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THIRD EDITION

Nutrition in Pediatrics

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Basic Science and Clinical Applications

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DEDICATIONS

To the memory of Myriam Puig, MD, PhD, a contributor to the second and third editions of this textbook. Dr. Puig succumbed to cancer in September 2002. Her professional life was dedicated to the nutritional health of underprivileged Venezuelan children and her publications to the benefit of nutrition for children everywhere.

— W. Allan Walker

To my colleagues, students, residents, and fellows, who continue to provide me with the stimulation and inspiration to learn and ask new questions, and to my daughters, Sarah Watkins and Leah Watkins Beane, and my wife, Mary Watkins, for their continued love and support.

— John B. Watkins

To Catherine and John Duggan, who nourished me from the beginning and inspired a career in medicine; to Michael, Brendan, and Emily Duggan, and the rest of the world's children, for their optimal nutrition; and to Deborah Molrine, for constant love and support.

— Christopher Duggan

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CONTENTS

PREFACE

Because the field of nutrition is actively evolving and creating major new principles in the care of the pediatric patient, we have embarked on the third edition of this textbook. The editors continue to support the premise that a comprehensive text as a reference source in pediatric nutrition is essential for the proper care of infants and children. As medical care in the twenty-first century is predicated on prevention of disease, the discipline of pediatric nutrition becomes that much more important. For example, we now know from the Barker hypothesis that intrauterine nutrition and weight gain during the first year of life are important predictors of chronic diseases of adulthood (cardiovascular disease, diabetes, and hypertension). In addition, as we attempt to cope with the worldwide epidemic of obesity and its concomitant "syndrome X," we recognize that a healthful diet and attention to weight gain must begin in early childhood before "bad" eating habits are established. Furthermore, as parents seek a more healthful lifestyle for themselves and their children, they are assessing conventional approaches to treatment of disease and are seeking alternative forms of treatment and prevention. An example of this alternative approach is the use of probiotics to treat diarrhea, prevent daycare infections, and cope with the "hygiene hypothesis" for the development of atopic disease. Therefore, an updated access to clinical research-based information on the appropriate use of nutrition as an alternative form of therapy is essential for the practicing physician.

As with the first edition, we commissioned a comprehensive review of the second edition of this textbook to ensure the most updated and extensive coverage of nutrition. This review led to the addition of several chapters to each major section of the book. In the "General Concepts" section, the macronutrient requirement for growth chapter has been expanded to three chapters separately dealing with fat, carbohydrate, and protein. We have added new chapters on nutritional epidemiology, food safety, and international nutrition. In a newly added section entitled "Physiology and Pathophysiology," we have considered the role of nutrition in major body functions and dysfunctions including gene expression, immunophysiology, brain development, obesity, and behavior. The "Perinatal Nutrition" section, added to the second edition, has been expanded further to include chapters on maternal nutrition and pregnancy outcome and fetal nutrition and imprinting. The section on specific disease states has been expanded to include "The Adolescent Athlete and Dietary Supplements," "Nutrition and the Prevention of Cancer in Childhood," and "Evaluation and Management of Obesity." In keeping with the changing approach of care to pediatric patients, chapters have been added in dietary supplements (nutraceuticals) and special diets in the "Nutrition Support" section. Finally, the Appendix has been expanded to provide a more comprehensive resource for nutritional assessment and requirements and updated information on enteral products. As in previous editions, authors have been newly selected or retained based on their expertise in the topic of their chapter and their willingness to provide the most updated views on the subject.

In general, we believe that the third edition will provide a comprehensive resource for the health care provider for children entering the twenty-first century.

For this edition, Dr. Christopher Duggan has been added as an editor. His comprehensive knowledge of clinical care for the hospitalized patient, experience in nutritional issues in developing countries, and extensive experience in clinical nutrition research have been welcomed by the editors.

The editors wish to again thank Ms. Suzzette McCarron for her organizational talents and her ability to liaison between authors, editors, and the publisher. Without her extensive efforts this textbook would never have been possible. We also thank Ms. Carlotta Hayes for her many contributions

The editors are also grateful to Mr. Brian Decker, Ms. Jamie White, and the able staff of BC Decker Inc for their help and support in further developing this edition and in the publication of this textbook.

W. Allan Walker
John B. Watkins
Christopher Duggan

PREFACE TO FIRST EDITION

The importance of nutrition in pediatrics has become more apparent in recent years as a result of significant observations that have helped both to define the specific needs of young infants to attain optimal growth and development and to prevent the expression of nutritionally related diseases at a later age. Of particular importance to industrialized societies is the awareness of subtle malnutrition present in pediatric patients in general as well as in underprivileged children of large cities and the hospitalized pediatric patient population. We now know that specific nutrient deficiency (e.g., zinc essential fatty acids) can occur in virtually any pediatric patient as well as in unique patient populations such as premature infants, food faddists, or families obsessed with weight reduction. Thus, the increased awareness of nutrition as an important component of the practice of pediatrics has prompted the creation of this book.

The purpose of this text is to offer a comprehensive review of general concepts of nutrition as they pertain to pediatrics as well as relevant information on the nutritional management of specific disease states. Accordingly, the text is divided into four major sections. In the first, general concepts of nutrition, such as nutrient requirements, nutritional assessment, and prevention of disease, are presented. In the second section, a systemic approach to the pathophysiology of nutrition as it pertains to other disciplines—immunology, endocrinology, pharmacology, and gastroenterology—is developed. The third and largest section comprehensively covers specific disease states and is directed at the nutritional management of these conditions, which include diabetes, cystic fibrosis, and anemias. A special effort has been made to provide updated information on the unique nutritional needs of patients with these diseases. These chapters are augmented by appropriate appendix material describing special diets and requirements of patients. In the final section, which presents an approach to nutritional support of pediatric patients, a major effort is directed at updating the reader on the more recent information about breast-feeding. Following a practical discussion concerning problems of nursing mothers, this section addresses enteric and parenteral support of pediatric patients with special needs for nutritional support. In short, this book serves as a comprehensive reference text for the practicing pediatrician, pediatric trainee, and subspecialist requiring nutritional information.

We want to thank our many authors selected to write chapters on subjects for which they have special expertise. By developing a specific format for the textbook and then selecting the most appropriate authors in their fields to develop the topics, we have provided the most comprehensive and updated text on pediatric nutrition presently available.

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CHAPTER 1

PEDIATRIC NUTRITION: A DISTINCT SUBSPECIALTY

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Scientific interest in nutrition has a long history.[1,2] Balance studies were conceived by Sanctorius in the 1620s. Lavoisier researched the oxidation of foods and Magendie discovered that protein was necessary for survival two centuries ago. In 1838, Franz Simon produced his classic dissertation, in Latin, on human milk biochemistry, which for the first time underpinned a rational basis for infant nutrition. It was over 100 years ago, in the late nineteenth century, that Rubner defined the energy content of foods and constructed the first calorimeter for measuring energy expenditure. By the early twentieth century, we already had a broad understanding of nutrient needs and an increasing understanding of micronutrients and of the effects of specific deficiencies (Funk coined the term "vitamines" in 1912). Sophisticated metabolic research on animals fed by continuous intravenous infusion flourished in the first three decades of the last century, and as early as 1944, we saw the first case of a child, age 5 months, fed successfully via the intravenous route.

In parallel with this long-term development of nutritional science has been an equally long-term appreciation of the clinical and public health importance of infant and child nutrition. In the earliest part of the last century, and well before, nutrition was a prominent and vital part of caring for infants. Unquestionably, in the eyes of early clinicians, how and what the infant was fed during health and illness were primary determinants of survival. The infant mortality rate in the United States in 1900 was 165 per 1,000.[1] The unacceptably high rate and the variability from one area of the country to the other related primarily to mode of feeding in infancy.

At that time, pediatrics, both as an academic specialty and in everyday practice, was in its own infancy. At the turn of the nineteenth century, there were probably fewer than a dozen practitioners in the United States who were exclusively devoted to pediatrics.[2] In the first presidential address to the American Pediatric Society in 1889, Abraham Jacobi discussed the rationale for having the specialty of pediatrics distinct from internal medicine: "Pediatrics deals with the entire organism at the very period during which it presents the most interesting features to the student of biology and medicine...there is scarcely a tissue or an organ which behaves exactly alike at different periods of life."[2]

A review of the topics covered in the annual presidential addresses to the American Pediatric Society during its first 35 years shows a frequent return to nutrition and nutrition-related subjects. In 1924, David M. Cowie suggested that feeding in infancy was then sufficiently based on sound physiologic principles and that pediatrics needed to focus more on nutrition and metabolism, among other things, of the older child.[2] By 1940, when the eleventh edition of *Holt's Diseases of Infancy and Childhood* was published, the editors unhesitatingly stated, "Nutrition in its broadest sense is the most important branch of pediatrics. A knowledge of its fundamental principles is essential to the physician if he is to apply preventive and corrective measures intelligently."[3]

WHY HAS PEDIATRIC NUTRITION NOT EMERGED AS A DISTINCT SUBSPECIALTY?

Given that nutrition is the oldest branch of pediatrics based on centuries of major research, it seems paradoxical that it has never emerged as a formal, distinct academic discipline. Indeed, considering its roots in and fundamental relationships to that which makes pediatrics unique—growth and maturation—why has nutrition taken a back seat to other subspecialties? The decline in the importance of nutrition in pediatrics can be explained in two ways.

First, the urgency that fostered nutrition research and the illnesses that made nutrition a prominent part of pediatric practice decreased progressively during the last century. The causes of infantile scurvy and rickets and other deficiency diseases were delineated during the early decades of the twentieth century. In fact, with the exception of iron deficiency, primary nutritional deficiencies are now virtually unknown in the United States and other developed countries, and infant mortality rates relate more to the general level of socioeconomic development than to nutritional practices. With the advent of refrigeration and appropriate milk processing technology, survival of artificially fed infants in clean environments is now routine.

Second, pediatrics has followed the path taken by internal medicine and surgery; the past 40 years have seen the growth of "organ-based" subspecialties: pediatric cardiology, neurology, nephrology, and so on, and, more recently, gastroenterology. The result of this evolutionary course was to imbed clinical nutrition in a variety of "focused" subspecialty areas. This arguably fostered a disease-specific orientation to nutrition and fragmentation of nutrition practice and research. Thus, enteral feeding has come under the wing of gastroenterologists, parenteral nutrition has interested gastroenterologists and pediatric surgeons as well, aspects of growth have fallen into the domain of endocrinology, neonatal nutrition has been taken on by neonatologists, eating disorders by psychologists and psychiatrists, food allergy by allergists and physicians in respiratory medicine, and so forth. This fragmentation and multiple ownership of pediatric nutrition have hindered development of the field as a distinct entity.

WHY IS PEDIATRIC NUTRITION RE-EMERGING IN IMPORTANCE?

In the past, the major focus in the field of nutrition has been one of meeting nutrient needs and the prevention of nutrient deficiencies. There has now been a fundamental sea change in orientation in this field. The major current interest in nutrition is its impact on health.[4] Our new understanding of the potential biologic impacts of nutrition on health has led us to frame two key new questions: Does nutrition matter in terms of patients' responses to their disease? Does it matter for long-term health and development?

With regard to the first, increasing evidence now indicates that good nutritional care may improve the clinical course of disease, reduce hospital stay, reduce the need for more expensive treatments, and, indeed, result in major reduction in health care costs. Such benefits of nutritional care are emerging over a broad range of pediatric domains such as gastroenterology (eg, Crohn's disease, short-bowel syndrome), surgery, renal medicine, care of disabled children (eg, cerebral palsy), infectious disease (eg, human immunodeficiency virus [HIV]), and oncology. Neonatology provides good examples of the effects of good nutrition on clinical course: nutritional practices may have a major influence on the incidence of life-threatening diseases (necrotizing enterocolitis and systemic sepsis),[5] may influence the need for expensive and potentially hazardous parenteral nutrition, and may significantly impact length of hospital stay.

However, the factor that has most influenced the reemergence of interest in pediatric nutrition is the increasing evidence for its effects on long-term health and development. The idea that early nutrition could have long-term consequences is part of a broader concept concerning the impact of early life events in general. To focus attention in this area, Lucas proposed using the term "programming,"[6] the idea that a stimulus or insult applied during a critical or sensitive period of development could have a long-lasting or lifetime impact on the structure or function of the organism. The first description of programming during a sensitive or critical period of development was by Spalding, who in 1873 defined the critical period for imprinting in newborn chicks.[7] Since then, developmentalists have described numerous examples of short-lived stimuli—both endogenous and exogenous—that have had lifetime effects.

What is the evidence that nutrition may behave in this programming way? Since the first studies by McCance in the 1960s, the evidence for such programming in animals is overwhelming. Brief periods of experimental nutritional manipulation in early life influence in adult life many outcomes of potential relevance to humans,[8] including blood pressure, insulin resistance, blood lipids, vascular disease, body fatness, bone health, gut function, endocrine status, learning, behavior, and longevity.[8–11] Nutritional programming effects have been seen in all species studied, including nonhuman primates.[9,10]

In the past 20 years, increasing evidence has shown that humans, like other species, may be highly sensitive to early nutrition in terms of later health outcomes. Deficiencies of single nutrients at critical periods can have long-lasting effects. Animal studies have documented the role of zinc deficiency in the development of neural tube defects in the fetus. Decreased folic acid intake in the periconceptional period also has been linked to neural tube defects in the human.[12]

Iron is another trace element that appears to play a critical role in development. Iron deficiency in rats, for example, produces reversed sleep cycles, altered pain threshold, and difficulty in learning. Dopamine D_2 receptors also are decreased. When the iron-deficient diet is begun at 10 days of age, later iron repletion is unable to reverse these defects completely.[13] In the human, the mechanisms of the detrimental effects of severe iron deficiency in early childhood on subsequent mental development are yet to be elucidated, but several studies suggest that such effects may be permanent.[14,15] On a molecular level, it is possible that iron is required at a critical time for the expression of one or several genes, and if this opportunity is lost, iron sufficiency is unable to reverse the path of development.

Many observational studies have linked growth, size, or nutrition in early life to the types of health outcome influenced by early nutrition in animals. Such observational data might be confounded, but, in more recent years, there has been long-term investment in randomized intervention studies. These trials have now shown that early diet during

the first weeks or months may influence, thus far up to 20 years later, such outcomes as blood pressure, blood lipids, insulin resistance, tendency to obesity, bone health, and cognitive performance.[8,16–18]

The effects of brief early nutritional interventions are often surprisingly large. Studies in the preterm infant show that feeding a standard versus preterm formula for just 1 month may result in a 12-point deficit in verbal IQ (in males) and a more than doubling of motor or cognitive impairment (both sexes) 7 to 8 years later.[15] In the same population, random assignment to banked donated breast milk rather than infant formula resulted in a reduction in diastolic blood pressure 13 to 16 years later of a magnitude greater than that induced by nonpharmacologic interventions used to manage hypertension in adult life (weight loss, exercise, salt restriction).[17]

These new data have major biologic and public health implications. They show that nutrition cannot simply be seen in terms of meeting nutritional needs. Rather, nutrition emerges as a major environmental influence on the genome, influencing lifetime health. It is also apparent that there is now a new onus on health professionals to ensure proper nutrition to optimize the short- and long-term health of sick individuals and healthy populations.

RATIONALE FOR A SEPARATE DISCIPLINE

Viewed in the historical context of a changing subspecialty paradigm and a new appreciation of nutrition's role at the molecular level with profound implications for health, the time would seem right for nutrition to be recognized as a distinct area of pediatric practice. But what other criteria should be fulfilled for nutrition to be formally developed as a pediatric subspecialty? Two questions must be addressed: Is there a defined area of pediatric care that requires specific nutritional expertise and are there readily identifiable deficiencies in current pediatric nutritional patient teaching and research that would benefit from such a development?

Defined Area of Expertise

There is a defined area of pediatric care that requires nutritional expertise. Nutritional advice is probably the most common category of advice sought by parents. Nutritional management problems are possibly the most common problems in pediatric hospital practice; virtually every sick premature infant and a high proportion of sick older children could benefit from specific and expert nutritional attention. Walk on any general ward and the number of patients needing advice from a pediatric cardiologist, nephrologist, or gastroenterologist will be far exceeded by those who would benefit from sound nutritional care.

However, beyond the routine practice of what we know, there are potentially important areas of new expertise that need to be sewn into nutrition practice. Just as a field such as cardiology owes its specialty status in part to the development of specialized techniques—catheterization, diagnostic imaging, etc—so could pediatric nutrition be underpinned by new tools awaiting exploitation in a clinical setting.[6] Isotope probes are available for exploring metabolic process and energy expenditure. Body composition devices (dual x-ray absorptiometry, impedance, isotope dilution, air displacement plethysmography, three-dimensional photonic scanning, ultrasonography, magnetic resonance imaging, etc) are ready to be pioneered in the complex management of sick infants and children. They also are likely to prove useful in the assessment of the impact of public health policy on the nutritional status of the childhood population (for instance, the value of interventions to reduce obesity, which are currently monitored by inappropriately nonspecific and crude methods). New tools are also available to measure and plot growth that will make the diagnosis and management of growth disorders, failure to thrive, and overweight less arbitrary and more precise. Such techniques require trained specialists.

Deficiencies in Patient Care

Subspecialists trained in pediatric nutrition would improve patient care. Specialty advice in nutrition is often sought from physicians whose primary interest is in another area.[19] This results in fragmentation of care and creates a lack of uniformity in how conditions are managed. A "standard of practice" does not exist. Nutrition knowledge has exploded to the point where clinicians in individual specialties no longer can be expected to have a comprehensive grasp even of all aspects relevant to their own practice. The fact that a high percentage of inpatients in any general or pediatric hospital continues to be found to be malnourished by "world-class" criteria suggests that care could be improved. With efforts to contain costs and the move to home care, patients are leaving hospital with more profound nutritional deficits than before, and the situation can be expected to become worse.

For many years in the United States, parenteral nutrition support in many hospitals was overseen by the surgical service, whereas enteral nutrition was handled by virtually any pediatrician. Even with the advent of nutrition support teams, most of the physicians involved have acquired their nutritional skills in an ad hoc fashion. If consultation about enteral nutrition is needed, the gastroenterologist, by default, has assumed responsibility and is likely to be called. To be sure, gastroenterology and nutrition are closely linked, and most pediatric gastroenterologists have considerable expertise in nutrition, especially as it affects their "organ system." But the pediatric gastroenterologist should not be expected to be well versed in all areas of nutrition because only a small part of nutrition science and practice is related directly to gastroenterology.

Deficiencies in Teaching

Teaching of nutrition in medical schools also is fragmented at best: "To almost everyone expressing an opinion about the teaching of nutrition in medical schools, it appears to be entirely unsatisfactory. Rare successes prove to be ephemeral and crucially dependent on individual commitment and outside funding."[20] In most medical schools, the basic science pertaining to nutrition is imbedded in biochemistry and, perhaps, physiology. Formal teaching of clinical nutrition is nearly nonexistent. What teaching there

is generally is done as part of primary care rotations or by subspecialists in other areas in pediatrics. Many medical students never observe breast-feeding and are never trained to make up a formula feed. Most house staff leave training with less than adequate understanding of the physiology and management of breast-feeding, the composition and appropriate use of standard or special infant formulas, or the appraisal of simple feeding problems and the rationale for nutrition advice or care during the second 6 months of life and beyond. Public health and preventive nutrition are equally neglected. McLaren has argued that were nutrition "given its rightful place" in the basic sciences, there would be no need for courses in nutrition or nutrition textbooks.[19] Clinical teaching would revolve around clinical dietetics. This would still leave nutrition primarily relating to and being practiced by organ-based specialties. Although this may be acceptable from the point of view of clinical practice, from the point of view of research, it will ultimately impede inquiry into the important areas.

Deficiencies in Research

The area that perhaps stands to gain most from the development of nutrition as a distinct discipline is research. Although basic laboratory and animal research in nutrition has been active, the key clinical research questions in pediatric nutrition are unlikely to be addressed as long as nutrition is divided among the traditional specialties. This is so because the orientation toward disease of most subspecialties will favor research to answer questions related to therapeutic dietetics (ie, treatment of disease). With infant survival from a nutritional point of view assured in most Western countries, the issue of how early nutrition should be optimized in terms of its effects on later health becomes of paramount importance.

The objective for clinical research in any field of health policy or clinical practice should be to prove outcome benefits for recommended approaches to management, generally by use of formal clinical trials that test the safety and efficacy of the intervention. This would be standard in established clinical areas. Thus, whether or not a clinician should treat high blood pressure, remove a malignancy rather than give chemotherapy, or repair a heart defect at birth rather than later in childhood and other decisions depend on proven clinical benefit for each management option. For example, physicians routinely treat high blood pressure precisely because lowering blood pressure has been shown to reduce morbidity and mortality from cardiovascular disease.

Research in childhood nutrition has been largely unsatisfactory in this respect. Research over the past 50 years has failed to address adequately whether adhering to the nutritional recommendations made by ad hoc groups and governmental bodies confers outcome benefits.[6] The critical issue of whether early nutrition, either in health or disease, influences long-term health or development has, until recently, barely been approached in formal studies. Thus, most recommendations of expert bodies on fundamental areas of practice are based largely on theoretic considerations derived from short-term physiologic experiments and epidemiologic studies rather than on outcome findings from intervention trials. Both physiology and epidemiology can be useful in identifying questions and framing hypotheses for such outcome trials, but neither can replace them.

The paucity of clinical outcome studies in pediatric nutrition contrasts sharply with the major research investment that has been made in pediatric nutritional physiology. Possibly more research effort has been applied here than in any other area of pediatrics. For instance, as far back as 1953, Macy and colleagues summarized the contents of 1,500 publications on the composition of breast milk—just one small area of infant nutrition.[21] The profusion of pediatric nutritional studies in the face of the paucity of outcome data justifying clinical practice suggests that clinical pediatric nutritional research has lacked direction. This lack of research direction, not seen to nearly the same extent in the recognized pediatric specialties, can be traced in part to the absence of guidance on research priorities from specialists trained in nutrition and from centers of excellence in pediatric nutrition.

CONCLUSION

Like the blind men approaching the elephant, each subspecialty comes up with a different view of nutrition. Each subspecialty creates a paradigm that determines how questions are framed and results are interpreted. Depending on one's primary interest, taurine may be thought of as a critical nutrient for neural development and function, a primary determinant of bile acid conjugation, or an osmoregulator of the brain during dehydration. Someone needs to see the elephant for what it is—to collate our knowledge in the field of nutrition, understand its significance for development, and apply it to clinical practice.

Functional specialties in medicine increasingly are interacting in a matrix fashion with organ-based specialties. Clinical nutrition fits comfortably into this new paradigm. The time appears to be right to foster clinical nutrition within pediatrics as a unique discipline. Such a development would address currently identifiable deficiencies in patient care, training, and, especially, research in clinical nutrition.

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CHAPTER 2

CLINICAL ASSESSMENT OF NUTRITIONAL STATUS

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Nutritional assessment is an integral part of patient care because nutritional status affects a patient's response to illness. Attention to nutritional status is especially important in pediatric patients because they are also undergoing the complex processes of growth and development, which are influenced by the genetic makeup of the individual and coexisting medical illness in addition to nutritional status. Thus, the assessment of nutritional and growth status is an essential part of clinical evaluation and care in the pediatric setting.

The assessment should allow for the early detection of both nutrient deficiencies and excesses. There is no single nutrition measurement that is best; therefore, a combination of different measures is required. Growth is an important indicator of health and nutritional status of a child, and a variety of growth charts are currently available to help with the assessment of growth. These include the 2000 Centers for Disease Control and Prevention (CDC) growth charts that represent the US population. Each growth measurement performed needs to be accurate and obtained at regular intervals. These longitudinal data will help identify at-risk patients (eg, those who are malnourished, obese, stunted; small-for-gestational-age infants; and those with refeeding syndrome) and will allow the monitoring of a patient's clinical response to nutritional therapy.

During infancy, childhood, and adolescence, many changes in growth and body composition occur. Therefore, clinicians must understand normal growth to recognize abnormal patterns. Clinicians also need to recognize the nutritional changes that occur with acute and chronic disease. With the epidemic of pediatric obesity, the proper identification of the overweight or obese patient is also important. A brief nutritional screening assessment may be used to identify patients in need of an in-depth assessment. A typical nutritional screening includes a brief medical and dietary history (including feeding ability), anthropometric measurements (eg, weight, stature), and possibly laboratory data. A full nutritional assessment includes more detailed medical and dietary histories (including a measure of dietary intake), a complete physical examination, further anthropometric and body composition measurements, sexual and skeletal maturation, laboratory data, and the estimation of nutritional requirements. A clinician's global assessment of the child based on these objective data and his/her clinical judgment is also important to consider in determining nutritional status.[1] Most often, health care professionals work as a team in gathering the information for the assessment of nutritional status of children.

MEDICAL HISTORY

Obtaining the medical history is central to the nutritional assessment. Past and present medical information, including the duration of the current illness, relevant symptoms, diagnostic tests and therapies (eg, chemotherapy, radiation), and medications, is documented. Because nutritional abnormalities are often associated with certain disease states, it is essential to identify underlying medical conditions and the concomitant medication history. Medications can cause nutritional deficiencies (eg, 6-mercaptopurine) and drug–nutrient interactions (eg, phenytoin and tube feedings; Table 2-1). Drug–nutrient interactions may occur between drugs (prescription and nonprescription) and foods, beverages, and dietary and vitamin/mineral supplements. Alterations in drug metabolism and absorption by food or pharmacologic interactions may be clinically significant.[2] Past medical history includes previous acute and chronic illness, hospitalizations, and operations. The history of past growth patterns (with previous growth charts, as possible), onset of puberty (for the child and other family members), and a developmental history (including feeding abilities) may also be included. Family history should include a medical history as well as the family's social and cultural background, especially as related to diet therapy and the use of alternative and complementary medicine. The review of systems includes oral motor function, dental development, and gastrointestinal symptoms such as vomiting, gastroesophageal reflux, diarrhea, and constipation.

