day), and skin (10 mg nitrogen/kg/day) must be more than replaced to achieve anabolism and growth. Children also require higher relative fat intake for normal growth than do adults (table 4).

However, in predicting energy requirements of critically ill children, one cannot utilize estimates of total EE for healthy, active, growing children. Rather, one must first determine basal energy requirements, then adjust for hypermetabolism (table 6). Additional calories should be added depending on

Table 5. Distribution of caloric needs in healthy, growing infants and children

Age years	BMR kcal/kg/day	Activity kcal/kg/day	Growth kcal/kg/day	Total kcal/kg/day	BMR/total calories, %
VLBW	47	15	67	130	36
<1	55	15	40	110	50
1	55	35	20	110	50
2	55	45	5	100	50
5	47	38	2	87	54
10	37	38	2	77	48

BMR = Basal metabolic rate; VLBW = very low body weight.

Table 6. Increases in resting energy expenditure with physiologic stress [73]

	Increase in EE, %
Fever	12% per °C[1]
Cardiac failure	15–25
Major surgery	20–30
Burns	10–100
Severe sepsis	40–50

[1] For core body temperatures of >37 °C.

the relative activity (or inactivity) of bed-ridden PICU patients. Neuromuscular blocking agents decrease EE by eliminating skeletal muscle contractions (fig. 4). Somatic growth is acutely inhibited due to stress-related decreases in GH and insulin-like growth factor-1 [5]. Using this approach, an estimate of the critically ill child's caloric needs can be made. Although Harris-Benedict equations have historically been used in adults, they are not often used in critically ill children. Indirect calorimetry may prove useful in more complex patients.

The concept of 'overfeeding' the critically ill child has significant importance. Global caloric overfeeding cannot reverse the obligate catabolism during acute hypermetabolic states and, indeed, is associated with clinical detriment and increased mortality. In adults, caloric administration of 150 versus 100% of the measured resting EE was associated with 40 compared to 28% mortality, respectively [14]. Carbohydrate excess dramatically increases $\dot{V}_{CO_2}$ and RQ, increasing minute ventilation requirements in high-risk patients who may have little respiratory reserve. Carbohydrate overfeeding does not reverse the domi-

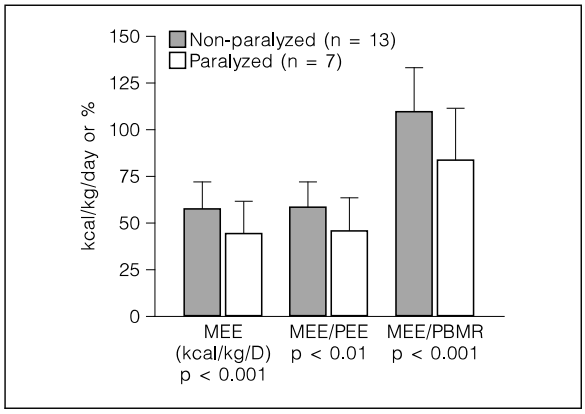

Fig. 4. Effect of neuromuscular blockade on energy expenditure. MEE = Measured EE, PEE = predicted EE, PBMR = predicted BMR [74].

nant role of fatty acid oxidation during critical illness, even though it can result in lipogenesis [15], liberating large amounts of carbon dioxide in the process (each molecule of glucose that is converted to palmitate liberates 14 molecules of CO_2). Dextrose at 125% basal EE does not substantially alter the distribution of energy sources utilized. Also, excess carbohydrate administration has been associated with fatty infiltration of the liver and deterioration of hepatic function [16]. On the other hand, lipid overfeeding can compromise immune and pulmonary function. Therefore, mixed substrate administration should be emphasized, with an avoidance of carbohydrate overfeeding.

As children recover, becoming anabolic, activity and somatic growth again become necessary considerations in determining energy requirements. When estimating caloric needs, a correction for 'catch-up growth' is used based on multiplying calculated 'maintenance' calorie determinations times the ratio of ideal body weight to the actual body weight. Infants with bronchopulmonary dysplasia or congenital heart disease may require 140–160 kcal/kg/day to achieve growth. Ultimately, administered calories must result in growth; if not, then more calories must be provided and factors contributing to growth failure must be evaluated and treated.

Techniques of Metabolic and Nutritional Support

The provision of optimal metabolic/nutritional support to critically ill patients has continued to evolve. During the late 1960s, caloric support by parenteral nutrition (PN) was developed and total parenteral support could

Table 7. Comparison of metabolic and nutritional support in children

	Metabolic support	Nutrition support
Indication	Acute illness	Starvation Failure to thrive
Goals	Minimize catabolism Prevent metabolic failure	Promote growth and anabolism
Protein	2–3.5 g/kg/day (20% of total calories)	1.5–2.5 g/kg/day (11–15% of total calories)
Fat	1–2 g/kg/day (20–50% of total calories)	2–4 g/kg/day (20–50% of total calories)
Glucose	5–10 g/kg/day (20–60% of total calories)	As tolerated (20–60% of total calories)

be realized. Concomitantly, improvements were made in delivering complex enteral formulas through various routes into the gastrointestinal (GI) tract. As hypermetabolism became better defined, metabolic support to prevent end-organ damage was increasingly promoted and the concept of 'substrate-limited metabolism' entering clinical practice. Metabolic support of ill patients differs from nutritional support of healthy children (table 7). However, these concepts have not been thoroughly investigated despite their application in the PICU.

Selection of the route of administration for nutritional-metabolic support depends primarily on the status of the GI tract and its ability to adequately absorb nutrients. For patients who cannot meet their needs through oral intake, GI intubation with enteral formula administration is the preferred method for caloric and nutrient delivery. Peripheral PN or total PN (TPN) are alternatives when GI function is inadequate. Numerous studies demonstrate advantages for early enteral feedings compared to PN in both adults and children [17, 18]. Improved tube delivery systems now allow early enteral nutrition (EN) in critically ill children. Although gut use is preferable, PN can easily be administered during GI compromise. Some indications for PN include short-bowel syndrome, ileus, severe dysmotility, inflammatory bowel disease, and necrotizing enterocolitis-like enteropathy. In general, PN is overused due to misperceptions regarding GI tract competence. General guidelines for the development of a nutrition-metabolic treatment plan are outlined in figure 5.

Enteral Nutrition

Assisted EN provides calories to persons who cannot meet their needs through oral (per os, PO) intake. EN also has several advantages over PN, including decreased cost, metabolic abnormalities, and infectious risk. The

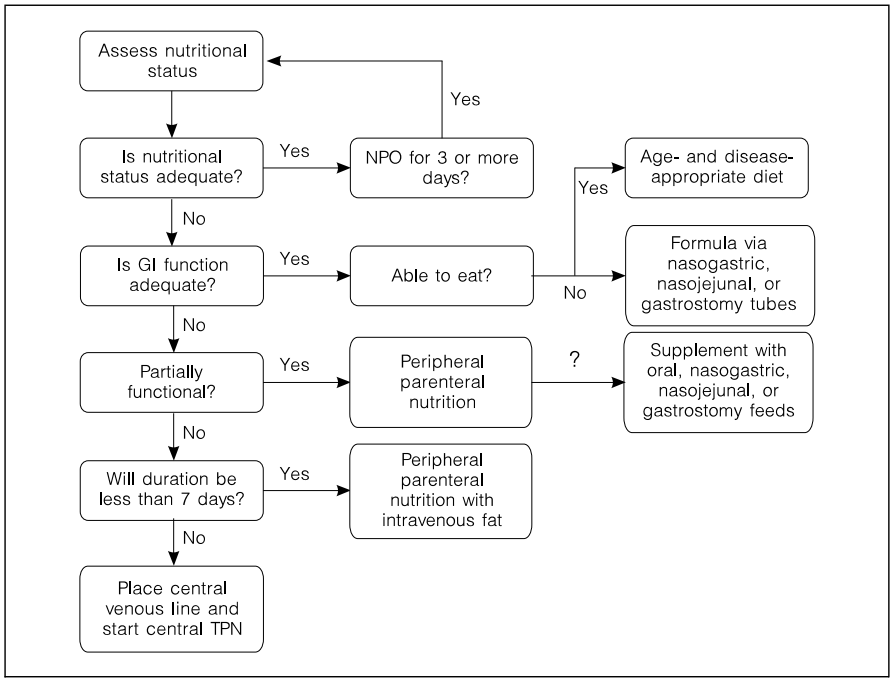

Fig. 5. Development of nutritional-metabolic treatment plan. Modified from Carlin et al. [75].

presence of nutrients in the intestinal lumen promote GI integrity, stimulating enteric secretions, hormones, and blood flow. EN may also contain specific components that cannot currently be provided parenterally and may facilitate nutritional recovery.

EN may help maintain the gut as a barrier to bacterial translocation. Enteric cellular metabolism is quite high: glutamine is the principle cellular fuel for the small intestine. Luminal nutrients support the gut mucosa and promote trophic hormone production. Intestinal mucosal atrophy can arise from starvation (absence of luminal nutrients), even when PN is provided. During hypermetabolism, enterocyte glutamine metabolism increases [19]. Glutamine is not present in current PN formulations and enterocyte glutamine supply exhaustion may further compromise mucosal integrity: a potential consequence of mucosal impairment is bacterial translocation which occurs in as many as 66% of adults on TPN [20]. Bacterial translocation does not seem to occur in individuals on complex enteral feeds [20].

Candidates for EN include children who have at least partial GI tract function. Even when gut use is limited, 2–3 ml/h of enteral formula maintains

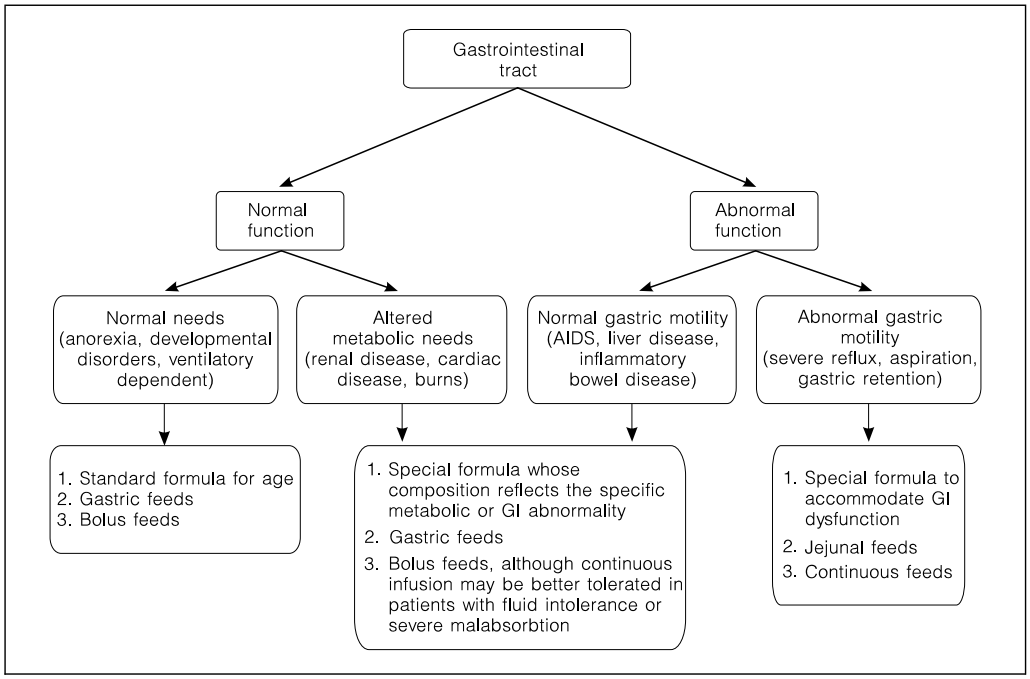

Fig. 6. An approach to enteral nutritional management [76].

trophic levels of several important GI hormones [21]. Clinical indications for EN are broad, including conditions where increased metabolite losses or nutritional-metabolic requirements are beyond the patient's PO intake capacity, where PO intake is limited by the patient's condition or therapy, or where EN is the primary management for the patient's disease. One general approach to EN management is shown in figure 6.

Enteral Nutrition Delivery Methods

Assisted EN may be delivered into the stomach or small intestine. The stomach may be accessed by orogastric or nasogastric feeding tubes; long-term gastric feeds may be provided after surgical gastrostomy or percutaneous-esophageal gastrostomy. Transpyloric feeding can be administered either after spontaneous passage of a weighted tube (often quite slow), or through direct intubation past the pylorus using fluoroscopic, pH-guided, or other techniques. Occasionally, surgical jejunostomy may be necessary.

Gastric feeding is most desirable as the stomach tolerates higher osmolarity formulas, gastric acid secretion in response to formula stimulates physiol-

ogic pancreatic responses, and gastric feeding has protective effects on the stomach's mucosa. If gastric feeds are contemplated, one must determine if gastric emptying is adequate or if gastroesophageal reflux is an issue. Patients with critical illness have multiple disease-related and iatrogenic factors affecting gastric emptying. Major factors influencing gastric emptying include: formula osmolality, fat content, lipid carbon chain length, and medications. Narcotics, benzodiazepines, and other analgesic, anesthetic, or sedative mediations commonly used in the PICU can significantly alter gastric emptying in a dose-dependent manner. Although neuromuscular blocking agents alone do not significantly influence gastric emptying, these drugs are used concomitantly with medications which do inhibit gut motility. Continuous gastric formula infusion is usually better tolerated than bolus methods, especially if gastric emptying is abnormal. Bolus feeding increases both total 24-hour $\dot{V}_{O_2}$ and peak $\dot{V}_{O_2}$ when compared to continuous feeding [22].

Ileus or dysmotility after trauma, surgery, or medications usually has more pronounced effects on gastric compared to small bowel motility. Transpyloric feeding eliminates issues related to gastric emptying. Small bowel feeds must always be given by continuous infusion and are usually the method of choice in patients with intestinal compromise. Small bowel feeds have been tolerated immediately after abdominal surgery in adult patients, with excellent results despite an apparent ileus [17]. Patients receiving neuromuscular blockade are frequently fed into the small bowel with minimal complications or difficulties [23]. Motility agents, such as cissapride or metoclopramide, are often beneficial in circumstances of impaired gastric emptying and intestinal dysmotility.

Complications of EN may occur. Misplacement of feeding tubes into the trachea, lung parenchyma, pleural space, and the cranium can occur. The tube itself may cause esophageal or gastric ulceration, mediastinal perforation, or bleeding from esophageal varicies. Gastroesophageal reflux with pulmonary aspiration is also not uncommon in critically ill patients and can be minimized with transpyloric feeding. Carbohydrate overfeeding can worsen respiratory status due to increased $\dot{V}_{CO_2}$ and minute ventilation requirements. Hyperosmolar formulas may contribute to diarrhea with subsequent fluid and electrolyte losses.

Starting and advancing EN should be individualized. Initially, monitoring should focus on patient tolerance, fluid balance, and electrolyte stability. Once intake goals are realized, evaluation of growth and weight gain should be ongoing. Transition from enteral to oral feeding should be part of a clearly defined treatment plan.

Feeding Composition

A variety of formulas are available for EN, varying significantly in nutritional composition, caloric density, and cost. Formulas used in the first year

of life have a different balance of nutrients and lower osmolarity than formulas used in older children and adults. Modified cow's milk formulas contain lactose and cow's milk protein and are generally recommended for feeding infants with normal digestive processes. Soy-based formulas are lactose-free and are recommended for lactose-intolerant infants. Predigested formulas (protein hydrolysates) are used in the setting of soy and cow's milk protein intolerance. Special modified formulas are available for patients with malabsorption, maldigestion, renal disease, and specific inborn errors of metabolism. Formulas used for EN in children older than 1 year old have similar diversity. Guidelines for formula choice are readily available [24].

In the critically ill child, special considerations may influence formula selection. Some children require higher caloric density formulas to meet caloric goals. Formulas with 24 kcal/oz (0.8 kcal/ml) are usually well tolerated in infants. Higher caloric densities may be used, but patients must be observed closely for signs of intolerance, including osmotic diarrhea, fluid and electrolyte abnormalities, and inability to tolerate renal solute load. Increased caloric density may affect gastric emptying. With patience, it is often possible to slowly increase infant formula caloric density as high as 30–40 kcal/oz. For older children, EN formulas with 1–2 kcal/ml (30–60 kcal/oz) are available.

Critically ill patients often have limited ability to digest or absorb complex carbohydrates, intact proteins, or fats. Mucosal brush border disaccharidases may be compromised after acute injury, limiting complex carbohydrate digestion. Frequently, glucose polymers are used in critically ill patients due to relatively better digestion and absorption; however, such formulas also significantly increase osmolarity. Carbohydrate absorption is easily assessed at the bedside by testing for reducing substances in liquid stool.

Protein absorption may also be compromised during critical illness. Bowel injury can increase mucosal permeability, further harming the intestine and triggering systemic inflammatory cascades. Cardiac failure and cardiopulmonary bypass may increase intestinal microvascular permeability. Elevated central venous pressures can result in intestinal edema and protein-losing enteropathy after palliative repair of congenital heart disease. Many elemental formulas contain free amino acids (AAs) as a source of protein; however, small peptides from whey protein hydrolysis are better absorbed than free AAs [18]. Predigested formulas (protein hydrolysates) are the principle EN preparation used for critically ill children.

Long-chain fats require bile salts and lipolytic activity to be digested, then enter the circulation through the lymphatic system. Medium-chain triglycerides (MCTs) are absorbed directly into the portal circulation and do not require miscelle formation. Since MCTs have less inhibition on gastric emptying, faster absorption, and more rapid conversion into energy than long-chain

triglycerides (LCTs), formulas containing MCTs may be beneficial in the PICU. In children with chylothorax, formulas with very high amounts of MCTs may permit EN while also decreasing lymphatic flow, allowing leaking thoracic lymphatics a chance to seal.

Adequate electrolytes, vitamins, and minerals must also be provided. The adequately functioning gut has efficient mechanisms for electrolyte and mineral absorption. Bile salts and micelle formation are required for fat-soluble vitamin absorption.

Several new formulas have been developed for critically ill patients. Some areas of investigation and controversy include the use of fish oils, branched chain AAs (BCAAs), arginine, and glutamine. The role of these products remains unclear, especially in the PICU, where little data exist.

Parenteral Nutrition

For patients in whom GI dysfunction renders EN insufficient to provide adequate nutrition-metabolic support, parenteral delivery of nutrition becomes necessary. PN can supplement partial enteral feeding. The selection of nutritional components must be individualized and accompanied by careful monitoring. Individual nutritional elements must be considered: carbohydrates, AAs, fats, vitamins, trace elements and minerals must all be provided.

Mixed metabolic fuels are necessary for optimal support. In infants receiving TPN, providing nonprotein calories as a glucose-lipid mixture has many advantages compared to glucose alone. Comparing isocaloric-isonitrogenous TPN, glucose-lipid mixtures reverse negative nitrogen balance, produce net fat oxidation, and significantly decrease $\dot{V}_{CO_2}$ and RQ. In the PICU, mixed metabolic fuels are beneficial and decrease minute ventilation secondary to a decrease in $\dot{V}_{CO_2}$ [25, 26].

Carbohydrate

The goal of glucose administration is to provide energy, hopefully sparing somatic protein. However, during hypermetabolic states, glucose infusion does not suppress glucagon, does not lower serum fatty acids, and may impair lipid oxidation. Triglyceride breakdown does not decrease with hypercaloric glucose administration. Although protein synthesis is unaffected by high glucose delivery, high glucose loads may elevate insulin levels, promoting smooth muscle proteolysis in preference to skeletal muscle. As previously discussed, carbohydrate excess, both as a percentage of total calories and in absolute amounts, must be avoided as inordinate administration can significantly increase $\dot{V}_{CO_2}$ and RQ, elevating ventilatory requirements.

Dextrose is the mainstay of PN. In aqueous monohydrate form, dextrose yields 3.4 kcal/g (compared to 4 kcal/g for enteral carbohydrate). In adult

patients, dextrose delivery of 4 mg/kg/min (5.7 g/kg/day) has been reported as an optimal rate; greater amounts result in fat conversion and a very high RQ. In infants and children, glucose utilization may maximally range from 8 to 13 mg/kg/min (11.2–19 g/kg/day): critically ill infants will often tolerate no more than 8–10 mg/kg/min, whereas malnourished children receiving nutritional repletion usually require higher rates [26].

Insulin administration during TPN is not beneficial. During acute metabolic stress, hyperglycemia is primarily due to gluconeogenesis from proteolysis and relative insulin insensitivity. Proteolysis is unresponsive to exogenous calories. In this situation, the addition of insulin does not increase protein synthesis [27], and may promote smooth muscle breakdown [28].

Fat Emulsions

Adipose tissue represents the largest reservoir of stored energy substrates; in children, it contains approximately 18% polyunsaturated, 45% monounsaturated, and 37% saturated fatty acids. This fatty acid distribution is similar to that in breast milk but differs significantly from commercially available lipid emulsions. No currently available emulsion has a monounsaturated fatty acid content similar to adipose tissue or breast milk. Parenteral fat emulsion use has evolved over several decades as our understanding of lipid metabolism has advanced.

The use of fat-free PN leads to clinical and biochemical essential fatty acid (EFA) deficiency. Individual fatty acids and polyunsaturated fatty acids (PUFAs) are vital for EFA metabolism, even though these compounds are not usually a major substrate for energy production. Parenteral fat was initially introduced to provide PUFAs as a necessary substitute for EFA without consideration of optimal energy production. Only 1–2% of total calories as EFA is necessary to prevent deficiency.

Currently, lipid emulsions are primarily used as an energy source in a balanced nutritional regimen. Administered fats may be metabolized for energy, stored as adipose, or serve other functions. The intravascular metabolism of lipid emulsion is illustrated in figure 7. Endothelial lipoprotein lipase is responsible for lipid emulsion LCT hydrolysis. In order to be recognized by these enzymatic systems, emulsion particles must first acquire surface lipoproteins, including apoprotein C-II, C-III, and E, primarily from high-density lipoproteins. High lipid infusion rates may exceed the ability of these systems to adequately clear and metabolize administered emulsions, necessitating slower and/or continuous infusions in sick patients.