TABLE 2-1 Examples of Some Common Drug–Nutrient Interactions

Drug	*Nutrient*
Amphotericin B	Hypokalemia, hypomagnesemia
Antacids	Vitamin D and iron deficiency, hypophosphatemia
Phenobarbital	Vitamin D deficiency
Cholestyramine	Vitamin A, D, E, and K malabsorption
Cyclosporin	Elevated triglycerides, hypokalemia, hypomagnesemia
H_2 blockers	Iron deficiency
Methotrexate	Folate deficiency
Phenytoin	Folate deficiency
Corticosteroids	Hyperglycemia, hypophosphatemia
Sucralfate	Hypophosphatemia
Sulfasalazine	Folate deficiency
Trimethoprim	Folate deficiency
Furosemide	Hypokalemia, hypomagnesemia, hypocalcemia

PHYSICAL EXAMINATION

Physical examination includes anthropometrics (see below), including weight, stature, head circumference, and arm measures. The frequency of measurements of well children (Table 2-2) follows the recommendations of the American Academy of Pediatrics.[3] The pattern of measurement for hospitalized patients depends on the age of the patient, illness, and degree of nutritional intervention (see Table 2-2). Nutritional assessments for patients with complex chronic disease states should be conducted every 1 to 2 months and less often in those with milder disease (every 6 to 12 months). The general physical examination includes an assessment of the patient's general condition and close examination of skin, hair, and teeth (see Table 2-3 and Appendix, Table A-12). This includes an assessment for pallor, clinical assessment of body fat stores, wasting of muscle mass, edema, skin rash, thinning of hair, and evidence of specific nutritional deficiencies. Examples of specific signs include the flag sign or the loss of hair color associated with a period of malnutrition followed by recovery with a return of normal hair color and texture to normal. Vitamin A deficiency causes follicular hyperkeratosis and night blindness. It is unusual to see classic signs of marasmus and kwashiorkor in developed countries. Examination of specific organ systems and obtaining medical record information is helpful in assessing the severity of the underlying disease process. It is also important to consider the clinician's clinical judgment in the assessment of nutritional status.[1] Documenting sexual development by Tanner staging is a routine part of the nutritional assessment of adolescents (see below). For a summary of signs and symptoms of specific nutritional abnormalities, see Table 2-3 (see also the Appendix, Table A-12).

DIETARY HISTORY

The dietary history is an essential component of the nutritional assessment. The dietary history provides information not only on the amount and quality of food consumed but also on the eating patterns and behaviors of the family. This part of the nutritional assessment also provides information on the number of meals, snacks, and beverages consumed; special foods eaten by the child and family; vitamin and mineral supplements ingested regularly; food allergies; intolerances; and unusual feeding behaviors. The child and family are asked about psychosocial factors that impact on food selection and intake, including family history, socioeconomic status, and use of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) and supplemental food programs, parent/caretaker's perception of the child's nutritional status, and religious and cultural considerations. Food-related factors may affect dietary intake and include food allergies, intolerances, self-imposed and prescribed diets, and feeding skills. These factors are also noted in the assessment.

Assessing the dietary intake of breast-fed infants is more difficult because the volume of milk consumed cannot be directly measured. An estimate is obtained by weighing the infant before and after feeds and using a conversion factor of 1 mL volume of breast milk consumed for each gram of weight gained. In formula-fed infants, the clinician should inquire about both the amount and type of formula consumed and the details of the method of preparation (concentrates, powders, modular additives).

The quantity and quality of dietary intake are assessed by prospective food records (with weighed or estimated food portions), retrospective 24-hour recalls (previous 24 hours or of a "typical" 24-hour period), or food frequency questionnaires.[4] The prospective food records are usually carried out for 3 to 7 days (including a combination of weekend and weekdays) and provide the most accurate assessment of actual intake. However, food records are used most often in the research setting because they are labor intensive and time consuming. As available, these records are analyzed and compared to the Dietary Reference Intakes (DRIs) (see below) using a computerized nutrient analysis program. A limitation of food records is that parents tend to overestimate intake and/or forget to record all foods eaten.[5] The retrospective 24-hour diet

TABLE 2-2 Suggested Schedule for Growth Assessments in Hospitalized and Healthy Children

Age	*Weight*	*Length or Height*	*Head Circumference*
Hospitalized child			
Preterm	Daily	Weekly	Weekly
Full term to 12 mo	3×/wk	Monthly	Monthly
1–2 yr	3×/wk	Monthly	Monthly
2–20 yr	2×/wk	Monthly	As indicated
Outpatient well-child visit			
0–2 mo	Monthly	Monthly	Monthly
2–6 mo	Every 2 mo	Every 2 mo	Every 2 mo
6–24 mo	Every 3 mo	Every 3 mo	Every 3 mo
2–6 yr	Annually	Annually	—
6–10 yr	Every 2 yr	Every 2 yr	—
11–20 yr	Annually	Annually	—

Adapted from American Academy of Pediatrics.[3]

TABLE 2-3 Selected Clinical Findings Associated with Nutritional Inadequacies

Area of Examination	*Finding*	*Considered Nutritional Inadequacy*
General	Underweight; short stature	↓Calories
	Edematous; decreased activity level	↓Protein
	Overweight	↑Calories
Hair	Ease of pluckability; sparse, depigmented; lack of curl; dull, altered texture; flag sign	↓Protein
Skin (general)	Xerosis, follicular keratosis	↓Vitamin A
	Symmetric dermatitis of skin exposed to sunlight, pressure, trauma	↓Niacin
	Edema	↓Protein
	Petechiae, purpura	↓Ascorbic acid
	Scrotal, vulval dermatitis	↓Riboflavin
	Generalized dermatitis	↓Zinc, essential fatty acids
	Erythematous rash around mouth and perianal area	↓Zinc
Skin (face)	Seborrheic dermatitis in nasolabial folds	↓Riboflavin
	Moon face; diffuse depigmentation	↓Protein
Subcutaneous tissue	Decreased	↓Calories
	Increased	↑Calories
Nails	Spoon-shaped; koilonychia	↓Iron
Eyes	Dry conjunctiva; keratomalacia; Bitot's spots	↓Vitamin A
	Circumcorneal injection	↓Riboflavin
Lips	Angular stomatitis	↓Riboflavin, Iron
	Cheilosis	↓B-complex vitamins
Gums	Swollen, bleeding	↓Vitamin C
	Reddened gingiva	↑Vitamin A
Teeth	Caries	↓Fluoride
	Stained teeth	Iron supplements
	Mottled, pitted enamel	↑Fluoride
	Hypoplastic enamel	↓Vitamins A, D
Tongue	Glossitis	↓Niacin, folate, riboflavin, vitamin B_{12}
Skeletal	Costochondral beading	↓Vitamins C, D
	Craniotabes; frontal bossing; epiphyseal enlargement	↓Vitamin D
	Bone tenderness	↓Vitamin C
Muscles	Decreased muscle mass	↓Protein, calories
	Tender calves	↓Thiamin
Neurologic	Ophthalmoplegia	↓Thiamin, vitamin E
	Hyporeflexia	↓Vitamin E
	Ataxia, sensory loss	↓Vitamins B_{12}, E
Endocrine and other	Hypothyroidism	↓Iodine
	Glucose intolerance	↓Chromium
	Altered taste	↓Zinc
	Delayed wound healing	↓Vitamin C, zinc

Adapted from Hubbard VA, Hubbard LR. Clinical assessment of nutritional status. In: Walker WA, Watkins JB, editors. Nutrition in pediatrics, basic science and clinical applications. 2nd ed. Hamilton (ON): BC Decker; 1997. p. 7–28.

recall provides a quicker assessment of dietary intake. For a 24-hour recall, the child/parent is asked to recall what and how much the child ate and drank over the past 24 hours. Recall accuracy depends on the child/parent's memory and ability to estimate portion sizes. Also, because this is only one day of intake, it may not be representative of the usual intake. When the child's intake is affected by acute illness, a 24-hour recall of a "typical day" is more useful to estimate usual intake. The 24-hour recall tends to underestimate food intake when compared with longer intervals of food records.[5]

Another way of assessing dietary intake is the food frequency questionnaire method. These questionnaires collect information on both the frequency and amount consumed of specific foods and are useful in the clinical setting to identify usual eating patterns. A limitation of the food frequency questionnaires is that the amounts of food are often over-reported.[5] All of these methods of dietary assessment are somewhat limited owing to gaps in the nutrient databases, which lack information about bioavailability, presence of inhibitors and enhancers of absorption, and nutrient availability of specific nutrients of interest.[6]

The most commonly used method of dietary assessment in hospitalized patients is the calorie count. This is a variation of the prospective food records as the amount of food consumed from a known quantity of food (as specified by a menu or list) is recorded. The accuracy of the calorie count assessments is limited by the number of individuals required for the completion of these forms throughout a 24-hour period (eg, the dietitian, the nurse for each shift, the child's family, the child). However, calorie counts are a useful part of nutritional assessment follow-up because these provide a rough assessment of the patient's appetite, intake, and compliance with nutrition recommendations.

ANTHROPOMETRICS AND BODY COMPOSITION

At a minimum, nutritional assessment of a child includes a measured weight, length or height, and head circumference (birth to age 3 years), and these measurements are followed over time to assess short- and long-term growth and nutritional status. For children with chronic disease, a midarm circumference (MAC) and triceps skinfold (TSF) thickness are also part of the assessment to determine body fat and protein stores. In addition, a dual-energy x-ray absorptiometry (DXA) scan may be added to more thoroughly assess body composition (percent fat, lean body, and fat mass) and bone mineral density (BMD) (see Chapter 4).

Accurate and reliable anthropometric and body composition measurements require the proper equipment and techniques. Training and practice in anthropometric technique cannot be overemphasized. All growth measures should be taken in triplicate and used as an average. The clinician's assessment for a child depends on the quality of these data. Equipment requirements for each measure are discussed below.

Weight

Weight is a measure of overall nutritional status with age, sex, and height/length required for optimal interpretation. Weight is determined using a digital or beam balance scale. Until the child is approximately 24 months or can cooperate and stand independently, a pan version of the scale is used. Weight should be measured in light or no clothing and without a diaper for infants. It is important that the scale is zeroed prior to each measurement and is calibrated using known weights at least monthly or on movement of the scale.[7] Weights are recorded to the nearest 0.01 kg in infants and 0.1 kg in older children.

Stature: Length or Height

A measure of stature is important for monitoring long-term nutritional status. Recumbent length is measured using a length board for children from birth to 2 or 3 years. The measurement of length requires two individuals. The first person positions the infant straight on the board so that the infant's head is against the headboard and in the Frankfort horizontal plane.[7] The Frankfort plane is the anatomic position when the lower margin of the orbit and the upper margin of the auditory meatus are in line. The second person holds the infant's knees flat to the table and heels flat against the movable footboard.[7] For children able to stand independently and cooperate, height is measured using a stadiometer, with a moveable headboard at a fixed 90-degree angle to the back of the stadiometer. The child is measured barefoot or in thin socks and in minimal clothing to allow the observer to check for correct positioning. For the measurement, the child stands erect, feet together, heels, buttocks, and back of head touching the stadiometer, and looking ahead in the Frankfort horizontal plane.[7] Because length overestimates height by approximately 0.5 to 1.5 cm,[8] it is essential to record the method of measurement during the transition from recumbent length to standing height. The change to standing height is also accompanied by the transition to pediatric (2 to 18 years) growth charts (see below). Both length and height measurements are recorded to the nearest 0.1 cm.

For children in whom stature measurements are not possible owing to physical constraints (eg, contractures, nonambulatory), alternative measures are available. Upper arm and lower leg lengths provide reliable and valid indexes of stature in children.[9,10] These measurements are conducted using sliding calipers in infants and an anthropometer for children. All measurements are recorded to the nearest 0.1 cm.

The shoulder to elbow length is used for the upper arm measurement.[11,12] In infants (birth to 24 months), the arm is bent to a 90-degree angle and the measurement is taken from the superior lateral surface of the acronium to the inferior surface of the elbow.[12] For older ages (2 to 18 years), the arm should hang in a relaxed position at the side, and the distance between the superior lateral surface of the acronium to the tip of the radius is measured.[12] Lower leg length is measured as the knee to heel length[12] for infants (0 to 24 months) and as a calf length[11,12] in older children (2 to 18 years). For infants, the superior surface of the knee to the heel is measured while the leg is bent at a right angle at the hip, knee, and ankle.[12] In older children, the medial tip of the tibia to the distal tip of the medial malleolus is measured while that leg is crossed over the opposite knee.[11,12] The right-side extremity should be measured for these alternative stature estimates.[12] If there are asymmetric extremity abnormalities, the measurement should be taken on the least affected side.

Head Circumference

Head growth, primarily owing to brain development, is most rapid within the first 3 years of life. Routine measurement of head circumference (the frontal occipital circumference) is a component of the nutritional assessment in children up to age 3 and longer in children who are at high nutritional risk. Head circumference is a less sensitive indicator of short-term nutritional status than weight and height because brain growth is generally preserved in cases of nutritional stress. Head circumference is not a helpful nutritional status measure in children with hydrocephalus, microcephaly, and macrocephaly.

Head circumference is measured using a flexible, nonstretch tape measure. The circumference should be taken at the maximum distance around the head, which is found by placing the measuring tape above the supraorbital ridge and extending around the occiput.[12,13] Care should be taken to keep the tape measure flat against the head and parallel on both sides. The measurements should be recorded to the nearest 0.1 cm.[13]

GROWTH CHARTS AND TABLES

Serial measurements are essential for optimal assessment of short- and long-term growth and nutritional status. A number of growth charts and tables are available for the comparison of weight, stature, and head circumference with reference populations by age and sex. Weight is also assessed relative to a child's height (weight for height, weight for height^2 or body mass index [BMI]) for an additional assessment. The types of charts and tables available for clinical assessment in infants and children are reviewed.

Premature Infant Growth Charts

For infants born prematurely, a variety of charts are available for the assessment of growth. Intrauterine growth–based charts are preferred over postnatal growth–based charts as the pattern and rate of normal intrauterine growth are the standard for growth of premature infants. Growth measurements are plotted based on corrected gestational age for the first 12 months of life. In clinical practice, the use of corrected gestational age may continue to 24 to 36 months, depending on the child's size and growth. The Lubchenco growth charts (see Appendix, Figure A-14) are the most widely used owing to ease of clinical use (weekly age intervals, commonly used percentiles) and include charts for weight, length, and head circumference.[14,15] The Babson charts (see Appendix, Figure A-13) are presented in biweekly age intervals up to 40 weeks gestation and as standard deviations, rather than

percentiles, so they are used less in clinical care.[16] More recently, weight charts based on larger national datasets of fetal growth have been published.[8,17] There is still a need for more up-to-date reference standards for length and head circumference.

Once a preterm infant reaches 40 weeks corrected gestational age, it is appropriate to monitor growth on the new CDC growth charts.[18] Former premature infants are plotted on these charts based on their corrected gestational age (as above). Although all premature infants may not achieve "good" placement on these growth charts, these charts provide the appropriate goal for growth. Also available are the Infant Health and Development Program (IHDP) charts for low birth weight (LBW, 1,501 to 2,500 g) and very low birth weight (VLBW, ≤ 1,500 g) premature infants for boys[19,20] and girls[21,22] and the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Growth Observational Study[23] projected growth charts and tables for VLBW infants (available online: <http://neonatal.rti.org>). These charts provide a comparison of how an LBW or VLBW premature infant grows relative to two reference populations of similar infants. The IHDP and NICHD postnatal charts represent actual, not ideal, patterns of growth for former premature infants. Therefore, these charts may be used in conjunction with but not in place of the CDC growth charts.

CDC Growth Charts, 2000

In 2000, the CDC and National Center for Health Statistics (NCHS) released an updated set of growth charts called the CDC growth charts (see Appendix, Figures A-1 to A-10).[18] Changes to the previously used 1979 NCHS growth charts[24] included (1) BMI (kg/m^2) charts for boys and girls (2 to 20 years); (2) 3rd and 97th percentiles for all charts and 85th percentile for the weight-for-stature and BMI-for-age charts; (3) improved transition from recumbent length to standing height measurements in the stature charts; (4) increased age range from 18 to 20 years; and (5) the use of a combination of breast- and formula-fed infants to establish the reference growth patterns.[18] These charts are available for boys and girls ages 0 to 36 months for weight, length, and head circumference by age and weight for length and ages 2 to 20 years for weight, height, and BMI for age and weight for height. The CDC growth charts are available on the Internet (<www.cdc.gov/growthcharts>).

Incremental Growth Velocity

Reference data are also available for incremental growth velocity for boys and girls in weight, stature, and head circumference from 0 to 18 years (see Appendix, Tables A-6 to A-10).[25–29] These data are presented in time intervals (1, 3, or 6 months) and approximate growth over time by percentile (3rd to 97th or 5th to 95th percentiles). In clinical practice, the incremental tables for weight, length, and head circumference[25,27,29] are helpful in the assessment of former premature infants and other children with growth failure from any cause. The growth increments are easily divided into daily, weekly, or monthly weight gain goals. This method of growth assessment is more sensitive in detecting growth faltering or catch-up growth than the growth charts.

Growth charts for the assessment of height and height velocity in relation to the stage of sexual maturity based on US reference data are also available (see Appendix Figures A-11 and A-12).[30] These charts provide height growth for early, middle, and late maturers by sex and age at which peak height velocity was reached and explain some of the variation in growth related to different stages of puberty. Height velocity charts are often used in the care of children with poor growth and chronic illnesses.

Special Growth Charts

Although the CDC growth charts are recommended for the growth and nutritional assessment for all children, a number of disease-specific charts have been published (eg, achondroplasia, Brachmann-de Lange syndrome, cerebral palsy, Down syndrome, Marfan syndrome, myelomeningocele, Noonan's syndrome, Prader-Willi syndrome, sickle cell disease, Silver-Russell syndrome, Turner's syndrome, Williams syndrome; see Appendix, Table A-13). Weight- and height-for-age growth charts are available for boys and girls ages 0 to 36 months and 2 to 18 years based on a large sample of children with Down syndrome.[31,32] However, many other special charts are based on small samples of children and include children with suboptimal nutritional status. Disease-specific charts may be helpful to use in conjunction with the CDC growth charts.

A set of growth charts is also available for the assessment of alternate stature measures,[9,10] including upper arm length (infants 0 to 24 months, girls 3 to 16 years, boys 3 to 18 years) and lower leg length (infants 0 to 24 months, girls 3 to 16 years, boys 3 to 18 years). Similar to other measures of stature, these linear growth measures are used along with weights to help determine a child's nutritional status.[12]

ASSESSMENT OF ANTHROPOMETRICS

Nutritional status indices are essential for the clinical interpretation of the growth measurements. Every nutritional assessment requires one or more of the following indices for interpretation.

Percentiles for Age and Sex

When each of the growth measures is plotted on a growth curve, a percentile or rank of the individual compared to the reference population is determined. For example, the 25th percentile weight for age means that the individual patient weighs the same or more than 25% of the reference population of the same age and sex, and the 75th percentile weight for age means that the individual patient weighs the same or more than 75% of the reference population of the same age and sex.[8] Percentiles are easily interpreted and used clinically. Available growth charts provide reference growth of children ranging from the 5th to 95th percentiles and now the 3rd to 97th percentiles. In clinical practice, the 5th to 95th percentile growth charts continue to be used in the screening and follow-up of healthy children, whereas the 3rd to 97th percentile growth charts may be used for

children with chronic illness or at nutritional risk. Weight-for-age and height-for-age percentiles are also used to screen for malnutrition using published classifications (see Appendix, Table A-11). Percent ideal body weight (IBW), based on appropriate height and weight for age (see below), is often used as an indicator of wasting or obesity. Height-for-age percentiles are an adequate measure of long-term nutritional status and are used for screening in healthy children with low height for age reflecting stunting. Height for age is generally interpreted as short (< 5th percentile), normal (5 to 95th percentile), and tall (> 95th percentile).

Genetic Growth Potential: Midparental Height

In the assessment of a child's stature, it is helpful to estimate the genetic potential for stature as determined by the biologic parents' adult height.[33] This is of particular interest in the child with short stature because it is important to determine if the child is healthy but short owing to family genetic background, disease, and/or poor nutrition. An adjustment for parental height is used for a child's length (0 to 36 months) or height (3 to 18 years) and is based on the mean of the height of both biologic parents. This allows adjustments to the child's stature for tall or short parents. The corrections are based on the Fels Institute and older NCHS data[24] and therefore are used in conjunction with the 1979 NCHS growth charts. Parental height adjustment is appropriate for use with most of the parents and children in the United States; however, it should not be used when the parents do not meet their genetic potential for height (eg, in situations of poor health and/or nutritional status during the parental childhood or adolescence).[33]

Weight for Height

Weight relative to height provides different information on the growth and nutritional status in an individual than either weight for age or height for age alone. Weight for height helps to determine and classify the nutritional status in the individual patient.[34] For children under the age of 6 years, weight for height is most frequently assessed by determining a percentile on the CDC growth charts.[18] Weight for height is generally interpreted as underweight (< 5th percentile), within normal variation (5th to 95th percentile), and overweight (> 95th percentile) and is used in screening healthy children. Weight-for-height measures are also used for screening classification of protein-calorie malnutrition (see Appendix, Table A-11).

BMI is another measure of weight relative to height. The new CDC growth charts provide BMI for age and sex from age 2 to 20 years.[18,35] With the availability of these new charts, BMI will be used more frequently as an assessment tool for children. However, because both weight and height in children change over time, unlike in adults, there is no fixed BMI value for the diagnosis of obesity in children (eg, BMI ≥ 30). The BMI percentile must be used for interpretation. In the United States, the 85th and 95th BMI percentiles for age and sex are used to define "at risk of overweight" and "overweight" in children.[36] From the International Obesity Task Force, cutoff points for BMI to define overweight and obesity in children based on cross-sectional growth studies from six countries (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, United States) are also available.[37] A recent study found similar predictions of underweight and overweight in children and adolescents (2 to 19 years) using the BMI-for-age and weight-for-height classifications.[38]

Percent Ideal Body Weight

Percent IBW is an additional indicator of nutritional status. Unlike weight for height, this measure can be used past the age of 6 years (the age limit for the weight-for-height curve). IBW for a child is determined from the CDC growth charts by using the following steps: (1) plotting the child's height for age; (2) extending a line horizontally to the 50th percentile height-for-age line; (3) extending a vertical line from the 50th percentile height for age to the corresponding 50th percentile weight; and (4) noting this IBW. Percent IBW is calculated as [(actual weight divided by IBW) × 100]. In clinical practice, percent IBW may be used to classify the degree of over- or undernutrition. An example of a set of clinical classifications is > 120% IBW as obese; 110 to 120% IBW as overweight; 90 to 110% IBW as normal range; 80 to 90% IBW as mild wasting; 70 to 80% IBW as moderate wasting; and < 70% IBW as severe wasting. IBW is also used as a clinical weight goal in the nutritional rehabilitation of a child.

Percent Weight Loss

Percent of usual body weight loss is an important clinical indicator of nutritional status and nutritional risk. Percent weight loss is calculated as [(previous weight – current weight)/previous weight – 100]. A 5% or greater weight loss in 1 month may be considered an indicator of nutritional risk in children.

Growth Velocity

Growth velocity (change in the growth parameter over time) is useful to detect a change in nutritional status and to monitor the effectiveness of nutritional and medical therapy. As discussed above, age- and sex-specific charts and tables are available for the evaluation of weight, stature, and head circumference growth over time.[25–30]

BODY COMPOSITION

In children with many acute and chronic diseases, the nutritional assessment requires measurement of body composition (body fat and protein stores) in addition to weight, stature, and head circumference (see Chapter 4).

Midarm Circumference

MAC can be used as a measurement of growth and an index of energy and protein stores and can provide information on fat patterning.[13] The measurement is taken at the midpoint of the upper arm, located halfway between the lateral tip of the acromion and the olecranon when the arm is flexed at a 90-degree angle (measured and marked). For the MAC measurement, the child should be upright with the arm relaxed by the side. A flexible, nonstretch

measuring tape is placed perpendicular to the long axis of the arm, tightened around the arm, and recorded to the nearest 0.1 cm.[13]

Triceps Skinfold Thickness

The TSF thickness is an indicator of subcutaneous fat (energy) stores and total body fat and provides information on fat patterning.[39] For the measurement, the child should be upright with the arm relaxed at the side. The TSF thickness is measured at the midpoint of the upper arm (defined above) over the center of the triceps muscle on the back of the arm (measured and marked beforehand). The anthropometrist lifts the skinfold with the thumb and index finger, approximately 1 cm above the marked midpoint, and places the calipers at the marked point. Four seconds after the handles of the calipers are released, the measurement is taken and the calipers are removed. This measurement should be taken in triplicate, used as an average, and recorded to the nearest 0.1 cm.[12]

Reference data (age and sex specific) are available for the assessment of MAC and TSF thickness as a percentage[40] (see Appendix, Tables A-4 and A-5). The MAC and TSF measurements (in mm) are used to calculate upper arm muscle area and fat area (formulas below).[12,40] These are clinical indicators of total body stores of muscle and fat[12]:

Upper arm muscle area (cm^2) = [MAC (cm) – (TSF (cm) × π)]^2/(4 × π), where π = 3.14.

Upper arm fat area (cm^2) = upper arm area (cm^2) – upper arm muscle area (cm^2), where upper arm area (cm^2) = MAC^2/(4 × π).

Dual-Energy X-Ray Absorptiometry

DXA is a noninvasive measurement of BMD. It is an indirect, low-radiation measurement that has increasing clinical utility. DXA scans are performed on the lumbar spine, hips, and whole body in adults and on the lumbar spine and whole body in infants, children, and adolescents. Although primarily used for the assessment of bones, whole-body scans also provide body composition measures of fat-free mass, fat mass, and percent body fat.[41] In addition, the DXA scans provide information on bone mineral content (BMC) in grams per centimeter or BMD in grams per square centimeter in different regions of the skeleton or the whole body. Values for the lumbar spine are used to assess bone health and are compared with reference data in healthy age- and sex-matched infants, children, and adolescents. Usually, an anteroposterior view of the lumbar vertebrae L1 to 4 or L2 to 4 is used for clinical interpretation. It takes approximately 20 minutes to complete both DXA scans (lumbar spine and whole body), including time for positioning. Younger children are measured while asleep, or sedation may be considered. Results for BMC and BMD are assessed using a z-score (standard deviation score), which compares the individual with the reference database. A z-score of 0 is the mean (similar to the 50th percentile on a growth chart) for the reference data, with +1, +2, –1, and –2 representing plus and minus 1 and 2 standard deviations of the reference mean. These results are expressed as z-scores and percent predicted. The World Health Organization (WHO) has defined osteoporosis in young, white, adult women as a BMD z-score of –2.5 or less (ie, 2.5 or more standard deviations below the reference mean).[42] A diagnostic criterion for men, children, and other races is not yet available.[42] In clinical practice, children with z-scores of –2 to + 2 are considered to have normal BMD, whereas a z-score of –1 to –2 is in the low normal group. A z-score of –2 to – is considered in the reduced range, whereas a value of –3 or less is considered to be in the significantly reduced range. Z-scores less than –2 are considered in the fracture range (Table 2-4).

The quality of the DXA-BMD reference ranges available for children is a limitation of this method. The sample sizes are low, and there is minimal detail for children across various pubertal groups. Additionally, the reference dataset is not heterogeneous nor representative of the ethnic diversity of the US population.[43] The advantages of the DXA are the low radiation exposure, fast scan time, and noninvasive nature. The precision of the instrument is excellent. The radiation dose is small (< 1 mrem, Hologic Delphi Clinical Bone Densitometer product specifications) or less than that received during a standard airline flight across the United States.[44] The frequency of measurements depends on the clinical needs (see Table 2-4). Patients with poor BMD measurements may need the scans every 6 to 12 months after the baseline assessment. Those individuals with values in the low normal range but with risk factors may need testing every 1 to 2 years. At-risk patients include those with chronic illness (eg, inflammatory bowel disease, cystic fibrosis, celiac disease), poor growth, and reduced physical activity and those receiving chronic medications (eg, corticosteroids, anticonvulsants).

A newer technique providing data on both cortical and trabecular bone is quantitative computed tomography (QCT). This test describes volumetric BMD and also differentiates between cortical and trabecular bone. Special high-resolution scanners have been developed to decrease radiation exposure for the peripheral skeleton, and this is currently a research tool. Bone health in children and adults is altered by intakes of calcium and vitamin D and weight-bearing physical activity. It is important to be aware of the risk factors for bone disease in children, including conditions such as chronic diarrhea, lactose intolerance, poor dietary intake, fat malabsorption, decreased physical activity, and the use of steroid medications.

TABLE 2-4 Suggested Bone Health Assessment by Dual-Energy X-Ray Absorptiometry

Z-Score	*Interpretation*	*Repeat Measurements*
2.0 or greater	Increased	Annually
+2 to –2	Normal	If clinical status changes
–1 to –2	Low normal	Every 1 to 2 yr
–2 to –3	Reduced	Annually
–3.0 or less	Significantly reduced	Every 6 to 12 mo

SEXUAL AND SKELETAL MATURATION

Because body composition and the rate of growth vary throughout childhood and adolescence, it is important to consider sexual/pubertal and skeletal maturation when assessing an individual patient's anthropometric measurements. For example, a small child who is physically immature (based on sexual and skeletal development) is less of a nutritional concern than a child who is small and appropriately mature for age. The physically immature child with likely growth delay has the potential to catch up to the size of her peers once she advances in maturity.

Sexual maturity is assessed using the Tanner staging system by the clinician physical examination[45] or as a pubertal self-assessment form completed by the child/parent.[46–49] Staging (1 to 5) is based on breast and pubic hair development for girls and genital and pubic hair development for boys (see Appendix, Tables A-1 and A-2).

Skeletal maturation (or bone age) is the second method for assessment of physical maturity. Bone age is assessed by a left hand-wrist radiograph and scored using the standards developed by Greulich and Pyle[50] or the newly revised TW3 method developed by Tanner and colleagues.[51] Bone age provides a measure of "how far a given individual has progressed along his or her road to full maturity"[52] regardless of chronologic age. Sexual and skeletal maturity provide a measure of physical maturity and are valuable in formulating the nutritional assessment of children and adolescents.

LABORATORY TESTS

Laboratory testing is a helpful but less essential part of a nutritional assessment in most children and is presented in detail in Chapter 3. Nutritional information can be obtained from plasma, serum, urine, stool, hair, and nail samples. The latter two are rarely used clinically. Depending on the underlying medical condition and related nutritional problems from the history and physical examination, a focused laboratory assessment may be obtained. Serum albumin and prealbumin reflect the adequacy of protein and calorie intake. Because the half-life of albumin is 14 to 20 days, it also reflects longer-term protein stores. The shorter half-life of prealbumin (2 to 3 days) is a better short-term indicator of calorie and protein intake. However, the usefulness of prealbumin in the hospitalized patient may be limited by the fact that it is decreased in the setting of stress, sepsis, and acute illness. Checking a C-reactive-protein level may help identify when the low prealbumin level is related to stress. Anemia can be attributable to multiple nutritional deficiencies (eg, iron, vitamin B_{12}, folate, vitamin C, protein, and vitamin E), and a careful analysis of the red blood cell indices and peripheral blood smear will help to determine what further nutritional laboratory tests should be obtained (eg, iron studies, vitamin levels). In premature infants, nutritional anemias can be attributable to iron, vitamin E, and copper deficiencies. Nutritional tests to check for bone health may include serum calcium, phosphorus, alkaline phosphatase, magnesium, and 25-hydroxyvitamin D. Additional information on bone health may be obtained from a parathormone level, radiography, and DXA scan. Specific vitamin and mineral levels can be checked when deficiency or excess states are suspected. A urine analysis, along with serum electrolytes, is useful in assessing the hydration status of the patient. See Table 2-3 for a list of selected clinical findings related to nutritional inadequacies and Chapter 3 for a more in-depth look at laboratory assessment of nutritional status.

NUTRITIONAL REQUIREMENTS

The estimation of nutritional requirements is the last step in a nutritional assessment. Recommendations for calorie and protein intake, as well as specific vitamins and minerals, are needed for patient care (see Chapters 5, 6, and 7). The history (medical and dietary), physical examination, and anthropometric and laboratory data obtained are used to help estimate these nutritional requirements. These provide a starting point for nutritional therapy and are modified over time based on the patient's ongoing health status and response to nutritional therapy. The adequacy of the nutritional therapy provided should be vigilantly monitored in children with failure to thrive (FTT) and obesity and in those patients with conditions requiring enteral or parenteral nutrition.

There are a number of methods to estimate caloric needs of children in the clinical setting, including the Dietary Reference Intakes (DRIs) for estimates of total energy needs, the WHO and Schofield prediction equations for estimates of resting energy expenditure (REE), and a direct measurement of REE. In 1989, the National Research Council published the Recommended Dietary Allowances (RDAs) to provide information about the nutrient needs of infants, children, and adolescents, in addition to adults. Longitudinal average dietary intake consistent with good health and appropriate growth in healthy children were used for these estimates.[53] The 1989 RDAs now have been replaced by a more comprehensive set of guidelines called the DRIs. In addition to the RDAs, the DRIs include Estimated Average Requirements, Adequate Intakes (AIs), and Tolerable Upper Intake Levels for most nutrients.[54] The DRIs are used in Canada and the United States, and nutrient intakes at the suggested levels promote nutrient function, biological and physical well-being, and disease prevention.[55] DRIs are available for vitamins, minerals (see Chapters 6 and 7), energy, and macronutrient recommendations (see Chapters 5 and 17). Generally, the DRIs address the nutritional needs of the healthy individual and population. Therefore, DRIs may require adjustments in the clinical setting because they do not address energy or nutrient requirements for individuals who are malnourished or have acute/chronic disease.

The DRI for energy in children 0 to 2 years is estimated from prediction equations derived from total energy expenditure (TEE, by the double-labeled water methods) and energy needs for tissue deposition for growth "at rates consistent with good health."[56] For chil-

dren at this young age, estimated energy requirements (EERs) vary based on weight. The EERs for children 3 to 8 years and 9 to 18 years are also from TEE and energy deposition costs (20 and 25 kcal/day, respectively) and are based on age, weight, height, and level of physical activity (see Appendix). The important role of moderate physical activity in achieving and maintaining the appropriate energy balance for optimal health is emphasized in these new recommendations. Levels of physical activity are categorized into four levels: sedentary, low active, active, and very active.[56,57] EER equations also are available for use in children ages 3 and above who are at "risk of overweight" defined as a BMI > 85th percentile and "overweight" as a BMI > 95th percentile.[36] DRIs provide an estimate of total energy needs in kcal/day and may be adjusted based on nutritional, medical, and growth needs of the individual patient.

The WHO and Schofield REE equations offer another method to estimate energy requirements. The WHO recommendations are based on the evaluation of several thousands of children and are clinically useful. The WHO equations (see Appendix, Table A-24) calculate REE by sex, age, and weight groups and approximate the basal metabolic rate.[58] Total daily energy needs are then estimated by multiplying the REE by a factor to adjust for physical activity, medical status, and/or the need for catch-up growth (Table 2-5). The Schofield equations (see Appendix) use sex, age, weight, and height of the child and may more accurately predict REE in children with altered growth and body composition (ie, FTT and obesity).[59] Schofield REE estimates are also adjusted for the patient's activity, stress, and growth needs (see Table 2-5) to approximate total daily energy needs. The new DRIs for total energy recommendations may replace these equations in clinical research settings.

The best way to determine an individual's REE and daily energy needs is by indirect calorimetry; however, this method is not readily available in all clinical settings. This technique measures oxygen consumption and carbon dioxide production when the child is resting in the early morning, typically after an age-appropriate fast (usually 12 hours). Sedation may be required for younger children. Results are expressed in kcal/day or kcal/kg/day and are compared to standard prediction equations (ie, WHO and Schofield).[60]

In summary, for the estimation of energy needs in the clinical setting, an REE based on indirect calorimetry is preferred for children with complex medical and nutritional needs. If an REE measurement cannot be obtained, then the WHO or Schofield equations are recommended. These estimates of REE are then adjusted based on activity, stress, and growth for an estimate of total daily energy needs for the individualized patient. As above, the new DRIs for total energy recommendations may replace these estimates in the clinical setting. However, these estimates of total energy expenditure are not as reliable as those values obtained by more accurate research methods (eg, doubly labeled water).[61] Finally, it should be remembered that all estimates are guidelines for the initiation of nutritional therapy. Adjustments in the nutritional regimen are made based on objective measures, such as weight gain, laboratory data, and medical condition.

TABLE 2-5 Disease and Physical Activity Factors for Adjustment of Resting Energy Expenditure (REE)

REE × 1.0–1.1	Well-nourished children, sedated on ventilator, extracorporeal membrane oxygenation; minimal stress
REE × 1.3	Well-nourished children with decreased activity, minor surgery, mild-to-moderate sedation; minimal stress
REE × 1.5	Ambulatory child with mild-to-moderate stress Inactive child with sepsis, cancer, trauma, extensive surgery Minimally active child with malnutrition and catch-up growth requirements
REE × 1.7	Active child with catch-up growth requirements Active child with severe stress

Adapted from Mascarenhas MR, Tershakovec AM, Stallings VA. Parenteral and enteral nutrition. In: Wyllie R, Hyams JS, editors. Pediatric gastrointestinal disease. Philadelphia: WB Saunders; 1999. p. 741–57.

DRIs also provide updated protein recommendations (see Appendix; also see Chapter 5). An AI for protein in infants 0 to 6 months is based on the mean protein intake of healthy breast-fed infants.[62] Nitrogen intake, nitrogen balance (the minimum protein intake necessary to maintain nitrogen balance), rates of protein deposition, and efficiency of protein use all influence protein requirements. For individuals 7 months through 18 years of age, the protein recommendations are based on a combination of these factors, plus a safety factor to account for individual variation.[62] The DRIs provide protein recommendations (g/kg/day) by age from birth to 8 years and by age and sex starting from 9 years. Individualized needs can be estimated by multiplying the age/sex appropriate g protein/kg/day by the body weight. As previously noted, DRIs may be further individualized based on the child's nutritional, medical, and growth needs and should be adjusted over time based on clinical status and response to nutritional intervention.

CONCLUSION

In pediatric care, infancy, childhood, and adolescence are recognized as unique phases because adequate nutrition must support both usual nutrient requirements and nutrients needed for optimal growth and development. However, nutritional status depends in part on current and past illnesses, and a child's response to illness is affected by his/her nutritional status. Thus, understanding and addressing the nutritional status of a hospitalized child are important components of clinical care. No one measure provides an adequate assessment of nutrition status. A nutritional assessment often includes the input of many members of the health care team. This chapter provides the factors to consider in the nutritional assessment and monitoring of a hospitalized child. Initial nutritional goals are adjusted over time as the child's medical and nutrition status change to provide optimal care.

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CHAPTER 3

LABORATORY ASSESSMENT OF NUTRITIONAL STATUS

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Adequately and appropriately assessing the nutritional status of an individual requires the integration of various information gathered by the clinician. Anthropometrics, dietary and medical history, clinical and physical assessment, and laboratory values provide medical personnel with the information to determine the adequacy of an individual's diet, detect nutritional deficiencies, and monitor the effect of treatment.[1] Of these parameters, laboratory values can provide objective confirmation of nutritional deficiencies that might be suspected from the dietary history or clinical physical findings and can allow detection of subclinical abnormalities before functional or anatomic lesions occur. Laboratory tests can also be used to monitor therapy of malnutrition in individuals with greater precision than is usually possible with dietary, anthropometric, or clinical assessment techniques.

Laboratory tests allow detection of underlying causes of malnutrition, such as inadequate dietary intake, malabsorption, increased nutrient requirements, or excretion or destruction of nutrients. These tests can provide a measure of depletion of tissue stores before deficiencies in functional nutrient pools occur. They can be used to determine quantitative alterations in biochemical levels of nutrients, their metabolites, or dependent enzyme activities that are often not detected by anthropometric or clinical methods (Figure 3-1).

Despite the availability of a plethora of proposed biochemical and immunologic assays, the laboratory assessment of nutritional status has so far failed to fulfill its promise for a number of reasons. There have been no widely accepted methods of integrating information about the various nutrients that need to be screened into a battery of a few standard, readily available, inexpensive tests. Part of the reason for this could be that most laboratory tests of nutritional status are too specific. Although they nicely quantitate levels of a certain nutrient in a specific body fluid at a particular time, these measurements might not correlate with values at other times or in other body pools, or with deficiencies of other nutrients. Furthermore, laboratory values can be misleading to a clinician because of the effects of disease, medication, body stress, and environmental conditions not related to the patient's nutritional status. Ideal specimens might not be obtained or could be contaminated, causing inaccurate values. Clinicians must take many factors into consideration when evaluating laboratory values.[2]

ANALYSIS IN BLOOD

One of the major underlying difficulties is that most nutrients are not distributed evenly in the body and are not confined to one body pool. Thus, a single determination of blood, urine, or even tissue concentrations of these nutrients does not always provide a reliable indication of distribution or functional metabolic significance. Amounts of a nutrient in plasma might form only a very small percentage of whole-body stores and could be unrelated to tissue levels. Plasma levels can be regulated so that normal levels are maintained in spite of a severe tissue deficiency. For example, plasma calcium comprises less than 2% of whole-body calcium, and there is an even smaller percentage in the functional form of ionized calcium. Regulated by hormones, plasma calcium levels can be in the normal range even in the presence of severe bone calcium depletion (rickets).

Thus, plasma or serum levels of nutrients might not always be reliable indicators of nutritional status. Although relevant tissues can sometimes be difficult to obtain for biopsy (eg, liver, bone, brain, or muscle), some nutrients (such as vitamin C) can be better assessed by measuring their levels in whole blood, red cells, or leukocytes because these are also centers of metabolic activity. Even more relevant are functional assays of the activity in red cells of certain enzymes that are dependent on a particular nutrient. Good examples of these include transketolase activity for thiamin, glutathione reductase for riboflavin, transaminase for pyridoxine, and glutathione peroxidase for selenium.

ANALYSIS IN HAIR AND NAILS

Because the measurement of vitamin and trace minerals in hair and nail clippings reflects deposition of stores over the long term rather than recent dietary intake, they it has little use in the clinical setting. Despite the apparent easy avail-

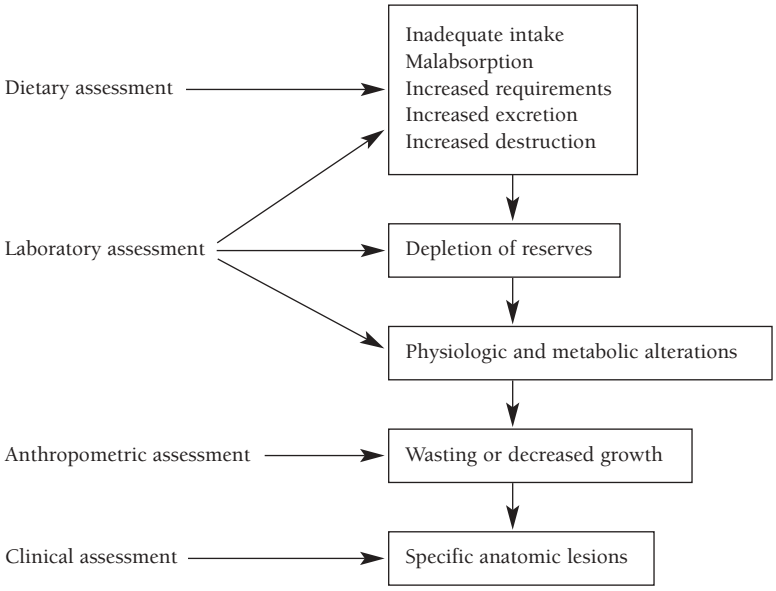

FIGURE 3-1 The levels of assessment of nutritional status as malnutrition progresses from inadequate intake to subclinical alterations to gross clinical signs and symptoms. Malnutrition can potentially be detected by laboratory assessment before it becomes clinically apparent.

ability of tissue samples, collection procedures remain problematic because of contamination by external agents (eg, cosmetics, shampoos, forceps, collection vials) and selection of appropriate specimens (telogen hairs). Many studies continue to address the effect of contamination on the accuracy of measurement and the appropriateness of the use of these samples for nutritional assessment.[3,4]

ANALYSIS IN URINE

Nutrients can be metabolized into inactive (or active) forms that cannot be directly assayed. Most nutrients are eventually excreted in the urine, and many methods involve measuring levels of nutrients or their metabolites in the urine, which can be decreased in deficiency states. Some examples of these metabolites are 2-methyl nicotinamide from niacin and 4-pyridoxic acid from pyridoxine (vitamin B_6). On the other hand, there might be increased urine excretion of metabolic products that accumulate because of a specific nutrient deficiency, for example, methylmalonic acid in vitamin B_{12} deficiency and formiminoglutamic acid in folate deficiency. Urine excretion of metabolites can also be measured after specific "loading" of a nutrient to determine relative depletion, as in the tryptophan load test for pyridoxine deficiency and tyrosine load test for vitamin C deficiency.

The problem with urine collections is that excretion from the bladder varies during the day, and concentrations are less reliable than cumulative daily total amounts. Ideally, a 24-hour urine collection should be used for assessment. Shorter samples continue to be studied for their accuracy when compared with 24-hour collections.[5,6]

METHODS OF ANALYSIS

Many nutrients are present in plasma in extremely low trace concentrations—in the nanogram to picogram per milliliter range. This has necessitated the development of extremely sophisticated assays, some of which are quite expensive. In many cases, these new techniques have replaced even more expensive bioassays, such as those still in use for biotin and pantothenic acid. The advent of multichannel sequential autoanalyzers has been a positive development in providing rapid, inexpensive analysis of a battery of enzymes and electrolytes in a small amount of serum, but they have not been specifically applied to nutritional assessment.

Emission flame photometry is a readily available method for analysis of major minerals, such as sodium, potassium, chloride, and calcium. Somewhat more involved, atomic absorption spectroscopy has now become the preferred method of analysis of many trace elements, such as zinc and copper. The fat-soluble vitamins (A, D, E, and K) and their metabolites can be measured by high-performance liquid chromatography.[7] Other techniques include radioimmunoassay, gas chromatography, thin-layer chromatography, and mass spectrometry.[8] The use of stable isotopes has led researchers to a better understanding of nutrition and metabolism. For example, much of the knowledge of neonatal nutrition has come from studies using stable isotopes.[9,10] Large-scale group or community studies most often use isotope studies for their populations. Using stable isotopes in a clinical setting might not be feasible.[11–13] Most of these methods are too expensive to allow consideration as routine nutritional screening tests.

VITAMIN AND MINERAL ASSESSMENT

With more than 40 essential nutrients to measure, including 13 vitamins and at least 14 trace elements, plus an inexhaustible list of related metabolites, enzymes, hormones, and functional parameters, no battery of laboratory tests can hope to provide a complete comprehensive assessment of all nutrients. Even if this were possible, com-

plete biochemical "normality" would not guarantee adequate health or nutrition, nor would immediate corrections necessarily be desirable in patients who have adapted to their nutritional state. For many nutrients, it is not clear that published normal biochemical values represent ideal levels. There are many genetic, racial, and regional differences in nutrient levels, some of which could represent chronic deficiency in the majority of the population. Iron status can be suboptimal in a large proportion of menstruating women, for example. Age and sex differences in normal levels must also be considered.[14–17] Indeed, the definition of *ideal* could be different to different evaluators. To a surgeon, ideal nutrition could mean lack of postoperative morbidity. To an epidemiologist, it might mean absence of chronic disease. To a pediatrician, it might mean adequate growth and development.

Determining the most useful laboratory values is an ongoing process. The ideal nutritional assessment test has yet to be developed. As proposed by Goldsmith, the ideal test would have a short half-life, have rapid response to improved nutritional intake, reflect moderate decreases in intake early, indicate current nutritional status, reflect the degree of deficit, and be unaffected by non-nutritional factors.[18] Laboratory assessment of nutritional status should not be an indiscriminate application of all possible tests. Rather, it should involve intelligent selection of appropriate tests in conjunction with dietary, anthropometric, and clinical information and consider availability, cost, predictive value, sensitivity, specificity, reliability, and validity.

Although assays for specific vitamins and minerals are covered in other chapters, Table 3-1 lists most of the readily available tests of nutritional status and their relative level of applicability. Generally accepted normal levels are listed in Table 3-2. In addition to the now-classic reference works of Sauberlich and colleagues[19] and Jelliffe and Jelliffe,[20] several reviews and symposia should be consulted for further details and values.[21–28]

ANALYSIS OF SPECIFIC NUTRIENTS

Energy

Although energy in the body is stored mainly as fat (approximately 100,000 kcal in the average adult), most usual diets supply most of this energy as carbohydrate.[29] Analysis of foods in the bomb calorimeter to measure energy intake exactly was pioneered by Atwater and Benedict in the early 1900s. Direct calorimetry precisely determines energy expenditures as metabolic heat production (M) by measuring work performed (W); heat loss by evaporation (E), radiation (R), conduction (K), and convection (C); and body temperature changes (S)[30]:

$$M = S + R + C + K + E + W$$

This requires complete thermal isolation in a chamber or suit and is available only in a few research centers.

Indirect calorimetry bases energy expenditure on oxygen consumption (21.14 kJ/L of oxygen consumed), which can be somewhat more easily obtained by collection and analysis of inspired and expired air. Although many assumptions and calculations must be made, relatively accurate estimates of energy expenditure can be made with portable collection bags and gas analyzers within a few minutes using the Haldane transformation equation[31,32]:

$$O_2 \text{ consumed} = \frac{V_{air\ exp} \times FN_2\ exp \times FO_2\ insp - V_{air\ exp} \times FO_2\ exp}{FN_2\ insp} \\ V_{air\ exp}\left(FN_2\ exp \times \frac{0.2093}{0.7094} - FO_2\ exp\right)$$

and adjusting for protein catabolism by the Weir equation[33,34]:

$$\text{MEE (kcal)} = 3.94 \times VO_2 + 1.06 \times VCO_2 - 2.17 \times \text{UUN}$$

or as modified by Cunningham[35]:

$$\text{MEE (kcal)} = 3.76 \times VO_2 + 1.25 \times VCO_2 - 1.09 \times \text{UUN}$$

Measurement of carbon dioxide consumption divided by oxygen consumption yields the respiratory quotient (RQ), which can give an indication of the relative source of metabolic fuel, carbohydrates giving an RQ of 1.0 and fats decreasing it toward 0.7[36]:

$$RQ = VCO_2/VO_2$$

Collection and analysis of expired carbon dioxide and oxygen intake require expensive instruments and are still subject to wide variation, depending on clinical and environmental conditions. Studies of indirect calorimetry continue to prove its usefulness in measuring resting energy expenditure (REE).[37,38] Unfortunately, indirect calorimetry is not always available to the clinician, and predicting energy needs falls to the use of equations.

If indirect calorimetry is not available, an estimate of basal metabolic rate (BMR) can be obtained by a number of equations, all widely researched in comparison to indirect calorimetry. The most widely known and, until the past few decades, the most widely used of these equations is the Harris-Benedict equation.[36] It should be noted that mistakes in transcribing the constant coefficient (ie, 655 for females and 66 for males) frequently lead to inaccurate estimates.[39,40] The Harris-Benedict equation was developed using information gathered on healthy individuals. The majority of research was done on the adult population. It is therefore difficult to justify its use on critically ill or hospitalized patients, especially in pediatrics.[41] A number of newer equations have been developed that can be used to determine energy needs in pediatrics and in a critical care setting.