The optimal quantity of fat administration in children is not known. A recent study in newborns receiving TPN compared lipid metabolism when 70, 50, 35, 15, or 0% of nonprotein calories were given as lipid emulsion: maximum

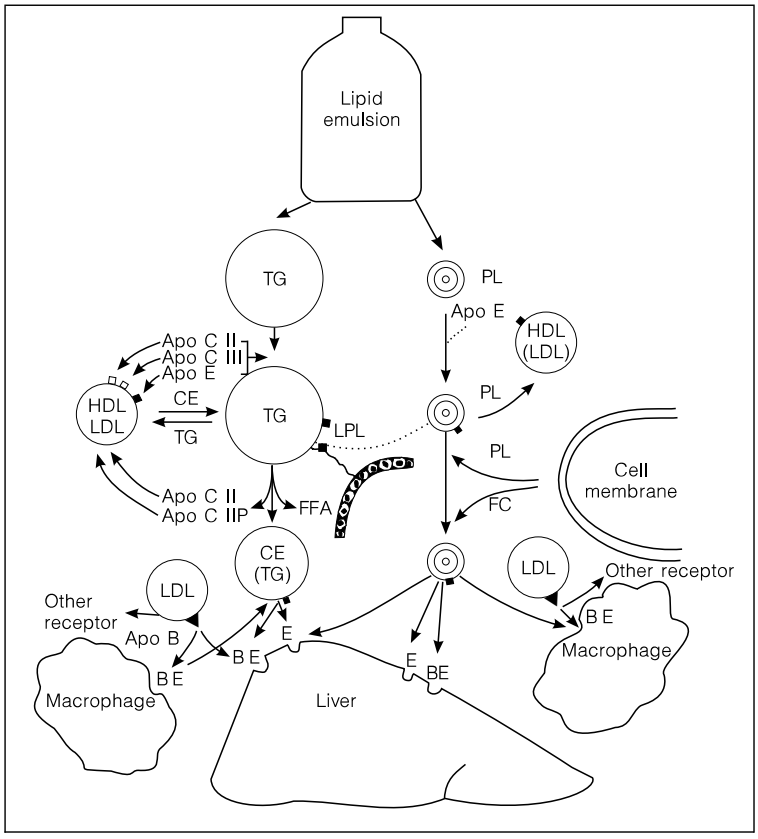

Fig. 7. Metabolism of intravenous lipid emulsion [77]. Intramuscular metabolism of both triglyceride (TG)-rich and phospholipid (PL)-rich particles present in a lipid emulsion. The four key steps previously outlined for the metabolism of endogenous chylomicrons are represented for the TG-rich emulsion particles. On the right side, the formation of PL-free cholesterol (FC) complexes having acquired apoprotein (Apo) E is represented, as is the competitive effect of liposomes for lipoprotein lipase (LPL). In the lower part, we have speculated on the potential competition of exogenous remnants between themselves and with endogenous lipoproteins for binding to the low-density lipoprotein (LDL) B, E receptor and the chylomicron remnant E receptor at the site of different tissues. HDL = High-density lipoprotein; FFA = free fatty acid. From Carpentier [77].

fat oxidation occurred with 50% lipid calories [25]. A similar study in newborn infants provided 18, 29, or 40% of nonprotein calories as fat and indicated that maximum fat oxidation occurred at 40% [26]. In these newborn infants, low-fat/high-carbohydrate intake was associated with increased minute ventilation, whereas moderate and high-fat intake minimized net protein oxidation.

There are clinically significant differences in commercially available 10 and 20% lipid emulsions, especially in their phospholipid content. Adjustments in the amount of phospholipid emulsifier have improved lipid clearance. The higher amount of phospholipid in 10% emulsions results in excessive phospholipid liposomes. These phospholipid liposomes contribute to the formation of lipoprotein X-like particles which have been detected in lipoprotein fractions from neonates receiving 10 but not 20% lipid emulsion [29]. Lipoprotein-X particles slow the peripheral hydrolysis of circulating triglycerides by lipoprotein lipase. Premature infants demonstrate significantly faster triglyceride clearance and lower serum phospholipid levels following administration of 4 g/kg/day of 20% lipid emulsion compared to 2 g/kg/day of 10% emulsion [30].

Over the last decade, considerable experience has been gained outside the USA using MCT/LCT emulsions to provide a more readily available energy source. Emulsions containing MCTs may be advantageous as hepatic and peripheral lipoprotein lipases hydrolyze MCT/LCT mixtures more rapidly than LCTs alone [31]. Since the intracellular metabolism of medium-chain fatty acids does not require carnitine, parenteral MCT/LCT mixtures are cleared and converted to energy more rapidly than currently available LCT emulsions [32]. Infants generate $^{13}CO_2$ from 1-^{13}C-labeled MCT emulsions more rapidly than from 1-^{13}C-labeled LCT [33].

Lipid emulsions have raised concerns regarding their possible effects on immune system function: the rate of fat emulsion administration and LCT-PUFA content have been implicated. In human trials, high dose lipid infusion over 8 h decreased reticuloendothelial system (RES) function (as measured by technicium-sulfur colloid clearance) whereas RES dysfunction was not seen with 24-hour infusion duration [34]. Slower lipid infusion rates also improve macrophage function in infants [35]. However, withholding lipids may cause other immune abnormalities, including lymphatic tissue atrophy, decreased antibody production, and increased infection susceptibility. LCT emulsions decrease bacterial clearance in animal models; substituting MCT, thus lowering PUFA content, improved bacterial clearance [36]. RES dysfunction with standard LCT emulsions compared to improved RES function with MCT/LCT administration has been demonstrated in a recent human investigation [37].

Controversy has arisen regarding possible effects on the immune system due to the high ω–6 PUFA content (e.g., linoleic acid, 18:2 ω-6) in lipid emulsions; ω–6 acids are substsrates for arachidonic acid pathways involved in the synthesis of prostanoids and leukotrienes. These PUFA metabolites may result in significant immune modulation, including decreased neutrophil chemotaxis, phagocytic function, and bactericidal activity. Rapid infusion of lipid emulsion may enhance thromboxane synthetase activity, thereby increasing thromboxane production. In newborn piglets, rapid lipid infusion (1 g/kg/h) resulted in

thromboxane-mediated pulmonary vasoconstriction which could be reversed by thromboxane antagonists [38]. Use of fish oil (ω–3) instead of soybean oil (ω–6) in a thermal injury animal model improved immune function; in burn patients, greater survival has been observed with ω–3 fatty acid use [39].

Questions have also been raised regarding emulsions and their effects on pulmonary function, particularly in premature infants and patients with acute lung injury. These topics have been recently reviewed [40]. Early studies correlated elevated triglyceride levels following bolus lipid administration with compromised arterial oxygenation; oxygenation improved following a heparin-mediated decrease in triglyceride levels. Premature infants less than 1 week old receiving bolus administration of 10% lipid emulsion have average serum triglyceride levels of >200 mg/dl and decreased P_aO_2; however, premature infants of >2 weeks postnatal age had mean serum triglyceride levels which remained below 150 mg/dl without a change in P_aO_2 [41]. Bolus lipid administration in animals results in pulmonary vasoconstriction and decreased P_aO_2, effects partially reversed by thromboxane antagonism [38]. In a series of ventilated adult patients with acute respiratory distress syndrome, infusion of 500 ml of 10% lipid emulsion increased alveolar-arterial oxygen gradient, whereas patients with other causes of respiratory failure maintained or improved their gradient [42]. Subsequent studies in very-low birth weight neonates have demonstrated that 20% lipid emulsion administered over 20 h has no effect on pulmonary function or blood gases [43]. In newborn infants, high-dose lipid administration (3g/kg/day) compared to a lower dose (1 g/kg/day) resulted in a small decrease in transcutaneous P_aO_2 (73.8 ± 2.8 to 68.8 ± 2.6 torr), accompanied by a decrease in $\dot{V}_{CO_2}$ and alveolar minute ventilation [44]. Since RQ improves without a change in $\dot{V}_{O_2}$ and changes in arterial oxygenation are minimal, higher lipid doses are favored. In contrast, MCT containing emulsions do not affect pulmonary hemodynamics or gas exchange despite bolus administration to septic patients or mechanically ventilated adults [45, 46].

Based on these considerations, our practice has been to aggressively use parenteral lipids (only the 20% lipid emulsion) in the PICU, starting at 1.0 g/kg/day and increasing by 1.0–1.5 g/kg/day until 30–50% of the calories are from fat. In patients with acute respiratory distress syndrome, a slower, but similar approach is utilized. Lipid emulsions are administered over 18–24 h, with daily determinations of serum triglycerides. Although it is usually possible to maintain serum triglyceride levels below 250 mg/dl, baseline levels in patients with sepsis may be 400–600 mg/dl or higher and do not contraindicate the institution of intralipid administration. Often, these levels decrease as lipid infusions are progressively increased. Hopefully, MCT containing emulsions will soon be available in the USA where they will likely have a significant role in the PICU. In fluid-restricted patients, 30% lipid emulsions may be help-

ful in reducing administered fluid volume; 30% emulsions contain the same 1.2 g/dl of phospholipid emulsifier as 10 and 20% emulsions. No data currently exist in the PICU population for 30% lipid emulsions.

Amino Acids

Crystalline AA solutions have been used for many years. The clinical use of specialized AA solutions is increasing. Caloric requirements are influenced by the source of protein, need for catch-up growth, losses, and increased metabolic demands. Ten to twenty percent of total calories should come from protein. In fluid-restricted patients, AA solutions with concentrations up to 15% AAs may permit adequate nutrition support. The commonly employed calculation of 'nonprotein calories to grams of nitrogen' can be misleading, as the relative contribution of carbohydrate and fat as nonprotein calorie sources is not considered. The use of simple percentages of each nutrient group allows better communication among health care providers. Given the approximation that protein provides 4 kcal/g and 0.16 g of nitrogen/g, then the following ratios of nonprotein calories to grams of nitrogen correspond to the indicated percent total calories from AAs: 100:1 = 20%; 150:1 = 14%; 200:1 = 11%, and 250:1 = 9%.

The controversy of whether AAs should be counted as calories remains unsettled. The view that all AAs are synthesized into structural proteins is over simplified, but counting all AAs as calories is equally over simplified, as renal losses, sructural protein synthesis, and other nonenergy-producing metabolism occurs. Exogenous protein products with short half-lives, such as fresh frozen plasma, cryoprecipitate, and albumin, are 'recycled' into the free AA pool and therefore also contribute to caloric intake. A rough approximation of counting half the AAs and half the infused protein products as calories may be reasonable, but this remains to be verified. There is no consensus as to how AAs and exogenous protein should be included in administered calorie calculations.

Initial uncontrolled studies in children implicated standard AA solutions in the development of TPN-associated cholestasis, with improvement after use of a specialized AA solution [47]. However, a subsequent retrospective review comparing standard and specialized AA solutions in infants could not demonstrate any improvement: only the duration of TPN use was correlated with cholestasis [48]. Clearly, prospective, randomized trials are necessary; yet, specialized solutions are common in many neonatal ICUs.

The use of BCAAs has been an area of active research. BCAAs have been postulated to minimize structural protein catabolism during acute stress and improve hepatic encephalopathy. BCAAs are not metabolized by the liver, and serve as an energy source for muscle. Studies in adults have demonstrated

decreased skeletal muscle breakdown and improved hepatic and skeletal muscle protein synthesis associated with BCAA use [49]. Recent experience in children has been contradictory [50, 51]. Further work is necessary to clarify the importance of BCAAs in critically ill children.

The use of BCAAs in hepatic encephalopathy is based on observations that the severity of hepatic encephalopathy correlates with the degree of decreased BCAAs and elevated aromatic AAs in plasma. Unfortunately, the use of BCAAs to correct these AA abnormalities does not produce objective improvements in clinical measurement in encephalopathy or serum ammonia. Two recent reviews summarise the conflicting results of BCAAs in fulminant hepatic failure [52, 53]. Further investigation is needed to support the use of BCAAs in children with liver disease.

Glutamine is the subject of intense recent investigation and controversy. It is the most abundant AA in plasma and muscle and the major energy source for intestinal enterocytes. Glutamine-supplemented TPN has been demonstrated to prevent and reverse intestinal atrophy associated with standard TPN use in animal models [54]. Subsequent animal studies have shown improved survival in an *Escherichia coli*-induced peritonitis model by the addition of 1.5% glutamine to standard TPN [55]. Others have disputed these beneficial effects [56]. In a randomized, controlled trial of adult bone marrow transplant recipients, glutamine supplementation resulted in increased nitrogen balance, fewer infections, and decreased hospital length of stay when compared to standard AA solutions [57]. In premature infants, glutamine-supplemented TPN resulted in shorter TPN duration, faster transition to enteral feedings, decreased duration of mechanical ventilation, and improved absorption of *D*-xylose when compared to control solutions [58]. Glutamine may become a significant constituent of TPN in the future.

Vascular Access

For the initiation of metabolic support with low tonicity PN, peripheral intravenous catheters often will be adequate and may be used for several days, obviating the need for more invasive and higher risk techniques. Dextrose concentrations above 12.5% must be given through a central vein due to the inability of peripheral veins to tolerate the hypertonicity of higher dextrose concentrations. The upper limit of tonicity generally tolerated in the peripheral veins is about 700 mosm; at higher tonicity, phlebitis and tissue damage from extravization become more common. Central vascular access is necessary if TPN is to be provided to critically ill infants and children.

Several types of central venous catheters are commonly used in the PICU. Polyurethane multilumen catheters usually allow a couple weeks of TPN delivery. Sialastic peripherally inserted central catheters allow central access for

several weeks with a low risk of infection. Broviac or Hickman-style tunneled catheters are used for chronic TPN administration and also have a low infection rate, although percutaneously placed multilumen catheters are more common in the PICU since they may be inserted at the bedside.

Numerous technical complications can occur with central vascular catheter placement. Pneumothorax is a common complication when catheters are placed into the internal jugular or subclavian veins; this complication is avoided by using the femoral vein. Other site- and procedural-related complications include: inadvertent arterial puncture or laceration; hematoma; hydrothorax; hemothorax; air embolism; brachial plexus injury; thoracic duct injury; arrhythmias, and ventricular perforation. Venous thrombus and catheter-related infections are common.

Infectious complications with prolonged catheter use for TPN are common. Numerous studies have examined catheter types, sites, and infection rates in critically ill patients [59]. Infection usually occurs as bacteria migrate into the catheter's cutaneous tunnel. With proper sterile technique, catheter infection rate depends on the cumulative duration of catheter use, with similar daily infection rates on early and late days of use [60]. The diagnosis of catheter infections may be difficult. In one series involving neonates, a significant decrease in catheter-associated gram-positive bacteremia was achieved by continuous infusion of low-dose vancomycin (25 μg/ml) mixed with TPN [61]. Despite the absence of vancomycin-resistant organisms in this report, the recent emergence of vancomycin-resistant enterococcus in other populations should limit this approach. Several studies have demonstrated an ability to treat catheter infections using the infected line, often with reported success rates as high as 75% [62]. Prophylactic line changes have recently been shown not to prevent catheter infections and probably increase technical complications [63].

Metabolic Complications of TPN

Several complications of TPN are common and relate to the constituents used and duration of therapy. AA solutions generally have little toxicity, although the lack of glutamine in commonly available preparations may affect mucosal integrity in the stressed patient, as previously discussed. Carbohydrate administration, when excessive, can dramatically increase carbon dioxide production resulting in ventilatory insufficiency in children with impaired respiratory reserve. Hyperglycemia may result in glucosuria and an obligatory osmotic diuresis. Intravenous fat administration, although very beneficial for metabolic-nutritional support, can result in thrombocytopenia, reduced neutrophil chemotaxis and bacterial clearance, and hypertriglyceridemia. Electrolyte abnormalities can result early in the course of TPN and can result in seizures, respiratory insufficiency, cardiac arrhythmias, and death.

Metabolic complications of TPN have been described [64], but are not completely understood. Excessive carbohydrate administration may contribute to hepatic steatosis [14]. Adults receiving TPN can have periportal fat infiltration, canalicular plugging, and centrilobular cholestasis. Elevated γ-glutamyltransferase, alkaline phosphatase, and hyperbilirubinemia may reflect cholestasis, cholelithiasis, or cholecystitis. Hepatic dysfunction, which manifests initially as cholestasis, appears to be more common in children [65]. The incidence is highest in premature infants (23–50%) [66] and in children with a surgical abdomen or peritonitis [65]. The severity of hepatic dysfunction may range from mild elevations in transaminases and bilirubin to frank hepatic failure. Clearly, the duration of TPN is a major factor. Uncomplicated TPN-related cholestasis usually resolves within 1–4 months after the cessation of TPN and the institution of EN [66]. TPN-associated liver disease is usually a relatively minor problem in the acute management of critically ill infants and children, but can be an issue with long-term patients. The use of cholecystokinin to improve bile flow may offer some benefit prior to the development of end-stage liver disease [67, 68]. EN should be instituted as early as possible in the hospitalized child. These areas have recently been reviewed [69, 70].

Conclusion

The metabolic and nutritional support of the critically ill child poses many challenges. We are still developing an understanding of the processes involved in the hypermetabolic response to injury and its impact on patient's physiologic abilities to recover from illness. Our ability to measure and assess the child's metabolic state during acute injury is still insufficient. Nonetheless, significant advances have been made in the support of these children through EN and PN. The trend towards earlier initiation of metabolic-nutrition support has improved the condition of critically ill children. Clearly, more research is needed in the PICU population.

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Nutritional Management of Cystic Fibrosis

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Gene Mutations in Cystic Fibrosis

Cystic fibrosis (CF) is the most common fatal autosomal recessive disease of Caucasians with an incidence of 1:2,000 in some populations [1]. CF is a disorder of a single gene that affects many organ systems but chronic, progressive respiratory tract disease is the main cause of mortality. CF affects the gastrointestinal tract in a variety of ways. It is the most common cause of exocrine pancreatic insufficiency (PI) in childhood which results in malnutrition and fat-soluble vitamin deficiencies. In the liver, inspissation of secretions within the bile ducts commonly causes focal biliary cirrhosis which leads to advanced multilobular cirrhosis in approximately 5% of patients. Intestinal manifestations caused by dehydration of intestinal contents in utero leads to bowel obstruction and perforation in utero and meconium ileus following birth.

Although the varied and complex phenotype of patients with CF has been documented for decades, only recently have investigators appreciated that the common sites of disease in the affected organs were limited to secretory epithelia. This knowledge led to studies focusing on epithelial pathophysiology to define the basic defect.

Figure 1 describes, in a simplified form, the mechanisms of chloride and sodium flux across epithelial cells. In normal epithelia (fig. 1a) chloride ions (Cl^-) enter the cell across the basolateral membrane and Cl^- is maintained

intracellularly above its electrochemical equilibrium. It exits the apical surface down an electrochemical gradient via Cl^- channels. Regulation of these channels is by phosphorylation in response to an increase in intracellular cyclic AMP (cAMP) concentration. Sodium ions (Na^+) enter the apical surface of the cell passively via Na^+ channels.

In CF epithelia (fig. 1b) the primary defect is in the apical membrane surface; cAMP agonists fail to open the apical chloride channels due to their absence or dysfunction. Knowles et al. [2] measured, in vivo, the potential difference across nasal epithelia and found that the relative electronegativity across the apical membrane was markedly increased in CF patients. This is due to a marked increase in inwardly directed Na^+ current in the CF epithelium. The relationship between the absence of cAMP-responsive chloride conductance and increased sodium transport has not been elucidated. It may be due to an increase in the number of sodium channels, increased ionic conductance or, as recently proposed, an increase in open probability of these channels [3] whose permeability is regulated by the cystic fibrosis transmembrane conductance regulator (CFTR).

A breakthrough occurred in 1989 when Tsui and co-workers [4–6] cloned the CF gene. The gene contains 27 coding exons spread over 230 kb. The protein product of this gene was designated CFTR. The structure of CFTR resembles a variety of bacterial, yeast, and mammalian transport proteins known as ABC transporters. A notable example of one of these is P-glycoprotein. Like P-glycoprotein, CFTR contains two different regions that are duplicated. There are two membrane-spanning domains, each consisting of six transmembrane segments and two nucleotide-binding domains. Unlike the other ABC transporters, CFTR contains a unique regulatory or R domain with an abundance of potential phosphorylation sites.

There is overwhelming evidence that CFTR is a cAMP-regulated Cl^- channel. The function of CFTR was elucidated from expression of CFTR in the apical membranes of cells which do not normally express the protein. Utilizing electrophysiological techniques, the regulatory and biophysical properties of CFTR were found to be identical to Cl^- channels [7].

These monumental studies have permitted investigators to begin to tie together the clinical spectrum and complexity of the disease with the basic pathophysiology and the molecular genetic defect. Since the cloning of the CFTR gene, almost 700 different mutations have been identified by the Cystic Fibrosis Genetic Analysis Consortium founded under the direction of Lap-Chee Tsui. Most of these mutations are extremely rare. The major disease-causing mutation is a 3 base-pair deletion leading to the loss of phenylalanine at position 508 of the protein product (ΔF508) which accounts for approximately 70% of all CF chromosomes.

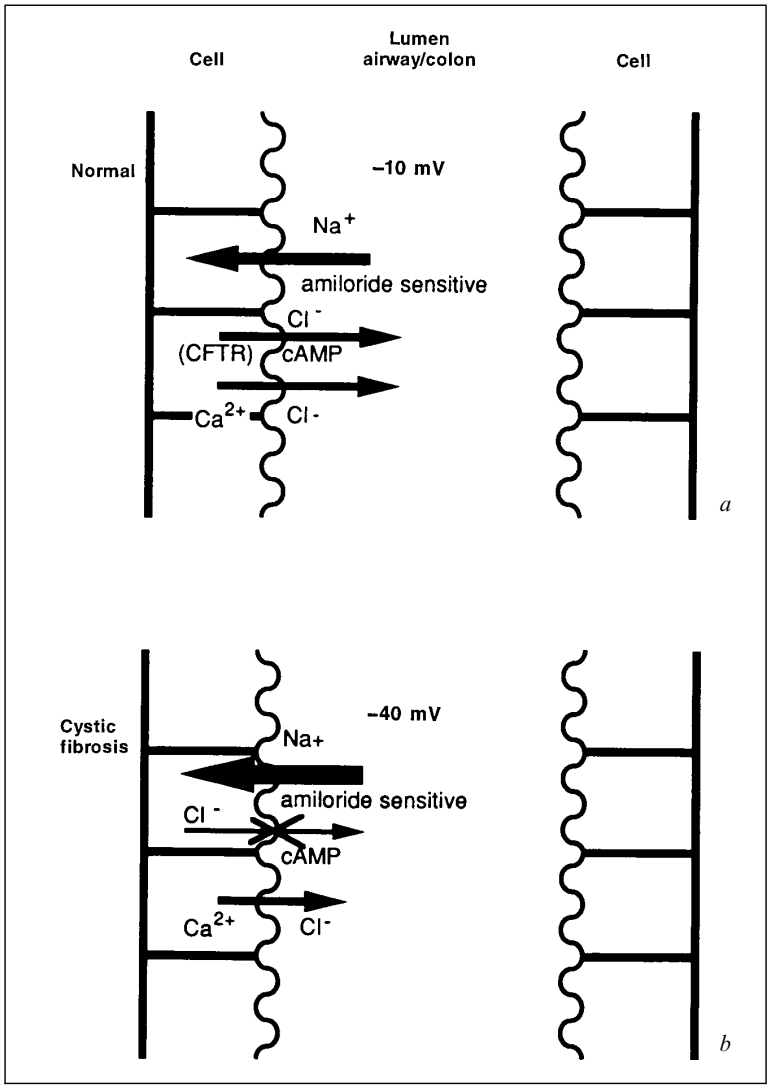

Fig. 1. Mechanisms of chloride and sodium flux across epithelial cells.