In the mid-1980s, a Food and Agricultural Organization/World Health Organization (FAO/WHO) committee established new predictive equations for estimating energy requirements.[42] Subsequent review and evaluation by Schofield led to equations that more closely relate to values obtained by indirect calorimetry, when factors are used for activity, stress, and disease state (Table 3-3).[43,44] Other predictive equations that have been proposed have been unable to relate as closely to measured energy requirements. Efforts

TABLE 3-1 Laboratory Tests for Nutritional Assessment

Nutrient	*Initial Screening*	*Secondary Monitoring*	*Special Investigations*
General status	Hemoglobin, hematocrit	Respiratory quotient	Total body K, total body N, indirect calorimetry
Protein	S albumin, S total protein, U protein (dipstick)	S transferrin, prealbumin, S retinol-binding protein, creatinine height index	U hydroxyproline index; S amino acid profiles, indices; nitrogen balance; stable isotope infusion
Fat		S triglycerides, S cholesterol	S lipoprotein electrophoresis, triene/tetraene ratio
Carbohydrate	S glucose, U sugar (dipstick)	GTT, lactose, sucrose tolerance tests	Breath hydrogen test
Vitamins			
A		S retinol, S carotene	S retinol-binding protein, dark adaptation test
C		S ascorbate	WBC ascorbate, blood ascorbate, tyrosine load test
D		S 25-(OH)-D; S calcium, phosphorus; S alkaline phosphatase; bone radiograph	S 1,25-$(OH)_2$-D (HPLC), S vitamin D^2 (HPLC), S PTH (RIA)
E		S tocopherol	RBC hemolysis test, tocopherol transport capacity
K		Prothrombin time	Clotting time, S vitamin K (HPLC)
Thiamin		RBC transketolase activity	24-hr U thiamin, TPP stimulation test
Riboflavin		RBC glutathione reductase activity	24-hr U riboflavin, blood pyruvate
Niacin		Whole blood NAD	24-hr U 2-Me nicotinamide, U 2-pyridone
B_6		S vitamin B_6, S pyridoxal phosphate	EGOT or EGPT index, U vitamin B_6, U 4-pyridoxic acid, tryptophan load test
B_{12}	Hemoglobin, RBC indices, RBC morphology	S vitamin B_{12}	U methylmalonic acid, RBC vitamin B_{12}, Schilling test
Folate	Hemoglobin, hematocrit, RBC indices, RBC morphology	S folate	U FIGLU, RBC folate
Pantothenate			S pantothenate, 24-hr U pantothenate
Biotin			Whole blood biotin, 24-hr U biotin
Minerals			
Calcium		S calcium, bone radiographs	Bone densitometry, calcium balance, S PTH
Phosphorus		S phosphorus	
Magnesium		S magnesium	
Iron	Hemoglobin, hematocrit, RBC indices, RBC morphology	S iron, S ferritin, S iron-binding capacity, S transferrin saturation	Marrow iron, free RBC protoporphyrin
Zinc		S zinc	RBC zinc, WBC zinc, salivary zinc, hair zinc, zinc isotope turnover
Copper		S copper, S ceruloplasmin	RBC copper, 24-hr U copper, hair copper, RBC superoxide dismutase, radiocopper turnover
Iodine		S thyroxine, S TSH	
Selenium		RBC selenium, RBC glutathione peroxidase	
Immune status	Total lymphocyte count, skin tests	S complement (C_3, CH_{50}), S immunoglobulins	Lymphocyte stimulation, T and B cell quantitation, WBC chemotaxis, NBT phagocytosis

EGOT = erythrocyte glutamic-oxaloacetic transaminase; EGPT = erythrocyte glutamic-pyruvic transaminase; FIGLU = formiminoglutamic acid; GTT = glucose tolerance test; HPLC = high-performance liquid chromatography; NAD = nicotinamide adenine dinucleotide; NBT = nitroblue tetrazolium; P = plasma; PTH = parathyroid hormone; RBC = red blood cell (leukocyte); RIA = radioimmunoassay; S = serum; TPP = thiamin pyrophosphate; TSH = thyroid-stimulating hormone; WBC = white blood cell (leukocyte).

to study predictive equations that will adequately assess energy requirements have only reinforced the fact that indirect calorimetry is the most accurate tool.[45–51]

In normal states, REE is about 10% above BMR, but this does not take into account additional requirements such as postoperative stress, burns, infection, or disease states, which can vary as much as 50% above or below BMR. Originally, calculations of BMR and REE were common for evaluation of thyroid function; their use today has shifted to research in obesity and in critically ill patients requiring nutritional support. Generally, critically ill patients require up to one and a half times their REE to prevent protein breakdown for gluconeogenesis. Precise measurements of individual energy requirements allow tailoring of nutritional support to prevent lean body mass breakdown without needlessly increasing oxygen consumption (which can compromise respiratory status) or fat deposition.

Finally, studies of energy metabolism over longer periods in subjects performing a variety of activities have used

TABLE 3-2 Guidelines for Criteria of Nutritional Status for Laboratory Evaluation

Nutrient and Units	*Age of Subject (yr)*	*Criteria of Status*		
		Deficient	*Marginal*	*Acceptable*
Hemoglobin (g/100 mL)*	6–23 mo	Up to 9.0	9.0– 9.9	10.0+
	2–5 mo	Up to 10.0	10.0–10.9	11.0+
	6–12	Up to 10.0	10.0–11.4	11.5+
	13–16 M	Up to 12.0	12.0–12.9	13.0+
	13–16 F	Up to 10.0	10.0–11.4	11.5+
	16+ M	Up to 12.0	12.0–13.9	14.0+
	16+ F	Up to 10.0	10.0–11.9	12.0+
	Pregnant (after 6 mo)	Up to 9.5	9.5–10.9	11.0+
Hematocrit (packed cell volume, %)*	Up to 2	Up to 28	28–30	31+
	2–5	Up to 30	30–33	34+
	6–12	Up to 30	30–35	36+
	13–16 M	Up to 37	37–39	40+
	13–16 F	Up to 31	31–35	36+
	16+ M	Up to 37	37–43	44+
	16+ F	Up to 31	31–37	33+
	Pregnant	Up to 30	30–32	33+
Serum albumin (g/100 mL)*	Up to 1	—	Up to 2.5	2.5+
	1–5	—	Up to 3.0	3.0+
	6–16	—	Up to 3.5	3.5+
	16+	Up to 2.8	2.8–3.4	3.5+
	Pregnant	Up to 3.0	3.0–3.4	3.5+
Serum protein (g/100 mL)*	Up to 1	—	Up to 5.0	5.0+
	1–5	—	Up to 5.5	5.5+
	6–16	—	Up to 6.0	6.0+
	16+	Up to 6.0	6.0–6.4	6.5+
	Pregnant	Up to 5.5	5.5–5.9	6.0+
Serum ascorbic acid (g/100 mL)*	All ages	Up to 0.1	0.1–0.19	0.2+
Plasma vitamin A (µg/100 mL)*	All ages	Up to 10	10–19	20+
Plasma carotene (µg/100 mL)*	All ages	Up to 20	20–39	40+
	Pregnant	—	40–79	80+
Serum iron (µg/100 mL)*	Up to 2	Up to 30	—	30+
	2–5	Up to 40	—	40+
	6–12	Up to 50	—	50+
	12+ M	Up to 60	—	60+
	12+ F	Up to 40	—	40+
Transferrin saturation (%)*	Up to 2	Up to 15.0	—	15.0+
	2–12	Up to 20.0	—	20.0+
	12+ M	Up to 20.0	—	20.0+
	12+ F	Up to 15.0	—	15.0+
Serum folacin (ng/mL)†	All ages	Up to 2.0	2.1–5.9	6.0+
Serum vitamin B_{12} (pg/mL)†	All ages	Up to 100	—	100+
Thiamin in urine (µg/g creatinine)*	1–3	Up to 120	120–175	175+
	4–5	Up to 85	85–120	120+
	6–9	Up to 70	70–180	180+
	10–15	Up to 55	55–150	150+
	16+	Up to 27	27– 65	65+
	Pregnant	Up to 21	21– 49	50+
Riboflavin in urine (µg/g creatinine)*	1–3	Up to 150	150–499	500+
	4–5	Up to 100	100–299	300+
	6–9	Up to 85	85–269	270+
	10–16	Up to 70	70–199	200+
	16+	Up to 27	27– 79	80+
	Pregnant	Up to 30	30– 89	90+
RBC transketolase-TPP-effect (ratio)†	All ages	25+	15– 25	Up to 15
RBC glutathione reductase-FAD-effect (ratio)†	All ages	1.2+	—	Up to 1.2
Tryptophan load (mg xanthurenic acid excreted)†	Adults (dose: 100 mg/kg body weight)	25+ (6 hr) 75+ (24 hr)	— —	Up to 25 Up to 75

Continues

TABLE 3-2 *Continued*

Nutrient and Units	*Age of Subject (yr)*	*Criteria of Status*		
		Deficient	*Marginal*	*Acceptable*
Urinary pyridoxine (μg/g creatinine)†	1–3	Up to 90	—	90+
	4–6	Up to 80	—	80+
	7–9	Up to 60	—	60+
	10–12	Up to 40	—	40+
	13–15	Up to 30	—	30+
	16+	Up to 20	—	20+
Urinary N methyl nicotinamide* (mg/g creatinine)	All ages	Up to 0.2	0.2–5.59	0.6+
	Pregnant	Up to 0.8	0.8–2.49	2.5+
Urinary pantothenic acid (μg)	All ages	Up to 200	—	200+
Plasma vitamin E (mg/100 mL)	All ages	Up to 0.2	0.2–0.6	0.6+
Transaminase index (ratio)				
EGOT	Adult	2.0 +	—	Up to 2.0
EGPT	Adult	1.25+	—	Up to 1.25

*Adapted from the US Department of Health, Education, and Welfare.[145]
†Criteria may vary with different methodology.
A = age (years); EGOT = erythrocyte glutamic oxalacetic transaminase; EGPT = erythrocyte glutamic pyruvic transaminase; F = female; H = height (cm); M = male; W = weight (kg).

the doubly labeled water method.[52–55] Water enriched with the stable isotopes deuterium and ^{18}O ($^{2}H_2$ ^{18}O) is administered in a single oral or intravenous dose and several blood or urine samples are obtained over the next 5 to 14 days. Because ^{18}O is excreted as both urinary water and respiratory carbon dioxide, but deuterium is excreted only as water, the different rates of excretion can be measured by mass spectrometry and can be used to calculate metabolic rate. Although they are useful in validating long-term energy needs compared to reports of dietary intake,[56–58] their clinical use in the acute care setting is difficult because of the time and expense involved in stable isotope enrichment and mass spectrometry.

TABLE 3-3 Equations for Estimating Resting Energy Expenditure in Children

Harris-Benedict
Men: 66.437 + (13.7516 × W) + (500.33 × H) – (6.755 × A)
Women: 655.0955 + (9.5634 × W) + (184.96 × H) – (4.6756 × A)
Infants: 22.10 + (31.05 × W) + (11.6 × H)

World Health Organization
Males
0–3 yr: (60.9 × W) – 54
3–10 yr: (22.7 × W) + 495
10–18 yr: (17.5 × W) + 651
Females
0–3 yr: (61 × W) – 51
3–10 yr: (22.5 × W) + 499
10–18 yr: (12.2 × W) + 746

Schofield
Males
0–3 yr: (0.167 × W) + (15.174 × H) – 617.6
3–10 yr: (19.59 × W) + (1.303 × H) + 414.9
10–18 yr: (16.25 × W) + (1.372 × H) + 515.5
Females
0–3 yr: (16.252 × W) + (10.232 × H) – 413.5
3–10 yr: (16.969 × W) + (1.618 × H) + 371.2
10–18 yr: (8.365 × W) + (4.65 × H) + 200.0

A = ages; H = height; W = weight.

PROTEIN

The assessment of protein nutrition has presented one of the most important yet most problematic questions in the history of nutrition. Widespread protein-energy malnutrition worldwide has fueled interest in determining protein status and requirements, especially in children.[59] Many methods have been devised for measuring protein use, but the central problem of protein turnover remains. Approximately 15% of the body mass consists of protein stored in the liver, muscles, intestines, and other tissues. This, however, is in dynamic equilibrium with the much smaller percentage of body protein carried as plasma amino acids. Concentrations of plasma proteins or amino acids do not necessarily represent their relative concentrations in tissue storage pools.[60–62]

Attempts to measure the flux between these metabolic and storage pools using labeled amino acids generally assume a steady state in which protein synthesis equals protein breakdown. Although radioisotopes were previously used to trace amino acid flux between protein pools, objections to their use in human subjects have led to studies using stable isotopes such as ^{13}C leucine and ^{15}N glycine. Because they require complicated mathematical calculations and mass spectrometer analysis, stable isotope infusions have generally been limited so far to research applications.[63,64] Thus, analysis of plasma proteins or amino acid levels cannot always be depended on to give a direct reflection of whole-body protein status. Of the thousands of plasma proteins, relatively few have been shown to have direct clinical significance as tests of health or nutritional status.[65] The future of protein analysis could lie in microassay chip technology now being developed for genetic analysis. Although the focus of this technology is currently on genetics and disease, it could be of use by clinicians for protein assessment.

Serum Albumin

Total serum proteins can be separated into albumins and globulins (α, β, and γ) by electrophoresis. Because γ-globulins can be increased in infection or malignancy, serum albumin levels are generally a better test of protein status than is total serum protein. Serum albumin levels have been one of the most popular measures of protein-calorie malnutrition, and levels below 3.5 g/dL are a hallmark of kwashiorkor. Although albumin remains widely used as a marker of nutritional status, the clinician must take into account multiple other factors affecting the result. Albumin levels can be normal in mild or even severe marasmus, despite markedly reduced muscle mass. Conversely, serum albumin levels can also be affected by other disease states (eg, rapid blood loss, protein-losing enteropathy), stress, surgery, fluid shifts, and even postural changes. Albumin turnover is fairly slow, with a half-life of about 20 days. Therefore, serum levels do not reflect recent dietary intake; albumin levels might not be reduced even after 3 weeks on a protein-free diet.[66–70]

Other Serum Proteins and Enzymes

Other transport proteins, such as thyroxine-binding prealbumin (transthyretin),[71] retinol-binding protein,[72] transferrin,[73] and ferritin,[74] have been proposed as better markers of protein malnutrition because of their shorter half-lives, but they can also be affected by caloric restriction, iron deficiency, or infection, as well as protein deficiency.[75] Prealbumin is secreted by the liver in a complex containing retinol, retinol-binding protein, and thyroxine (T_4) and thus is also known as transthyretin. Although vitamin A deficiency can affect secretion of retinol-binding protein, it does not affect plasma levels of prealbumin.[76–80] Ferritin is an acute-phase reactant and can be elevated in liver disease or various inflammatory states.

Other plasma proteins that have been proposed as markers of nutritional status include fibronectin[81] and insulin-like growth factor-1 (IGF-1).[82,83] IGF-1 and IGF-1–binding proteins have both been widely studied for their connection with nutritional status.[84,85] Studies have shown that levels of both IGF-I and IGF-1–binding proteins are affected when calories or protein are restricted.[86,87] IGF-I and IGF-binding proteins might not have the same disadvantages as other proteins when used for assessment. Both values appear to be sensitive indicators in an acute setting to changes in nutritional status.[88,89]

Concentrations of various enzymes in plasma have been widely used in diagnosis of many disease states but, for that very reason, are less specific for protein deficiency. Plasma concentrations of pseudocholinesterase, alkaline phosphatase, amylase, and lipase are reported to be reduced in kwashiorkor, whereas lactic dehydrogenase, isocitrate dehydrogenase, and transaminase are increased. In children, elevated plasma ribonuclease activity can be increased in even mild to moderate malnutrition; comparison of plasma and urine activities can distinguish between moderate and severe malnutrition.[90,91]

Attempts have been made to use plasma amino acid profiles to assess nutritional status. Because concentrations of amino acids are not regulated and do not directly reflect tissue uptake and flux, use in clinical settings has not been widely received. Amino acid values are also affected by infection, injury, and other stressors.[92]

Urinary Protein Excretion

Another approach to the assessment of protein status uses urinary excretion of protein breakdown substances. Creatinine is a degradation product of muscle creatine, and urinary excretion of creatinine has been used since 1905 as a measure of lean body mass. The creatinine height index compares urinary creatinine excretion over 24 hours to a control value and has been widely used as a measure of protein depletion in kwashiorkor and marasmus.[93]

Other urinary excretion ratios using creatinine as a standard, such as the urea-creatinine ratio, the sulfur-creatinine ratio, and the urinary hydroxyproline index, have been investigated but tend to reflect recent dietary protein intake rather than long-term nutritional status. Furthermore, these methods all require a 24-hour urine sample to minimize daily fluctuations in urine excretion, and this might not always be easy to obtain. Efforts to short-cut this difficulty have been frustrated by the variability of spot urine creatinine excretion.[94]

Nitrogen Balance Studies

Nitrogen balance studies can be useful in assessing individual protein status, although traditionally they have been used more in controlled metabolic research studies to determine protein requirements in populations or food protein quality. Nitrogen balance measurements can give a direct short-term comparison of dietary nitrogen intake versus fecal and urine excretion.[95] Nitrogen retention is calculated by subtracting fecal and urine nitrogen from oral intake:

$$\text{N retention} = \text{N intake} - \text{fecal N} - \text{urine N}$$

Ideally, this should be performed for several days on a constant protein intake in steady-state conditions. Nitrogen intake can be estimated by dividing dietary protein intake (in grams) by 6.25. Nitrogen output is best analyzed by the rather time-consuming Kjeldahl method of sulfuric acid distillation but can also be estimated in adults by urine urea nitrogen,[96] using an estimate of 4 g/day for stool and skin losses, although this could be much less in children:

$$\text{N retention} = (\text{protein intake}/6.25) - \text{urine urea N} - 4$$

Although nitrogen balance studies are used often in a clinical setting, they should not be used as the only means of assessing protein balance.[97–100]

Lipids

Plasma Lipids and Lipoproteins

Assessment of the fat status of individuals is complicated by similar considerations of storage and metabolic pools. Although fat stores in the body represent a considerable reserve of energy, only a small percentage of this fat is present in the plasma as free fatty acids. Additionally, much of

the free fatty acids and triglycerides in the plasma are derived from endogenous synthesis rather than from recent dietary intake. Triglycerides are transported in the blood along with cholesterol and proteins as lipoproteins. These can be separated by ultracentrifugation or electrophoresis as very-low-density lipoprotein or prebeta, low-density lipoprotein (LDL) or beta, and high-density lipoprotein (HDL) or alpha.[101,102]

Whereas elevated total plasma cholesterol and LDL cholesterol levels are associated with atherosclerosis,[103] higher HDL levels could be protective.[104] Studies of plasma lipids in adults have demonstrated links between multiple risk factors and cardiovascular disease. Risk factors include age, sex, history of hypertension, smoking, diabetes, high LDL levels, and low HDL levels. Various criteria have been developed, such as the Adult Treatment Panel III, to provide clinicians with guidelines for assessment of cardiovascular risk. Family history and various diseases also affect cholesterol levels and do not necessarily reflect nutritional deficiency or excess.[105] Studies in children are few, and recommendations for appropriate levels in the very young have not been assessed.

Essential Fatty Acid Deficiency

Although nutritional fat deficiencies are rare, a greater appreciation of essential fatty acid deficiency has occurred in association with a syndrome of dermatitis, poor growth, and degenerative changes in several tissues.[106,107]

Certain fatty acids cannot be synthesized in the body but must be supplied in the diet. They are important as precursors for cholesterol, prostaglandins, and cell membranes.[108]

This requirement comprises 1 to 2% of total caloric intake, but even this might not be provided if a patient is receiving total parenteral nutrition without periodic intravenous fat supplements.[109] Essential fatty acid deficiency can be assessed by elevation of the triene-tetraene ratio because nonessential eicosatrienoic acid (20:3, a triene) levels rise, whereas arachidonic acid (20:4, a tetraene) levels fall.[110,111] Linolenic acid could be another essential fatty acid; there has been a recent report of typical essential fatty acid deficiency symptoms occurring when linoleic acid but not linolenic acid was supplied for several months.[112]

Body Composition and Obesity

Obesity is less often assessed by biochemical parameters than by anthropometric measurements because most techniques for determining total body fat are practical only for research purposes. Potassium is distributed fairly evenly in fat-free tissue and contains a small percentage of the natural radioisotope ^{40}K. Very sensitive gamma counters can thus detect the amount of radioactive potassium in lean body mass, which can be subtracted from the total body mass to determine total body fat.[111,112] Because adipose tissue is very low in water content, total body fat can also be estimated by dilution of injected tritium, deuterium, or stable ^{18}O in the total body water compartment and subtracting that measurement from total body mass. Alternatively, determination of body density by plethysmography or immersion in water can differentiate between a relative amount of fat (with a lower specific gravity of 0.9) versus other tissues.[113]

Recent availability of dual photon absorptiometers, usually used to measure bone density, has led to their being adapted for body composition measurements because lean body tissue and fat can be differentiated and quantitated with a high degree of precision.[114,115]

Bioelectric impedance has been developed as a quick, inexpensive, and noninvasive measurement of lean body mass, which conducts electrical charge better than fat. However, measurements can be affected by changes in tissue fluid content, such as edema or dehydration.[116–120] Body composition is reviewed in more detail in Chapter 4, "Body Composition and Growth."

Carbohydrates

Obviously, serum glucose levels are regulated by insulin and other factors so that they do not directly reflect nutritional stores or requirements.[121,122] Alterations in serum glucose levels are thus more likely to be the result of impaired regulatory mechanisms (eg, in diabetes mellitus) than of nutritional deficiencies. Rarely, hypoglycemia can be the result of lack of carbohydrate substrate, as in neonatal hypoglycemia, childhood ketotic hypoglycemia, or glycogen synthetase deficiency.[123,124] However, hypoglycemia is too often diagnosed in otherwise healthy persons on the basis of a borderline serum glucose level, either fasting or after a glucose tolerance test, and this should not be considered a nutritional disease.

Glucose tolerance tests and other oral carbohydrate tolerance tests (lactose, sucrose, xylose) have also been used to assess carbohydrate malabsorption, although breath hydrogen testing is superior for this purpose.[125,126] If an oral dose of carbohydrate is malabsorbed, it will pass into the colon, where bacteria will metabolize it to hydrogen. The hydrogen, which is not produced elsewhere in the body, is excreted in the breath, where it can be collected and measured by gas chromatography. Stable isotopes are used to study glucose metabolism but are better suited for research purposes and large populations than for clinical assessment.[127]

IMMUNE STATUS

Although not always sufficiently appreciated, interactions between nutritional status and infections have been amply demonstrated for some time. Not only do infections adversely affect nutritional status, but malnutrition also predisposes the patient to a host of infections: parasitic, viral, bacterial, and fungal.[128] Investigations by Chandra and Kumari[129,130] and others have elucidated some of the immune dysfunctions that accompany protein-calorie malnutrition and specific nutrient deficiencies[131] and mediate impaired resistance to infection (Table 3-4). Conversely, immunologic assays have been proposed as functional tests of nutritional status, tests that reflect the functional ability of the individual to resist infection, instead of mere static measurements of a single nutrient.[132,133]

Immune responses can be divided into three categories: (1) cellular, principally involving T lymphocytes; (2) humoral, including serum and secretory antibodies; and (3) nonspecific, including phagocytosis, complement, and mucosal immunity. Protein-energy malnutrition affects immune responses in all three of these areas but has been most often associated with profound defects in cell-mediated immunity.[134] Skin tests for a number of antigens, such as *Monilia* (*Candida*), streptokinase-streptodornase, *Trichophyton*, and mumps are normally positive (> 5 mm induration after 72 hours) if there has been prior exposure to these antigens in the environment. However, there is a consistent loss of this cutaneous delayed-type hypersensitivity in moderate to severe protein-calorie malnutrition, and skin tests have been used as a sensitive indicator of functional malnutrition in field surveys as well as in hospital settings.[135] Although they do not require blood samples, skin tests do have the disadvantage that they cannot be read until 48 to 72 hours after taking the sample. If common recall antigens do not provoke any response, deliberate contact sensitization with dinitrochlorobenzene and subsequent rechallenge can be performed.[136]

Decreased cell-mediated immunity in malnutrition is also manifest as a decrease in lymphoid tissue, including thymus, tonsils, lymph nodes, and peripheral lymphocytes.[137] A quick estimate of the total lymphocyte count (TLC) can be easily obtained by multiplying the white cell count (WBC) by the percentage of lymphocytes seen on the peripheral smear:

$$TLC = WBC \times \% \text{ lymphocytes}$$

A decrease in the total lymphocyte count to less than 1,500/mm^3 is seen in some, but not all, malnourished patients, although many other conditions can cause lymphopenia as well. Nonspecific transformation of lymphocytes into blast forms by phytohemagglutinin and pokeweed mitogen in the lymphocyte stimulation test is occasionally impaired in severe malnutrition,[138] but this is not a consistent observation.

B lymphocyte response in malnutrition is less affected, and quantitative serum immunoglobulins can be elevated, although this finding could be attributable to constant low-grade infection.[139,140] The complement cascade is important in cytolytic responses, and levels of all complement proteins, except C4, are markedly decreased in protein-energy malnutrition. The most commonly available assays for complement function are C3 and CH50 (50% hemolysis).[141,142] Finally, phagocyte function can be impaired in malnutrition, with decreased leukocyte chemotaxis and decreased intracellular bacterial killing, although these phenomena might be more attributable to infection than to malnutrition per se.[143,144] Leukocyte mobility and chemotaxis can be measured in vivo with a Rebuck skin window or in vitro in a Boyden chamber after separation of leukocytes. The nitroblue tetrazolium dye test measures reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activity, which accompanies bacterial killing. Specific nutrient deficiencies also cause immune system dysfunction, notably iron, zinc, vitamin A, vitamin B_{12}, pyridoxine, and folate deficiency.

TABLE 3-4 Immunologic Changes in Malnutrition

A. Cell-mediated immunity
1. Delayed hypersensitivity (skin tests to PPD, *Candida*, SKSD, *Trichophyton*, DNCB)
2. Lymphocytes (normal absolute lymphocyte count)
a. ↓ T lymphocytes (E rosettes)
b. ↓ T helper cells, normal T suppressors
3. Lymphocyte proliferation
a. Normal to ↓ PHA stimulation
b. Normal to ↑pokeweed mitogen stimulation
4. ↓ Lymphoid tissue (tonsils, thymus, lymph node, pancreatic tissue)
5. ↓ Thymic hormone
6. Normal lymphokine activity (MIF)
B. Humoral immunity
1. Serum immunoglobulins (normal to ↑ IgG, IgM, IgA; ↑ IgE)
2. ↓ Secretory immunoglobulins (↓ SIgA)
3. Antibody response (normal to ↑ typhoid, pneumococcal polysaccharide; ↓ to normal diphtheria toxoid, yellow fever)
C. Nonspecific immunity
1. ↓ Phagocyte function
a. ↓ Chemotaxis (with infection)
b. ↓ Intracellular bacterial and candidal killing
c. Normal phagocytosis
2. ↓ Lysozyme activity
3. Complement levels
a. ↓ C_3, CH_{50}
b. ↑ Immune complexes
4. ↓ Interferon production
5. ↓ Mucosal immunity

Adapted from Gotoff SP.[172]
DNCB = dinitrochlorobenzene; ↓ = decreased; ↑ = increased; MIF = migration inhibiting factor; PHA = phytohemagglutinin; PPD = purified protein derivative; SKSD = streptokinase-streptodornase.

APPLICATIONS

Nutritional Field Surveys

In nutritional field surveys, large numbers of relatively healthy people are sampled to determine the prevalence of malnutrition in the population. Because samples are usually collected by mobile field units removed from central laboratories, problems such as refrigeration, centrifugation, and timing put severe restraints on the types of assays possible. Twenty-four-hour urine collections are usually not practical, and reliance must be placed on spot urine samples. Blood samples are generally limited to what can be obtained from one venipuncture, and invasive tests are usually out of the question. In surveys of young children in developing countries, even venipuncture is difficult, and laboratory tests are often limited to a fingerstick hematocrit and blood smear.

Careful selection of tests is of utmost importance to minimize needless duplication of information and to emphasize nutrients that are most likely to be deficient in the populations sampled. Standardization of collection, analysis, and reporting procedures must be maintained, and samples are generally transported to a central laboratory for processing. Some of the most elaborate nutritional surveys undertaken were the Ten-State Nutrition Survey (1968–1970) and its successors, the National Health and

Nutrition Examination Surveys (NHANES). Results from the Third NHANES (1988–1994) continue to be studied and reported. Some of the biochemical tests used in these surveys are listed in Table 3-5.[145–147]

Hospital Malnutrition

Although most of the classic epidemic vitamin deficiency diseases are now rarely seen in the United States, malnutrition in hospitalized patients is still a major problem. Until recently, nutritional assessment of hospitalized patients was rarely systematically or even routinely performed. Increasing attention has been paid to the widespread malnutrition detected by anthropometric and laboratory tests in acute care hospitals.[148] Hendricks and colleagues, using anthropometrics, laboratory assessment, and clinical nutrition assessment, repeated a study on the prevalence of malnutrition in a children's hospital.[149] Although a decrease in malnutrition was found, malnutrition was still prevalent in patients with chronic medical conditions, in children less than 2 years of age, and in patients older than 18 years. Although the need for nutritional assessment has been realized, both adult and pediatric patients still appear at risk for malnutrition, especially in a hospital setting.

Because of the proliferation of possible laboratory tests for the assessment of nutritional status, attempts have been made to identify those values that are clinically significant. Although detection of malnutrition is of interest, the relationship of nutritional values to morbidity and mortality is even more important clinically. A recent study by Naber and colleagues determined that malnutrition was predictive of complications in nonsurgical patients.[150]

Interest in identifying specific patients at risk for excess morbidity and postoperative complications has been the focus of trials of perioperative nutritional rehabilitation, either enterally or parenterally.[151–153] A large, multicenter trial reported that preoperative parenteral nutrition was cost-effective only in a select group of patients who were considered severely malnourished[154] using a Nutrition Risk Index based on serum albumin levels and weight loss.[155]

Using stepwise regression analysis, Buzby and colleagues[156] and Mullen[157] devised a Prognostic Nutritional Index (PNI) for patients about to undergo surgery, based on only four readily measured values (serum albumin [Alb], transferrin [Tfn], triceps skinfold [TSF], and delayed-type hypersensitivity skin tests [DTH]):

$$PNI = 158 - 16.6\,(Alb) - 7.8\,(TSF) - 0.20\,(Tfn) - 5.8\,(DTH)$$

Patients with a high-risk PNI of greater than 50 had increased postoperative complications, infections, and mortality. Harvey and colleagues used a similar index,[158] which includes information about specific diagnosis (cancer) and presence of infection:

$$PNI = 0.91\,(Alb) - 1.0\,(DTH) - 1.44\,(sepsis) + 0.98\,(Dx) - 1.09$$

Seltzer and colleagues reduced the number of values further, using serum albumin and total lymphocyte counts as a means of providing an instant nutritional assessment to determine the need for nutritional therapy.[159,160] Rainey-MacDonald and colleagues also found that the triceps skinfold and cutaneous-delayed hypersensitivity tests, which take 2 days to read, were redundant and added little to the predictive value of serum albumin and transferrin levels.[161] Other investigators,[162,163] despite using techniques such as Boolean analysis and receiver-operating characteristic curve analysis, have not found a substantially good predictive value between any of these biochemical and anthropometric standards and morbidity or changes in body composition.

Indeed, Baker and colleagues suggest that most of the common laboratory tests for nutritional assessment (serum albumin, triceps skinfold, total lymphocyte count, weight, creatinine height index, and delayed cutaneous hypersensitivity) had less sensitivity and specificity than a comprehensive bedside clinical assessment, including simple diet history, physical examination, and knowledge of disease state (Figure 3-2).[164] Furthermore, they showed that any combination of laboratory tests had no better prognostic value than a subjective global clinical assessment.[165–167]

Despite a wide range of available laboratory tests, no simple test or battery of tests has yet proved completely satisfactory for a definitive assessment of nutritional status, and one should include anthropometric and clinical as well as laboratory information for best results (Table 3-6).[168–170] Clinicians continue to create valuable tools that address all aspects of nutritional assessment. For example, WAVE (weight, activity, variety, and excess) is a recent development that provides a quick assessment for clinicians and recommendations for their patients.[171] Assessment tools such as this, in combination with laboratory values, can be useful in determining nutritional status.

TABLE 3–5 Laboratory Tests of Nutritional Status Employed in the Health and Nutrition Examination Surveys

Hemoglobin
Hematocrit
Serum iron
Serum iron-binding capacity
Blood folacin
Total serum protein
Serum albumin
Serum vitamin C
Plasma carotene
Plasma vitamin A
Urinary creatinine
Urinary thiamin
Urinary riboflavin
Urinary iodine

CONCLUSIONS AND RECOMMENDATIONS

Myriad laboratory tests are available for the assessment of nutritional status. Many methods have been devised for quantitation of different proteins, lipids, vitamins, and minerals in the serum, urine, and other body fluids. Unfortunately, no one test or battery of tests gives a completely satisfactory picture of the global nutritional state of the individual. Most common, inexpensive, easily available tests are not sensitive enough to detect early malnutrition before it becomes clinically significant. Conversely, most assays tend to be too specific to reflect abnormalities in a broad

(Select appropriate category with a checkmark or enter numeric value where indicated by "#")

A. History
1. Weight change
Overall loss in past 6 months: amount = # _____ kg; % loss = # _____
Change in past 2 weeks: _____ increase,
_____ no change,
_____ decrease.

2. Dietary intake change (relative to normal)
_____ No change,
_____ Change _____ duration = # _____ weeks.
_____ type: _____ suboptimal solid diet, _____ full liquid diet
_____ hypocaloric liquids, _____ starvation.

3. Gastrointestinal symptoms (that persisted for > 2 weeks)
_____ none, _____ nausea, _____ vomiting, _____ diarrhea, _____ anorexia.

4. Functional capacity
_____ No dysfunction (eg, full capacity),
_____ Dysfunction _____ duration = # _____ weeks.
_____ type: _____ working suboptimally,
_____ ambulatory,
_____ bedridden.

5. Disease and its relation to nutritional requirements
Primary diagnosis (specify) _____
Metabolic demand (stress): _____ no stress, _____ low stress,
_____ moderate stress, _____ high stress.

B. Physical (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe).
_____ loss of subcutaneous fat (triceps, chest)
_____ muscle wasting (quadriceps, deltoids)
_____ ankle edema
_____ sacral edema
_____ ascites

C. SGA rating (select one)
_____ A = Well nourished
_____ B = Moderately (or suspected of being) malnourished
_____ C = Severely malnourished

FIGURE 3-2 Form for subjective global assessment (SGA). Adapted from Baker JP et al.[164]

TABLE 3-6 Initial Screening Tests for Nutritional Assessment

Dietary assessment
24-hour recall or
Typical day recall or
72-hour diary or
Food frequency questionnaire
Anthropometric assessment
Height and height-for-age percentiles
Weight and weight-for-age percentiles, weight-for-height percentiles
Triceps skinfolds and arm circumference
Laboratory assessment
Complete blood count, including hemoglobin, hematocrit, WBC and differential, RBC smear
Serum albumin (or prealbumin or retinol-binding-protein), total protein
Serum electrolyte: sodium, potassium, chloride, bicarbonate
Renal function tests: blood urea nitrogen, creatinine
Serum glucose, triglycerides (fasting)
Serum cholesterol, HDL cholesterol, LDL cholesterol
Serum calcium, phosphorus, magnesium
Liver function tests: alanine aminotransferase, bilirubin
Urinalysis (dipstick)
Clinical assessment
Clinical history
Subjective global assessment
Physical examination

HDL = high-density lipoprotein; LDL = low-density lipoprotein; RBC = red blood cell; WBC = white blood cell.

range of nutrients. Although laboratory assessment has the advantage of providing reproducible, quantitative data, it is not always possible to determine tissue stores or functional reserve from a single serum or urine sample. Many tests require timed collections, complicated analytic methods, and expensive instruments and are more suited for specific research investigations than for clinical screening.

Recent efforts to develop a simple, streamlined battery of tests to detect hospital malnutrition have focused on the prognostic value of tests that predict clinical complications. Although no standard formula has achieved wide use, most include measurements of protein nutrition (serum albumin) and immune status (skin tests or lymphocyte count). However, these quick estimations might not have better predictive value than a global clinical assessment. Thus, laboratory assessment of nutritional status requires an intelligent selection of tests to fit the clinical situation. It should augment the dietary, clinical, and anthropometric data that should also be gathered and evaluated and should not be overemphasized to their exclusion. Used in this way, laboratory data will allow better quantification, reproducibility, and objectivity in the assessment of nutritional status.

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CHAPTER 4

BODY COMPOSITION AND GROWTH

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Growth is the maturation process characterized by change, compensation, and adaptation; it is genetically predetermined and significantly affected by hormonal, nutritional, and environmental factors. The size and shape of an individual are a result of the dynamic events preceding the time of assessment. The measurement of body composition allows the observer a closer look at the physiologic changes seen during growth and disease.

The recognition of the importance of body composition changes in different areas of acute, chronic, and preventive medicine has prompted an increased interest in studying and refining techniques of measuring these changes.[1] The accurate definition of nutritional status cannot be based only on height and weight. Some measure of body composition is also needed to distinguish, for example, the obese from the overweight, muscular individual.[2] In certain diseases, such as protein-energy malnutrition, cystic fibrosis, inflammatory bowel disease, chronic renal disease, and acquired immune deficiency syndrome (AIDS), which produce malnutrition or fluid and electrolyte derangement, weight measurements can overestimate the nutritional well-being of the patient. In addition, it might be possible, with nutritional rehabilitation, to achieve normal weight in the presence of inadequately repleted body composition or with an excess of fat or water.[3]

The study of body composition allows better comprehension of the effects of the genetic, nutritional, and physical activity factors on fat, muscle, and bone development.[4] It permits the study of the prevalence of obesity in children and youth and allows for better documentation of genetics and tracking of body fatness and bone accretion during the first two or three decades of life, along with their effect on the development of chronic diseases such as diabetes, cardiovascular disease, hypertension, and osteoporosis later in life. In this sense, it is important to define not only the amount of the different components but also the time in which they increase and their regional variations to delineate their possible relations to health risks[5–8] and the best strategies for risk prevention. Changes in the different compartments of the body that occur during fetal life and through infancy, childhood, adolescence, adulthood, and aging are presented in the first part of the chapter. An emphasis is placed on the distribution of fluid, fat, muscle, and bone mass in the different stages of the life cycle during health and disease.

The capacity to measure the body compartments in living human beings has permitted a better understanding of human energy metabolism. With the availability of certain techniques that can be used in the clinical setting, the measurement of body composition has become an indispensable tool in the monitoring of changes of fat and fat-free mass during growth, in circumstances of athletic conditioning, or in the nutritional management of patients with acute or chronic illness. In the past few years, increasing numbers of researchers have used body composition determinations in clinical studies. An understanding of the various methods and measurements of body composition is crucial in the interpretation of this pediatric and nutrition literature. Each method explores body composition from a different perspective, studying the chemical components or taking advantage of certain physical principles. On the whole, the use of different methods in the same set of subjects has allowed the cross-validation of the various techniques and has permitted a more detailed understanding of body composition. A glossary of the most commonly used body composition terms is given in Table 4-1.

CHANGES IN BODY COMPOSITION WITH GROWTH

A schematic representation of the changes in body composition throughout life is shown in Figure 4-1. More specific details of the compositional variation during growth are presented in Table 4-2. Figure 4-2 depicts changes in body compartments during fetal development; this graph can be helpful when assessing the growth of a preterm infant.[13]

Changes in Body Fat Mass

Fat is the most variable of body components, ranging from about 5% to more than 50% of body weight; the normal range is narrower, between about 10 and 30%.[14] During intrauterine life, the differentiation of fat starts in the sec-

Table 4-1 Glossary of Body Composition Terms

Term	*Definition*
Fat mass	All ether-extractable lipids in the body, including nonessential lipid (~90%), mainly triglyceride and essential lipid
Essential lipid	Lipid in bone marrow and cell membranes, and phospholipids in neurons
Adipose tissue	Fat (80–85%) plus its supporting cellular and extracellular structures (2% protein and 13–18% water)
Lean body mass	Part of the body free of adipose tissue
Fat-free mass	Nonfat mass, with four major constituents: water, protein, glycogen, and mineral; lean body mass plus the nonfat components of adipose tissue
Total body water (TBW)	Total water in the body
Intracellular water (ICW)	Water content of the cellular compartment
Extracellular water (ECW)	Nonmetabolizing fluid surrounding cells; distributed in two main compartments: plasma and interstitial fluid
Body cell mass	Cellular components of the body
Extracellular solids	Extracellular chemical compounds distributed in organic (collagen, reticular, and elastic fibers) and nonorganic (total body bone mineral + Na, bicarbonate, and citrate)
Bone mineral content (BMC)	Bone mineral content (g/cm) measured by absorptiometric techniques
Bone mineral density (BMD)	Ratio of BMC/bone width (g/cm^2) measured by absorptiometric techniques

ond trimester of gestation, approximately between the 14th and 24th weeks of pregnancy. It becomes evident in the head (buccal pad area) and neck, progressing rapidly to the trunk, arms, and, finally, the lower limbs. At the beginning of the third trimester, at about the 28th week, adipose tissue is already present in the principal body fat deposit areas. Therefore, it appears that the second trimester of pregnancy is a sensitive period for the development of fat tissue.[15]

The possibility that nutritional alterations at critical periods of development are the source of nutritional states such as adult obesity has been suggested by certain authors.[16] Follow-up studies[17] of infants exposed to famine prenatally or early in life and of infants of diabetic mothers[18–23] strongly suggest that prenatal and perinatal under- or overnutrition influences the development of fatness and its related diseases in later life. Intrauterine conditions could be exclusively or partially responsible for associations between birth weight and adult body composition. A Belgian study examining the relationship between birth weight and adult body composition suggested that genetic factors and the fetal-placental environment are responsible for observed differences in body composition among male twins.[24] Even before birth, there appear to be regional differences in fat accumulation that could have important significance for the future. Cell characteristics and normal growth patterns differ from one fat depot to another. After birth, hormonal responsiveness of fat tissue varies according to its location.[25]

The infant in utero increases its fat content from 2.5% at 1 kg of weight to a fat mass of 13.7% for boys and 14.9% for girls in the full-term newborn.[9,26] From birth, the accumulation of fat progresses rapidly to peak at 29.1% in boys and 32.0% in girls at age 6 months,[12] probably owing to a high intake of energy and little activity.[14] An interesting finding in this area is that breast-fed infants have a different accumulation of fat than formula-fed infants do.[27,28] Breast-fed infants have less fat, with the greatest differences evident between 9 and 15 months of age.[29] Differences in body fat also depend on the proportion of protein and the type of fat contained in certain formulas.[30] With increasing age, fat content drops, and the values fall to a minimum of 12.8% at 7 years in boys and 16.4% at 6 years in girls, with a discrete increase afterward, the "adiposity rebound,"[31] to 13.7% in boys and 19.4% in girls at the age of 10.[9]

Although there are sexual differences in body composition at birth or even sooner, the predominance of fatness in girls becomes remarkable during the adolescent years. In both sexes, puberty is characterized by substantial increases in both adipocyte size and total number and by a

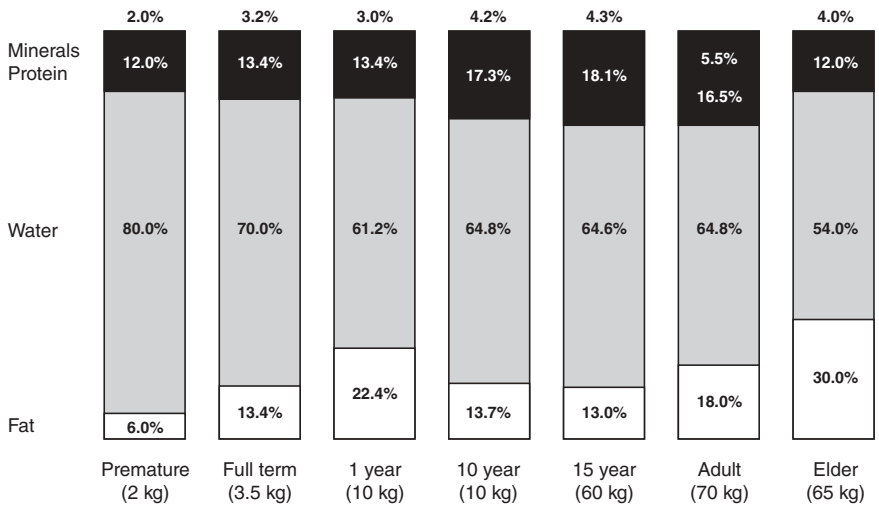

FIGURE 4-1 Changes in proportions of body composition with growth and aging.

TABLE 4-2 Body Composition of Reference Children and Adolescents

			Percentage of Body Weight						
Age (yr)	*Length (cm)*	*Weight (kg)*	*Fat*	*Protein*	*Mineral*	*Carbohydrate*	*TBW*	*ECW*	*ICW*
Boys									
Birth	51.6	3.5	13.7	12.9	3.2	0.5	69.6	42.5	27.0
0.5	67.9	8.04	29.1	10.9	2.4	0.5	57.2	32.9	24.3
1	76.1	10.03	25.6	12.3	2.7	0.5	59.0	31.6	27.4
1.5	82.6	11.43	24.5	12.9	3.0	0.5	59.1	30.1	29.4
2	87.6	12.46	25.4	13.5	3.1	0.5	58.1	26.6	30.7
5	109.9	18.7	14.6	15.8	3.7	0.5	65.4	30.0	35.4
10	137.5	31.4	13.7	16.8	4.1	0.5	64.8	26.7	38.0
12.5	153.0	42.3	16.3	16.4	4.1	0.6	62.7	26.4	36.4
15.5	171.5	59.5	13.0	17.4	4.5	0.6	64.6	25.8	38.8
18.5	177.0	69.9	12.9	17.7	4.8	0.7	64.1	24.7	39.4
Girls									
Birth	50.5	3.3	14.9	12.8	3.2	0.5	68.6	42.0	26.7
0.5	66.5	7.6	32.0	10.4	2.3	0.5	54.9	31.7	23.2
1	75.3	9.5	27.6	12.2	2.7	0.5	56.9	29.7	27.4
1.5	82.0	10.94	26.3	12.7	2.9	0.5	57.8	29.0	28.5
2	87.7	12.02	25.4	13.1	3.0	0.5	57.7	29.0	29.4
5	108.4	17.7	16.7	15.0	3.1	0.5	64.6	31.0	33.6
10	138.3	32.6	19.4	15.0	3.1	0.5	62.0	28.1	33.9
12.5	154.6	43.8	21.5	15.4	4.2	0.5	58.5	25.6	32.9
15.5	162.1	55.0	24.7	14.9	4.5	0.5	55.5	23.7	31.8
18.5	164.0	57.0	25.0	14.9	4.4	0.7	55.2	23.5	31.7

Adapted from Fomon SJ et al,[9] Haschke F,[10,11] and Butte NF et al.[12]
ECW = extracellular water; ICW = intracellular water; TBW = total body water.

centripetal change in fat distribution, which is especially marked in males.[32,33] In terms of fat percentage, males reach peak values during early adolescence and then show a decrease throughout adolescent growth, whereas females, after an initial decline, show a continuous increase in fat percentage throughout their eighteenth year. There are also significant gender differences in subcutaneous fat distribution, with a preponderance of adipose tissue in the upper part of the body (above the umbilicus) in males and in the lower part in females. This tendency for concentration of fat in the abdomen of males and the hips of females is seen at least as early as 4 years, with this sex difference in fat distribution becoming marked during adolescence.[34] Some of this variation can be attributed to the effects of adrenal and ovarian hormones. In females, a significant secretion of estrogen and progesterone induces a slight increase in trochanteric adipocyte volume and number, whereas in males, the latter are significantly reduced by androgens.[25]

With aging, body fat in men slowly increases from about 18% in those 18 to 25 years of age to 36% in those

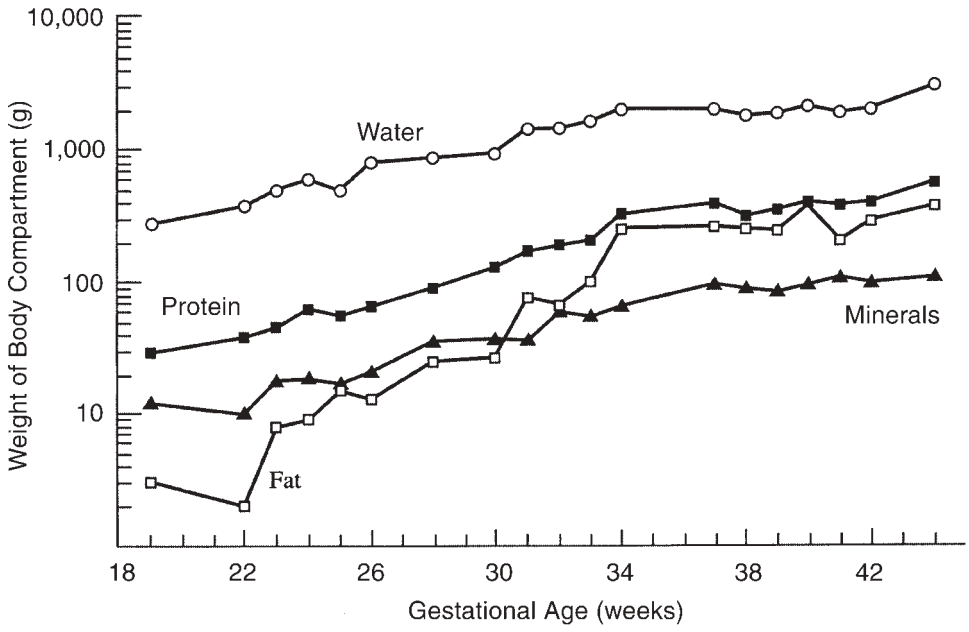

FIGURE 4-2 Changes in body composition during fetal development and early life. Reproduced from Ellis KJ.[13]

65 to 85 years old; in women, a gradual increase from 33 to 45% is found in similar age groups.[35] The preponderance of fat in females at all ages, especially in the lower part of the body, could be related to their capacity for childbearing as an adaptation mechanism for the preservation of the species. There is a need for important reserves for the fetus and newborn.[8] Nevertheless, in a minority of normal males and females, the adipose tissue distribution presents the sexual differentiation of the opposite sex.[8] In women with the android fat distribution, the risk factors for developing diabetes, hypertension, or hyperlipidemia are similar to those of men. In these women, there is no clear explanation for this different pattern of fat distribution, although it has been suggested that they might have an inherited increased sensitivity of their adipocytes to androgens and possibly to cortisol.[8]

Ethnic differences in fat accumulation during growth have been described. A study of white, black, and Hispanic girls reported a higher percentage of body fat in the Hispanic and black groups than in the white group when adjusted for body size. Bone mineral content and lean tissue mass were also greater in black girls than in white or Hispanic girls.[36] A similar study of multiethnic boys showed greater bone mineral content in the black children, but the highest percentage of body fat was found in the Hispanic group and the lowest body fat values were found in the black boys.[37] White children have a more peripheral distribution of body fat than Latin American, Japanese, or black children. Black children tend to have a more centralized pattern. These ethnic differences are evident as early as the preschool period and continue throughout adolescence.[38] The pattern of less peripheral fat has also been found in studies of children from several Latin American countries.[39] It could reflect genetic differences as well as different lifestyles and nutritional and health habits. Ethnic differences have also been found among Asian adolescents[40] and adults.[41] These studies suggest the need for ethnicity-specific references for body composition values.