CF is characterized by wide variability in clinical expression; patients may be diagnosed with different clinical features from the neonatal period to adulthood with differing severity of the involved organs. Before the CFTR gene was cloned, researchers from Toronto observed a remarkable concordance of pancreatic function status within affected family members. This suggested that genetic factors directly influence the severity of pancreatic disease. Eighty-

Table 1. Classification of CF gene mutation as severe or mild with respect to pancreatic function [adapted from 8]

Severe (Classes I, II or III)	Mild (Classes IV or V)	Variable (Classes IV or V)
ΔF508	R117H	G85E
I148T	R334W	2789 + 5G → A
G480C	R347P	
G551D	A455E	
R560T	P574H	
N1303K	3849 + 10 kb C → T	
G542X	G551S	
W1282X	P5748	
621 + 1G → T	R352Q	
1717 − 1G → T	T338I	
556delA		

five percent of patients require exogenous pancreatic enzyme supplements with meals to attempt to correct nutrient maldigestion due to PI. The remaining patients possess sufficient residual exocrine pancreatic function to permit normal digestion without the need for pancreatic enzyme supplementation. The latter group are pancreatic sufficient (PS). As a group, PS patients have better pulmonary function, lower mean sweat chloride levels and better overall survival than age-matched PI patients. When the gene for CF was cloned, it was shown that in the majority of cases, each genotype was associated with PI or PS only. Thus, the phenotype for pancreatic function is determined by the genotype at the gene locus. We have classified CFTR mutations according to the underlying genetic defect using the terms 'mild' or 'severe' which correlate with pancreatic sufficiency and pancreatic insufficiency phenotypes respectively. Homozygosity for the ΔF508 mutation is strongly associated with PI. PS occurs in patients who have one or two mild mutations, whereas PI occurs in patients who have two severe alleles. Thus, mutations conferring the PS phenotype appear to be dominant. Patients carrying severe mutations tend to be diagnosed in infancy or childhood due to the presence of meconium ileus or the signs and symptoms of malnutrition or malabsorption. PI is therefore associated with the malabsorption of macro- and micronutrients which in turn may contribute to the poorer nutritional status. PS patients tend to be diagnosed later due to lack of maldigestion and milder disease generally. Table 1 lists CFTR mutations as severe or mild with respect to pancreatic function [8]. In addition, some recently described less clearly defined mutations are listed.

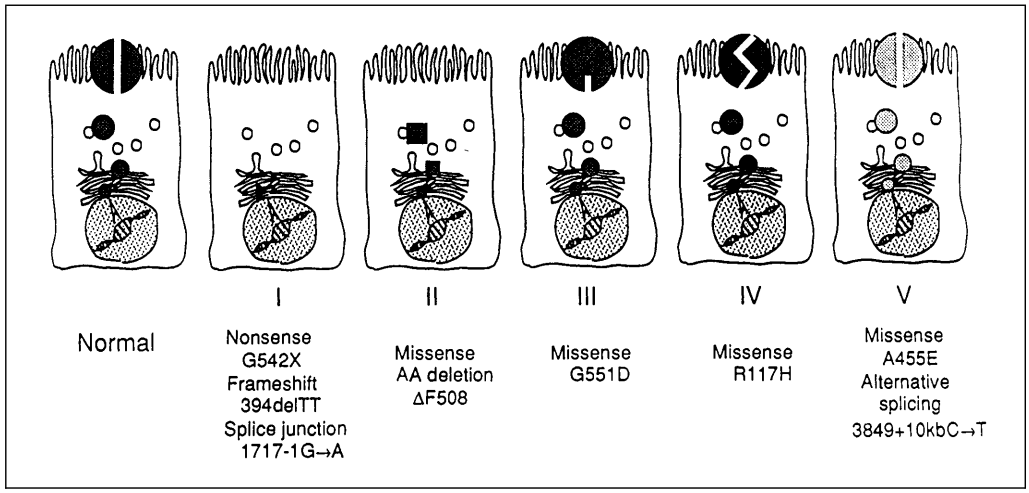

Fig. 2. Molecular consequences of CFTR mutations, as proposed by Tsui and coworkers [9].

Understanding How Mutations Cause CFTR Dysfunction

Several classification systems have been developed in an attempt to define the large number of CFTR gene mutations on the basis of their functional effects. Figure 2 shows five general mechanisms, as proposed by Tsui, which elucidate various ways by which CFTR gene mutations may influence CFTR-mediated apical Cl^- secretion [9]. Class I represents gene mutations in which the intact CFTR protein is not formed. Most mutations belonging to Class I possess nonsense codons which cause premature termination signals, or have similar effects on mRNA synthesis due to splice-site or frame-shift abnormalities. Since no functional CFTR protein is produced, no apical CFTR Cl^- channel function is present. Class II mutations represent mutant proteins which fail to reach the apical membrane under physiological conditions due to a defect in trafficking. These include the most common mutation, ΔF508. In vitro studies of epithelial cells expressing ΔF508 have shown that reduction of the incubation temperature from 37 °C to between 23 and 30 °C facilitates effective passage of the mutant protein to the apical surface of the cell membrane. Class III mutants include those that reach the apical membrane but fail to respond to activation by cAMP under physiological conditions. Most of these mutations are missense mutations situated in the first nucleotide binding fold of CFTR; G551D is an example of a Class III mutation. Class IV mutations produce protein that reaches the apical membrane, generate a

cAMP-regulated apical membrane chloride current, but have altered ionic properties resulting in the reduction of the amount of current; R117H is an example of a Class IV mutation. Class V mutations result in reduced synthesis of normal functioning CFTR, as a result of defective processing (A445E), or aberrant splicing at alternative sites, e.g. 3849 +10 kb C→T.

Classification of mutations into functional classes provide useful insights into the relationship between genotype and clinical phenotype. Patients with Class I, II and III mutations are similar in that there is no functional Cl^- channel, therefore, almost all of these patients are PI. However, patients with Class IV or V mutations in which some residual CFTR Cl^- channel conductance is retained, might be expected to have a less severe phenotype. Thus, patients with Class I, II and III mutations are more likely to have severe manifestations of disease: persistent maldigestion of nutrients is likely in the presence of PI, despite enzyme supplementation. Lung disease may progress more rapidly, which, as we will discuss, could have a deleterious effect on nutritional status. In contrast, patients with one or two Class IV or V mutations, due to the PS phenotype, will absorb nutrients normally without enzyme supplements and are less likely to experience severe lung disease. These factors are likely to contribute to better nutritional status. This review addresses the pathogenesis of the various factors that contribute to an energy deficit and describes an approach to nutritional evaluation and therapy.

Overview of Nutritional Problems in Cystic Fibrosis

Chronic undernutrition with significant weight retardation and linear growth failure has long been recognized as a general problem among CF patient populations. Previously, researchers felt that undernutrition was an inherent consequence of the disease, while others argued that it resulted from physiologic adaptation to advanced pulmonary disease. Early studies with CF patients, however, showed a strong association between the degree of malnutrition and the severity of pulmonary disease. Survival, in turn, was inversely correlated with the severity of lung disease. It has been suggested that malnutrition and the severity of pulmonary disease are causally associated, but it is not clear whether prevention of malnutrition and growth failure would slow the progression of lung disease and improve survival. The past decade has seen considerable interest in evaluating the multiple interdependent variables that give rise to chronic malnutrition and growth failure. In most CF centers around the world, nutritional support is now viewed as an integral part of the multidisciplinary care of patients with CF, and aggressive programs have been instituted to prevent malnutrition.

Table 2. Characteristics of CF clinic populations in Boston and Toronto (1982) [adapted from 10]

	Boston	Toronto
Number of patients	499	534
Male/female, %	57/43	58/42
Age, years		
Mean ± SD	15.9 ± 9.6	15.2 ± 8.3
Range	0–45	0–43
Median survival (50%), years	21	30

Growth retardation in CF patients is now viewed to result from an unfavorable energy balance rather than a factor inherent to the disease. Over 15 years ago, in contrast to results of studies elsewhere, reports from the Toronto CF clinic indicated that most patients closely conformed to the normal distribution of growth in the general population. Cross-sectional data from the Toronto clinic showed a normal distribution of height percentiles in males and females. In females, however, particularly after adolescence, weight distribution was skewed toward the lower centiles but weight retardation was far less evident than in reports from other centers. In a comparative study of two CF clinic populations of similar size and age distribution (Toronto and Boston), Corey et al. [10] found a marked difference in median age of survival: 21 years in Boston versus 30 in Toronto (table 2). Furthermore, after 10 years of age there was a dramatic separation in survival curves between the two centers. Pulmonary function was no different in the two clinic populations. Males and females attending the Toronto clinic, however, were taller than those in the Boston clinic, and males in Toronto were heavier. With the exception of nutritional management of their patients, the general approach to patient care, particularly pulmonary care, was similar in the two clinics. It was suggested that the higher survival rate in the Toronto CF population could be attributed to superior nutritional status.

An examination of dietary practices in the two clinics revealed a striking difference in philosophy. The approach in Boston, which closely resembled the prevailing approach in most centers throughout the world, was to prescribe a low-fat carbohydrate-rich diet. It was reasoned that reduction in dietary fat would improve bowel symptoms and reduce stool bulk. Recognizing the problem of maldigestion and poor absorption of long-chain triglycerides, many centers advocated the use of artificial diets with protein hydrolysates and substitution of long-chain fat with medium-chain triglycerides (MCT). How-

ever, several reports showed no long-term benefits to growth when protein hydrolysates and MCT were used as supplements or substitutes. As a consequence, CF patients were managed with a calorie-restricted, unpalatable diet and they were prohibited from the many energy-rich foods that comprise some of the more tasty choices in a 'normal' Western diet. Chronic malnutrition from reduced energy intake appears to have been an unfortunate, iatrogenic effect in most CF programs throughout the world.

Since the early 1970s, the Toronto group had advocated a calorically enriched diet by encouraging rather than restricting dietary fat and recommending sufficient enzyme supplements to optimize digestion [11]. Because fat is the most energy-rich, economical, and appetizing energy source, patients were encouraged to eat larger portions than their peers, to add fat in the form of butter or untrimmed meat and to eat high-calorie snacks between meals and before bed. Fat malabsorption occurred, but with optimal pancreatic enzyme supplements, net absorbed energy improved and better growth resulted. In recent years it is gratifying to see that most CF caregivers have adopted a similar philosophy for the nutritional care of their patients. Coincidentally, it is generally accepted that the primary objective of nutritional management is to achieve normal nutrition and growth for children of all ages and to maintain normal nutritional status in adulthood. This view is reflected by the following statement from a Consensus Conference, organized by the United States Cystic Fibrosis Foundation, on Nutritional Assessment and Management in Cystic Fibrosis: 'There is no reason to accept nutritional failure and/or impaired growth in any individual with CF' [12].

Pathogenesis of Energy Imbalance

A variety of complex, related and unrelated factors may give rise to energy imbalance in patients with CF. The net effect on growth potential varies considerably from patient to patient, according to marked differences in disease expression and with disease progression. In simple terms, an energy deficit results from an imbalance between energy needs and intake (table 3) and is determined by three factors: energy losses, energy expenditure and energy intake.

Energy Losses

Fecal nutrient losses from maldigestion/malabsorption may contribute to energy imbalance. Only 1–2% of residual pancreatic capacity for secreting digestive enzymes is required to prevent maldigestion [13], and yet the majority of CF patients (approximately 85%) have evidence of pancreatic failure at diagnosis.

Table 3. Energy imbalance in CF

Increased needs	Reduced intake
Increased intestinal losses	Reduced intake
Pancreatic insufficiency	latrogenic fat restriction
Bile salt metabolism	Esophagitis
Hepatobiliary disease	Anorexia
Regurgitation from reflux	Feeding disorders
	Depression
Increased urinary losses	
Diabetes mellitus	
Increased energy expenditure	
Pulmonary disease	
Primary defect?	

In those who exhibit maldigestion, very good correlations exist between residual pancreatic function (colipase secretion) and the severity of fat malabsorption (fig. 3). Some patients with documented steatorrhea, therefore, have variable, but very limited residual pancreatic function. This observation explains one of the numerous factors contributing to the variability of response to nutrient digestion of patients with PI given pancreatic enzyme supplements with meals. Despite improvements in the enzymatic potency and intestinal delivery of ingested pancreatic enzyme supplements, many patients continue to have severe steatorrhea and azotorrhea, even when they receive amounts of enzyme supplements that greatly exceed normal physiological needs.

In the absence of adequate pancreatic bicarbonate secretion [14], gastric acid entering the duodenum may lower intestinal pH until well into the jejunum. The acid-resistant coating of the microsphere enzyme preparations may not dissolve adequately in the proximal intestine. Pancreatic lipase is readily denatured below pH 4, and even if not denatured, enzymatic activity is considerably reduced at a low pH. Bile acids are readily precipitated in an acid milieu [15], and duodenal bile acid concentration may fall below the critical micellar concentration, thereby exacerbating fat maldigestion. Precipitated bile salts also appear to be lost from the enterohepatic circulation in greater quantities, thus reducing the total bile salt pool and altering the glycocholate: taurocholate ratio. Bile salt losses are further exacerbated by the binding of salts to unabsorbed protein or neutral lipid. It is proposed that viscid, thick intestinal mucus, with altered physical properties, may have a deleterious effect on the thickness and biophysical properties of the intestinal unstirred layer, further limiting nutrient absorption.

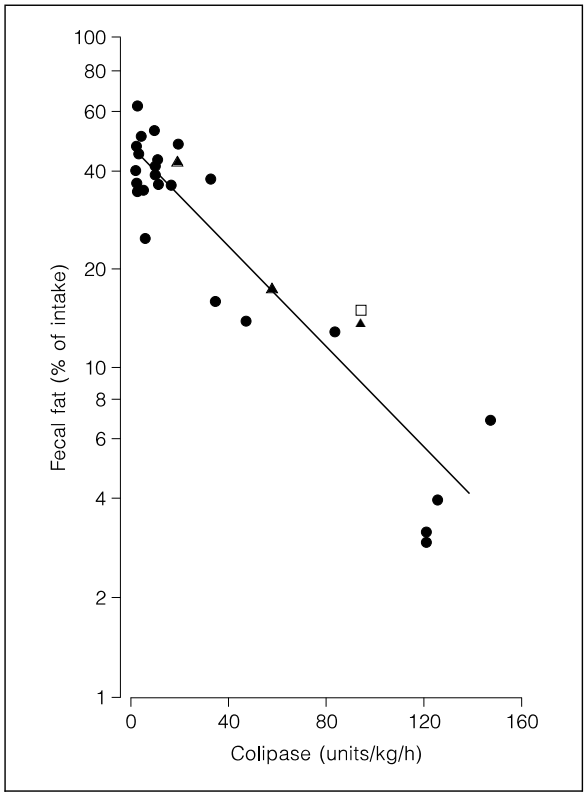

Fig. 3. Correlations between residual pancreatic function (colipase secretion) and the severity of fat malabsorption.

Two other factors, more prevalent in adolescents and adult patients with CF, may contribute to energy losses. Diabetes mellitus, if not adequately controlled, may increase caloric losses due to glycosuria and adversely affect protein metabolism. Furthermore, insulinopenia may adversely affect protein metabolism. Advanced liver disease with multifocal biliary cirrhosis may result in inadequate bile salt secretion, which in turn may increase the severity of fat malabsorption.

Energy Intake

Actual energy intakes in healthy patients with CF have been poorly documented. Nevertheless, it is widely accepted that energy intake should exceed normal requirements; crude estimates have suggested that patients may require 120–150% of the recommended daily allowance (RDA) for age and sex. When

we accurately evaluated nutrient intakes of a group of healthy adolescents, we were surprised to learn that energy intakes were close to the normal range for age, body weight, and sex [16]. Patients with normal growth percentiles for height and weight did show moderately higher energy intakes than those with growth retardation. Some CF centers, which have developed more liberal attitudes to dietary fat intake, have noted a corresponding improvement in energy intake and growth [17]. However, in most reports nutrient intakes were found to be close to the normal range.

Patients with CF are especially prone to complications that might limit oral intake. Esophagitis induced by gastroesophageal reflux (GER) is quite common particularly in patients with advanced pulmonary disease and is frequently associated with pain and anorexia. GER may also cause energy loss through vomiting following bouts of coughing [18]. The distal intestinal obstruction syndrome (DIOS), an unusual form of subacute obstruction within the distal ileum and proximal colon [19], is seen in some adolescents and adults with pancreatic failure. It frequently causes recurrent, crampy abdominal pain that is often aggravated by eating. Other abdominal symptoms, including extrahepatic biliary obstruction, cholangitis, advanced liver disease, and severe constipation, seem less likely to be associated with reduced dietary intake.

Respiratory exacerbations usually cause restricted oral intake by inducing anorexia and frequently there is acute weight loss. With improvement in respiratory symptoms, patients with mild pulmonary disease usually show rapid catch-up in weight. However, in the terminal stages of pulmonary disease when energy needs are high, chronic anorexia is a consistent feature. Further, patients with a severe chronic disease are prone to bouts of clinical depression, which in the adolescent or adult may be associated with loss of appetite and anorexia.

Over the past few years we have seen a number of younger children (infancy to 8 years of age) with reduced nutrient intake due to behavioral feeding difficulties; nutrient absorption is usually appropriate and energy expenditure is within the normal range. Behavioral intervention alone has hardly ever proved successful in the short term; consequently, in a minority of patients we have had to resort to supplemental nocturnal feeding with gastrostomy tubes to achieve satisfactory nutritional rehabilitation. This nutrition support modality appears to reduce parental anxiety and facilitates the implementation of behavior modification feeding programs.

Energy Expenditure and Metabolism

In recent years, a number of studies have focused on examining the rates of energy expenditure in patients with CF. In 1984, Pencharz et al. [20] evaluated the relationship between heart rate and energy expenditure, using an exercise cycle with graded workloads. Simultaneous measurements of oxygen

consumption and carbon dioxide production were taken using a closed-circuit indirect calorimeter and heart-rate telemetry. The subjects, who were malnourished and had moderate to advanced pulmonary disease, were receiving nutritional rehabilitation by continuous nasogastric tube feeding with a semi-elemental formula. Absorbed energy intake was calculated by subtracting stool energy content from the energy content of the feed. The energy needs of the patients were shown to be 25–80% higher than those of healthy persons of the same age, sex and size. It was hypothesized that energy expenditure increased because of the increased work of breathing in patients with advanced lung disease. Consequently, a patient with advanced lung disease might not be able to ingest sufficient calories to meet energy needs, resulting in energy imbalance and weight loss. In a subsequent study, resting energy expenditure (REE) was measured by continuous computerized open-circuit indirect calorimetry in 71 patients (8.9–35.5 years) who were not suffering from an acute respiratory infection [21]. Nutritional status and pulmonary function were studied simultaneously. REE was found to be extremely variable, but was above normal in most cases ranging from 95 to 153% of predicted values for age, sex and weight. REE was negatively correlated with pulmonary function and positively correlated with nutritional status (percentage of body fat). In addition, in agreement with the observations of others, pulmonary function was positively correlated with nutritional status. These findings have since been confirmed by Buchdahl et al. [22], who demonstrated that patients with CF had a REE of 9% above body weight and 7% above lean body mass, respectively, in comparison with healthy controls.

These two studies hinted at the possibility that the CF gene might have a direct effect on basal metabolism. Feigal and Shapiro [23] had earlier reported that mitochondria from cultured fibroblasts from CF homozygotes and heterozygotes had increased O_2 consumption associated with calcium transport. Rates in the homozygote were 2 times as high and in the heterozygote 1.5 times as high as those in controls. In a subsequent study of CF nasal epithelium, oxygen consumption exceeded that of control tissue by 2–3 times [24]. Shepherd et al. [25] investigated total daily energy expenditure using the doubly labeled water method in clinically well, appropriately nourished CF infants without clinical evidence of lung disease. The data were compared with studies in healthy infants. This methodology permits measurement of total energy expenditure in unrestricted subjects. CF infants had rates of energy expenditure 25% higher than values obtained in healthy infants matched for age and body weight. We were concerned about some methodologic difficulties that were brought to the attention of the investigative group [26]. Over the next 2 years, when additional subjects were evaluated, the differences between the infants with CF and the controls disappeared.

When the gene responsible for CF was identified, it was suggested that the gene product was directly involved in the regulation of ion transport across membranes [5], since CFTR shared structural similarity with several other membrane transport proteins. Furthermore, as CFTR is a cAMP-regulated chloride channel, the gating of this channel is an energy-requiring process. Following the hypothesis that the genetic defect may affect basal metabolism, O'Rawe et al. [27] reported that REE was increased by 25% in subjects homozygous for the most common CF mutation (Δ508) and by 10% in those with ΔF508 on one chromosome and an undefined CF gene mutation on the other. Unfortunately, their study did not adequately control for potentially confounding factors such as the severity of lung function or nutritional status. This is important, because we had shown that lung function has an effect on REE [21], and that undernutrition resulted in a decreased REE [28]. In a subsequent study we controlled for the two confounding variables by studying normally nourished males with CF who had minimal lung disease [29]. We observed little if any increase in REE and we were unable to demonstrate any difference in REE between patient groups with different genotypes. Thus, if there is a 'primary biochemical' or 'CF-related' cause for increased REE in patients with CF, its effects must be minimal. Conversely, lung disease appeared to be a major determinant of an increase in REE. When forced expiratory volume in 1 s (FEV_1) fell below 75% of predicted, the subject's REE rose in a curvilinear (quadratic) fashion (fig. 4). Thus, it appears that deteriorating lung function is the major factor associated with an increase in REE. O'Rawe et al. [30] published a detailed report of their study, in which they controlled for nutritional status but not for lung function. The FEV_1 data for their homozygous group (ΔF508/ΔF508) was 48–64% of predicted (mean 56%) and for their heterozygous group (ΔF508/other) was 52–74% of predicted (mean 63). It is therefore not surprising, if the pulmonary function data shown in fig. 4 are considered, that the REE values in each group were increased to 121 and 109% of predicted, respectively. The authors did attempt to correct for the effects of lung function, using analysis of covariance; however, their data are open to the alternate explanation, namely that REE rises as lung function deteriorates [21].

Protein synthesis is one of the major components of basal metabolic rate. We hypothesized that the increase in REE might, in part, be due to an increase in protein synthesis. We therefore measured REE and whole-body protein synthesis in normal controls, in undernourished patients with CF and in patients with anorexia nervosa, who served as disease controls by matching nutritional status to the CF patients [31]. Contrary to our hypothesis, there were no differences in protein synthesis between the three groups. However, the patients with anorexia nervosa had reduced REE while

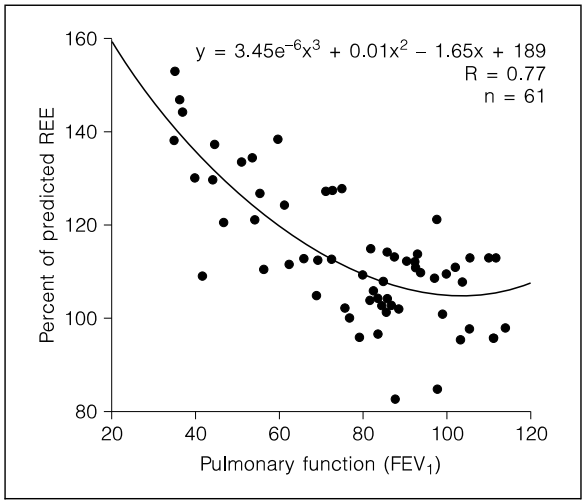

Fig. 4. When patients' FEV_1 fell to below 75% of that predicted, REE rose in a curvilinear fashion.

the CF patients had increased REE compared with controls. Protein synthesis and REE was then measured in CF patients during renourishment with nocturnal supplemental feedings. REE rose significantly with refeeding but no changes were seen in protein synthesis [28]. However, following refeeding, the patients with anorexia nervosa increased their REE in a similar pattern to the undernourished patients with CF [28, 32]. The increase in REE with refeeding provides evidence that the CF patient does adapt to a negative energy balance in the same manner as patients with self-imposed food restriction [32]. In conclusion, at least two factors appear to affect REE in the undernourished CF patient with impaired lung function. The first is a normal response to a negative energy balance, and the second appears to be related to the severity of lung disease. The precise causes of increased REE due to moderate to severe lung disease remain to be elucidated. However, the evidence is compelling that alterations in protein metabolism are not responsible [28, 31].

REE may be increased by drugs used in the management of CF. Prior to chest physiotherapy, for example, many patients use inhaled symphomimetic amines as bronchodilators. One of these, the β-agonist salbutamol, has been shown to be absorbed systemically through the respiratory tree and to induce a significant increase in REE (approximately 10%) over a period of 3 h following inhalation [33].

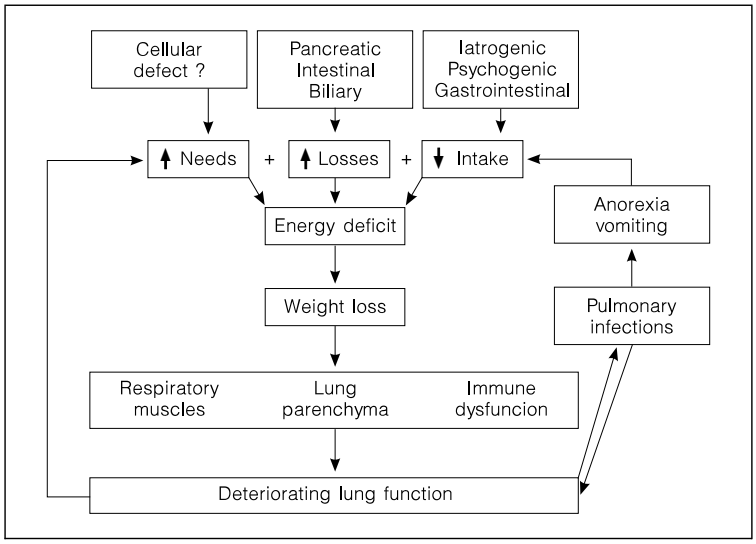

Fig. 5. Pathogenesis of energy imbalance in CF.

In practical terms, energy requirements should be determined by assessing total daily energy expenditure (TDEE). A significant increase in TDEE probably would result in a negative energy balance, which if left untreated would lead to undernutrition. It is interesting that patients with moderate lung impairment adapt to an increased REE by reducing their activity levels, thereby maintaining TDEE at levels comparable to controls [34].

Pathogenesis of an Energy Deficit

We have proposed a model to explain the pathogenesis of the energy deficit in CF patients (fig. 5), which helps to define the web of interdependent variables giving rise to chronic malnutrition and growth failure in some patients. It must be re-emphasized, however, that most patients with CF can maintain normal growth velocity and nutritional status by voluntary intake of calories, particularly when lung function remains relatively unimpaired [10]. Expressed another way, most patients are capable of compensating for the various factors that may contribute to an energy deficit. We and others have speculated that malnutrition is closely interrelated with decline in pulmonary function, but a cause-effect relationship remains to be proven. As lung disease worsens, most commonly in older adolescents and young adults, several factors come into play that might predispose the patient to an energy deficit. The frequency and severity of pulmonary infections may increase, inducing anorexia and lung infections per se increase REE. Chest infections often give rise

to vomiting, which may further reduce intake. These factors, in combination with the increase in REE that accompanies advancing lung disease, may lead to an energy deficit. Weight loss will result, initially producing a significant loss of adipose tissue but with time a loss of lean tissue along with muscle wasting. Respiratory muscle wasting would adversely affect respiratory motion and prevent effective coughing, thereby further contributing to the deterioration of lung function. Malnutrition is known to adversely affect lung elasticity and a variety of aspects of immune function. Taken together, factors giving rise to chronic malnutrition would appear to contribute to progressive deterioration of lung function. In essence, a vicious cycle is established, leading inevitably to end-stage pulmonary failure and death.

Deficits of Essential Nutrients

Deficits of essential micronutrients can occur as a result of primary malnutrition or secondary features of the disease, such as pancreatic failure [35]. By way of example, CF patients with PI frequently malabsorb fat-soluble vitamins, and thus risk developing signs and symptoms of nutritional deficiency.

Water-Soluble Vitamins

With the exception of vitamin B_{12}, water-soluble vitamins are well absorbed and there is no evidence of clinically significant deficiencies in well-nourished patients. In PI patients, vitamin B_{12} absorption can be normalized with adequate pancreatic enzyme replacement therapy. Vitamin B_{12} administration is not necessary, apart from patients with meconium ileus who have undergone extensive ileal resection.

Fat-Soluble Vitamins

Deficiencies of vitamins A, D, E and K have been demonstrated at diagnosis [35, 36]. Fat-soluble vitamin supplements are a necessary part of the nutritional care of CF patients with PI or severe liver disease. Vitamins A and E are of the greatest concern. CF patients generate increased oxygen-free radicals from activated neutrophils due to chronic lung inflammation and are deficient of antioxidants due to pancreatic insufficiency. This provides further evidence for adequate vitamin A and E supplementation which have been shown to have antioxidant effects [37]. Vitamin D deficiency is more of a concern with inadequate sunlight exposure [38] or with advanced cholestatic liver disease. Current recommendations for supplementation with fat-soluble vitamins were provided in the proceedings of a recent consensus conference on nutrition assessment and management [12].

Trace Metal Deficiencies

No obvious defect of the trace metal absorption or metabolism has been observed in CF. Plasma zinc levels, for example, appear to be low only in patients with moderate to severe malnutrition, and the levels correlate directly with plasma proteins, retinol-binding protein, and vitamin A [39]. Plasma levels of copper and ceruloplasmin may be elevated in patients with CF, but usually in proportion to the severity of pulmonary disease, because ceruloplasmin is an acute-phase reactant [39]. No reliable evidence supports the concept that selenium is of any clinical significance [40]. Symptomatic hypomagnesemia, with evidence of a positive Trousseau sign, tremulousness, muscle cramps and weakness, may develop in patients receiving aminoglycosides [41] and is also reported to be a secondary complication in patients treated for DIOS with repeated oral doses of N-acetylcysteine and balanced electrolyte solutions.

Iron-deficiency anemia with low serum ferritin is frequently seen in patients with advanced pulmonary disease, but may also be seen in the stable patient [42]. In patients with pulmonary insufficiency, polycythemia seems to occur less commonly than in other pulmonary disorders of comparable severity, suggesting that these patients have a relative anemia. However, hemoglobin values do respond to nutritional repletion of the undernourished patient [43]. The precise mechanism of iron-deficiency anemia is poorly understood, since there is no evidence of a defect of iron absorption or metabolism.

Essential Fatty Acid Deficiency

In infancy, particularly before diagnosis, clinical features of essential fatty acid deficiency (EFAD) can occur with desquamating skin lesions, increased susceptibility to infection, poor wound healing, thrombocytopenia, and growth retardation. In older patients who are adequately treated, clinical evidence of EFAD is extremely rare. Most patients with PI, nevertheless, have biochemical abnormalities of blood and tissue lipids [44]. Changes include decreased linoleic and increased palmitoleic, oleic, and eicosanoic acids. It has been suggested that these biochemical abnormalities reflect an underlying defect of fatty acid metabolism [45], while others have argued that the low plasma and tissue levels are due to increased metabolic usage in undernourished patients [46]. In a survey of 32 patients, we found that low plasma essential fatty acid levels were confined to patients with less than 5% of pancreatic function [47]. Furthermore, Parsons et al. [48] concluded that suboptimal caloric intake and undernutrition are important determinants in the development of EFAD. EFAD levels in tissues were restored by providing malnourished CF patients with caloric supplements via nasogastric tube feeding. The evidence at present points to the conclusion that EFAD is secondary to the negative energy balance and not related to the primary genetic defect.

Nutritional Evaluation and Therapy

Clinical Evaluation

Nutritional support, an integral part of the multidisciplinary care of patients with CF, requires close clinical evaluation, monitoring of growth rates, and appropriate dietary counseling. At diagnosis, height and weight (percentiles) should be carefully measured, and anthropometric measurements taken (skin folds, mid-arm circumference). During routine follow-up visits, growth should be carefully monitored, and where necessary, dietary counseling provided. When patients receive an adequate diet, normal growth can be expected until impeded by advanced respiratory disease. Patients who fail to grow at a normal rate deserve careful evaluation, particularly young children with little pulmonary disease.

Close involvement by a qualified, experienced dietitian is invaluable. Both energy intake and compliance with pancreatic enzyme supplements should be carefully evaluated; in addition, the adequacy of stool fat absorption (72-hour fecal fat) should be determined and fat and energy intake documented during administration of regular pancreatic enzyme supplements. The dose of enzymes may need to be adjusted within recommended guidelines [49] with or without the judicious use of agents to inhibit or neutralize gastric acid secretion and monitoring the effect of changes by 72-hour fecal fat balance studies.

Patients with mild pulmonary disease will often lose weight during an acute respiratory infection but achieve rapid catch up in growth after recovery. Those suffering from recurrent abdominal pain due to DIOS often reduce caloric intake to control their symptoms. In these cases aggressive treatment may be necessary; in our experience, this is best achieved by intestinal lavage with a balanced electrolyte solution containing polyethylene glycol [50]. Similarly, symptoms of esophagitis due to gastroesophageal reflux [18] must be sought and aggressive treatment instituted, because severe symptoms will reduce caloric intake. Generally, patients with hepatic disease will grow normally except in those with advanced multilobular cirrhosis or in rare instances of hepatic decompensation.

The diet must be calorically adequate for individual energy needs and should be as normal for age and peer group as possible. Actually, energy requirements of patients with CF are extremely variable, for the reasons described earlier. Dietary intake may be affected by a patient's level of self-esteem and general feeling of well-being. It is therefore essential that patients who have nutritional difficulties receive psychological support, especially in adolescence and adulthood. Exercise programs aimed at improving physical capacity are considered important. Improved muscle mass may lead to a sense of accomplishment and stimulate an interest in providing nutritional support

for physical goals. Patients with diabetes need additional counseling to provide adequate nutritional support.

As a general rule, protein intakes of children with CF are more than adequate [16], but nitrogen balance may be particularly sensitive to insufficient total energy intake. Provided the latter is adequate, we recommend that protein intake equal the RDA for age, sex and weight. As we have discussed in some detail, the use of fat as a source of energy, provides an excellent supply of palatable, energy-rich calories. The limited reserves of essential fatty acids in CF patients and the vulnerability of malnourished patients to EFAD require specific attention. Although there is no evidence to suggest that biochemical EFAD has a major clinical impact, we have recommended a diet that contains adequate quantities of linoleic acid to maintain normal or close to normal fatty acid profiles. However, as a precursor of the eicosanoid leukotriene B_4, it has been hypothesized that the use of ω–6 fatty acids may augment the levels of proinflammatory mediators. Experiments adding the ω–3 fatty acid eicosapentanoic acid to polymorphonucleocytes from CF patients suppressed the synthesis of proinflammatory products of arachidonic acid [51]. Thus, initial studies have investigated the preferential dietary supplementation of ω–3 fatty acids (fish oil) in CF and a double-blind 12-month trial is currently in progress (Dr. B. Koletzko, oral communication, 21st European CF Conf., June 1997). There is no known defect in the transport of monosaccharides, and some investigators have even suggested enhanced glucose absorption. Complex carbohydrates are quite well tolerated and are good sources of energy. Supplemented doses of fat-soluble vitamins are indicated in patients with PI or severe hepatobiliary disease; generally 2–3 times normal intake is recommended.

Laboratory Evaluation

At diagnosis, all patients require a careful assessment of pancreatic and nutritional status. To determine pancreatic status and the need for pancreatic enzymes, we recommend a quantitative evaluation of fecal fat losses over a minimum period of 72 h, while accurately measuring fat intake. At the same time, it will be possible to record total calorie intake. Less useful substitutes include documentation of fat on stool microscopy, stool steatocrit, stool trypsin chymotrypsin or elastase activity, serum carotene and vitamin A and E levels. Some of these tests like the stool steatocrit are useful for monitoring response to treatment on return visits. Serum levels of immunoreactive trypsinogen may be reduced in the patient with PI, but only after the age of 7–8 years [52]. The most accurate method of assessing pancreatic function is the direct pancreatic stimulation test [13], but this invasive, difficult test should be reserved for evaluating patients with suspected PS, in order to better define reserve exocrine function.

Routine laboratory studies of nutritional status in patients with CF were recently reviewed and a consensus report has been published [12]. It was recommended that a complete blood count, plasma retinol, and α-tocopherol be performed at diagnosis and yearly as part of routine care. If low levels of retinol and/or α-tocopherol are detected, the patient needs a more complete evaluation of fat absorption and liver function, and an increase in the dose of vitamins A and E. If there is evidence of iron deficiency in routine hematologic studies, then iron status must be measured more accurately, i.e. serum iron, transferrin and ferritin.

Electrolytes, acid-base status and serum albumin should be measured at diagnosis. However, serum albumin, as a routine method of monitoring nutritional status, is of no real value. Electrolytes and acid-base measurements are indicated with prolonged fever, vomiting or in the summer heat, particularly in breast-fed infants. Infants may well need a salt supplement on hot summer days. Shorter half-life proteins like transferrin, retinol-binding protein and prealbumin are unnecessary, since they offer no advantage over serum albumin combined with anthopometry.

Age-Related Nutritional Guidelines

Standard guidelines for the nutritional evaluation and support of patients with CF must be modified according to individual and age-specific needs, and to specific complications of the disease.

Our approach is to assess each patient from the perspective of energy balance. Key factors include energy intake, absorption and expenditure. Intake is determined from diet records, usually over 3–5 days. Nutrient absorption should be measured by coefficient of fat absorption following 3-day stool collection combined with a 3-day food record. Energy expenditure is measured using open-circuit indirect calorimetry [21]. Most centers will not have access to indirect calorimetry. Therefore, on the basis of the Toronto experience, a method of estimating the REE of a patient with CF has been published, based on normal standards, lung function, age and gender. Estimated REE enables the calculation of daily energy needs. The reader is referred to the consensus report for further details [12].

Infancy to two years: The majority of patients with CF are diagnosed in infancy because of meconium ileus or a nutritional disturbance. The time of diagnosis is a crucial period for instituting therapeutic interventions, dietary counseling, and nutrition education. Furthermore, this is a phase of rapid growth and high energy needs.

Newly diagnosed infants may be profoundly anorexic and indifferent to food. Infants presenting with severe malnutrition characterized by hypoalbuminemia, edema and anemia require close attention. In addition, during the

neonatal period active nutritional management is imperative after surgery for meconium ileus. A short course of intravenous nutrition and/or enteral tube feeding may be the only way to ensure adequate nutrition in the first few weeks of care. In general, patients improve rapidly with adequate attention to caloric requirements, vitamin needs and pancreatic enzyme supplementation; routine oral feeding with a standard age-appropriate formula becomes possible very quickly. In some instances a formula with a higher caloric density may be needed. In many infants with CF, normal growth can be sustained on human milk, provided adequate attention is paid to their caloric needs and sodium requirements. Protein hydrolysates, medium-chain triglycerides and polysaccharide supplements are rarely required. In a randomized, prospective study comparing a regular cow's milk-based formula with a protein hydrolysate formula, growth velocity and severity of nutrient maldigestion were no different in the two treatment groups [53].

There is evidence from several controlled trials that the neonatal screening programs offered in some centers may have an effect on prognosis including nutritional status. By early diagnosis many of the nutritional problems may be addressed before symptoms of malnutrition occur [54].

Two to five years: At this age, children develop some independent feeding habits, expressed through clear food preferences. Calorie intake varies considerably from day to day. Since feeding habits are developing at this age, it is important to maintain close attention to energy balance and nutrient needs, using an organized system of guidance and dietary counseling.

Six to twelve years: Children in this age group are expected to develop a greater sense of personal responsibility for their treatment and daily activities. This, in turn, may cause difficulties with drug compliance (pancreatic enzymes and vitamins); in addition, peer pressure may have an impact on their choice of nutrients.

Adolescent years: The period of adolescence is associated with an increase in energy requirements due to accelerated growth, pubertal development and, in many instances, a high level of physical activity. Poor growth and delayed development of puberty can create considerable emotional stress. Peer pressure may cause patients to deny their disease. Although the reasons have not been clearly defined, females with CF appear to be at the greatest risk of undernutrition and growth failure. During adolescence, patients with more advanced pulmonary disease are at risk of suffering from the ill effects of energy imbalance.

Adulthood: In most adults with CF, if close attention is paid to energy needs and food intake, it is possible to maintain adequate energy balance for maintenance of good nutritional status especially when lung function is not severely impaired. However, affected adults, especially females, will suffer

weight loss in association with advanced pulmonary disease. These patients develop an energy imbalance since they seem unable to maintain adequate energy intake by voluntary means.

Nutritional Intervention

A variety of approaches to artificial nutritional supplementation have been taken in patients who fail to respond to routine nutritional management. The hope is that early restoration of nutritional status may improve the quality of life and extend survival by ameliorating the rate of decline in respiratory function. High-energy liquid dietary supplements are used with regularity in most CF centers. Although they are convenient to use and may be successful for short-term nutritional rehabilitation, no reliable information is available regarding long-term efficacy. It is our impression that many of these energy-rich supplements are at best substitutes for normal dietary habits and do not result in long-term improvement in nutritional status. Patients with growth failure or weight loss, particularly those with deteriorating pulmonary function, therefore may be considered candidates for more invasive, artificial forms of supplementary nutrition. We have critically reviewed the literature on this subject.

Short-Term Studies

A variety of short-term parenteral and enteral feeding techniques have been used in malnourished patients with CF. Shepherd et al. [55] evaluated malnourished patients with CF (mean age 5.4 years) 6 months before and 6 months after a 3-week period of parenteral nutrition. During the pretreatment period, while receiving 'conventional' dietary management, the patients showed inadequate growth velocity, but 6 months after the short period of intravenous nutrition they appeared to exhibit continuing catch-up growth, fewer pulmonary infections and a significant improvement in clinical score.

Other studies have failed to show lasting improvement following short-term nutritional support. The improved nutritional status in the patients in Shepherd's study could be explained by aggressive pulmonary management while the patients were hospitalized. In addition, the very young age of their patients suggests that closer attention to voluntary nutrition may well have prevented the problem at the outset. Mansell et al. [56], who evaluated older malnourished CF patients (aged 10–17 years), also demonstrated improvement in nutritional status following a 1-month period of supplemental parenteral nutrition, during which patients were provided 120% of their energy needs.

Immediately following supplementation, body weight, triceps skinfold thickness, and mid-arm muscle circumference increased significantly. Maximum inspiratory airway pressure also increased, suggesting improvement in respiratory muscle strength, but none of the indices of lung function improved. One month after parenteral nutrition, however, the patients were once again malnourished, falling back to levels similar to those seen before treatment. In a study from Montreal [57], supplemental feeding by nasogastric tube was instituted while patients were in hospital and was continued at home for 4 weeks. Patients showed considerable weight gain, attributable to increased caloric intake, but the nutritional changes were transient and not accompanied by long-term improvement in growth. In a study from our center, Pencharz et al. [20] evaluated body composition, nutritional status, and energy needs of 6 undernourished adolescents and adults with CF. Lean body mass was preserved but there was significant wasting of adipose tissue. Following a brief period of nasogastric feeding with a semielemental diet, the effects of refeeding on body composition were reassessed. After refeeding, body weight, body fat and total body potassium increased significantly, but fat-free body mass and total body nitrogen did not change. None of the subjects were able to continue nasogastric tube feeding for longer than 2–3 months because of nasal irritation and coughing up the tube. Thus, nutritional benefits derived from brief periods of supplemental nutrition are short-lived and do not produce long-term improvement in growth or function. The failure of brief periods of supplemental feeding to effect a long-term nutritional benefit is not surprising if the pathogenesis of the energy imbalance is considered (fig. 5), since the underlying causative factors are not reversed.

Long-Term Studies

Since the effects of brief periods of energy supplemention on chronically malnourished patients with CF appear to be transient, long-term approaches have been evaluated in an attempt to achieve and maintain normal nutrition status in patients unable to meet their own energy needs. In addition, it was thought that reversal of malnutrition might have a favorable influence on the course of pulmonary disease and consequently on survival.

Three major studies addressed the problem by using nocturnal enteral supplements [58–60]. In a study from Toronto [59], 14 patients (mean age 12.9 years) were given nocturnal supplemental feeding of a semielemental formula by gastrostomy tube for an average period of 1 year. The adolescent and adult patients were suffering from moderate to severe lung disease and all were markedly wasted or stunted. Gastrostomy tubes were placed endoscopically under local anesthesia. A contemporary group of patients with CF (matched for age, sex, nutritional status and pulmonary function)

drawn from the clinic's computerized data bank, were pair-matched to the study group. In a second Canadian study [58], 10 malnourished CF patients (mean age 13.6 years) with moderate to severe lung disease were provided with nocturnal supplemental feeding of an intact formula by a needle jejunostomy tube for periods of 10–36 months. Pancreatic enzyme supplements were added to the formula. In the third study, Shepherd et al. [60] evaluated 10 undernourished CF patients (mean age 8.9 years) who were unable to maintain normal growth by oral means. They were followed during a 1-year course of nutritional supplement with a balanced-peptide or a semielemental formula given overnight by nasogastric or gastrostomy feeding. These patients were compared concurrently with patients receiving conventional nutritional therapy and matched for height, sex and pulmonary function. In all three studies, normal activity and regular meals were permitted during daytime hours.