The tracking of total body fat and fat distribution measurements has not been clearly demonstrated in children. Serial and repetitive measurements of body fat distribution might decrease intraindividual variation and improve reliability of tracking over time.[42] It appears that the majority of overweight 1 year olds display normal levels of fatness as adolescents and adults and that whereas overweight in early childhood is not well correlated with adult obesity, overweight in later childhood and adolescence is.[34]

Long-term follow-up studies have found that truncal fat predominance and increased body mass index (BMI) in childhood were associated with an increased risk of central obesity in adulthood.[43] Correlations have been shown between body fatness and risk factors for coronary heart disease and diabetes as early as 7 years of age,[44] and correlations between body fatness and serum lipid and lipoprotein concentrations have also been found at younger ages.[45] Moreover, overweight in adolescent males has been associated with increased risk of mortality from all causes and from coronary heart disease after 55 years of follow-up.[46]

In addition to total body fat, the location of fat plays an important role in the risks of developing cardiovascular disease, diabetes, hypertension, gallbladder disease, stroke, and overall mortality. It appears that at least three principal components of body fat are associated with health outcome: total amount of fat expressed as a percentage of body weight,[47] amount of subcutaneous truncal or abdominal fat,[48] and quantity of visceral fat located within the intra-abdominal cavity.[7,49] Adult diabetogenic or atherogenic obesity tends to be more centripetal than peripheral, more the abdominal "apple" shape than the gluteofemoral "pear" shape, more intra-abdominal visceral than extra-abdominal subcutaneous, more in the upper body (nape, cheeks, neck, shoulders, upper half of the trunk, and abdomen) than in the lower body; this holds true for both men and women with android distribution of fat.[8]

Risk factors for the development of obesity can be considered as either genetic[50,51] or environmental from changes in diet, exercise, or lifestyle.[52] Several authors have reported a correlation between body fat and the amount of time spent watching television,[53–55] whereas others have not found this association.[56,57] Along with other benefits, regular exercise results in decreased body fat and increased bone mineralization and muscle mass.[58] In general, athletes have a lower percentage of body fat and greater lean body mass than their nonathletic peers. However, there is considerable variability among individuals and types of activities. Athletes participating in sports in which body weight is supported (eg, swimming, cycling, kayaking) or in which body weight is not translocated (eg, throwing, lifting) tend to have a higher percentage of body fat than athletes who participate in sports that require horizontal or vertical translation of body weight (eg, running, jumping).[2,59] In sports in which weight is a factor, such as gymnastics, ballet, and wrestling, the effort to decrease body fat can affect performance and induce eating disorders. This phenomenon has occurred in both male and female athletes.[2,60] In obese adult patients, intensive and extensive aerobic exercise training not only can induce moderate to high fat losses but can also reduce central subcutaneous fat, which is more noticeable in males.[61]

The increased percentage of body fat seen in the elderly population is probably attributable to decreased physical activity. With aging, there is a decline in muscle strength and muscle mass that could be counteracted by regular physical exercise. The capacity to increase muscle mass and muscle strength is retained into old age. Physical training, especially resistance exercise of significant intensity, frequency, and duration, could retard the loss in muscle mass closely associated with bone mineral decline and increase in body fat. Hence, the associated abnormalities of diabetes, coronary heart disease, osteoporosis, and fractures could also be reduced.[62]

With some method of measuring body composition, the physician should assess the contribution of fat to the variation of body weight in order to make the appropriate recommendations concerning nutrition, exercise, or lifestyle to promote lifelong health.

Changes in Body Water

Water content is greatest during fetal life—about 88.6% of body weight at 24 weeks gestation and approximately 75% at term. After birth, it drops rapidly and is about 60% at age 4 months. From then until adolescence, it ranges between 60 and 65%.[14] During the first years of life, the extracellular water (ECW) volume exceeds the intracellular water (ICW) volume, and with growth this relationship changes: the ratio of extracellular to intracellular fluid volume declines during growth. ICW initially is about 25 to 30% of body weight but by adolescence constitutes 35 to 40%, principally because the child's muscle mass increases. At the same time, ECW slowly drops from about 40% to approximately 20 to 25% of body weight.[14] In the elderly there is a diminution of total body water (TBW).[63]

Small-for-gestational-age full-term and preterm infants have a greater proportion of body water at birth than do their appropriately grown peers, suggesting that fetal growth deficits in this population are not attributable to abnormalities in body water regulation.[64] In disease states such as malnutrition, there is an expansion of ECW; similar patterns have been observed after surgery, in patients with cancer, and in sepsis.[65] The ECW-to-ICW ratio appears to be an accurate predictor of clinical outcome and mortality,[65] and it has been proposed as a marker of the quality or health of the fat-free mass.[66] Moreover, a strong correlation between ECW-to-ICW ratio changes and protein and energy intakes has been found. For this reason, the availability of these measurements could aid the clinician in monitoring nutritional rehabilitation in the acute care of critically ill patients.[65]

Changes in Body Mineral Content

Throughout life, bone is constantly being formed and resorbed. The process of bone modeling, characterized by changes in the shape of bones, takes place from birth until the cessation of longitudinal bone growth. Thereafter, bone tissue within the existing skeletal structure is continuously being formed and resorbed, through the remodeling process, with minimal change in bone volume.[6] The skeleton develops through infancy, childhood, and puberty, reaching maturity by late adolescence. The rate of bone modeling varies greatly during these different biologic stages. The skeletal mass of infants doubles during the first year of life, and approximately 37% of the total skeletal mass of adults is accumulated during adolescence.[67] The annual increment in bone mineral density (BMD) values is high during the first 3 years of life and decreases thereafter until puberty, as occurs with height growth velocity. During puberty, an increase also occurs in BMD values, which peaks in late adolescence, corresponding to Tanner stage IV, and continues at a slow rate to adulthood.[68] The adult reference man has a calcium content of 1.2 kg.[69]

Until 10 weeks gestation, the human skeleton is composed entirely of cartilage, a tissue quite distinct histologically and chemically from cortical bone. At about 10 weeks, a primary center of ossification begins to develop in the shafts of long bones (eg, femur) and the collagen laid down is calcified by the deposition of mineral into it. The osseous tissue gradually extends along the shaft, replacing the cartilage and also forming the spongy trabecular bone of the metaphyses.[70] At around 22 weeks gestation, cartilage comprises 42% of the total skeleton in the 500 g fetus; it is 33% in the full-term fetus.[71] The skeleton of a full-term infant contains about 30 g of calcium, most of which was deposited during the last trimester of intrauterine life.[6] Fetal intrauterine calcium accretion increases exponentially during the last trimester of pregnancy, from 130 mg/kg/day at 28 weeks gestation to 150 mg/kg/day at 36 to 38 weeks gestation.[72] These values are so high that human milk can supply to a premature infant only a fraction of the amounts needed to emulate the intrauterine accretion rate.[71] Insufficient intake of calcium and phosphate is the primary cause of osteopenia and rickets of prematurity.[73] In studies of premature infants when calcium and phosphate intake is increased by supplementing their mother's milk[74] or their formula, bone mineralization increases significantly, paralleling the intrauterine rate in some studies.[75–78]

Absorptiometric techniques have permitted the study of bone mineralization measured as bone mineral content or BMD during growth. Intrauterine bone mineralization has been determined by measuring the BMD in appropriate-for-gestational-age infants born at between 30 and 41 weeks gestation[79] and between 22 and 42 weeks gestation.[80] BMD and bone width at birth were found to correlate with gestational age and birth weight.[73] These values of BMD between 30 and 41 weeks gestation have been used as reference curves[81] to compare various feeding regimens in the premature infant.

BMD increases over the first year of life, at a slower rate during the first 6 months, and varies with the type of feeding.[73,82,83] Higher BMD values have been found in supplemented breast-fed infants[74] or cow's milk formula–fed full-term and premature infants[84,85] when compared with those in unsupplemented breast-fed infants. In a longitudinal study of hospitalized preterm infants fed either preterm formula or fortified breast milk, those fed preterm formula demonstrated a greater increase in BMD; however, the significance of this increase was nullified when adjusted for differences in weight gain. Whether there is a relationship of these differences to specific nutrient intake and long-term effects on bone calcium accretion has yet to be determined.[86] Lower values have been observed in infants receiving breast milk or soy-based formula when compared with infants receiving cow's milk formula.[85,87,88] In later studies with soy formulas modified to improve the suspensibility of minerals, no differences in BMD were found when compared with results with cow's milk formula.[82,83,89] The long-term consequences of the differences in BMD with various types of feedings in early infancy are as yet unknown. However, in two studies of bone mineralization at 1 to 6 years of age, the BMD of children who had been breast-fed was similar to that of those who were formula-fed.[90,91]

No gender or ethnicity differences in BMD content have been found in full-term newborns[92] or children up to the age of 4 years.[90,91] After that, there is a wide variation in BMD as a function of age, gender, and ethnicity.[91,93–96] Boys appear to have slightly higher BMD values in the radius

(predominantly cortical bone) than girls do, and blacks have higher values than whites.[91,94,97,98] With the onset of puberty, the difference between males and females increases significantly. Ethnic differences in BMD among blacks, whites, and Asians have also been reported in adolescents and adults.[96,99,100]

In the lumbar spine (predominantly trabecular bone), there is a gradual linear increase in BMD with age in both sexes before puberty, at approximately 9 to 10 years of age,[68,95,97,101] followed by accelerated increments during puberty.[95,96,101] Thereafter, BMD values are higher in girls, possibly because of earlier pubertal development, until the age of 15 years,[95,97,101] with marked slowing afterwards. In girls, peak bone mass in the spine and femoral neck is probably achieved by 15 years of age.[97] In boys, the most rapid increase in axial BMD occurs at 13 years of age, with the steepest increase at 15 and 16 years and no slowing until 17 years of age.[101] In males, peak bone mass is not achieved until the age of 17 or 18 years.[97]

These absorptiometric data, showing the relatively greater importance in accumulating bone mass of early adolescence in girls compared with late adolescence, agree with studies done with other methods. Abrams, in a study of calcium kinetics in girls 4.9 to 16.7 years old using intravenous ^{42}Ca, found that calcium deposition and the size of the exchangeable pool in bone reached a maximum during early puberty and decreased in late puberty,[102] suggesting that the greatest period of calcium transfer to the bone is in the prepubertal and early pubertal periods. Also, the measurement of lumbar spine in adolescent and adult females by quantitative computed tomography (CT) has suggested that vertebral trabecular bone could reach its peak near the end of the second decade of life.[96] Because peak bone mass accumulation is achieved during adolescence, current recommendations for calcium nutrition reflect a greater requirement for these age groups (Appendix 2). Prevention of osteoporosis consists primarily of maximizing peak bone mass during the years of growth and skeletal consolidation.[6]

Genetic factors are probably the strongest predictors of peak bone density. It has been suggested that genetics contribute 70 to 80% of the variance in bone mass, with the environment contributing the remaining 20 to 30%.[103,104] Premenopausal daughters of postmenopausal women with osteoporosis have lower bone mass than other women of the same age.[105] Moreover, BMD correlates more closely in monozygotic than in dizygotic twins.[106]

Within the modifiable environmental factors, calcium intake could play a significant role in peak bone mass. For the growing individual, there is a significant positive relationship between calcium intake and retention. This has been observed in the studies of infants presented earlier and in studies of BMD in children and adolescents.[94,103] Variations in calcium nutrition early in life could account for as much as 5 to 10% of the difference in peak bone mass; such a difference probably contributes to more than 50% of the difference in hip-fracture rate later in life.[6,104] Finally, it has also been found that weight-bearing activity and physical exercise during childhood have a positive impact on peak bone mass.[101,104] During adult life and in the elderly, the role of exercise in preserving bone mass has also been reported in several studies.[104,107]

With this in mind, osteoporosis has become the domain of the pediatrician as the interplay of genetics, nutrition, and activity is better understood and preventive measures can be undertaken. There is an increasing prevalence of obesity in children, and children who are overweight could have an increased risk of fractures owing to lower BMD.[108,109] In practical terms, the pediatrician should encourage the attainment of normal body weight for height and the adequate intake of calcium during the first 3 years of life and also during the prepubertal and pubertal stages, when the highest rates of bone mineralization take place.[68]

Changes in Body Skeletal Muscle Mass

There is no definitive in vivo method of measuring total muscle mass. Neither total body potassium (TBK) nor total body nitrogen (TBN) can identify muscle cells specifically.[110] Although two metabolic end products released from myocytes—creatinine and 3-methyl histidine—have been used to estimate whole body muscle mass, their application is limited by the constraints stated in detail below.[111,112] However, in certain well-controlled conditions, they can give accurate results.[110]

Regional body muscle composition can be assessed by means of imaging techniques and also with absorptiometric techniques.[111] Gross estimates of muscle mass can also be obtained with anthropometric measurements of midarm circumferences or areas. This technique is particularly useful in the clinical setting when followed over time and validated against other methodologies.[113,114]

Skeletal muscle represents 22 to 25% (approximately 850 g) of the mass of a newborn infant and approximately 30 to 45% (approximately 28 kg) of the total body weight of an adult, although the range in values reported for the adult is highly variable. The skeletal muscle of a newborn contains 27% of TBN, 33% of TBK, and 28% of TBW.[69] The chemical change in the composition of skeletal muscle during early development is a decrease in the percentage of water and an increase in the protein concentration. As the fibers increase in number and size, the extracellular material, which makes up a large part of fetal skeletal muscle, is replaced by muscle fibers.[70] The muscle mass constitutes the largest part of the soft tissue mass, except in extremely obese individuals, in whom adipose tissue might predominate.[70,115] Depending on gender, age, and health status, between one-third and half of total body protein is within skeletal muscle.[111]

The process of growth of the total muscle mass is not uniform and develops slowly during childhood, with a growth spurt in the adolescent years, which is more intense and prolonged in boys than in girls.[69] The development of muscle mass is influenced by several factors, including age, sex, nutrition, hormonal and metabolic states, and exercise. Estimated muscle mass as a percentage of body weight increases from 42 to 54% in boys between 5 and 17 years of age. In girls, it increases from about 40 to 45% between 5 and 13 years of age, decreas-

ing somewhat thereafter. This decrease is probably attributable to the relatively higher accumulation of fat in the adolescent female. At all ages from birth to adulthood, muscle mass predominates in males.[115] With advancing age, there is a substantial decrease in muscle mass.[62] At 70 years of age, skeletal muscle has lost 40% of its peak weight in early adult life.[35]

This sarcopenia that occurs in the elderly could be delayed by regular exercise.[62] Physical activity should be promoted during the early periods of life to create positive habits that can continue thereafter, favoring the muscle, bone, and cardiovascular systems, to decrease the tendency toward obesity.

Changes in Body Visceral Mass

Growth and development of the viscera are associated with the same changes in chemical composition as those seen in muscle mass, namely, a decrease in the proportion of water and an increase in the proportion of protein. Extracellular elements such as sodium and chloride decrease, whereas intracellular elements such as potassium and magnesium either remain the same or increase.

The brain grows rapidly from midgestation to 18 months after birth, when it reaches about 70% of its adult mass. Growth and development of the brain are characterized by a decrease in the percentage of water and an increase in protein, but the brain differs from most other tissues in that lipids form an integral part of the structure. Myelination begins before birth, but most of it takes place between birth and 3 years of age, when the brain is 80 to 90% of its mass at maturity. Up to the age of 3 years there is a considerable increase in the concentration of lipid, with a consequent decrease in the percentage of water. After 3 years, the changes in composition are relatively small.[70]

During the myelination period there is a rapid accumulation in the brain of the ω-3 and ω-6 long-chain polyunsaturated fatty acids (PUFAs)—docosahexaenoic acid (DHA; 22:6ω-3), arachidonic acid (AA) (20:4ω-6), and adrenic acid (22:4ω-6)—which are important structural components of the cell membrane phospholipids.[116] The type of lipid that accumulates in the brain during these first few years is influenced by early nutrition and might have functional implications, especially related to visual maturation and cognitive development.[117–120] Preterm infants who receive formulas with a high linoleic-to-α-linolenic acid ratio and practically devoid of longer-chain PUFAs show a marked decrease in the DHA-to-AA ratio in brain and retina.[116] On the other hand, human milk contains enough precursors and long-chain PUFAs to fulfill the infant's requirements for brain growth.[121] These factors have led to the study and development of infant formulas containing DHA and AA, with hopes of mimicking the fatty acid accretion pattern of breast-fed infants in babies who are formula-fed.[116,122,123]

The other major organs—liver, kidney, lung, heart, skin, and spleen—also change in chemical composition in the same way, with a decrease in the proportion of water and an increase in protein. The kidney has more sodium and less potassium at each age than muscle or liver does. In the skin, the protein increases, but it also changes in type: in the fetus, less than 20% by mass is collagen; the rest is mainly elastin. By term, the collagen represents 63% and in the adult 90%.[70] Finally, the immune system is also an important component of the body's lean nonmuscle compartment; lymphocytes alone account for approximately 2% of total body weight and 8% of fat-free solid in the adult. The status of the immune system is intimately related to body composition via the known effects of cytokines on muscle protein metabolism.[124]

The proportion of body weight contributed by major organs and tissues is presented in Table 4-3. At any age, muscle, skeleton, skin, liver, and brain account for more than 70% of body mass. With increasing age, some organs, such as liver, spleen, and kidneys, appear to atrophy, whereas hypertrophy is common in others, such as prostate, lungs, and heart.[35]

Chemical and General Changes in Fat-Free Mass

In general, fat-free mass increases rapidly during the late fetal and newborn period, followed by a rapid deceleration between the first and third years of life. Afterward, growth velocity slows until about 10 years of age, when the adolescent growth spurt is initiated. During the first years of life, there is a slight predominance of fat-free mass in males, which becomes significant during the adolescent period. The pattern of growth in fat-free mass is correlated with height.[69] At the other end of the life cycle, aging is marked by a progressive loss of lean body mass, especially skeletal muscle and bone mass.[62]

Concept of Chemical Maturity

Most healthy young adults have achieved chemical stability of their fat-free mass. This concept of chemical maturity was introduced by Moulton in 1923. Realizing the chemical changes that occur during growth, he found that the body composition of most species approached that of the adult when puberty was reached.[58] At this point, fat-free mass becomes relatively constant, with a water content between 72 and 74%, a protein content of approximately 19%, a potassium content of 60 to 70 mmol/kg in men and 50 to 60 mmol/kg in women, and a mineral content of

Table 4-3 Contributions of Organs and Major Tissues to Body Weight

	Percentage of Body Weight			
			Adult	
Organ or Tissue	*Fetus (20–24 wk)*	*Full-Term Newborn*	*Male*	*Female*
Skeletal muscle	25.0	25.0	40.0	29.3
Skeleton	22.0	18.0	17.1	17.1
Skin	13.0	15.0	3.7	3.1
Liver	4.0	5.0	2.6	2.4
Brain	13.0	13.0	2.0	2.1
Lungs	3.3	1.5	1.4	1.4
Kidneys	3.1	1.6	0.4	0.5
Heart	0.6	0.5	0.5	0.4
Spleen	—	0.2	0.3	0.3

Adapted from White DR et al.[70]

6.8%.[58,125] The completion of chemical maturation is also reflected in the stabilization of various constants relating one component of body composition to another, such as potassium to nitrogen and ECW to ICW, and intracellular potassium concentration.[14] Because conditions such as pregnancy, extreme old age, disease, nutritional status, and physical build can affect fat-free mass composition, the usefulness of these constants is debatable.

The changes in fat-free mass body composition as a function of age are shown in Figure 4-3. Variation in chemical maturity during growth is greater than the changes associated with aging. During growth, chemical maturity occurs at different stages for different constituents of fat-free mass. Muscles, visceral tissues, and bone all reach chemical maturity at different rates. For example, bone mineral maturation appears not to occur until the third decade of life. Body potassium, mainly reflecting increases in muscle mass, increases gradually from birth to 20 years of age in males and until 17 to 18 years of age in females. It then starts to descend and at about the age of 85 years is generally equal to that of a 13- or 14-year-old boy[69] (Figure 4-3A). In children, fat-free mass contains relatively more water than in adults. The hydration constant of fat-free mass ranges from 80.2% in the newborn to 75% in early puberty and to 73% in adults (Figure 4-3B). Protein content increases from about 15% at birth to about 19.5% in boys and 18.7% in girls at age 10 years.[9] Approximately 0.5% of body weight (0.6% of fat-free mass) is carbohydrate. Bone mineral content rises during childhood and especially in adolescence. It gradually increases from 3.7% of fat-free mass in infants to 5.2% in the prepubescent male, 6.2% in the postpubescent male at around 15.5 years of age, and then reaches 6.8% in the adult.[58] Bone gain continues during the third decade of life and then plateaus. Bone loss begins in the fourth or fifth decade of life, varying from one skeletal site to another and between sexes[104] (Figure 4-3C).

The relative content of water, protein, and minerals determines the density of the fat-free mass. During growth, as water content decreases and protein and mineral content rise, there is an increase in body density. Water and bone mineral are the principal factors in the change in density of the fat-free mass, water because it is the largest constituent of the fat-free mass and bone mineral because its density is very high, at 3.0 g/cc^2. With aging there is a decline in body density[69,126,127] (Figure 4-3D). Consequently, body composition in children is not correctly estimated if adult constants are used. For example, fat is

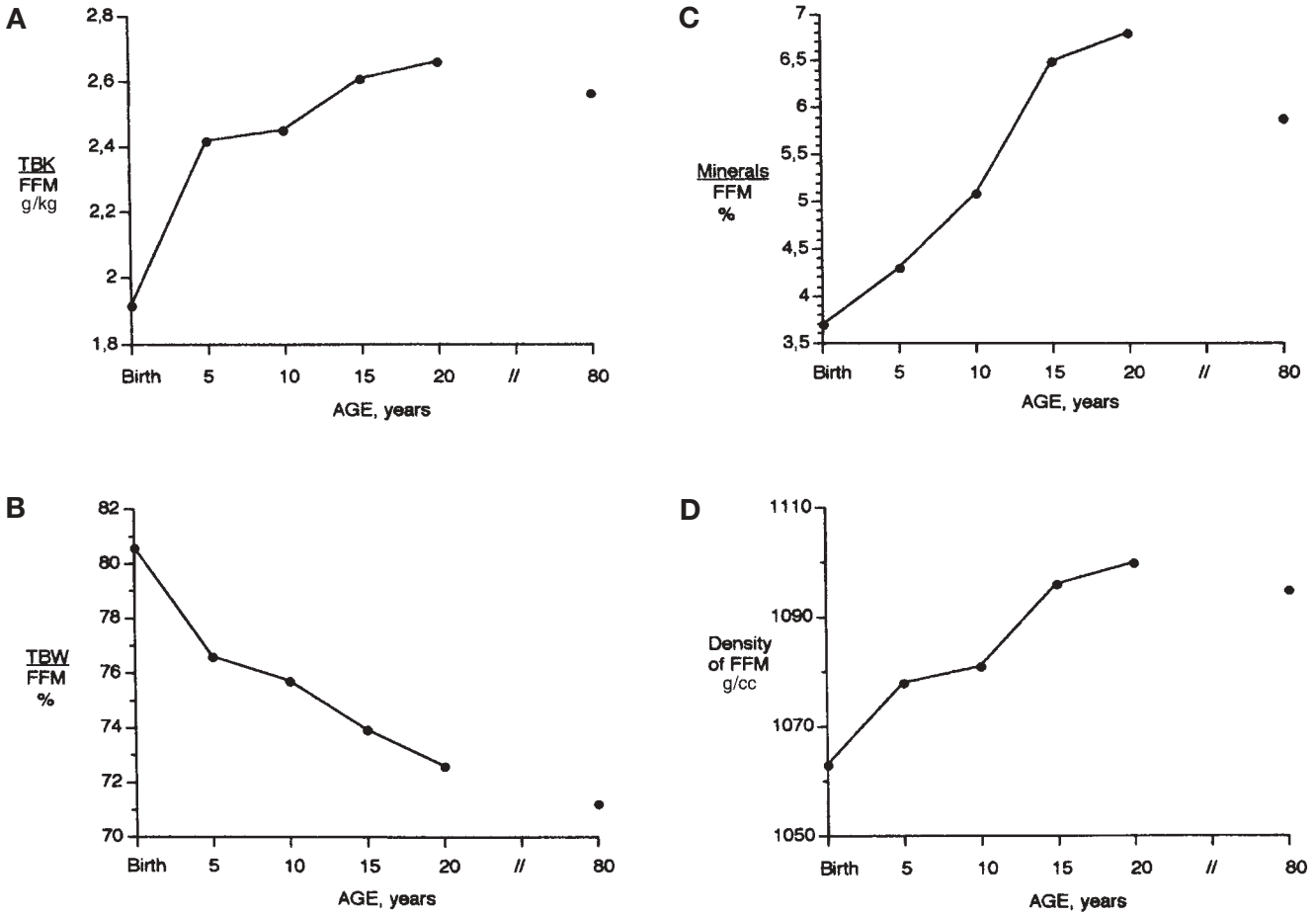

FIGURE 4-3 Changes in fat-free mass (FFM) body composition as a function of age. *A,* Total body potassium (TBK) in relation to FFM. *B,* Total body water (TBW) in relation to FFM. *C,* Bone mineral content in relation to FFM. *D,* Density of the FFM. Adapted from Fomon SJ et al,[9] Haschke F,[10] Lohman TG,[58] and Heymsfield SB et al.[126,127]

underestimated when calculated on the basis of TBW and overestimated when calculated on the basis of TBK or body density.[125] Constants adjusted for age and gender during childhood and adolescence have been developed for fat-free mass constituents,[58] making it possible to derive percent fat equations for each age and gender group.[4]

Changes in Linear Growth

Height velocity reaches its peak of 10 to 12 cm/month between 16 and 30 weeks gestation and decreases to 3 cm/month (36 cm/year) at birth. The postnatal curve is signaled by a deceleration in linear growth to 15 cm/year at the end of the first year, 9 cm/year at the end of the second year, and 8 cm/year at the end of the third year. Between the ages of 4 and 5 years, it is 6.5 cm/year, and from then to the time of puberty the growth velocity per year stabilizes to approximately 5 to 6 cm/year.