In each study, long-term enteral supplemental feeding resulted in a significant improvement in catch-up growth and positive changes in body composition. There appeared to be beneficial effects on pulmonary function but the effect on survival remains unanswered. In the two Canadian studies [58, 59], nutritional supplements appeared to slow the rate of deterioration of pulmonary function. In Shepherd's study [60], respiratory function deteriorated in the control group but appeared to improve in the patient group; however, the patients were considerably younger than those in the two Canadian studies.

Following our evaluation of the effects of these studies of long-term gastrostomy supplemental feeding [59], we established a multidisciplinary approach to the evaluation and care of the failing patient with CF. This approach uses the services of dietitians, nutrition support nurses, social workers and physicians. Patients identified as having an energy imbalance problem are seen first by the dietitian. If diet counseling and/or voluntary supplements are not effective, the patient is referred for assessment for long-term gastrostomy feeding. This involves both a family and social evaluation and assessment by a clinical nutritionist. Once all the factors for and against nutritional intervention are considered by the multidisciplinary team, the patient and family are brought into the decision-making process.

Currently only 24 of the 550 patients (2.5%) attending our pediatric and adult CF clinics are receiving nocturnal gastrostomy feeds. Few patients have been able to discontinue gastrostomy feeding, since their energy needs remain elevated. In the past few years we have moved from endoscopically-placed, percutaneous gastrostomy tubes to placement by an interventionist radiologist under diagnostic imaging control [61]. This procedure is well tolerated, and patients are discharged about 3 days after gastrostomy insertion.

Conclusion

If close attention is paid to the individual patient's energy needs and nutritional status, undernutrition can be prevented or promptly treated. In the vast majority of patients, normal growth and nutrition can be achieved with the rational use of a normal, high-energy diet. However, in a small group of patients, advanced lung disease causes a rise in energy expenditure, and energy imbalance may result. At this stage, long-term, invasive methods of nutritional support should be considered. In patients with more advanced lung disease who are candidates for a lung transplant, maintenance of good nutritional status before surgery is an important prognostic factor [62]. Aggressive nutritional therapy, however, is likely to be unsuccessful and may even cause considerable complications during the terminal stages when the patient is suffering from end-stage cardiopulmonary failure [43].

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Nutrition in Pediatric Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is a term which refers to two conditions, Crohn's disease and ulcerative colitis. Although each represents a distinct clinical pathological entity, in practice these diseases are often indistinguishable. The chronic, relapsing nature of these disorders can be particularly difficult for children and adolescents. Both result in a variety of debilitating symptoms which can interfere with daily activities, linear growth, sexual maturation and psychosocial development.

Malnutrition/Growth Failure

Approximately 85% of children with Crohn's disease and 65% of children with ulcerative colitis show significant weight loss at the time of diagnosis [1]. Growth failure and delay in sexual maturation are common features of IBD in the preadolescent and adolescent. Children with Crohn's disease are primarily at risk, though those with ulcerative colitis can also be affected. Studies have suggested that anywhere from 30 to 60% of children who develop IBD prior to or during puberty will undergo a period of marked impairment of linear growth during adolescence [2, 3]. Permanent impairment of linear growth is seen in 20–30% of young adults whose IBD (especially Crohn's disease) was diagnosed in childhood or early adolescence [4]. The primary

reason for poor weight gain, growth failure and delayed development is often inadequate nutritional intake, while maldigestion and malabsorption are less significant factors. For the adolescent to manifest a growth spurt and for puberty to progress normally, the older child and teenager with IBD must consume a diet containing 75–90 kcal/kg/day, often an insurmountable task. Eating often initiates symptoms of cramps and diarrhea which can ultimately result in patients avoiding food. Likewise, there appears to be a component of anorexia seen even in patients with isolated colonic disease. Whether this anorexia is related to dysmotility of the gastrointestinal tract and/or to inflammatory mediators produced by the disease process is as yet unclear.

Inadequate dietary intake also occurs because of self imposed or iatrogenically prescribed dietary restrictions which lack sound scientific or clinical basis. Inappropriate restrictions often further reduce both the caloric value and the palatability of the food provided. Losses of macro- and micronutrients, bacterial overgrowth, and bowel resection can also contribute to malnutrition.

Protein loss from inflamed bowel is common and contributes to the catabolic state of patients. Fat malabsorption is less common but can be seen in patients with significant ileal disease or following ileal resection. Carbohydrate malabsorption (e.g., lactose intolerance from small bowel, Crohn's) is rarely of major nutritional significance although it may contribute to symptoms and aggravate the 'fear of eating' seen in some patients. Fistulae, fever, and corticosteroids may contribute to an increase in nutritional requirements (table 1).

Metabolic Changes

Increased energy expenditure associated with active inflammation has been suggested as a mechanism that contributes to malnutrition in patients with IBD. The few pediatric studies are conflicting. Studies in adults have found that resting energy expenditure measured by indirect calorimetry in patients with IBD is equivalent to the predicted energy expenditure in healthy adults [5, 6]. Interestingly, these studies have noted an increase in resting energy expenditure in relationship to the magnitude of weight loss. Some authors have suggested that the higher metabolic rate seen in these underweight patients with IBD is related to a proportionally greater decrease in body fat with sparing of lean body mass. A recent paper [7] utilizing a combined body scan technique which allowed for measuring total energy expenditure from energy intake and changes in energy stores, showed that there was no difference between adults with Crohn's disease and other ill patients. In other words,

Table 1. Etiology of malnutrition in inflammatory bowel disease

Poor caloric intake
Disease induced
Dietary restrictions (iatrogenic, parental or self-imposed)
Malabsorption/intestinal losses
Decreased surface area (disease, resection)
Bacterial overgrowth
Bile acid deficiency (ileal resection, severe ileitis)
Protein-losing enteropathy
Blood loss
Micronutrient losses (diarrhea, fistulae)
Increased requirements
Infection, fever
Inflammatory process (?)
Need for catch-up growth
Drugs
Sulfasalazine (folate)
Steroids (calcium, protein catabolism)
Cholestyramine

it is sufficient to nourish adult Crohn's patients with approximately 30–35 kcal/kg/day as one would nourish any ill adult. There are no increased energy needs. They observed that as disease activity increased, energy expenditure from physical activity was decreased thus maintaining equilibrium of total energy expenditure. In a similar study, Muller et al. [8] evaluated adults receiving continuous enteral nutrition for Crohn's disease. Positive energy balance was achieved with 31 kcal/kg/day. Noteworthy in this study was that there was an accumulation of carbohydrate and protein associated with weight gain but an actual depletion in fat mass, suggesting that fat is more of an energy substrate during active Crohn's disease than glucose. In contrast, Royall et al. [9] analyzed patients after 3 weeks of enteral nutrition for Crohn's disease, utilizing a four-compartment model, and demonstrated that patients with active disease had lost a significant amount of body fat, to 70% of healthy controls. There was a relative sparing of lean mass and proportionally a greater loss of fat mass. Those patients on corticosteroids had difficulty increasing their protein status during enteral therapy. However, for the group as a whole, there was improved weight gain with normal proportions of body composition (64% water, 18% protein, 18% fat). Data such as these are not available for pediatric patients, and given differences in energy needs per kilogram of body

weight as well as hormonal differences in a variety of age groups, it is unlikely that adult and pediatric data would be comparable.

Micronutrients

Micronutrient deficiencies are usually determined by measuring serum levels of the micronutrients in patients with IBD. Although most of the data are gleaned from adults, deficiencies are also seen in the children. The reasons for micronutrient deficiencies are similar to those for growth failure and protein energy malnutrition.

Low serum folate occurs in 40–60% of patients with IBD. Deficiency is due to poor intake, small bowel disease, and the use of sulfasalazine which interferes with folate absorption. Vitamin B_{12} deficiency is seen most commonly in patients who have had ileal resection and occasionally in patients with extensive ileitis. Other water-soluble vitamins are not significantly diminished although poor intake of B_6, B_2, and pantothenic acid have been described. Vitamin D deficiency is common in Crohn's disease, often related to the severity of the disease. Patients with bile acid malabsorption after ileal resection resulting in fat malabsorption are at highest risk. Oral antibiotics may contribute to vitamin K deficiency, which is rarely of clinical significance.

There is controversy surrounding trace element deficiencies, specifically that of zinc. Zinc deficiency has been shown to cause retarded growth, delayed sexual development and delayed bone age. Serum Zn levels are often but not invariably low in children with IBD and growth failure, but the levels often can be shown to directly correlate with the serum albumin concentration, as zinc is bound to albumin [10]. There are, however, reports of Zn malabsorption or excessive stool losses of Zn [11]. Zinc tolerance tests are abnormal in some growth-retarded IBD patients, but similar findings may also be seen in children with IBD without growth delay [10]. Serum levels of calcium fluctuate with the serum albumin level. There are, however, patients who have abnormal calcium metabolism related to fat malabsorption or steroid use which may predispose them to renal calcium oxalate stones. Occasionally, inappropriate restriction of dairy products may contribute to poor calcium intake. Magnesium deficiency occurs but is very uncommon. Urinary magnesium concentrations may be a better indicator of magnesium status in patients with IBD, than serum magnesium levels. Copper deficiency (possibly secondary to inadequate supplementation) has recently been shown to be a complication of parenteral nutrition in adults with Crohn's disease. Other trace element deficiencies are rare except as would be expected in the use of long-term parenteral nutrition without trace element supplementation.

Assessment of Nutritional Status

In assessing the growth, energy, and protein status of a child with IBD, dynamic evaluation of changes over time are more valuable than measurements at single time points. This is true both at the time of initial evaluation and during subsequent examinations.

Height and weight measurements can be expressed in a number of ways to assess growth and nutritional status. Weight for age and height for age percentiles are useful indications of acute and chronic malnutrition. This is especially true when percentiles can be compared to those in years prior to the onset of IBD. Follow-up of changes along these growth curves after diagnosis can be a measure of the efficacy of medical and nutritional therapies. Weight for height curves are also useful. However, caution must be used in interpreting these data, as stunting can result in a severely growth-retarded individual with a normal weight for height percentile.

A corollary to the use of percentile curves is the evaluation of growth expressed as height and weight velocities. When measured sequentially, these serve as sensitive growth indicators. Velocities are expressed as increments per year since growth occurs in spurts and rates derived for shorter periods of time may be inaccurate. Prepubertal girls have an expected minimum growth of 4 cm/year and prepubertal boys 3.7 cm/year. Velocity curves may point out significant slowing in growth for an individual patient and unmask growth failure more quickly than height for chronological age curves. Because adolescents with IBD often have delays both in puberty and bone age, height velocity must also be interpreted in the context of the stage of sexual maturation and bone age as opposed to chronological age alone. Bone age determination is, therefore, a useful measurement to help predict and monitor the (potential for) future growth. For example, a Tanner-III 15-year-old male with a bone age of 12 should have nutritional and medical intervention to treat his growth failure even if he is asymptomatic. It is hoped that this patient will attain catch-up growth because of the gap in his bone age versus chronologic age. On the other hand, the same patient with a bone age of 15 is at high risk for permanent growth failure.

Protein and energy stores can be assessed by standard anthropometric measurements, including midarm circumference and triceps skinfold thickness. Since interobserver variability often causes significant error, these measurements are taken sequentially by the same staff member. Other methods for measuring body composition including bioelectrical impedance, stable isotopes, under water weighing, CT scans, TOBEC and DEXA are at this time mostly research tools, not readily available, nor clinically validated in children.

Laboratory measurements are rarely helpful in the assessment of macronutrient status. Low serum albumin, a common biochemical abnormality, usually reflects the severity of the inflammatory process and enteric protein loss. Measurement of the prealbumin, transferrin, and retinol-binding proteins is somewhat more useful in documenting acute protein depletion. Given the protein loss in stool, nitrogen balance studies utilizing urinary urea or urinary nitrogen alone are usually inadequate. However, an estimate of the severity of protein loss can be obtained by measuring stool α_1-antitrypsin levels, which correlate with enteral protein loss. Assessment of the patient's caloric intake is often useful in managing the nutritional consequences of IBD. A written 3-day diet record is preferable to a 24-hour recall, especially in the pediatric population, and the dietitian must enlist the adolescent patient as a partner in this process.

Therapy

Nutritional therapies in children with IBD have dual roles. Clearly, patients suffering from malnutrition and concomitant growth failure will require nutritional support. In addition, nutritional therapies, either alone or as an adjunct to medications, can also be used to induce a remission of disease activity.

General Recommendations

As part of the routine management of any child with IBD, nutritional counseling to assure adequate nutriture and growth is essential. All patients, even those without overt signs of malnutrition or growth failure, should receive counseling either from the treating physician or from a dietitian well versed in the disease process. Our approach is designed to insure adequate caloric intake, since very often these patients need up to 75–85 kcal/kg/day for adequate growth. Thus, we discourage any dietary restrictions unless there is a clear medical indication. We do not, for example, routinely restrict lactose, even in patients with small bowel Crohn's disease, unless patients are symptomatic, are diagnosed as being lactose malabsorbers with a lactose breath hydrogen test, and intolerant of dairy despite exotenous lactase supplementation. Low-residue diets are not routinely prescribed, unless the patient has an intestinal stricture. Parental desire for a 'good diet' thereby restricting high calorie 'junk food' often is a stumbling block to maintaining appropriate caloric intake. Given the discomfort and anorexia associated with this illness, it is our policy to encourage patients to eat foods they enjoy while trying to maintain good micronutrient balance with either certain foods or with supplemental vitamins. Nutritional supplementation with high calorie liquid

formulas or other products can be utilized for the patient who demonstrates insufficient caloric intake, before significant growth failure occurs. On the other hand, one needs to recognize that the majority of these supplemental products have only fair palatability and only the highly motivated patient will continue to use them long term.

Micronutrient supplementation is not routine. Most patients are encouraged to use a single supplemental multivitamin a day, especially if their diet is felt to be inadequate. Folate supplementation may be necessary in patients receiving Azulfidine, which inhibits folate absorption. The vast majority of IBD patients who do not have significant bleeding will be found to have anemia associated with low serum iron yet with normal or high levels of serum ferritin. This reflects the anemia of chronic inflammation, whereby iron stores are normal but are unable to be utilized secondary to the inflammatory process. Supplementation with iron in these patients is generally ineffective. There are, as yet, no large scale studies of erythropoietin levels or therapy in IBD. One controlled study, in adults, showed that 82% of patients with IBD and low relative erythropoietin levels, responded to a 12-week course of erythropoietin [12]. More data are needed before widespread measurement and therapy with erythropoietin can be recommended.

Nutritional Therapy of Malnutrition and Growth Failure in IBD

In the prepubertal adolescent, the potential for catch-up growth is limited because of bone maturation and eventual epiphyseal fusion. Early aggressive intervention in patients with growth failure is imperative. The goal of the nutritional therapy is to allow for the reversal of growth arrest and for catch-up growth, thereby hopefully returning to the individual patient's premorbid growth channel. The reversal of growth arrest requires an appropriate body weight for height, while catch-up growth may require additional calories over and above that necessary to maintain weight for height. Thus, caloric intake for catch-up growth should be estimated according to the patient's ideal weight for age rather than their actual weight.

The most common approach initially is the use of high calorie supplements taken orally. These will result in weight gain and catch-up growth only if utilized for a sustained period of time which may often be difficult. Thus, many centers utilize nocturnal nasogastric feedings as a standard therapy for malnutrition and growth failure in adolescents with IBD. Utilizing overnight nasogastric feedings, with the tube placed nightly by the patient themselves, rarely interferes with normal daily activities. Such an intervention has been shown in a number of studies to effectively reverse growth failure [13, 14]. Supplementation, whether oral or nasogastric, may need to continue for a period of years, to maximize growth in these patients. It should be noted,

however, that a number of these patients will continue to manifest permanent growth impairment possibly related to their using corticosteroids.

The choice or type of formula used, whether polymeric or monomeric, should be individualized based on the patient's clinical status, extent of disease and previous surgery. However, for the purposes of growth failure, polymeric formulas have been shown to be quite effective. Some groups utilize an intermittent approach, that is once a month for 4 months or for 3–4 months over a 1-year period [14]. We have tended to continue the nasogastric feeds for longer consecutive periods, mostly because of its additional therapeutic benefit as will be discussed later [13]. Certainly, if the time for catch-up growth is limited as evidenced by the patient's bone age, then a more aggressive approach, one which will achieve the most in the shortest period of time, should be taken.

There are rarely contraindications to enteral nutritional support. The most significant problem is patient noncompliance. Very often, however, the most motivated patients are the ones with the severest growth retardation and pubertal delay who have become increasingly embarrassed by comparison with their healthy teenage friends.

Parenteral nutritional support, also given overnight, can achieve weight gain and reverse growth failure in IBD. Many adolescents who are unable or unwilling to self-intubate for nocturnal nasogastric feeds are willing to utilize an indwelling catheter and administer nocturnal parenteral nutrition. Cost, potential infectious and metabolic complications and difficulty of administration make parenteral nutritional support less preferable than enteral feedings. However, parenteral nutrition is an efficacious alternative which, if managed by a team well versed in its use and risks, can be quite a safe approach.

There is a group of patients, especially those who have short segment small bowel Crohn's disease with growth failure, who will benefit from surgical resection of the diseased segment. Not all patients, however, achieve improved growth postoperatively and the risk of recurrence must be taken into account before the decision to operate is made. In general, a surgical approach to growth failure in the adolescent with Crohn's disease should be reserved for the patient who has exhausted medical and nutritional therapies without success.

Nutrition as Primary Therapy for IBD

Although classically, nutritional therapy has been considered an adjunct to medical and surgical therapy for IBD, over the last 10–15 years there has been considerable interest in nutrition as primary therapy especially in patients with Crohn's disease. Earlier studies utilized parenteral nutrition, but more recently there have been a number of studies exploring enteral nutrition as a primary therapy.

The majority of the controlled trials are those which have evaluated nutritional therapy for the induction of short-term remission in acute or relapsing Crohn's disease. These studies have compared various types of enteral feedings to corticosteroids, enteral feedings to parenteral nutrition, or different types of enteral nutrition to each other. A number of these studies are summarized in table 2.

There have been at least six studies which have compared monomeric (elemental) diets to standard corticosteroid therapy, with two of these being in pediatric patients. Most of these reports range in number from 15 to 37 patients with patients being treated anywhere from 2 to 6 weeks. As noted in table 2, a monomeric diet appears to be as efficacious in inducing remission as standard steroid therapy in patients with Crohn's disease.

In another group of four different reports, steroid therapy was compared to an alogomeric (semi-elemental) diet. Only one of these studies involved pediatric patients and that study was the only one that indicated an equal effect of the oligomeric diet to steroids. In fact, the largest group, involving over 100 patients [19], showed that steroids induced remission 80% of the time versus only 53% of the time for the oligomeric diet.

There are two recent studies, one of which involves pediatric patients [20], that compare polymeric diets to steroids. Both involve only small numbers of patients. However, both show that polymeric diets are equivalent to steroids in inducing remission in patients with Crohn's disease. Major differences in methodology and numbers of patients makes it difficult to compare these studies and to explain why polymeric diets might be superior to oligomeric diets.

Similar results are obtained when monomeric diets are compared to polymeric diets. In five separate studies, all in adults, the majority showed that polymeric diets were equal to monomeric diets in the induction of remission. Only one suggested that elemental diets were superior to polymeric diets, while one showed that polymeric diets were better. In the majority of these reports, relapse rates were higher when tube feedings were discontinued.

Griffiths et al. [21] recently performed a meta-analysis of randomized controlled trials of enteral nutrition as a primary treatment of active Crohn's disease. Exclusive enteral nutrition was compared with corticosteroids, and elemental with non-elemental formulas. In 8 trials comprising 413 patients, corticosteroids were found to be more effective than enteral nutrition. In 5 trials comprising 134 patients, there was no difference in the efficacy of elemental versus non-elemental formulas.

The use of parenteral nutrition has also been shown to be efficacious in both patients with Crohn's disease and ulcerative colitis. There have been a myriad of retrospective studies dating from 1973 that indicate that parenteral

Table 2. Induction of remission with nutrition support in IBD: Prospective randomized controlled trials and number of patients with short-term remission

Author	Steroid therapy	Monomeric diet
O'Morain et al. [15], 1984	8/10 (80%)	9/11 (82%)
Saverymuttu, 1985	16/16 (100%)	15/21 (71%)
Okada, 1990	3/10 (30%)	8/10 (80%)
Seidman et al. [16][a], 1991	6/9 (66%)	8/10 (80%)
Thomas et al. [17][a], 1993	7/7 (100%)	9/9 (100%)
Gorard, 1993	17/20 (85%)	10/13 (77%)
Author	**Steroid therapy**	**Oligomeric diet**
Malchow, 1990	32/44 (73%)	21/51 (41%)
Sanderson et al. [18][a], 1987	6/7 (86%)	7/8 (88%)
Lochs et al. [19], 1991	41/52 (79%)	29/55 (53%)
Lindor, 1992	7/10 (70%)	3/9 (33%)
Author	**Steroid therapy**	**Polymeric diet**
Gonzalez-Huix, 1993	15/17 (88%)	12/15 (80%)
Ruuska et al. [20][a], 1994	9/9 (100%)	10/10 (100%)
Author	**Monomeric diet**	**Polymeric diet**
Giaffer, 1990	12/16 (75%)	5/14 (36%)
Park, 1991	2/7 (29%)	5/7 (71%)
Raouf, 1991	9/13 (69%)	8/11 (73%)
Royall, 1994	16/19 (84%)	15/20 (75%)[b]
Rigaud, 1991	10/15 (67%)	11/15 (73%)
Author	**TPN/NPO**	**Enteral nutrition**
Alun-Jones [23], 1987	14/19 (88%)	11/17 (85%)[c]
Greenberg et al. [24], 1988	12/17 (71%)	11/19 (58%)[d]
Wright and Adler [25], 1990	4/5 (80%)	3/6 (50%)[e]
Gonzalez-Huix et al. [26], 1993	10/20 (50%)	12/22 (55%)[d]

Numbers in parentheses are short-term remission rates. TPN = Total parenteral nutrition; NPO = nothing per os.

[a] Pediatric studies.

[b] Peptides.

[c] Monomeric diet per os.

[d] Polymeric diet via nasogastric tube.

[e] Oligomeric diet per os.

nutrition can induce remission in Crohn's disease. There are likewise 3 prospective uncontrolled trials and 5 controlled prospective trials that show efficacy ranging from 60 to 100% induction of remission [22].

There have also been 3 papers on Crohn's disease and 1 on ulcerative colitis [23–26] that have compared total parenteral nutrition to either a polymeric or an oligomeric diet. Despite differences which appear significant as in the studies by Greenberg et al. [24] (71 versus 58%) and Wright et al. [25] (80 versus 50%), because of the small number of patients, the results do not meet significance. Thus, there is only the suggestion that enteral nutrition, whether in Crohn's disease or ulcerative colitis, produces remission rates equivalent to those of parenteral nutrition. A recent uncontrolled trial in pediatric patients [27] with Crohn's disease showed a 72% remission rate in a group of 65 children given a semi-elemental diet for 4 weeks. In this particular study, 43% relapsed within 6 months and 61% within 12 months. This is very much in keeping with many of the previously mentioned studies. Of interest, however, was that if patients continued a semi-elemental diet the relapse rate was much lower (46 versus 83% relapse within 12 months) [27].

A recent critical review of the literature [28] also concludes that intense parenteral or enteral nutritional support has a role in achieving remission in Crohn's disease. Although the data do not support one type of nutritional intervention over another, the authors suggest that enteral nutrition be used if possible, as it is less costly and potentially less complicated.

There have also been a number of studies that have investigated exclusion diets as a primary therapy for Crohn's disease based on the premise that certain dietary antigens exacerbate Crohn's. Riordan et al. [29] induced remission in patients using an elemental diet and compared patients who were then either given corticosteroids or an exclusion diet, whereby they introduced a single food each day and excluded any foods that produced gastrointestinal symptoms. Sixty-six percent of the corticosteroid group relapsed versus only 30% in the diet group. Although this type of practice of food testing and exclusion is time-consuming and requires significant dietary counseling, the authors suggested that an exclusion diet may be a worthwhile approach for patients to maintain remission of Crohn's disease. Pearson et al. [30], however, found that although almost 50% of patients who were put into remission by an elemental diet did identify certain foods that cause sensitivity, these sensitivities were quite variable and not persistent. They felt that although food intolerance does occur in Crohn's disease it is of 'insufficient importance to warrant putting all patients through elimination diets'. They did, however, suggest that reintroduction of foods after induction of remission by an elemental diet needs to be done slowly. In a recent pediatric study, Polk et al. [31] found that a combination of a peptide-based formula given for 1 month followed by a 2-

week exclusion diet and a 2-week low-residue diet regimen for 2 of 4 months in a cycle during a 1-year period improved growth failure and decreased disease activity in children with Crohn's disease compared to the year prior to this therapy. The numbers, however, were very small (6 patients) and apparently none of the patients identified foods associated with symptoms during the exclusion diet phase. Thus, there is still considerable controversy about the role of exclusion diets in Crohn's disease.

In ulcerative colitis there seems to be little benefit in the use of total parenteral nutrition or enteral nutrition as primary therapy. Case reports and retrospective studies show minimal therapeutic benefit from total parenteral nutrition in ulcerative colitis [22]. One pediatric study [32] demonstrated limited benefit from parenteral nutrition in avoiding surgery in ulcerative colitis, although there was a 50% remission rate (4/8). There are 2 prospective controlled trials in adults with ulcerative colitis that show no therapeutic advantage of parenteral nutrition over either intravenous fluids or oral diet [33, 34]. In one study mentioned previously [28], parenteral nutrition and enteral nutrition were equivalent (50%) in inducing remission in a small number of adults with ulcerative colitis. This is in contrast to 2 retrospective reports which showed only a 33% remission rate associated with enteral diets [22]. It would seem, therefore, that nutritional support, whether it is enteral or parenteral although possibly of some value as an adjunct to medical therapy for ulcerative colitis, is of limited value as a primary therapy for these patients.

Mechanisms of Action

Many different theories have been proposed as to why diet therapy is efficacious in inducing remission in Crohn's disease. When the initial studies utilizing elemental diets were successful, many felt that the elimination of intraluminal antigens and 'bowel rest' helped induce remission. This was also the explanation for the beneficial effect of parenteral nutrition. However, benefits from polymeric diets point to other pathogeneses and suggest that this mechanism is probably not an important factor in inducing remission in Crohn's disease. Nutritional repletion in any form is more than likely the critical factor in inducing remission.

One can only speculate as to how replenishment or correction of macro- and micronutrient deficiencies improve clinical status in patients with Crohn's disease. In theory, improved lymphocyte counts related to improved nutrition may help diminish intestinal disease activity. Various immunoglobulins have been shown to be increased by elemental diets including gut IgA. There has also been a suggestion that improved nutritional status also improves intestinal mucosal permeability which may be a factor in decreasing the inflammatory process. It is also possible that certain particular nutrients such as glutamine

which is a primary substrate for enterocytes, improves intestinal healing. As of yet, there have been no prospective controlled studies comparing glutamine-containing formulas to those without glutamine. Many enteral diets do contain glutamine which may be beneficial.

A recent paper has suggested that the mechanism of action of certain enteral diets in Crohn's disease is related to low levels of fat and to specific types of fat content (decreased linoleic acid) which actually limit the precursors for arachidonic acid-derived eicosanoid synthesis [35].

Micronutrient repletion may also influence outcome in Crohn's disease. Both vitamin C and vitamin A are involved in improving lymphocyte functions and vitamin A more than likely has a role in epithelial cell turnover.

Clinical Approach

In general, if one intends to induce remission in IBD without utilizing medications, then nasogastric infusions, usually nocturnal, are considered to be the least invasive and most efficacious. Unfortunately, the relapse rate is considerable when the diet is discontinued. Protocols investigating long-term intermittent elemental diets are currently under way. As mentioned previously, one preliminary report suggests that continuing nasogastric supplemental feeds with a semielemental diet diminishes the relapse rate (over a 12-month period) and increases height velocity [27].

Given the risks and cost of parenteral nutrition we prefer nocturnal nasogastric feedings of either a polymeric or elemental diet to induce and maintain remission. In our practice, parenteral nutrition is utilized either as an adjunct to medical therapy or to reverse growth failure only in those patients who have either failed or refused enteral nutrition support.

Research Issues/Concepts for the Future

Short Chain Fatty Acids

It has been our personal observation and that of others that patients with acute colitis may do better when they are fed enterally. It is well known that anaerobic fermentation of carbohydrates such as fiber, polysaccharides, starches, and simple carbohydrates that are delivered to the colon will produce short chain fatty acids including acetate, butyrate, and propionate. These compounds have been shown to be utilized by the colonic mucosa as a source of energy. Children with Crohn's ileocolitis and ulcerative colitis have been shown to have increased fecal concentrations of n-butyrate, possibly related to an abnormality of colonocyte butyrate utilization [36]. Short chain fatty acids have been utilized as a therapy for diversion colitis [37] when used in

an enema preparation. A recent uncontrolled study in adults with refractory ulcerative colitis found a 60% response rate with butyrate enemas [38]. Consideration of the use of fiber in enteral diets for colitis patients or short chain fatty acids in enema preparations will require further study.

Polyunsaturated Fatty Acids

There has been considerable recent interest in the possibility that dietary polyunsaturated fatty acids which are then metabolized to eicosanoids may have some efficacy in modifying various autoimmune disorders. Eicosapentaenoic acid has been studied in systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and in asthma. There are a number of preliminary studies suggesting the therapeutic efficacy of eicosapentaenoic acid in IBD and a recent European study that appears promising [39].

Glutamine/Arginine

Glutamine is the preferred metabolic fuel for the small intestinal mucosa. The most abundant amino acid in plasma, it represents over 50% of the amino acids in skeletal muscle and stimulates lymphocytes and other rapidly dividing cells. Many now consider glutamine a 'conditionally essential' amino acid in catabolic and stressed patients. In these patients low muscle and serum glutamine levels have been shown to occur fairly rapidly and some improvement in outcome has been noted in patients with glutamine-supplemented parenteral nutrition. As yet, there are no good studies demonstrating the effects of glutamine-supplemented parenteral nutrition or enteral nutrition in IBD. Likewise, arginine has been considered a conditionally essential 'amino acid' in stressed individuals, it stimulates immune function, and seems to increase nitrogen retention and wound healing in a select group of patients.

Team Approach to Care/Logistics

To adequately care for chronically ill children with IBD and their families requires an integrated team approach. Our team includes pediatric gastroenterologists, a gastrointestinal nurse clinician as well as a nutrition support nurse clinician, a pediatric nutritionist, and ancillary services such as child psychiatry, pediatric pathology, pediatric surgery, and pediatric radiology.

The nutrition team must work in tandem with other members of the team to best understand each individual patient's particular needs and tendencies. Very often, decisions about the type of nutritional therapy will be made by the attending gastroenterologist following the evaluation and recommendations of the nurses, nutritionist, and psychiatrist. The nutritionist's role is that

of evaluating the adequacy of the child's diet as well as counseling. If nasogastric nutrition support is indicated, then the nurse clinician begins the process of teaching the patient self intubation. This can be done as an outpatient, first in an office setting supervised by the nurse clinician, and then with follow-up at home by the home care staff. The current availability of sophisticated high tech home care companies makes these arrangements quite simple. However, appropriate communication between the physician, nurse clinician (who acts as the coordinator), the family and home care company is essential. Although it has not been our practice to use gastrostomy tubes, a number of centers have begun to place them in a select group of patients who refuse nasogastric feeds. A recent paper from Canada describes the successful use of gastrostomies in a group of 20 children who required enteral nutrition support [40].

For those children who fail tube feedings, we then will begin nocturnal parenteral nutrition. This will often require a short hospital stay in order to place an indwelling central venous catheter (Broviac/Hickman) and to initiate the parenteral nutrition. Recently, we have successfully utilized peripherally inserted central venous catheters for short-term (6 months) nocturnal parenteral nutrition, obviating the need for a hospital stay. Parent and family education is also performed. Given the risks of parenteral nutrition, there is considerable teaching time necessary to ensure proper care and handling of the catheter, site, equipment and parenteral nutrition solutions. Patients are usually monitored on a regular basis by our nutritionist, nurse clinician, and a dedicated nutrition support physician. As the patient's clinical status improves and his/her oral intake increases, the parenteral nutrition is weaned. Patients are often seen monthly, although more frequent laboratory tests can be obtained by the home care company and communicated to the team.

Ongoing monitoring of the efficacy of treatment on weight gain and growth is essential in deciding the duration of both enteral and parenteral therapy. If the patient is otherwise well and has progressed over time to reach what is felt to be their final height, or if there is radiographic evidence of closed epiphyses, then the nutrition support can be discontinued.

Education for patients and their families involves a variety of modalities, including audiovisual presentations. Patients who have learned the technique of inserting a nasogastric tube for nutritional supplementation often meet with others about to embark on such a program. In similar fashion, self-help support groups for parents and other family members of adolescents with IBD can be of enormous benefit. Volunteers whose children suffer from IBD help counsel other parents, especially during critical periods such as time of diagnosis, initiation of nutrition support, or recommendations for surgery. Seminars and written educational materials on a variety of subjects including

general good nutrition, nutrition support, self image, quality of life, sexuality, and marriage are quite helpful.

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Short Bowel Syndrome

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Short bowel syndrome refers to the clinical effects of extensive small bowel resection. It includes diarrhea, fluid and electrolyte disturbances and malabsorption associated with malnutrition. In order to understand the effects of the short bowel syndrome it is important to review some essential aspects of gastrointestinal physiology.

Physiological Considerations

Gastric Emptying

The rate at which a meal enters the intestine is regulated by the rate of gastric emptying. Gastric emptying of liquids depends upon their osmolarity. For digestible solids the emptying is regulated by the particle size. However, of greater importance in relation to the short bowel syndrome is the fact that chyme entering the distal intestine inhibits gastric emptying [1].

Small Bowel

Small bowel motility is three times slower in the ileum than in the jejunum [2]. In addition the ileocecal valve may slow transit, especially when the ileum has been resected [3].

The adult small bowel receives about 5–6 liters of endogenous secretions and 2–3 liters of exogenous fluids per day. It reabsorbs most of this volume in the small bowel. The amount reabsorbed in the small intestine depends upon the nature of the meal [4]. With a meat and salad meal most of the fluid is absorbed in the jejunum, whereas with a milk and doughnut meal less is absorbed proximally and more distally. In addition the absorptive processes are different in the jejunum as compared with the ileum. These differences

depend partly on the nature of the electrolyte transport processes and partly on the permeability of the intercellular junctions.

In general, water absorption is a passive process resulting from the active transport of nutrients and electrolytes. The transport of sodium creates an electrochemical gradient and also drives the uptake of carbohydrates and amino acids across the intestinal mucosa. In addition in the ileum there is neutral sodium chloride absorption. However, the net absorption depends not only upon these processes but upon the extent of back diffusion of the transported material back into the intestinal lumen through 'leaky' intercellular junctions. In the jejunum these junctions are very leaky and thus jejunal contents are always isotonic. Fluid absorption in this region of the bowel is very inefficient when compared with the ileum. It has been estimated that the efficiency of water absorption is 44 and 70% of the ingested load in the jejunum and ileum, respectively. For sodium the corresponding estimates are 13 and 72% [5]. Hence the ileum is important in the conservation of fluid and electrolytes.

Colon

The colon has the slowest transit varying between 24 and 150 h. The intercellular junctions are the tightest in this part of the bowel and the efficiency of water and salt absorption in the colon exceeds 90% [5]. In addition carbohydrate is fermented in the colon to short-chain fatty acids (SCFAs) having two important actions. First SCFAs enhance salt and water absorption [6]. Second the energy content of malabsorbed carbohydrates is salvaged by being absorbed as SCFAs. Our recent data suggest that in short bowel patients this salvage may be greater than in normals [7]. Thus, the colon becomes an important organ for fluid and electrolyte conservation and for the salvage of malabsorbed energy substrates in patients with a short bowel.

Unique Functions of the Ileum

The ileum uniquely absorbs vitamin B_{12} and bile salts. Bile salts are essential for the efficient absorption of fats and fat-soluble vitamins. Normally the demand for bile salts imposed by fat absorption cannot be met by synthesis alone. This full need is only met by ileal resorption of bile salts which are then recycled into the intestine. With ileal resection the loss of bile salts increases and is not met by an increase in synthesis. The bile salt pool is depleted and fat absorption is reduced. In addition loss of bile salts into the colon affects the colonocytes and reduces the ability of the colon to reabsorb salt and water resulting in increased diarrhea. In the colon bile salts are also dehydroxylated to deoxy bile salts which induce colonic water secretion.

Effects of Intestinal Resection

Motility

Gastric motility is enhanced following small bowel resection [8]. While proximal resection does not increase the rate of intestinal transit, ileal resection significantly accelerates intestinal transit [8, 9]. In this situation the colon aids in slowing intestinal transit so that in patients with a short bowel without a colon, a marker fed by mouth was completely excreted in a few hours [10].

Absorption of Fluid and Electrolytes

The effect of intestinal resection depends upon the extent and site of resection. Proximal resection results in no bowel disturbance because the ileum and colon absorb the increased fluid and electrolyte load efficiently. The remaining ileum continues to absorb bile salts and thus there is little reaching the colon to impede salt and water resorption. In contrast when the ileum is resected, the colon receives a much larger load of fluid and electrolytes and also receives bile salts which reduce its ability to absorb salt and water, resulting in diarrhea. In addition if the colon is resected the ability to maintain fluid and electrolyte homeostasis is severely impaired [11].

Absorption of Nutrients

Absorption of nutrients occurs throughout the small bowel and the removal of the jejunum alone results in the ileum taking over most of the lost function. In this situation there is no malabsorption [12]. In contrast even a loss of 100 cm of ileum causes steatorrhea [13]. The degree of malabsorption increases with the length of resection and the variety of nutrients malabsorbed increases [14, 15]. Balance studies of energy absorption showed that the absorption of fat and carbohydrate were equally reduced to between 50 and 75% of intake [16]. However, nitrogen absorption was reduced to a lesser extent, namely to 81% of intake. In the study of Ladefoged et al. [15], the degree of calcium, magnesium, zinc and phosphorus absorption was reduced but did not correlate with the remaining length of bowel, and it was recommended that in these patients parenteral nutrition be mandatory. Our studies showed similar reduction in absorption, but only half required parenteral replacement. The data taken as a whole suggest that it is easier to meet the needs for energy and nitrogen by increasing oral intake than the needs for electrolytes and divalent ions. A review of the literature prior to the availability of parenteral nutrition shows that resections of up to 33% result in no malnutrition and those of up to 50% could be tolerated without special aids, but those in excess of 75% require nutritional support to avoid severe malnutrition [17–27].

Adaptation of the Intestine

Following resection, the remaining small bowel hypertrophies and increases absorptive function [28–31]. This process enhances the ability of the remaining bowel to recover the lost function and is thus an important compensatory process. The factors which influence this adaptation are complex and are discussed below as are the effects of total parenteral nutrition (TPN).

Eating exposes the gastrointestinal tract to a unique set of stimuli which does not occur when it is kept constantly empty; a process called bowel rest. The advent of TPN resulted in the ability to rest the bowel for short or long periods of time without causing malnutrition, a situation which had not been possible previously. This process nourished the body but excluded the gut from nutrient and hormonal stimuli which occur during the ingestion of an oral diet. The advent of defined formula diets (DFDs) without residue and diets composed of monomers such as glucose instead of polymeric starch, modified the stimuli received by the gut when exposed to a normal diet. It should also be recognized that since nutrients are absorbed progressively along the length of the bowel, the jejunum is exposed to a higher concentration of nutrients than the ileum. Resection of the proximal bowel results in the ileum receiving more nutrients. Resection of the ileum on the other hand does not alter the jejunal nutrient load but may reduce stimuli from hormones released by the ileum.

Effect of Excluding Food from the Bowel Lumen

Hypoplasia of the mucosa is the most obvious change in experimental animals, when food is excluded from the lumen. At the same time body composition can be simultaneously maintained by the use of TPN. These facts have been extensively documented, and the interested reader is referred to a recent review by Lo and Walker [32].

In growing or neonatal animals, TPN and bowel rest will maintain normal body growth but will result in reduced bowel length, gastric and pancreatic hypoplasia [33–36]. Despite the occurrence of mucosal hypoplasia, the development of disaccharidase enzymes and glucose transport is accelerated and mucosal levels of these enzymes increased in neonatal animals receiving TPN [34, 36]. Hypoplasia occurred mainly in the proximal small bowel and is less evident distally [35]. In adult animals the effect of TPN and bowel rest diminished mucosal mass but stimulated glucose absorption per milligram of mucosal protein [37]. In addition TPN and bowel rest increased intestinal permeability [38] and altered the response to endotoxin [39].

Does the Nature of Enteral Nutrition Cause Hypoplasia?

It is not simply the lack of food, but also the nature of the diet that influences mucosal bulk. In neonatal studies mother's milk is no beter than formula [35]. However, refined intragastric liquid feeds cause relative hypoplasia as compared with a solid diet [33, 40].

Factors Influencing Bowel Atrophy

In general it appears that the decreased digestive and absorptive activities of the mucosa during bowel rest are the major reasons for hypoplasia. This concept is supported by the fact that simply increasing the tonicity of the bowel contents results in an increase of the mucosal mass [41]. Absorption of amino acids results in a nonspecific increase of mucosal function and mass [42]. Finally disaccharide hydrolysis followed by absorption stimulates mucosal growth to a greater extent than equivalent monosaccharide absorption [43]. Another factor affecting the mucosa appears to be biliary-pancreatic secretion. Transplantation of the ampulla causes mucosal hypoplasia while infusion of cholecystokinin and secretion stimulate mucosal growth [44, 45]. Recently SCFAs were shown to prevent or reduce mucosal atrophy in animals receiving TPN and bowel rest, even when given parenterally [46–48]. Dietary fiber is the main source of colonic fermentable substrate for SCFA production. Therefore, fiber in the diet aids the maintenance of mucosal mass and DFDs are not quite as good as a solid diet in this regard. Glutamine is a nutrient for the bowel mucosa and the supplementation of TPN with glutamine preserves gastric and colonic mass in TPN-fed animals but does not preserve small bowel mucosal height [49].

Does Bowel Rest Induce Gut Atrophy in Man?

In the rat, bowel rest with TPN causes atrophy in days [50], but in man even after 21 days of bowel rest with TPN there is no change in gut hormone production after a meal [51] or any histological atrophy [52, 53]. In children bowel rest caused atrophy only when prolonged beyond 9 months [53]. However, there is a reduction in the size of the microvilli and a fall in brush border enzyme activity [52].

In summary animal data suggest that when the bowel is not used, it atrophies. Mucosal atrophy is due to a combination of the lack of functional stimulation and the absence of hormonal, biliary and pancreatic secretion. The only convincing trophic factors are SCFAs and perhaps glutamine. Finally the dramatic mucosal atrophy seen in animals on bowel rest while receiving TPN does not occur in humans even after a few weeks of bowel rest. There are thus few data to suggest that patients on TPN for short periods need to be fed progressively to avoid malabsorption.

Complications

Gastric Hypersecretion and Peptic Ulceration

Gastric hypersecretion occurs immediately after intestinal resection and tends to be transient. However, in some patients peptic ulceration may occur. Treatment with H_2 blockers has been found to be successful [54, 55].

Cholelithiasis

After ileal resection there is interruption of the enterohepatic cycle of bile salts. As a consequence, bile salt loss occurs in excess of the ability of the liver to increase synthesis and the bile salt concentration in bile falls. The reduction in the concentration of chenodeoxycholate in the bile increases cholesterol secretion [56]. This combination makes the bile lithogenic. Clinically in this situation an increased incidence of gallstones has been observed [57]. Recently a study in experimental animals has shown an increased incidence of pigment stones [58].

Renal Stones

Hyperoxaluria occurs in short bowel patients due to increased absorption of oxalate by the colon [59]. Bile salts in the colon increase oxalate absorption [60]. Hyperoxaluria is associated with renal stone formation and the propensity to form stones is reduced by reduced citrate [61]. Treatment involves taking a low oxalate diet, taking cholestyramine to bind bile salts and use of citrate to prevent stone formation.

D-Lactic Acidosis

In some patients with a short bowel a syndrome of slurred speech, ataxia and altered affect occurs in episodes [62]. Superficially the patient appears 'drunk'. The cause of this syndrome is fermentation of malabsorbed carbohydrate in the colon to *D*-lactate and absorption of this metabolite [63]. The treatment of this condition involves the use of a low carbohydrate diet [64].

Nutritional Treatment

Based on the considerations already discussed, the approach to a patient with intestinal resection depends upon the extent of the resection, the presence of continuing intestinal disease that reduces the functional length of the intestine, the site of resected bowel and time for adaptation. The progress of the patient with time will lead to modifications of therapy. However, there are several therapeutic avenues applicable to all patients. First these

general approaches are considered and then the specific applications are discussed.