Girls of Anglo-Saxon descent start the pubertal growth spurt at about 12 years of age, with a peak height velocity of 9 cm/year. Boys start the growth spurt at about 14 years of age, with a peak velocity of 10 cm/year. Total increments in stature after peak height velocity are slightly larger in males than in females. The annual increments decrease significantly after peak height velocity is achieved.[128] In the Fels longitudinal study, adult stature was reached at an average age of 21.2 years for males and 17.3 years for females. In girls, growth in stature continued at a slower rate for almost 5 years after menarche.[128]

Changes in height gain are linked to pubertal status. Some regions of the world show variations in pubertal onset. In Latin American countries, children show an early maturation pattern. The pubertal spurt occurs 1 to 1.5 years before it does in children of Anglo-Saxon descent.[39] The age at which puberty occurs varies among populations and individuals. Therefore, body composition changes are better related to physiologic age than to chronologic age, and some indication of pubertal staging is necessary in studies concerning this age period.

Changes with Weight Loss or Weight Gain

At birth, normal weight velocity is approximately 7 to 9 kg/year; it decreases to 3.5 kg/year at the end of the first year and 2.5 kg/year at the end of the second year and then remains fairly stable at around 2 kg/year until puberty. Changes in weight that result from dietary intervention or that occur spontaneously almost always comprise both fat-free mass and fat. However, the relative contribution of each body component to the total weight change is dependent on several factors.[1,39] In the circumstances of weight reduction, fat mass decreases, but the fat-free mass also diminishes in proportion to the initial body fat content.[1]

The situation is similar for individuals who gain significant amounts of body weight in response to intake. The composition of the weight gain is a function of body fat content: thin individuals put on proportionately more lean, at least initially during weight gain, than do those with larger body fat burdens.[1] In obese subjects, weight gain is between 20 and 30% fat-free mass. In subjects of normal or low weight, such as malnourished children, premature infants, or patients with anorexia nervosa, the proportion of weight gained as fat-free mass is larger, around 60 to 75%, depending on the individual and type of diet. On the other hand, people with sedentary lifestyles and aging individuals tend to accumulate proportionately more fat during weight gain.[39]

Changes in Body Composition in Malnutrition

Malnutrition and disease can cause body composition alterations beyond those expected from underfeeding. Moreover, many of the methods used in measuring body composition changes assume certain conditions that are generally not present in these children. For example, they might have electrolyte derangement and altered body water distributions related to their condition that can invalidate the results of some techniques.[129] However, some of the changes are already well known.

Children with severe protein-energy malnutrition generally have increased TBW in relation to body weight. ECW as a percentage of TBW is also increased. These changes are indicative of severe losses of cell mass and body fat. The cells seem to retract and lose potassium, magnesium, and phosphorus. Total body sodium is increased both extracellularly and intracellularly. The extracellular increase of sodium is generally less than the increase in ECW. This results in hyponatremia with a relative increase in total body sodium. TBK is decreased, although serum potassium levels are usually normal. Deficiencies in magnesium, calcium, phosphorus, and trace elements (zinc, copper, selenium, and chromium) with bone demineralization have also been reported. Total body protein is depleted, especially in kwashiorkor. There is a marked loss of muscle mass, primarily as a result of a decrease in cell size rather than cell number. If the process of energy deficiency continues, the result is slowing or cessation in linear growth and stunting.[39,130] The alterations in ECW, sodium, and potassium should be taken into account in the early management of children with acute malnutrition. The process of recovery should start carefully and slowly by correcting the water and electrolyte derangement to avoid dangers associated with refeeding syndrome, particularly heart failure.[39,129,130] See Chapter 10, "Protein-Energy Malnutrition," for more details.

In marasmus, initially there is a loss in fat mass and ICW. The body cell mass diminishes, at the expense, especially, of muscle protein. In the edematous form of kwashiorkor, there is a loss in muscle and visceral protein, with a relative preservation of subcutaneous fat. The ICW decreases. There is expansion of the extracellular compartment with edema and hypoproteinemia. As the process develops, it becomes manifest with marked losses in muscle mass and an increase in ECW. The effect of this progression can obscure the severity of the malnutrition if body weight alone is used to assess the child. In the combined form of protein-energy malnutrition there are abnormalities in all body compartments.[39,130] Malnourished children can continue to show aberrations in body composition even after regaining weight.[131]

BODY COMPOSITION MODELS

Traditionally, body compartments have been divided into fat mass and fat-free mass. The fat mass includes all ether-extractable lipids in the body. The fat-free mass has four major constituents: water, protein, glycogen, and minerals.[132] Adipose tissue includes the fat and its supporting cellular and extracellular structures.[93,133] Lean body mass refers to the part of the body free of adipose tissue, whereas fat-free mass consists of lean body mass plus the nonfat components of adipose tissue.[133] In very obese individuals, the excess adipose tissue can increase fat-free mass without increasing lean body mass. Therefore, because lean body mass and fat-free mass are not synonyms, it is most accurate to use the terms fat mass and fat-free mass in the two-compartment model of body composition.[133]

Several methods of body composition measurement rely on the two-compartment model of fat mass and fat-free mass, each assumed to be in constant composition. In general, these methods first measure one constituent of the fat-free mass, such as density, water, or potassium. Then they assume that the concentration of that constituent of the fat-free mass is a known constant and that the other components of the fat-free mass also maintain a relatively constant composition to calculate the total fat-free mass. Fat-free mass is then subtracted from body weight to calculate fat mass. The two-compartment model continues to be widely used, mainly because of the simplicity of its interpretation.[93] Both of the assumptions noted above, however, are questionable because the fat-free mass changes with a variety of conditions.[2,4,35,58,124] To address this problem, multicompartment models of body composition assessment have been developed in which more than one constituent of the fat-free mass of each subject is measured.[126,132,134]

MULTICOMPARTMENT MODELS

Recent advances in methodology have allowed the measurement of several body compartments to overcome the limitations of many assumptions. As a result, body composition analysis has evolved from the traditional two-compartment system of fat and fat-free mass to models based on four or more body-weight fractions. Now body composition in humans can be studied using several models at different levels of complexity (Figure 4-4)[13,127,135]: (1) atomic, (2) molecular, (3) cellular, (4) functional, and (5) whole body. The direct or indirect methods used to measure components at the five levels are presented in Table 4-4. Several of these methods are reviewed later.

Atomic Level In the human body, there are approximately 50 different elements, but just six (oxygen, carbon, hydrogen, nitrogen, calcium, and phosphorus) account for more than 98% of body weight. Oxygen constitutes more than 60% of total body mass. The remaining 44 elements make up less than 2% of body weight.[135] Traditionally, elemental analysis of humans was possible only in cadavers, which was confounded by the possible alterations caused by disease and death. The availability of whole-body counting and neutron activation analysis, combined with a measurement of TBW, allows the measure of eight elements directly (hydrogen, carbon, nitrogen, calcium, phosphorus, sodium, potassium, and chlorine). This information is used to calculate the body content of three more elements (oxygen, magnesium, and sulfur). There are consequently 11 body components determined at the atomic level; these comprise at least 99% of body weight in living humans.[127,136] Equations have been developed using atomic components to calculate higher levels of body composition (Table 4-4).

Molecular Level The molecular model of body composition is usually based on three main chemical groups: water, mineral, and organic.[132] The minerals are further separated into bone mineral and soft tissue components, and the organics are mainly defined by protein and fat components. Therefore,

Body weight = lipid mass (fat) + total body protein + bone mineral + soft tissue mineral + TBW.[13,93,132]

At this level, TBW by isotope dilution and bone mineral by whole-body dual-photon absorptiometry can be deter-

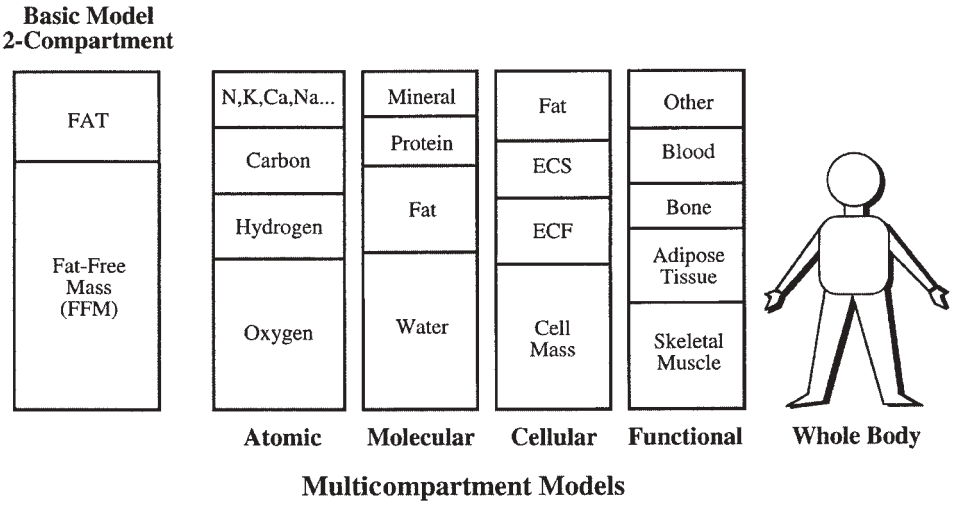

FIGURE 4-4 Body composition models. Reproduced from Ellis KJ.[13]

mined directly.[135] The remaining components must be estimated indirectly. For example, protein can be determined from TBN by making two assumptions: that all body nitrogen is in protein and that 16% of protein is nitrogen.[135,136] Total body fat can be calculated by subtracting the nonlipid carbon from total body carbon and then converting this into fat, assuming that triglyceride is 77.4% carbon.[137] Bone mineral can also be calculated from total body calcium. An important aspect of these estimates drawn from elements is that no known age dependencies are recognized.[126] The main assumption is that the proportions of carbon, nitrogen, and calcium are known and constant within lipid, protein, and bone mineral, respectively.

Cellular Level At the cellular level, the body is divided into four main compartments: cells, extracellular fluid, extracellular solids, and fat. Body cell mass reflects the cellular components of the body. The extracellular fluid is the fluid surrounding the cells. Extracellular solids consist of organic and inorganic chemical compounds. The organic extracellular solids include collagen, reticular, and elastic fibers. The inorganic extracellular solids represent the total body bone mineral (primarily calcium, phosphorus, and oxygen) and other inorganic components such as bicarbonate, citrate, magnesium, and sodium.[135]

At this level, the volume of extracellular fluid and its plasma subcompartment can be quantified directly by dilution methods. Body cell mass can be estimated by the difference between TBW and ECW or by the measurement of TBK. Extracellular solids can be estimated from elements measured by neutron activation analysis (NAA).[135,136]

Functional Level The fourth level of complexity comprises tissues, organs, and systems. Three specific tissues are particularly important in body composition studies: bone, adipose tissue, and muscle, which together comprise approximately 75% of body weight.[135]

The direct methods used to estimate the major compartments at this level are the imaging techniques, such as CT, nuclear magnetic resonance imaging (MRI), and ultrasonography. They can directly determine the regional and total body adipose tissue, skeletal muscle, liver, kidney, and spleen volumes. Brain volume can also be evaluated by CT, and heart mass can be estimated by echocardiography.[132] Dual-photon and dual-energy x-ray absorptiometry (DXA) can be used to estimate fat tissue, bone, and skeletal muscle mass.[138–140] Measurement of total body potassium, nitrogen, and calcium by NAA allows the indirect estimation of skeletal muscle mass and bone mass.

Whole Body Level The whole body level of body composition measurement concerns body size, shape, and exterior and physical characteristics.[135] The techniques used in their estimation are mainly anthropometry and densitometry. Anthropometric evaluations, although less accurate, are simpler and easier to perform than are some of the measurements at the other four levels. Thus, the anthropometric techniques are often well suited for large-scale studies or for field work. Air-displacement plethys-

TABLE 4-4 Equations and Methods for Measuring Body Composition by Level

Atomic Level	
Na, Cl, Ca, N, C, P	Neutron activation analysis
K	^{40}K counting
H_2O	Isotope dilution
Body weight = TB O + TB C + TB H + TB N + TB Ca + TB P + TB K+ TB Cl + TB Na + TB Mg + etc.	
Molecular Level	
Fat	Carbon in fat*/0.774
Total body water	Isotope dilution
Total body protein	TB N × 6.25
Bone mineral	TB Ca/0.364 Dual energy x-ray absorptiometry
Soft tissue mineral	
K	TB K
Mg	TB K × 0.06
H_2PO_{4-}	TB K × 1.7
Na	TB Na
Cl	TB Cl
HCO_{3-}	TB Cl × 0.43
Body weight = lipid mass (fat) + total body water + total body protein + bone mineral + soft tissue mineral	
Cellular Level	
Body cell mass	0.00833 × TB K
Extracellular water	Isotope dilution Bioelectric impedance analysis
Extracellular solids	TB Na + TB Cl + TB HCO_{3-} + TB Ca TB Ca/0.177
Fat	Carbon in fat*/0.774
Body weight = body cell mass + extracellular water + extracellular solids + fat	
Functional Level	
Adipose tissue	Dual energy x-ray absorptiometry Computed tomography Magnetic resonance imaging Ultrasonography Infrared interactance Anthropometry
Skeletal muscle	0.0196 × TB K – 0.0261 × TB N
Bone	TB Ca Dual energy x-ray absorptiometry Quantitative computed tomography
Other tissues	Dual energy x-ray absorptiometry Computed tomography Magnetic resonance imaging Ultrasonography
Body weight = adipose tissue + skeletal muscle + bone + other tissues	
Whole Body Level	
Anthropometry	
Densitometry	
Total body electric conductivity	
Bioelectric impedance analysis	

Adapted from Ellis KJ,[13] Wang ZM et al,[135] Heymsfield SB, et al,[136] and Brans YW.[144]
*Carbon in fat = TB C – [(3.37 × TB N) + (0.052 × TB Ca) + (0.085 × TB Cl)].
TB = total body.

mography, a densitometric method, is showing promise in children as an acceptable alternative to underwater weighing for determining body volume. It is important to recognize that changes in regional distribution are not measurable at this level.

BODY COMPOSITION MEASUREMENT METHODS

Direct measurement techniques quantify a compartment directly, and indirect methods are based on certain constant, established relationships between compartments that allow the calculation of other components from the direct measurements.[126] All indirect methods for the measurement of body composition have limitations because they make assumptions related to the method or to the interrelations among the different compartments. Because the body composition of children is in constant flux, many of these assumptions of steady-state relationships, based on adult data, are questionable. Therefore, whenever possible, the constants used in the calculations should be based on age, sex, and ethnicity reference data.

These reference data should be obtained with the use of several methods of body composition measurement at different levels in the same subjects to establish the steady-state relationships among compartments at different ages and for both sexes.[126] Unfortunately, there are few laboratories that are able to perform these studies, and they are located principally in large research departments. Nevertheless, the information obtained at these sophisticated facilities will allow the development of more accurate age-, gender-, and ethnicity-related references and constants. These will permit better comprehension of the changes in body composition and a more accurate calibration of the less precise but more practical and portable methods, which can be used in the office or field.

Neutron Activation Analysis

The NAA method of body composition measurement takes advantage of the principle that a given dose of neutrons generates a known amount of radioactivity within a defined mass of substance. If neutrons from a suitable source irradiate the body, some of these neutrons are captured in the atomic nuclei of body elements. The nuclei thus become unstable, and particulate or electromagnetic radiation is emitted to regain stability. These emissions (often gamma rays) can be observed directly (prompt emission) or later owing to the effects of the emissions on other atoms (delayed emission).[141] The total activity therefore reflects the total mass of the substance. A particular element can be identified by the characteristic energy of the electromagnetic radiation it emits, together with the decay rate. This method has been used in adults to determine the amount of a number of elements in the body using three different systems[134]: delayed gamma NAA (total body calcium, sodium, chlorine, and phosphorus), prompt gamma NAA (TBN), and inelastic neutron scattering (total body carbon).[135] Three chemical compartments (protein, mineral, and fat) can be estimated from these elements.[126,132]

This method should permit better understanding of human body composition because of the number of elements it can assay, yet its use in children will be limited because of the radiation exposure.[134] For the in vivo measurement of body nitrogen by NAA, low-dose (30 mrem) radiation techniques have been developed, and some limited data exist regarding TBN in children.[3] In the case of NAA of body calcium, it is the most sensitive and specific method for the detection of changes in total bone mass; however, the associated radiation exposure (> 280 mrem, total body) is substantially higher than that associated with TBN measurement.[142] New techniques for elemental analysis in humans should continue to be developed to improve the practicality of this precise measurement of body composition changes.[143]

Body Potassium Counting

The great advantage of this technique is that it relies on the natural occurrence of radioactive ^{40}K, which emits a characteristic gamma ray at 1.46 MeV.[93,112] It exists in the body at a fixed proportion to total K, assumed to be constant at 0.0118% for all potassium in the biosphere. Thus, no external radiation is necessary for this determination. However, the equipment needed is expensive, and great care must be taken to isolate the detectors from other sources of radioactive decay that might interfere with the measurements.[110]

In the adult, knowledge of TBK permits estimation of the fat-free mass or the body cell mass,[133] assuming constant relationships between TBK and these compartments. In the child, because the potassium content of the fat-free mass increases with growth (Figure 4-3A), age- and gender-adjusted constants should be used when available.[2,58]

Hydrometry

Water-containing body compartments can be measured by tracer dilution techniques. A known dose of a tracer is administered orally or intravenously, and then samples of body fluids are analyzed for tracer content after a sufficient time lapse to allow penetration to the compartment of interest. Corrections for overexpansion, nonequilibrium, and excretion of the tracers are needed to appropriately interpret the data obtained.[13]

Total Body Water The most common method of measuring TBW in children is by isotope dilution using the stable isotopes deuterium (D_2O) or oxygen 18 ($H_2{}^{18}O$). The use of the radioactive tracer tritium (^3H_2O) is contraindicated in children. Deuterium overestimates the total body water space by 0.5 to 5% because of a presumed exchange with hydrogen ions in organic material. However, the advantage of deuterium over $H_2{}^{18}O$ is that it is less expensive.[2] Subjects are asked to drink or are injected with a known amount of labeled water, and after a suitable period of equilibration, the concentration of the isotope in breath, urine, saliva, or plasma is determined.[133]

The measurement of TBW has been used for estimating the nonfat compartment of the body because neutral fat does not bind water and it is assumed that the weight of

water to fat-free body mass ratio is a constant (total body water:fat-free mass = 1:0.732).[132] This assumption is not true in children because the hydration constant changes with age (Figure 4-3B) and can vary among individuals of the same age. As already stated, age- and gender-adjusted hydration constants should be used in calculations.

Extracellular Water. Bromide has been the most widely accepted marker used in estimating ECW volume by dilution.[144] It is nontoxic, produces no discomfort in low concentrations, and can be measured in blood or saliva. Sucrose has also been used in premature babies.[145] ICW can be determined from the subtraction of ECW from TBW; however, this technique typically accumulates a significant measurement error of ± 2 to 3 L in an adult.[13]

Bioelectric Impedance Analysis

Bioelectric impedance analysis (BIA) is based on the principle that lean tissue will conduct a high-frequency electric current better than fat tissue. Body cell fluids are responsible for electric conduction, and the cell membranes determine capacitance. Conductivity is far greater in fat-free mass than in the fat mass of the body because the fat-free mass contains virtually all of the water and conducting electrolytes of the body.

Impedance is the frequency-dependent opposition of a conductor to the flow of an alternating electric current.[146] The impedance of a geometric system is related to conductor length and configuration, as well as to the cross-sectional area and the signal frequency. At low frequencies, the bioelectric current flows primarily through extracellular fluids. As frequency increases, the capacitance aspects of the body (cell membranes, tissue interfaces) start to retard the current, producing an increase in reactance. At high frequencies, the current penetrates all body tissues completely, and again reactance is diminished. With multifrequency bioelectric impedance, the differentiation of total and extracellular body water can be accomplished.[146,147] The bioelectric impedance method for estimating body composition is noninvasive, rapid, inexpensive, portable, easy to do, and applicable to field conditions. Hence, BIA has potential for use with individuals across a broad age spectrum and in a variety of settings.

The precision and accuracy of BIA have been questioned, however, and some authors have stated that its estimates are no more accurate than the ones obtained by anthropometry or DXA, particularly among obese children.[148,149] Diurnal variations have been observed with BIA measurements, although this has also been seen with measures of height.[150] Other concerns include inconsistencies caused by differences in body shape among individuals of the same stature. In regard to children and adolescents, the geometry of the conductor changes during growth as size increases and shape varies, which influences impedance. Also, during growth the composition of the fat-free mass changes markedly as the relative contributions of water decrease and those of protein and minerals increase. Several different prediction equations for calculating TBW, fat-free mass, and ECW have been published for a variety of age groups and types of measurements.[13] Altered states of hydration or a disturbance in the intracellular-to-extracellular fluid ratio can alter BIA findings,[93] and the equipment is highly sensitive to changes in temperature or humidity. Finally, some authors have raised questions about the applicability of the basic equation[151] and have stated that this technique offers no advantage over body weight in predicting body composition changes.[2,93,151] In spite of these reservations, BIA continues to be used in research studies,[55,152–155] and it appears that under well-controlled conditions, using adequate reference data and proper equations, the results can be valuable.

Total Body Electroconductivity

Total body electroconductivity (TOBEC) relies on the properties of hydrated lean tissue and ECW to conduct electric energy when subjected to appropriate radio frequencies.[133] The subject is placed in a measurement chamber consisting of a large cylindrical coil that generates an electric current at a specific radio frequency, which in turn generates an electromagnetic field inside the coil. When a subject is placed in this field, currents are induced that dissipate some of the energy of the electromagnetic field, which is recorded as a change in the coil impedance. The difference between the coil impedance when empty and when the subject is in the field is a function of the subject's conductivity. The electrolytes dissolved in the body water pool are responsible for the conductive properties, and because the dissolved electrolytes are distributed almost exclusively throughout the fat-free mass, a transformed TOBEC signal will vary in proportion to the total volume of fat-free mass.[156]

The TOBEC method is quick and requires minimal cooperation on the part of the subject, who may remain in street clothes.[2] The precision of the measurements appears to be good; however, the accuracy of the measurements could be limited if the population being studied differs from the reference population used to generate the prediction equations.[133] Moreover, changes in electrolyte composition of the body, such as might occur in some diseases, might result in changes in impedance independent of the changes in fat-free mass.[112] Finally, other major limitations are the lack of portability and the cost of the equipment.

Absorptiometry

In absorptiometry, the individual is scanned with photons at two different energy levels and the differential absorption of photons is measured. The photons are generated either by a ^{153}gadolinium source (with dual-photon absorptiometry) or an x-ray source (with DXA). This technique is safe, the average radiation dose is 1 to 3 mrem per scan, it is noninvasive, and its measurements are independent of assumptions of invariant relationships among body components.[112,138] DXA has emerged as a practical standard for validating other techniques of body composition assessment. It is a highly precise and accurate method for evaluating bone status as well as developmental and age-related changes in total fat and fat-free tissues.[139,140,157–159] In addition, this method has the potential for estimating

regional distribution of fat, fat-free mineral-free soft tissue, and bone status; it has also been applied to estimating muscle mass.[111]

DXA has been safely and accurately used in studies of healthy and sick newborns,[92,158,160–163] infants, and children.[44] A portable, low-cost DXA technique for measurement of bone mineral in the forearm of preterm infants has been presented.[164] Pediatric software for use with DXA has been validated and is more precise for use in children than adult software.[165] It should be noted that this technique does not measure absolute bone mass but instead provides a relative measure expressed as bone mineral content in grams per centimeter or BMD in grams per square centimeter.[93] In theory, a triple-energy x-ray absorptiometric technique could measure estimates of body water and protein mass in addition to bone and fat mass; feasibility studies are under way.[13]

Imaging Techniques

Advances in imaging technologies have allowed extensive, direct, in vivo analysis of body composition. These imaging methods are CT and nuclear MRI.[166] CT scanning requires exposure to a significant amount of radiation, whereas MRI does not.[167] Both methods share the problem of deriving an estimate of the composition of the whole body from certain slices. The estimate improves as more images are included in the measurement.[167]

Both CT and MRI provide a visual image of adipose tissue and nonfat tissue within the entire section of the body scanned. The cross-sectional images can be obtained at any level within the body, making possible precise site-specific calculations of subcutaneous and visceral fat content.[166–170] By scanning multiple sections of the body (up to 28 in some techniques[171]) and by summing the volume of adipose tissue in each section serially, it is possible to estimate the total volume of fat within the body.[133,167,168,171] A primary advantage of obtaining multiple images over the entire body is that it permits the analysis of separate anatomic regions, thereby allowing a detailed assessment of regional adipose tissue distribution.[172] These images can also provide an estimation of tissue and organ volumes.[167,173]

CT images provide more accurate information about compartment density and thus are better at differentiating body tissues than is MRI. CT scanning, however, transmits a high level of radiation exposure when determining body composition owing to the need for several scans taken at different levels. This limits the use of CT in children and also in studies requiring repeated measurements on the same subjects.[174] MRI can provide similar information without radiation. This permits serial determinations on the same subjects and also studies in children.[169] Although CT and MRI methods are particularly useful for accurate body composition measurements in the research setting, their risk, availability, and cost generally preclude their routine use in clinical practice.