General Therapeutic Approaches

Initially an assessment should be made to determine whether the patient has had a resection which is unlikely to cause serious malabsorption. These are those with a jejunal resection leaving an intact ileum and colon. Such patients need observation and are likely to recover full bowel function without the need for nutritional or other therapeutic support. Others who have had a resection of less than 100 cm of terminal ileum will only require the use of a bile salt binder, cholestyramine 4–12 g/day to control bile salt-induced diarrhea. The remaining patients with a greater length of resection should be treated as follows.

Initial Treatment after Resection

Control of Diarrhea

Diarrhea is due to a combination of increased secretions, increased motility and osmotic stimulation of water secretion due to malabsorption of luminal contents. Initially diarrhea is controlled by keeping the patient nil per os to reduce any osmotic component. Gastric hypersecretion can be controlled by the continuous infusion of appropriate doses of H_2 blockers such as cimetidine. In addition loperamide can be used to slow gastric and intestinal transit. If loperamide does not work then codeine or phenoxylate may be tried.

Intravenous Fluids

In the immediate postoperative period all patients will require intravenous fluids and electrolytes to replace losses. Sodium and potassium chloride as well as magnesium are the most important ions to be replaced and plasma levels of the ions should be monitored frequently. Fluid is infused according to measured losses and to maintain an adequate urine output. The infusion is tapered as oral intake is increased.

Oral Feeding

The next consideration is to determine the nature of oral feeds. In patients who have more than 60–80 cm of bowel left, refeeding should be progressive with a view ultimately to feeding a normal oral diet. By contrast in patients who have little small bowel left, the initial target should be small volume isotonic feeds containing a glucose-electrolyte content similar to the oral rehydration solution. The composition of this solution should be glucose 3.4%

with sodium 85–90 m*M*, potassium 12 m*M*, bicarbonate 9 m*M* and chloride 80–90 m*M* for adults. The sodium concentration should be reduced for infants. Such a solution avoids osmotic stimulation of secretion and yet stimulates the bowel to absorb, thus promoting adaptation. For those with intermediate lengths of bowel progressive feeding should be attempted with the following plan. The same carbohydrate-electrolyte feeds as above should be started. A mixture of a similar composition has been shown to be well absorbed by patients with massive resection who have previously been dependent on intravenous fluids [65]. The diet should be lactose-free since lactase levels in such patients are reduced [66]. Vitamin B_{12} absorption should be measured and if subnormal injections of 200 mg/month should be started.

While it is popular to try DFDs in these patients, studies by McIntyre et al. [67] have shown that they are not absorbed better than a solid diet.

Early observations suggested that a low fat diet with added medium-chain triglyceride together with a high carbohydrate content was better for patients with a short bowel [68–70]. The theory behind these suggestions was the finding that malabsorbed long-chain fatty acids can cause colonic water secretion resulting in higher fecal output with steatorrhea and consequently greater loss of divalent ions. However, such studies were not controlled and medium chain triglyceride can also cause osmotic diarrhea. Using a controlled cross over design in two studies [10, 16], we showed that a high-fat diet was comparable to a high-carbohydrate diet in regard to total fluid, energy, nitrogen, sodium, potassium and divalent ion absorption. We therefore recommend a low lactose diet containing high calories from both fat and carbohydrate and a high nitrogen intake. In adults who require about 30 kcal/kg/day we aim to increase intake gradually to about 60 kcal/kg/day to provide sufficient absorbed calories despite malabsorption. The rationale for this approach is discussed by Woolf et al. [16]. Supplements of potassium, magnesium and zinc are given while monitoring serum levels.

Parenteral Nutrition

In patients with less than 60 cm of remaining small bowel and in those with a combined small bowel and colon resection, parenteral nutrition is lifesaving. It is started in such patients within a few days of the resection and initially 32 kcal/kg of a mixed energy substrate and 1 g/kg amino acids is infused with sodium 150–200 m*M*, potassium 60–100 m*M*, calcium 9–11 m*M*, magnesium 7–15 m*M* and zinc 70–100 μmol/day. Among trace elements zinc is the most important as we have found large losses in patients with a high endogenous output of intestinal fluids. Oral feeds are simultaneously started and attempts are made to reduce parenteral feeding as oral feeds are increased. It will become apparent whether the patient needs parenteral feed-

ing on a long-term basis. If that is the case then the patient should be started on a program of home parenteral nutrition (HPN). We have found that as the bowel adapts over months and even years the patient requires less parenteral feeding and ultimately about 30% of our patients initially requiring HPN can be weaned off HPN by using up to 2 liters of oral rehydration solution, high calorie diet and supplements of potassium, magnesium, calcium, fat-soluble vitamins and zinc. They are monitored regularly until the weight is stable and they are electrolyte balanced. Hypomagnesemia is particularly a serious problem in these patients. Ingestion of magnesium salts orally enhances diarrhea and therefore it often becomes difficult to use magnesium supplements orally. The author has successfully used magnesium heptogluconate for this purpose. This preparation is available as a palatable liquid which is added to the gastrolyte supplement in quantities of 30 m*M*/day. If this approach is not successful then magnesium sulfate is injected intramuscularly in doses of 12 m*M* 1–3 times a week to supplement the oral intake.

Vitamin supplementation needs comment. These patients can absorb water-soluble vitamins but have difficulty absorbing fat-soluble vitamins. They require large doses of vitamins A, D and E to maintain normal levels. Also pills often pass out whole in these patients, hence liquid preparations have to be used. The author recommends the measurement of these vitamin levels and supplementation with aqueous preparations of vitamin A and E (Aqasol A and E) and 1,25-dihydroxy-vitamin D in doses which normalize the plasma levels. Normalization may not be possible with oral vitamins in some individuals especially vitamin E levels.

In others an oral diet with intravenous fluid and electrolytes becomes necessary and in the remainder full parenteral nutrition is given.

Special Considerations

Somatostatin Analogue. A long-acting somatostatin analogue has become available and can be given subcutaneously. All studies have shown a reduction in the volume of output and an increase in sodium or chloride absorption [71–73]. However, the reduction does not seem to be sufficient to avoid parenteral nutrition in patients who require it [72].

Jejunal Resection with Intact Ileum and Colon. Patients in this category can be fed orally immediately and rarely have any problems.

Ileal Resection of <100 cm with Colon Largely Intact. Patients in this category have so-called choleraic diarrhea, and are best helped by the administration of 4 g of cholestyramine three times a day to bind bile salts left unab-

sorbed by the resected ileum. Vitamin B_{12} absorption should be measured and, if low, should be injected intramuscularly in doses of 100–200 μg/month.

Ileal Resection of >100–200 cm with Colon Largely Intact. This group of patients has little difficulty in maintaining nutrition with an oral diet, but has fatty acid diarrhea. For such a patient fat restriction is mandatory. With the larger resection the bile salt pool is depleted and cholestyramine is no longer beneficial. Parenteral vitamin B_{12} replacement is required.

Resection in >200 cm of Small Bowel and Lesser Resection with Associated Colectomy. Patients of this class require the graduated adaptation program indicated previously under general considerations.

Resection leaving <60 cm Small Bowel or Only Duodenum: Massive Bowel Resection. Patients in this category need HPN indefinitely. However, many patients even in this category may show a surprising degree of adaptation and require less parenteral nutrition and benefit from orally absorbed nutrients. The indication to reduce parenteral nutrition is weight gain beyond the desired limit and the fact that reduced infusion does not cause electrolyte imbalance and dehydration.

Conclusion

The short bowel syndrome is a very variable condition which can be as mild as that following terminal ileal resection to a very debilitating condition which follows total ileal and colonic resection with end-jejunostomy. The management varies with the extent and site of resection and the adaptation of the remaining bowel.

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Is Obesity an Imbalance in Energy Expenditure and Energy Intake? Is Leptin the Answer?

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Epidemiologic Features of Childhood Obesity

Prevalence, Persistence and Emergence

The prevalence of childhood obesity in the USA has increased dramatically during the last three decades. Data from the National Health and Nutrition Examination Survey III, from the years 1988–1991, showed that the prevalence of obesity based on body mass index (BMI), from children aged 6–17 years was 10.9% based on the 95th percentile and 22% based on the 85th percentile [1]. The 85th and 95th percentiles of BMI are approximately 120 and 140% of ideal body weight for height, respectively. The obesity prevalence increased during the period examined among all gender and age groups [1]. This increase was greatest for African-Americans among all gender and age groups [1].

In a sample of 6,000 children from Birmingham, Ala., the prevalence of obesity in girls at age 5 was 10% in Caucasians and 23% in African-Americans, rising to 27% in Caucasians and 47% in African-Americans by age 11 [2]. In boys, the prevalence of obesity at age 5 was 6% in Caucasians and 13% in African-Americans, rising to 22% in Caucasians and 29% in African-Americans by age 11. In Canadian children [3], the prevalence of obesity increased by approximately 50% (depending on the criteria used for obesity) between 1981 and 1988.

Epidemiologic studies suggest that possibly three critical periods exist for the development of childhood obesity [4]. These periods include gestation and early infancy, 5–7 years of age, and adolescence [4]. A longitudinal study [5] suggests that weight gain in infancy is a poor predictor of 9-year-old obesity.

However, impending or actual obesity began at ages 6–9 years [5]. Obesity that begins early in life increases the risk of obesity-related morbidity later in life [6]. However, the link between obesity and increased health risk is not well understood, particularly in children. Long-term follow-up from the Harvard Growth Study of the 1920s has shown that overweight adolescent males incur a twofold increase in risk of death by coronary heart disease [6]. The persistence of obesity into adulthood has been determined in several cohort studies. The percentage of obese children who become obese adults is 14% if they were obese at age 6 months [7], 41% if they were obese at age 7 years [8], 70% if they were obese at 10–13 years of age [9, 10], and 80% if they were obese at adolescence [11–14]. Further, the risk of obesity for progeny of two obese parents is around 50% for children close to the end of adolescence, but it may be around 30% for a pre-adolescent child [14]. This suggests that a significant proportion of obesity develops in late childhood and that late childhood obesity is a significant risk factor for the persistence of obesity into adulthood [6].

Demographics

Socioeconomic status and race are predictors of obesity [11–15]. One study [15] demonstrated a strong inverse relationship between socioeconomic status and obesity in children, while another study [12] reported an inverse relationship between income and obesity in females from childhood to adolescence. The mechanism by which socioeconomic status affects obesity is unclear. Our Birmingham data indicate that African-American females are fatter than Caucasian females through childhood [2]. After adolescence, African-American females have higher prevalence rates of obesity than Caucasian females [12]. African-American women have a higher age-adjusted mean BMI and skinfolds thickness than Caucasian women from their twenties onward [16, 17]. As adults, African-American females have increased morbidity and mortality due to abnormal glucose metabolism, hypertension, dyslipoproteinemia, and other diseases associated with obesity [16, 17]. Obesity in adolescence is the most powerful predictor of these risk factors [6]. The prevention of obesity in childhood and adolescence may be an effective means of decreasing the associated mortality and morbidity in adults, and particularly in African-American females [6].

Familial Aggregation

Fifty percent of the progeny of two obese parents become obese by the end of adolescence compared to only 8–12% of the progeny of lean or medium weight parents [14]. The relative contributions of genetic factors and the environment within the family to explain this familial aggregation of obesity

were examined in adoption [18, 19] and twin [19,20] studies. In the Danish adoption study [18], the results showed a positive relationship between adoptee weight class (thin, median weight, overweight, and obese) and the BMI of the biologic parents, but there was no apparent relationship between adoptee weight class and the BMI of the adoptive parents. The relationship between biologic parents and adoptees was present across the entire range of weight classes [18]. The investigators concluded that genetic influences have an important role in determining obesity in adults, whereas the family environment alone has no apparent effect [18]. In the Swedish adoption study [19], the genetic and environmental contributions to the BMI were examined in twins (identical and fraternal) reared apart or together. The results of intrapair correlations of the values for BMI of identical twins reared apart were 0.70 for men and 0.66 for women [19]. The intrapair correlation coefficients of BMI among identical twins reared together were 0.74 for men and 0.66 for women [19]. This apparent similarity, that is independent of childhood environment, has minimal influence [19]. The response to long-term overfeeding was studied in 12 pairs of nonobese healthy young adult male monozygotic twins [20]. Individual changes in body composition and topography of fat deposition varied significantly during the overfeeding period [20]. The similarity in response to overfeeding with each twin pair was significant with respect to body weight, percentage body fat, fat mass, and estimated subcutaneous fat, with about three times more variance among pairs than within pairs [20]. After adjustment for the gains in fat mass, the within-pair similarity was particularly evident with respect to the changes in regional fat distribution and the amount of abdominal visceral fat, with about six times more variance among pairs than within pairs [20]. Taken together, these studies suggest that there are significant genetic influences on the amount and the distribution of body fat. However, the metabolic basis of this genetic predisposition was not examined.

Classifications and Health Concerns

Childhood obesity can be classified as either exogenous/simple obesity or endocrine/genetic obesity. Children with simple obesity, which accounts for 99% of childhood obesity, are tall for age (height over 50th percentile), have normal or advanced bone age, are mentally normal, have no physical abnormalities and frequently have a family history of obesity. The endocrine and genetic syndromes associated with obesity account for $<1\%$ of childhood obesity. The main features of these children are: they are short for age; have delayed bone age; are mentally retarded; have associated physical abnormalities, and have an infrequent family history of obesity. Childhood obesity is associated with the following medical complications: psychosocial; orthopedic problems of hip and legs; cardiovascular such as hypertension and hyperlipidemia;

respiratory such as sleep apnea and Pickwickian syndrome; skin striae and irritation; glucose intolerance, and gallbladder disease.

During the last several years there has been an increasing interest in the study of obesity in children. In particular, there have been extensive developments in the study of energy expenditure (EE) and energy intake. The aim of this article is to summarize recent advances in this area with an emphasis on studies in pre-adolescent children.

Energy Expenditure

Advances in the area of total EE (TEE) have occurred with the increased utilization of the double-labeled water technique. Cross-sectional assessments [21–25] of TEE in free-living children using double-labeled water have shown that TEE in young children is approximately 25% the current recommendations for energy intake [26]. This discrepancy may be explained by either: (i) inaccuracy of prior energy intake data that were used to derive the recommendations, or (ii) a substantial reduction in EE in children over the last few decades, presumably due to a decline in physical activity [27]. Either way, recent research data imply that new nutritional guidelines need to be formulated for young children in order to ensure that the recommended energy intake closely matches TEE [27]. This may require reducing recommended levels of energy intake or recommending increased physical activity or both. Studies of EE in children have also been useful for examining the role of EE in the development of obesity.

EE in Infancy

Reduced EE was an important factor in the rapid weight gain during the first year of life in Caucasian infants born to overweight mothers [28]. The contribution of EE to weight gain was investigated in a small group of infants born to lean and overweight mothers. TEE (adjusted for body weight) measured at 3 months of age was related to weight gain during the first year of life. No significant differences were observed between infants who became overweight (weight/length > 90th percentile according to the National Center for Health Statistics values [29]) by the age of 1 year (50% of infants born to overweight mothers) and those who did not, with respect to weight, length, and skinfolds thicknesses at 3 days and 3 months of age [28]. However, the average TEE at 3 months of age was 21% lower in the infants who became overweight than in normal-weight infants. In this study the components of EE were not measured. Overall, this age group has a low long-term persistence of obesity [5, 7], although the persistence of obesity in this study cohort has

not been reported. A major strength of this study was the inclusion of a longitudinal component. A higher rate for long-term persistence of obesity would be expected in children who become obese in late childhood. In another study there was no relationship between the TEE (adjusted for body composition) at 3 months of age and indices of body fatness at 9 months and 2 years of age in normal full-term Caucasian infants born to nonobese mothers [30]. In both studies the TEE was measured using the double-labeled water technique and the indices of body fatness included BMI and the sum of the triceps and subscapular skinfold measurements. The former study included infants of obese and nonobese mothers, whereas the latter included only infants of nonobese mothers. The discrepancy between these studies suggests that the mechanisms may be different for the development of obesity in genetic versus spontaneous obesity and that obesity may have heterogeneous etiologies. These studies suggest the need for a genetically predisposed sample since the children of obese parents are fivefold more prone to obesity than children of nonobese parents, and their obesity is more persistent [9, 13, 14].

EE in Childhood

Caucasian children, aged 4–5 years, with at least one obese parent had lower EE than children with nonobese parents; neither group of children was considered obese at baseline [31]. The TEE (adjusted for body weight) was estimated from the integrated pulse rate for the day, based on the measured relationship between oxygen consumption and pulse rate. Heart rate monitoring is known to be an imprecise estimate of TEE in children. These children were restudied 12 years later [32]. The TEE was adjusted for body composition. Among the adolescent boys, parental obesity predicted more rapid growth of lean body mass, but not adiposity [32]. Among the adolescent girls, lower energy intake per kilogram at baseline predicted higher BMI and adiposity 12 years later [32]. No pubertal staging was done in this study. This study suggests that a low EE per kilogram body weight may be associated with a precocious pattern of growth and development in children predisposed to obesity [32].

EE in Adolescents

Native Americans are prone to obesity and the Pima Indians are the only minority group that has been investigated metabolically. Low TEE (adjusted for body composition) in adult Pima Indians has been found to predict subsequent weight gain [33, 34]. These investigators observed a familial effect on resting EE (REE) and 24-hour TEE. These studies suggest that reduced EE contributes to the familial aggregation of obesity [33, 34]. The 24-hour EE, determined using a whole-room indirect calorimeter, during weight maintenance and/or in

response to overfeeding was compared in peripubertal (mean $\pm$ SD, 12.4 $\pm$ 1.4 years) Pima Indian children with both parents obese and children with both parents of normal weight [35]. At baseline, the offspring of obese parents were already heavier, fatter, and had advanced sexual maturity when compared with the offspring of normal-weight parents [35]. When adjusted for differences in body weight and composition, 24-hour EE was similar at baseline and during overfeeding in both groups of children [35]. In another study [36], similar results were obtained when heavier and fatter Pima Indian children were compared to thin Caucasian children at baseline. The fact that children born to obese parents were already overweight may have obscured an initial impairment in EE even though attempts were made to correct for differences in body composition. Using the double-labeled water technique, a cross-sectional study in Caucasian adolescents suggests that absolute TEE is higher in obese adolescents, but is similar between lean and obese after normalizing for differences in body composition [37]. Obese children are commonly taller, have more lean body mass, and reach sexual maturity earlier that normal-weight children [11–14]. The increase in TEE in obese children and adolescents suggests that increases in body weight are paralleled by increases in lean body mass and therefore in TEE [33]. All of these observations suggest that children should be studied before the development of obesity.

Using double-labeled water technique to measure TEE, obese adolescent boys increased daily EE by 12% after a training program; half of this increase was attributed to the exercise and the remainder was due to an increase in spontaneous physical activity [38]. In intervention studies, it would be interesting to measure each of the components of EE in order to distinguish which change with training. This information would be particularly useful since previous studies in adults have shown that TEE may not necessarily increase in response to exercise because of compensatory reductions in other components of daily EE [39].

Television on EE

An area of interest has been the effects of television viewing on energy intake and physical activity in children. Children and adolescents who watched more television have a greater prevalence of obesity and superobesity than those who watched less television [40]. The association persisted when controlled for prior obesity, geographic region, season, population density, race, socioeconomic class and a variety of other family variables [40]. Television viewing may affect both energy intake and expenditure. EE may be reduced because less energy is expended while watching television than is required for more active play. Also, television viewing may promote increased energy intake by the consumption of calorically dense foods advertised on television and

by increased between-meal snacking. This study [40] does not discriminate between these possible causes. A recent study concluded that the failure of some obese adults to lose weight while eating a diet they reported as low in calories is due to an energy intake substantially higher than reported and an overestimation of physical activity, not to an abnormality in thermogenesis [41].

Finally, an area of interest has been whether television viewing affects REE in children. One study [42] in 10-year-old normal-weight or obese girls showed that REE was lower by 14% when measured while the girls watched an episode of 'The Wonder Years' compared to measurements performed while the girls were asked to sit quietly. This finding could be interpreted to mean that either: (i) television viewing reduces REE, or (ii) children fidget more when asked to sit quietly, thus leading to an increase in REE. The latter interpretation was supported, at least in part, by another study [43] which showed that 10-year-old normal-weight or obese girls had increased movement during measurement of REE when asked to sit quietly versus watching a videotaped episode of 'The Cosby Show'. However, although fidgeting was positively correlated with minute-to-minute variation in REE, there was no relationship between fidgeting and the absolute magnitude of REE [43].

Energy and Macronutrient Intake

Although obesity is commonly believed to be a result of excess calorie intake, many studies in children have failed to find a significant correlation between total calorie intake and fatness [44–47]. Earlier research [48] supports the view that obese children consume more energy than nonobese children. More recently, a study [49] examined the relationship between dietary intake (using 24-hour diet recalls) and body fatness (based on skinfold data) in 48 pre-adolescent children. Results revealed that obese children had greater crude energy intake than nonobese children, but when adjusted for weight, they consumed less calories.

Recent research has focused on diet composition because of the uncertain association between energy intake and adiposity. This is emerging as an important area of research based on the theories of Flatt [50] suggesting that dietary fat is stored more efficiently than carbohydrate. Thus in adults, excess consumption of carbohydrate tends to be oxidized whereas excess fat intake tends to be stored [51]. The role of diet composition in the development of obesity in children, however, has not been extensively studied.

The question arises as to what extent obese children prefer high-fat foods, since a high-fat diet may contribute to weight gain in an efficient manner. In children, however, there are very little data on the relationship between the

sensory qualities of fat and subsequent intake. Children as young as 18 months of age have been reported to prefer high-fat foods such as hot dogs [52]. In a prospective study following children from age 6 months to 4 years, 47–65% of children who at age 2 consumed a high-fat diet compared to their peers continued to be among those in the upper tertile for fat intake at age 4 [53]. In another study [54], it was found that the majority of the most frequently consumed foods by 7- to 10-year-old urban school children in the USA contained at least 50% of calories from fat. There is some evidence to suggest a physiological basis for preference of high-fat foods in children [55]. Through associative conditioning experiments, 20 children 2–5 years of age were given opportunities to consume either a high-fat (220 kcal/100 g) or low-fat (110 kcal/100 g) yogurt [55]. Following repeated consumption, the children showed a clear preference for the yogurt flavor with the higher fat content. It was concluded that the high-fat yogurt generated post-ingestive satiety cues and thus provides evidence that the post-ingestive consequences of high-fat foods contribute to children's liking of these foods.

The consumption of high-fat diets by children is probably influenced by familial factors. One study [56] analyzed 3-day diet records of 1,597 individuals from 375 families and found familial similarity for energy and nutrient intake in the diet. Another study [57] confirmed that the fat content of children's diet is influenced by parental diet. There were significant parent–child correlations for total carbohydrate, total fat, and total calorie intake in 294 families with children aged 6–19 years. Additionally, food acceptance in children is related to the frequency of exposure to that food [58]. Finally, parent–child feeding strategies have been shown to affect their children's eating behavior. Although children in general can regulate their eating behavior in order to obtain a diet adequate in calories and nutrients [59], parents who used more controlling measures in feeding practices had children who were less able to consume appropriate calorie levels [60].

Leptin

In 1994 the notion that genetic abnormalities contribute to obesity gained important support with the identification of the *ob* gene and its protein product [61]. The *ob* protein, named 'leptin' from the Greek *leptos*, meaning thin, is produced in adipose tissue and is thought to act as an afferent satiety signal in a feedback loop that putatively affects the appetite and satiety centers of the brain [62]. The ultimate effect of this loop is to regulate body-fat mass. Leptin informs the brain of the amount of adipose tissue present in the body. In *ob*/*ob* mice, which are markedly hyperphagic and obese, the *ob* gene is

mutated and no leptin is produced; when given leptin, they stop eating and lose weight. The same does not seem to be true for most obese humans. In normal-weight and obese adults [63–65] and in normal-weight and obese children [66], serum leptin concentrations and the levels of *ob* mRNA in adipocytes correlate with body weight, and there is a strong positive correlation between serum leptin concentrations and the percentage of body fat, the BMI, and basal serum insulin concentrations. Serum leptin concentrations in normal-weight children [66] are comparable with those found in normal-weight adults [63]. Leptin concentrations in obese children [66] are comparable with those found in obese adults [63]. These results suggest that the adipocytes of humans produce leptin when the adipose mass increases and that there is resistance to the action of leptin, at the level of the hypothalamus [62, 67], causing increased appetite and decreased EE despite adequate leptin production by adipocytes; in this way the increase in adipose-tissue mass is maintained [62]. The problem in the obese humans is decreased sensitivity to leptin, but the nature and actions of the effector system for leptin are not known [62].

Children, unlike adults, are in a dynamic relationship with their energy needs for growth and development. Leptin concentrations decrease with advanced Tanner stage in both normal-weight and obese children independent of adiposity [66]. It is hypothesized that prepubertal children manifest a central insensitivity to leptin or relative 'leptin resistance' in the service of their dynamic energy needs [66]. As adolescents approach the end of puberty, energy needs and adipose stores stabilize, and leptin sensitivity returns. In an animal analogue, the association between leptin and pubertal development has been described. One study [68] found that in the *ob*/*ob* mice, which produce no leptin because of a defective *ob* gene, puberty does not advance until exogenous leptin is administered. Although the mechanism has yet to be described, it is likely that leptin plays a role in human growth and development.

The significant correlation between the serum leptin concentration and the percentage of body fat suggests that adipocytes are signaling the brain about the size of the adipose-tissue depot [63]. If the action of leptin in humans is similar to that in mice [69–71], appetite should decrease and EE should increase, which together should result in weight loss. The finding of increased serum leptin concentrations in obese humans suggests decreased sensitivity to leptin, although the detection of leptin by immunologic methods does not prove that it is biologically active [63]. *No functional and structural abnormalities of the leptin-effector system in humans are currently known.* However, diet-induced obesity in normal mice is an example of decreased sensitivity to leptin, because larger doses of leptin were required to induce weight loss in these mice than in leptin-deficient mice [71]. The *db*/*db* mouse provides an example of unresponsiveness to leptin [70, 71]. In summary, leptin, the protein product

of the *ob* gene, is detectable in serum; its concentration is correlated with the percentage of body fat and is elevated in obese humans [63]. These results suggest that obesity in humans is more likely to be due to central mechanisms regulating food intake and EE than to defective signaling by adipocytes to these central mechanisms [63].

Leptin may thus be considered a hormone of adipocytes, but beyond the relation with BMI, little is known about the regulation of its secretions. In humans [63] and in animals [68–71], caloric restriction reduces serum leptin concentrations and *ob* mRNA levels in adipose tissue, and refeeding increases these levels. The effects of fasting can be mimicked by norepinephrine and the effect of feeding by either insulin and glucocorticoids [72–74].

The decrease in *ob* gene expression in hungry animals that have been fasting and its increase by insulin and glucocorticoids (the concentration of which, like that of insulin, increases after meals) are compatible with the concept that leptin could be a satiety factor [62]. A loop system may be envisioned in which food intake could trigger insulin and glucocorticoid output, thereby favoring fat accumulation and then secretion of leptin, subsequently causing satiation [62]. If leptin is a satiety hormone and food intake is controlled by the hypothalamus, one may ask how leptin is linked to food intake [62]. One line may be through the appetite-stimulating hypothalamic peptide neuropeptide Y [62]. High hypothalamic concentrations of neuropeptide Y elicit food intake, whereas low concentrations have the opposite effect [67]. In most animal models of obesity, hypothalamic concentrations of neuropeptide Y are high, and intracerebroventricular infusions of neuropeptide Y cause obesity in normal rats [67]. The main metabolic change induced by neuropeptide Y is increased secretion of insulin and glucocorticoid, which in turn leads to fat accretion, obesity, and insulin resistance in muscle – a step leading to non-insulin-dependent diabetes mellitus. Intracerebroventricular infusions of neuropeptide Y also cause an increase in adipose-tissue leptin mRNA level. Thus, high neuropeptide Y concentrations in the brain cause most features of obesity syndromes [67]. Therefore, with regard to obese humans [63], and by the studies of several animal models [68–71], one fundamental mechanism of obesity is insensitivity to the action of leptin, presumably in the hypothalamus. Whether the insensitivity to leptin is due to mutations of the gene for leptin receptors in the brain, post-receptor abnormalities in leptin signal transduction, or other abnormalities in hypothalamic function is unknown. Other factors contributing to the dysfunction of this system and therefore to obesity may include neuropeptide Y-induced hyperphagia, deficiency of production or action of anorexigenic hypothalamic neuropeptides, and increased secretion of insulin and glucocorticoid [72–74]. Because these latter two hormones stimulate leptin output, leptin, provided it is func-

tional and its receptors are unaltered, represents an afferent pathway allowing for decreasing neuropeptide Y-ergic activity and decreased food intake [62]. Normal body-fat mass may thus be maintained by means of a central-peripheral loop system which is dysregulated in obese humans.

Conclusions

Obesity occurs as a result of a complex interaction between genetic and environmental factors. Obesity arises from a failure in the regulation of energy balance leading to a mismatch between energy intake and EE, such that intake exceeds expenditure. The mechanism of this dysregulation is unknown, and it is not clear whether obesity develops because of an excess in energy intake relative to expenditure, a reduced EE relative to intake, or a combination of both. The discovery of leptin represents a remarkable breakthrough in the understanding of the pathophysiology of obesity. For scientists who have proposed that obesity is the result of a dysregulation system linking the brain, food ingestion, and adipose-tissue mass, the system has acquired a long-awaited missing link with the discovery of leptin. However, no case of obesity has been explained on the basis of known gene products. Human obesity most likely is polygenic, requiring more than 50 genes which influence behavior and metabolism. The prevalence of obesity in children [1] and adults [75] has increased dramatically during the last three decades. This increase in prevalence cannot be explained by genetic changes but rather by a gene expression of the environmental influence. The future of obesity research is an exciting new frontier. Many anticipated discoveries are just beyond the horizon.

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Author Index

Babineau, T.J. 22
Blackburn, G.L. 22
Branski, D. 50

Daum, F. 210
Deckelbaum, R.J. 40
Dimand, R. 154
Dinari, G. 210
Durie, P.R. 182

Figueroa-Colon, R. 240
Freier, S. 50
Friel, C.M. 22

Heyman, M.B. 136

Ish-Shalom, S. 110

Jeejeebhoy, K.N. 12, 227

Kallas, H.J. 154
Kaluski, D.N. 40
Kaluski, E. 40
Kuchan, M. 80

Lebenthal, E. 64
Lerner, A. 110

Madar, Z. 95
Masor, M. 80

Pencharz, P.B. 182

Reif, S. 64
Reifen, R. 122
Rozen, G.S. 110

Simpser, E. 210
So, A.L. 136
Stark, A.H. 95
Suskind, R.M. 1

Thompson, A. 12

Udall, J.N., Jr. 1

Walker-Smith, J.A. 50
Wasantwisut, E. 122
Wilschanski, M. 182
Winship, T. 80

Subject Index

Acquired immunodeficiency syndrome
  malnutrition association 145–147
  nutritional support 147–150
  progression in children 145
Acute injury
  energy expenditure determination 158, 159, 162–164
  hypermetabolism and clinical consequences 155–158
  nutritional assessment in children
    anthropometry 160
    biochemical markers 160, 161
    clinical signs 161
    dietary evaluation 161
  nutritional support in pediatric intensive care unit
    assisted enteral nutrition
      advantages over parenteral nutrition 165, 166
      approach to management 167
      candidates 166, 167
      delivery methods 167, 168
      feeding composition 168–170
    caloric requirement determination 161–164
    total parenteral nutrition
      amino acids 175, 176
      candidates 164, 165, 170
      carbohydrates 170, 171
      fat emulsions 171–175
      metabolic complications 177, 178
      vascular access 176, 177
  phases of physiologic response 155
  substrate utilization determination 158, 159
Amino acids, *see* specific amino acids
Arginine
  ammonia detoxification 26
  hormone secretagogue 26, 27
  immune system stimulation 27, 28, 138
  inflammatory bowel disease treatment 223
  supplementation in sepsis 28
  wound healing role 27
Atherosclerosis, *see* Coronary heart disease

Biosphere study, caloric restriction effects on cardiovascular parameters 9, 10
Bone remodeling
  basic multicellular units 111
  growth factor regulation 111
  hormonal regulation
    calcitonin 112
    glucocorticoids 112
    growth hormone 112
    insulin 112
    parathyroid hormone 111, 112
    sex steroids 112, 114
    thyroid hormone 112
    vitamin D 112
Branched-chain amino acids
  hepatic encephalopathy treatment 29–31
  total parenteral nutrition 29, 30, 175, 176

Bronchopulmonary dysplasia, vitamin A therapy 128

Calcitonin, bone remodeling role 112
Calcium
  dietary requirements for optimal skeletal growth 115
  food sources 115, 116
  peak bone mass and intake 113–115
Caloric restriction, effects on longevity and disease 8–10
Carbohydrates, *see also* Fiber
  classification
    cellulose 66
    disaccharides 65
    glucose polymers 66
    monosaccharides 65
    polysaccharides 66
  content in infant nutrition 67, 68
  digestion and absorption
    disaccharides 69, 70
    monosaccharides 69
    ontogeny 70–72
    overview 68
    starch 70
  energy source in infancy 64
  malabsorption
    clinical implications 72
    fructose intolerance 69, 73, 74
    glucoamylase deficiency 70, 77
    glucose-galactose malabsorption 73
    lactose intolerance 69, 74, 75
    mechanism 72
    sorbitol intolerance 74
    sucrase isomaltase deficiency 69, 75, 76
    trehalose intolerance 69, 70, 77
  starch sources
    modified food starches 68
    oats 67
    rice 66
    wheat 66, 67
  total parenteral nutrition in pediatric intensive care unit 170, 171
Cholesterol, *see also* Coronary heart disease, Hyperlipidemia
  hypercholesterolemia management in children 45–47
  lipoprotein carriers 41
  screening 42, 43
Colon
  carbohydrate salvage 228
  fiber
    fate 96, 97
    morphology, effects of diet
      length 97, 98
      smooth muscle thickness 98, 99
      ultrastructure 97
  total parenteral nutrition effects 230, 231
Common variable immunodeficiency 139, 141
Coronary heart disease, *see also* Cholesterol, Hyperlipidemia
  development in childhood 42
  lipoprotein levels 40–42
  population approach in prevention 44, 45
  prevalence 40
Crohn's disease
  assessment of nutritional status 214, 215
  malnutrition and growth failure 210, 211, 216, 217
  metabolic changes 211–213
  nutritional therapy
    amino acids 223
    general recommendations 215, 216
    malnutrition and growth failure 216, 217
    mechanisms of action 221, 222
    polyunsaturated fatty acids 223
    primary therapy 217, 218, 220, 221
    relapse rate 222
    short-chain fatty acids 222, 223
  team approach to care and logistics 223–225
  vitamin and trace element deficiencies 213, 222
Cystic fibrosis
  energy imbalance, pathogenesis
    energy expenditure and metabolism 192–196
    energy intake 191, 192
    energy losses 189–191
    model 196, 197
  growth retardation 188
  incidence 182

intestinal manifestations 182
ion flux across epithelial cells 182, 183
nutrient deficiencies
essential fatty acids 198
trace metals 198
vitamins 197
nutritional support
age-related guidelines 201–203
clinical evaluation 199, 200
history 187–189
laboratory evaluation 200, 201
long-term studies 204, 205
short-term studies 203, 204
transmembrane conductance regulator
gene 183
mutations
clinical manifestations 183–185
mechanisms of dysfunction 186, 187

Dietary fiber, *see* Fiber

Energy, recommended dietary allowances 3, 4
Energy expenditure
adolescence 244, 245
childhood 244
cystic fibrosis 192–196
determination in acute injury 158, 159, 162–164
infancy 243, 244
television effects 245, 246
Enteral nutrition, assisted
advantages over parenteral nutrition 165, 166
approach to management 167
candidates 166, 167
delivery methods 167, 168
feeding composition 168–170

Fat emulsions, total parenteral nutrition in pediatric intensive care unit 171–175
ω-3 Fatty acids
inflammation protection 34
inflammatory bowel disease treatment 223
membrane composition 33
metabolites 33
nutritional supplementation in disease 34, 35
total parenteral nutrition in pediatric intensive care unit 174
ω-6 Fatty acids
inflammation role 33–35
long-chained triglycerides 32
metabolites 33
Fiber
classification 95
components 95
dietary recommendations for children 6, 99, 103, 105, 106
fate in intestines
colon 96, 97
small intestine 96
high-fiber diets, safety for children
micronutrient availability effects 102, 104, 105
mineral absorption impairment 104
vitamin absorption impairment 105
intestine morphology, effects of diet
length 97, 98
smooth muscle thickness 98, 99
ultrastructure 97
laxation, effects of dietary fiber 100, 101
obesity, dietary prevention and treatment in children 101, 102
physical properties 95, 96
Food allergy, *see* Food protein hypersensitivity
Food guide pyramid 7, 8
Food protein hypersensitivity
antigenic proteins 51, 52
clinical features 55, 56
definition 51, 61
diagnosis and differential diagnosis 56–58
epidemiology 51
follow-up 60
genetics 52
humoral immune response 54
milk allergy 51, 52, 58–60
nucleotide supplementation of formula, effects on tolerance 90
pathogenesis 52, 53
prognosis 60, 61
secondary disease 52

Food protein hypersensitivity (continued)
tolerance 54, 55
treatment 50, 58–61
trends in morbidity 50, 61
uptake of antigens 53
Fructose intolerance 69, 73, 74

Gastric emptying, rate 227, 229
Glucoamylase deficiency 70, 77
Glucocorticoids, bone remodeling role 112
Glutamine
concentration in blood 23
inflammatory bowel disease treatment 223
role in gastrointestinal tract 23–25
supplementation in disease 24–26
total parenteral nutrition 23–26, 176
Glycine, prevention of reperfusion injury 31
Growth hormone, bone remodeling role 112

Hepatic encephalopathy, branched-chain amino acid treatment 29–31
Human immunodeficiency virus, *see also* Acquired immunodeficiency syndrome
malnutrition in infection 145, 146
T cell destruction 145
Hypercholesterolemia, *see* Cholesterol
Hyperlipidemia, *see also* Cholesterol, Coronary heart disease
coronary heart disease association 40, 41
population approach in prevention 44, 45
screening in children 42–44
secondary disease in children 41, 42

Immunodeficiency, *see also* Acquired immunodeficiency syndrome
malnutrition association
interrelationship and vicious cycle 139
micronutrient deficiency 137, 138
protein-energy malnutrition 136, 137
nutritional support 143, 144, 148–151
primary disorders
common variable immunodeficiency 139, 141
gastrointestinal symptoms 139, 141, 142
severe combined immunodeficiency 139, 141
table 140
secondary disorders
corticosteroid side effects 144, 145
human immunodeficiency virus infection and acquired immunodeficiency syndrome 145–150
immunosuppressive drugs 142–144
Inflammatory bowel disease
assessment of nutritional status 214, 215
malnutrition and growth failure 210, 211, 216, 217
metabolic changes 211–213
nutritional therapy
amino acids 223
general recommendations 215, 216
malnutrition and growth failure 216, 217
mechanisms of action 221, 222
polyunsaturated fatty acids 223
primary therapy 217, 218, 220, 221
relapse rate 222
short-chain fatty acids 222, 223
team approach to care and logistics 223–225
vitamin and trace element deficiencies 213
Injury, *see* Acute injury
Insulin, bone remodeling role 112
Intestines, *see* Colon, Inflammatory bowel disease, Small intestine
Isoleucine, *see* Branched-chain amino acids

Lactose intolerance 69, 74, 75
Leptin
gene 247
regulation 249, 250
serum concentration in obesity 248, 249
Leucine, *see* Branched-chain amino acids

Magnesium, deficiency and osteoporosis 117
Medium-chained triglycerides
enteral nutrition in pediatric intensive care unit 169, 170

metabolism 35, 36
nutritional supplementation in disease 35, 36
Milk allergy, *see* Food protein hypersensitivity
Minerals, recommended dietary allowances 5, 6
Multisystem organ failure, glutamine deficiency role 24, 25
Muscle, *see* Skeletal muscle

Nautral killer cell, nucleotide nutrition effects in neonates 87, 89
Neuropeptide Y, control of appetite 249, 250
Nuclear magnetic resonance, evaluation of skeletal muscle energetics 16–18
Nucleotides
breast milk composition and bioavailability 82–84
immune system effects in neonates
cell-mediated immunity 84, 87–91
humoral immunity 84–87
mechanisms 91, 92, 138
infant formula supplementation
effects
diarrhea incidence 89, 91, 92
food allergy 90
upper respiratory tract infection incidence 89, 90
history 81
nutritional supplementation in disease 32
overview of functions 80, 81

Obesity, childhood
classification and health concerns 242, 243
demographics 241
emergence 240, 241
energy and macronutrient intake 246, 247
energy expenditure
adolescence 244, 245
childhood 244
infancy 243, 244
television effects 245, 246
familial aggregation 241, 242
fiber, dietary prevention and treatment in children 101, 102
leptin
gene 247
regulation of gene 249, 250
serum concentration in obesity 248, 249
prevalence 240
Osteoporosis, *see also* Bone remodeling, Peak bone mass
age of onset 110
idiopathic juvenile osteoporosis 118, 119
risk factors
drug therapy 117
inactivity 117
malabsorption diseases 117, 118
smoking 117

Parathyroid hormone, bone remodeling role 111, 112
Parenteral nutrition, *see* Total parenteral nutrition
Peak bone mass
dietary influences
calcium 113–117
caloric intake 116
magnesium intake 117
heredity 113
Pediatric intensive care unit, *see* Acute injury
Protein, *see also* specific amino acids
metabolism in illness 22
recommended dietary allowances 2–4
Protein-energy malnutrition
immunodeficiency association 136, 137
prevalence in hospitalized children 154

Recommended dietary allowances
energy 3, 4
evidence for basis 1, 2
limitations 1, 5, 6
minerals 5, 6
protein 2–4
trace elements 2, 3
vitamins 4, 5

Retinol-binding protein, vitamin A metabolism 124, 128

Severe combined immunodeficiency 139, 141
Sex steroids, bone remodeling role 112, 114
SGLT1, monosaccharide transport and malabsorption defects 69, 73
Short bowel syndrome
  complications 232
  effects
    absorption
      fluids and electrolytes 229
      nutrients 229
    gastrointestinal motility 229
  nutritional therapy
    general approaches 233
    initial treatment 233–235
    parenteral nutrition 234, 235
    treatment by resection length 235, 236
  somatostatin therapy 235
  total parenteral nutrition effects on intestine 230, 231
Skeletal muscle
  energetics 13, 14
  hand grip strength, measurement of function 12
  malnutrition effects
    energetics 16–18
    function 13, 18, 19
  oxidative phosphorylation and malnutrition 15, 16
  phosphorous-31 nuclear magnetic resonance, evaluation of energetics 16–18
Small intestine
  fiber
    fate 96
    morphology, effects of diet
      length 97, 98
      smooth muscle thickness 98, 99
      ultrastructure 97
  ileum function 228
  motility 227
  total parenteral nutrition effects 230, 231
  water absorption 228
Sorbitol intolerance 74
Sucrase isomaltase deficiency 69, 75, 76

T cell(s), nucleotide nutrition effects in neonates 84, 87–91
Television, energy expenditure effects 245, 246
Thyroid hormone, bone remodeling role 112
Tolerance, *see* Food protein hypersensitivity
Total parenteral nutrition
  amino acids 23–26, 29, 30, 175, 176
  candidates 164, 165, 170
  carbohydrates 170, 171
  effects on intestine 230, 231
  fat emulsions 171–175
  metabolic complications 177, 178
  vascular access 176, 177
Trace elements
  deficiencies
    cystic fibrosis 198
    inflammatory bowel disease 213
  high-fiber diets, absorption impairment 105
  recommended dietary allowances 2, 3
Trehalose intolerance 69, 70, 77

Ulcerative colitis
  assessment of nutritional status 214, 215
  malnutrition and growth failure 210, 211, 216, 217
  metabolic changes 211
  nutritional therapy
    amino acids 223
    general recommendations 215, 216
    malnutrition and growth failure 216, 217
      mechanisms of action 221, 222
    polyunsaturated fatty acids 223
    primary therapy 218, 220, 221
    relapse rate 222
    short-chain fatty acids 222, 223

team approach to care and logistics 223–225
vitamin and trace element deficiencies 213

Valine, *see* Branched-chain amino acids
Vitamins, *see also* Vitamin A, Vitamin D
deficiencies
cystic fibrosis 197
inflammatory bowel disease 213
high-fiber diets, absorption impairment 105
recommended dietary allowances 4, 5
Vitamin A
assessment of status
body reserves 129, 130
breast milk 130
ecological indicators 131
functional indicators 131
impression cytology 131
serum 130
breast milk availability 125, 130
components 122
dietary requirements 125
food sources 123
functions
cell differentiation 126, 127
immune function 127
overview 122
reproduction 127
vision 122, 126
interaction with other nutrients 127, 128
metabolism 123–125
therapy
bronchopulmonary dysplasia 128
cancer 129
infectious disease 128, 129
toxicity 126
xerophthalmia in deficiency
clinical manifestations 129
intervention 132, 133
prevalence 131, 132
risk factors 132
Vitamin D, bone remodeling role 112

World Health Organization, nutritional goals 8

Xerophthalmia, *see* Vitamin A