Anthropometry

Anthropometric measurements of body composition are relatively fast and noninvasive and require a minimum of equipment compared to laboratory techniques. They are used in clinical settings and in public health studies to identify individuals who are vulnerable to under- or overnutrition and to evaluate the effectiveness of nutrition intervention programs.[49] Skinfold and circumference anthropometrics are almost as fundamental among body composition methods as height and weight; every new criterion method will require translation into the universal language of anthropometry.

More than 40 anthropometric dimensions have been proposed,[175] but the principal anthropometric measurements are height, weight, skinfold thickness, circumferences, body segments, and body breadths. Indices include BMI (body weight/stature^2, in kg/m^2), body fat distribution (such as trunk/extremity skinfold thicknesses), or the waist-to-hip and waist-to-thigh circumference ratios. Some of these methods have been validated against more direct measures of body composition. Waist circumference was shown to be a better predictor of truncal fat mass than waist-to-hip ratio when compared with DXA measurements in a large study of children aged 3 to 19.[176] This easy and inexpensive technique could prove to be useful in many pediatric settings as more is learned about central body fat distribution and its associated risks. BMI is part of routine anthropometric monitoring with standardized curves from National Center for Health Statistics data on the latest version of the Centers for Disease Control and Prevention pediatric growth charts (Appendix 1). The validity of BMI as a marker of overweight status has been demonstrated.[177] Upper-arm fat and muscle areas, based on skinfold measurements and circumferences, have been used as predictors of fat mass and lean body mass, respectively.

Skinfold measurements give a more accurate estimate of percentage of fat than weight and height alone. Human skin is 0.5 to 2 mm thick, so most of a skinfold measurement is the subcutaneous fatfold.[2] Skin fatfold thickness measurements are said to provide an estimate of the size of the subcutaneous fat depot, which in turn provides an estimate of total body fat. This extrapolation assumes that the thickness of the subcutaneous mantle reflects the total amount of fat in the body and that the sites chosen represent the average thickness of the entire mantle.[69] These assumptions might be untrue. In fact, the subcutaneous adipose tissue is only about 30 to 40% of total body adipose tissue, and there is a regional variation in fat thickness. There is also an interindividual variation in the subcutaneous fat distribution. Moreover, the relationship between subcutaneous and internal fat is not linear, and it varies with body weight, body build, and age.[134] Nevertheless, in well-controlled studies, some authors have found that in children skinfold measurements are highly correlated (r = .90 for boys and .84 for girls), with estimates of either total body fat or percent body fat from other techniques.[178]

In practice, skinfold thicknesses are measured at standardized regions by an experienced examiner using calipers of known quality.[133] The most commonly used calipers are Harpenden, Holtain, and Lange. The triceps skinfold thickness has been the site most frequently selected for a single, indirect measure of body fat, but no

single body region appears to have skinfold sites that are consistently representative of the whole subcutaneous fat layer. It is recommended that one use at least one limb skinfold (left triceps) and one body skinfold (left scapular) to account for the different distribution of subcutaneous fat, but whenever possible, multiple skinfold measurements should be used to obtain better estimates of body fat mass and its regional distribution.[14]

Many equations to predict body composition using anthropometric measurements such as height, weight, skinfold, and circumference measurements have been developed.[125,175] The prediction equations tend to be specific for the population measured and might not be valid for other populations. Despite careful attention to measurement sites, considerable intraindividual and interindividual variations occur, resulting in different predictions of body fat between examinations and examiners. The best results are obtained by experienced examiners who measure at the exact locations used by the investigators who developed the predictive equations[128] or in situations in which the subjects are similar in body type. There is a large body of literature, however, using anthropometric techniques in which reliability is not so clear.[98,113,114] For example, in very obese patients and in the presence of generalized edema, it is difficult to obtain accurate and reproducible estimates.[2,65]

Densitometry

Densitometry is a technique that requires the direct measurement of body density or separate estimation of total body weight and total body volume. Underwater weighing is the most common method used for determining body density in adults. The principle of underwater weighing is that the weight of a submerged human being is directly related to that person's average body density.[133] By weighing the subject in air and then in water and making appropriate corrections for temperature and air in the respiratory system, it is possible to estimate body density assuming the appropriate densities of fat (0.9 g/cm^3) and fat-free mass (1.1 g/cm^3). The technique is restricted to subjects who can cooperate because total submersion and breath holding at some reproducible lung volume are required. Hence, underwater weighing is not feasible in infants and children nor in most hospitalized patients. The method also might be inappropriate for use in children because, during maturation, the density of the fat-free mass changes (Figure 4-3D), thus invalidating one of the basic assumptions of the method (constant density of the fat-free mass).[134] However, age- and gender-adjusted constants for fat-free mass could be used.[58]

Air-displacement plethysmography (ADP) has recently been demonstrated to be a practical and valid alternative to underwater weighing for measuring body density. Rather than measuring a subject's displacement of water, the displacement of air from an enclosed chamber is measured to indirectly determine body volume and subsequently calculate body density. The BOD POD system (Life Measurement, Concord, CA) is a commercially available ADP system that has been studied with children and adults. The BOD POD is a chamber that allows a quick, noninvasive, simple measure of the two-compartment body composition model. Although it has been correlated closely with underwater weighing results in average adults,[179] its relationship to subjects outside the normal range of body fat has been less favorable.[180] The BOD POD has been successfully used in children aged 5 to 14 years, with acceptable precision for body density measurements.[181] Younger and more heterogeneous populations of children have not been studied. More studies are needed to validate this method with a multicompartment body composition model.[180]

Near-Infrared Interactance

Near-infrared interactance (NIRI) is based on the principles of light absorption and reflection using near-infrared spectroscopy.[112] It involves transmission of electromagnetic radiation through a probe into subcutaneous tissue and analysis of the reflected and scattered energy from that electromagnetic radiation to estimate the chemical composition of the sample. Like skinfold measurements, NIRI relies on the subcutaneous depot to extrapolate compositional data to the whole body and therefore is inherently limited in scope.[112,133] It could, however, be a reasonable alternative when skinfold measurements are refused or not possible.[182] This method has been used in infants, but its results correlated with subcutaneous adipose tissue thickness only when the latter was thin.[183]

There are many methods of measuring body composition; some are more practical than others for office or field determinations. Each method evaluates one or several components of the body using different technical approaches. The multicompartment model serves as the validation tool to cross-reference the reliability and precision of these technical measurements. The physician should become acquainted with several methods of assessing body composition for use in clinical practice and literature review.

CONCLUSIONS

During growth, body composition changes. Chemical maturity occurs at different stages for the various constituents of the fat-free mass. The water content of the fat-free mass decreases, whereas the protein, potassium, and bone mineral content increase, affecting the density of fat-free mass, which also increases. The fat mass varies greatly during the life cycle, depending on heredity, nutrition, and lifestyle.

Body weight alone cannot be used as an acceptable measure of nutritional efficacy or status. An assessment of the composition of weight gain is needed to ascertain the appropriateness of this gain. The elaboration of growth standards in terms of body composition in childhood and adolescence, and in relation to sexual maturation, could allow the recognition of abnormalities in specific body components in disorders affecting growth and puberty; it could also allow recognition of the moment when a differing pattern of distribution or accretion appears in relation to age, gender, ethnicity, or illness.

The evaluation of body fat with some body composition method should allow the pediatrician to define deviations in body weight and to act in the prevention or treatment of

early obesity. In this sense, the beneficial role of exercise and the negative roles of sedentarism and possibly of television have to be taken into account. The possibility of critical periods for fat accretion and an understanding of the long-term consequences of different body fat distributions might have important implications in the nutritional management of children and adolescents.

As new and more accurate methods emerge, and with the combination of different methods in the multicompartment model, the values for the reference fetus, child, or adolescent might be more precisely defined by state-of-the-art techniques. Age, gender, and ethnicity standards will allow the use of less expensive, surrogate field methods suitable for office practice and for population studies. The ideal field method should be inexpensive, easy to use, reliable, noninvasive, portable, validated, and calibrated. No perfect method is yet available. However, the clinician has a variety of methods that can be used. The methods selected can provide valuable estimates if their limitations and assumptions are recognized.

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CHAPTER 5.1

MACRONUTRIENT REQUIREMENTS FOR GROWTH: FAT AND FATTY ACIDS

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Fat is a major source of fuel energy for children of all ages, providing high relative caloric density compared to protein and carbohydrate. In addition, it aids in the absorption of fat-soluble vitamins A, D, E, and K and carotenoids and is a source of essential fatty acids (EFAs). Although carbohydrate and protein foods can fully substitute as a source of energy, failure to supply EFAs will lead to retardation of growth and development, learning deficiencies, impaired visual and neurologic development, and other abnormalities, including those related to immune-inflammatory responses.[1]

Dietary fat consists primarily (98%) of triacylglycerol, composed of one glycerol molecule esterified with three fatty acid molecules, and smaller amounts of phospholipids and sterols. Other fats or lipids also contain carbohydrate, amino acid, phosphate, and choline moieties, as well as fatty acid esters, such as sphingosine (a major base of sphingolipids), glycolipids, phospholipids, and sterol esters. Cholesteryl esters are composed of a single fatty acid esterified to cholesterol. Fatty acids provide a ready energy source for most organs and tissues in the body, with the exception of red blood cells and brain cells. Carnitine transferase is the carrier system for transporting long-chain fatty acids into mitochondria, where β-oxidation and energy production occurs. The brain can use ketones derived from fatty acids as an energy source. Excess triglycerides are stored in adipose tissue.

Although strong evidence exists for the need of EFAs in the diet, for example, linoleic acid and α-linolenic acid, there is little evidence that dietary cholesterol is necessary for normal growth and development in mammals because in both animals and humans, sufficient cholesterol is produced endogenously to meet all needs for growth and development.[2] The best evidence for the latter lies in that, in utero, all or almost all cholesterol is synthesized endogenously by the fetus during the most rapid phase of growth and development.[3,4] In addition, millions of vegetarian children worldwide who do not consume any animal-derived products grow and develop normally. Similarly, there seems to be no special requirement for phospholipids as long as sufficient choline is present in the diet.

Fatty acids are hydrocarbon chains that contain a methyl (—CH_3) and a carboxyl (—COOH) end. Fatty acids vary by the number of carbon atoms in the chain and by the presence and position of double bonds (unsaturation). In biochemical shorthand, the number of carbon atoms in the chain of fatty acids is written first and then the number of double bonds. The position of the first double bond from the methyl end of the chain is written with the prefix "ω" or "n." Most fatty acids have an even number of carbon atoms because they are synthesized or degraded two carbon units at a time. An example of a short-chain fatty acid is $CH_3CH_2CH_2COOH$, butyric acid, written as $C_{4:0}$.

Fatty acids are derived from both animal and plant foods and are classified into several categories:

- Saturated fatty acids
- Monounsaturated fatty acids
- Polyunsaturated fatty acids (PUFAs; n-6 and n-3 fatty acids)
- *Trans*–fatty acids

Saturated fatty acids contain no double bonds, monounsaturated fatty acids contain a single double bond, and polyunsaturated fatty acids (PUFAs) contain more than one double bond. The major saturated fatty acids in food derived from animals are palmitic ($C_{16:0}$) and stearic acids ($C_{18:0}$). Oleic acid ($C_{18:1}$ ω-9) is the most prevalent monounsaturated fatty acid and is derived from plants or synthesized by animals. Linoleic acid ($C_{18:2}$ ω-6) is the major PUFA derived from plants; α-linolenic acid ($C_{18:3}$ ω-3) is also found in plant oils, and its derivatives, eicosapentaenoic acid (EPA) ($C_{20:5}$ ω-3) and docosahexaenoic acid (DHA) ($C_{22:6}$ ω-3), are produced in animals (fish are an important source) that ingest them. Human milk contains substantial quantities of C_{18} precursors of the ω-3 and ω-6 families as well as their C_{20} and C_{22} derivatives.[5]

Trans–fatty acids are unsaturated fatty acids that contain at least one double bond in the *trans* configuration. When the two hydrogen atoms are on opposite sides of the double bond, the configuration is termed *trans*; when the two hydrogen atoms are on the same side of the double bond, the configuration is termed *cis*. The *trans* double-bond angle is larger than the *cis* configuration, and this results in a more extended fatty acid chain, more similar to that of saturated fatty acids. In addition, fatty acids having a *trans* double bond have different physical properties compared with *cis* fatty acids. Partial hydrogenation of polyunsaturated oils results in an increase of *trans*–fatty acid content and the hardening of fat. Dietary *trans*–fatty acids are derived naturally from meat and dairy products in children's diets and to a greater extent from products made from hydrogenated fat. It has been difficult to accurately quantitate dietary intake of *trans*–fatty acids, however, because of the limited amount of data available on the content of *trans*–fatty acids in commonly consumed foods.

Clinical studies have demonstrated that consumption of *trans*–fatty acids or hydrogenated fat results in higher blood cholesterol levels than consumption of *cis*–fatty acids or naturally occurring oils. Relative to saturated fatty acids, however, *trans*–fatty acids or hydrogenated fat results in lower blood cholesterol levels. Clarification is needed on issues related to the potentially detrimental effects of *trans*–fatty acids or hydrogenated fat compared with saturated fat with respect to decreasing high-density lipoprotein (HDL) cholesterol levels and increasing Lp(a) levels alone and compared with their benefits in decreasing total and low-density lipoprotein (LDL) cholesterol levels.[6,7]

ESSENTIAL FATTY ACIDS

The fatty acids essential for humans are linoleic acid and linolenic acid. Linoleic acid and its derivative, arachidonic acid (AA) ($C_{20:4}$ ω-6), function as precursors for eicosanoids, which include prostaglandins and leukotrienes, components of numerous cellular signaling mechanisms. α-Linolenic acid and its ω-3 derivatives compete for the enzymes involved in the synthesis of AA and oppose many of the activities of its derivatives.[8] Long-chain derivatives of linolenic acids are present in structural lipids and are components of brain, nerve, and other cellular membranes.

The pathways of linoleic and linolenic acid metabolism and related prostaglandin metabolism are shown in Figures 5.1-1 and 5.1-2. Thromboxane derived from AA (an omega-6 fatty acid) is a potent mediator of platelet aggregation, whereas the similarly derived prostacyclin is an anticoagulant and vasodilator. In contrast, thromboxane, derived from omega-3 fatty acids, is a weak mediator of platelet aggregation, whereas the prostacyclins derived from omega-3 fatty acids are mediators of inflammatory and allergic responses and are essential for normal second-messenger action.[9–11] The biologic antioxidant vitamin E appears to help regulate prostaglandin production and prevents oxidation of unsaturated fatty acids. A diet high in polyunsaturated fat should contain an appropriate amount of vitamin E (at least 0.5 mg tocopherol equivalent per gram linoleic acid) to ensure the normal metabolism of these fatty aids. Failure to do so has been associated with a hemolytic state in infants, particularly when extra iron (a free radical generator) is added to the diet.[12]

ABSORPTION OF DIETARY FAT

Digestion of dietary fat starts in the stomach.[13] A lipase termed lingual lipase, because it was first found at the base of the tongue in the rat, initiates triglyceride hydrolysis. The released nonesterified fatty acids emulsify the fat droplets. In the duodenum, bile salts enhance emulsification and pancreatic lipase activity. Colipase fixes lipase to the emulsified fat droplet. Until the age of 6 months, infants can have low concentrations of pancreatic lipase

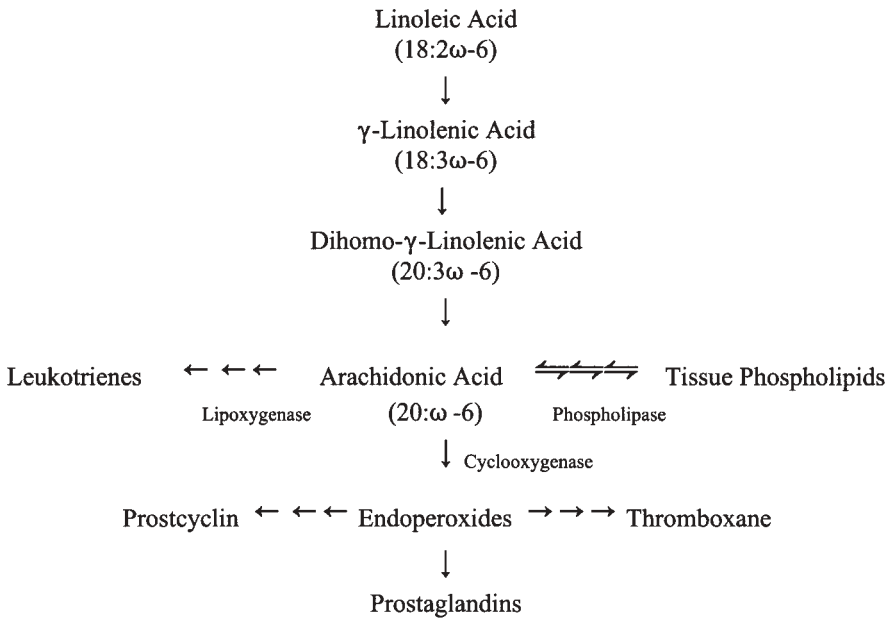

FIGURE 5.1-1 Metabolic pathways of linoleic and arachidonic acid.

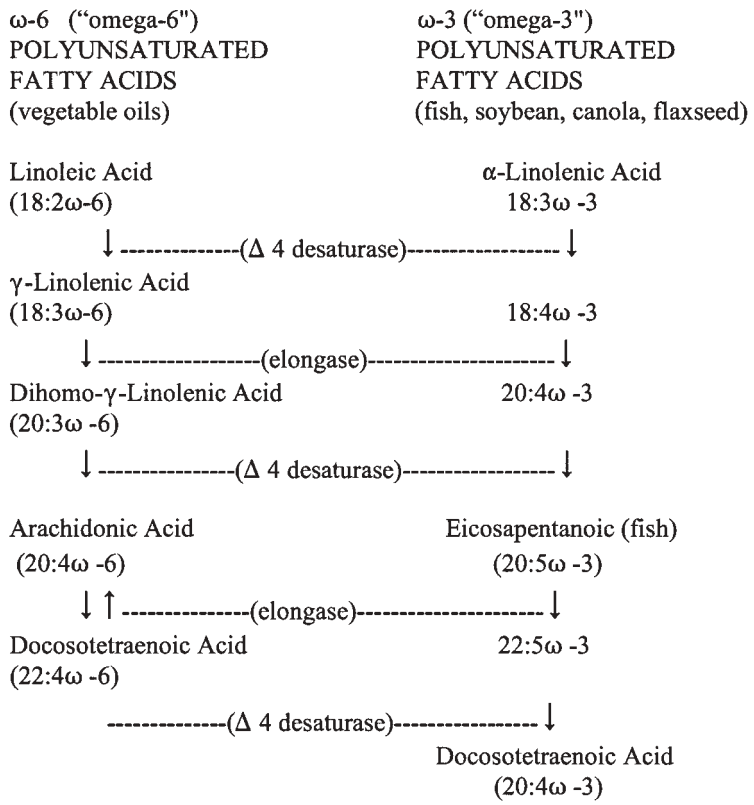

FIGURE 5.1-2 Metabolic pathways of the two essential fatty acids, linoleic (ω-6) and linolenic (ω-3) acids.

and bile acids in the intestinal lumen, which may result in up to 10 to 15% of ingested fat to remain unabsorbed. The ability to absorb fat is facilitated in the breast-fed infant because breast milk contains a bile salt–stimulated lipase.[14]

Bile acid–phospholipid aggregates, termed micelles, provide a large surface area for the action of pancreatic lipase or human milk lipase, which mainly removes the two outer fatty acids from the glycerol and leaves an easily absorbable monoglyceride. The triglyceride is enzymatically reassembled from the monoglyceride and two fatty acids in the upper small bowel mucosa. Long-chain triglycerides are then coated with protein and extruded as chylomicrons into the lymphatics. Medium- and short-chain fatty acids (with 2 to 10 carbon atoms) partially short-circuit this complex system and can be absorbed directly into the portal venous system. The longer the chain length of saturated fatty acids, the slower the rate of absorption. The introduction of double bonds into the longer fatty acids may cause calcium wastage by the information of insoluble soaps.

DEFICIENCY

Hansen and colleagues, in the late 1950s, proved that a fat component present in vegetable oils, linoleic acid, was essential in the human diet.[15] Cow's milk fat contains much less of the EFAs than does human milk fat, which has led manufacturers of some infant formulas to add vegetable oils to a base of skim cow's milk. Symptoms of EFA deficiency in infants may result when linoleic acid is less than 1% of energy intake. Deficiency of linoleic or AA is characterized by symptoms such as scaly skin, hair loss, diarrhea, and impaired wound healing in humans. Such deficiency may result from feeding infants a diet of fat-free milk, prescribing a special fat-free diet for specific pathologic conditions, or a prolonged course of fat-free intravenous alimentation. Absence of trace amounts of linolenic acid causes visual and behavioral symptoms in animals and perhaps in humans.[5,16] In patients with cystic fibrosis and hepatobiliary disease, steatorrhea may also result in malabsorption of EFAs.

Human milk contains 3 to 7% of energy as linoleic acid and a significant amount of omega-3 linolenic acid and its derivatives, depending on the maternal diet. Most commercial infant formulas contain more than 10% of fat as linoleic acid, and all contain some linolenic acid. Unmodified cow's milk contains only about 1% linoleic acid, which is less than the presumed daily requirement of 2.7%. Adequate intakes of linolenic acid and its long-chain derivatives are especially important for premature infants.

RECOMMENDED INTAKES OF EFAS

Both linoleic acid ($C_{18:2}$ ω-6) and α-linolenic acid ($C_{18:3}$ ω-3) are nutritionally essential and must be included in the diets of infants and children to ensure normal growth, cell membrane maintenance, lipid metabolism, and prostaglandin synthesis.

Linoleic and linolenic acids are absolute requirements for the diet of infants. The American Academy of Pediatrics' (AAP) Committee on Nutrition recommends that infants receive at least 3% of total energy from linoleic acid and 0.3% of energy from linolenic acid.[17] For preterm infants, the International Union of Nutritional Sciences recommends higher intakes of linoleic acid and linolenic acid, at 4 to 5% of energy as linoleic acid and 0.5% of

energy from linolenic acid. Because of the need for rapid neurologic growth in preterm infants, the latter group has also made recommendations that preterm infants receive long-chain n-6 fatty acids (C_{20} and C_{22}) as 0.5% of total energy and long-chain n-3 fatty acids (C_{20} and C_{22}) at 0.25% of energy.[18]

The Food and Nutrition Board of the Institute of Medicine, National Academy of Science, after an extensive review of the literature, recently published Dietary Reference Intakes for macronutrients, including those for n-6 and n-3 PUFAs in infants and children. Their recommendations for adequate intakes of these fatty acids are summarized in Table 5.1-1.

A number of studies have suggested that conversion of the precursor EFAs, linoleic acid to AA and linolenic acid to EPA and DHA, is less efficient in formula-fed infants compared with breast-fed infants because the latter have higher plasma concentrations of these long-chain PUFAs. Preterm infants are at greater risk of deficiency, however, because these fatty acids are normally supplied to the fetus from maternal plasma throughout pregnancy.

Human milk contains small amounts of both C_{20} and C_{22} n-6 fatty acids. In the past decade, therefore, a number of randomized clinical trials were conducted to evaluate the benefits of adding these fatty acids to infant formula. Several studies involving preterm babies demonstrated enhanced early visual acuity for infants fed DHA ($C_{22:6}$ n-3) supplemented formula compared with an alternate formula supplemented with its precursor, α-linolenic acid ($C_{18:3}$ n-3).[19–23] These results suggest that, similar to findings in animal studies, the DHA content of the brain may depend more heavily on the dietary supply of DHA rather than on its precursor, α-linolenic acid. A recent study reporting poorer growth (shorter length) in long-chain PUFA–supplemented preterm infants at 18 months of age compared with breast-fed or control-fed (preterm formula without long-chain PUFAs) infants has raised concern, however, and the results of additional clinical trials will be needed to fully assess the risks and benefits of preterm formulas supplemented with long-chain fatty acids.[24]

Among term infants, the results of similar clinical trials have been mixed. Some studies have reported improved visual acuity or better neurodevelopmental outcomes in infants fed formula supplemented with C_{20} and C_{22} n-6 fatty acids, whereas the results have been negative in other studies. These studies, however, vary with respect to design, composition of the formulas used, duration of supplementation, age at testing, and types of outcome measures employed. Table 5.1-2 summarizes the findings for recent clinical trials in term infants.[25–36]

Based on the evidence provided by these studies, formulas supplemented with AA and DHA have been approved for feeding infants in North America and Europe. In the United States, these supplemented formulas contain AA as 0.40 to 0.64% of total fatty acids and DHA as 0.15 to 0.32% of total fatty acids. There is still controversy, however, as to whether the supplementation of infant formula with long-chain PUFAs results in any long-term visual or developmental benefits to the child.

TABLE 5.1-1 Adequate Intake of n-3 and n-6 Polyunsaturated Fatty Acids for Infants and of Linoleic Acid and α-Linolenic Acid for Older Children and Adolescents

Age of Child	*n-6 Polyunsaturated Fatty Acids*	*n-3 Polyunsaturated Fatty Acids*
0–6 mo	4.4 g/d (8% of energy)	0.5 g/d (1% of energy)
7–12 mo	4.6 g/d (6% of energy)	0.5 g/d (1% of energy)
	Linoleic Acid	*α-Linolenic Acid*
1–3 yr	7 g/d	0.7 g/d (1% of energy)
4–8 yr	10 g/d	0.9 g/d (1% of energy)
Boys		
9–13 yr	12 g/d	1.2 g/d
14–18 yr	16 g/d	1.6 g/d
Girls		
9–13 yr	10 g/d	1.0 g/d
14–18 yr	11 g/d	1.1 g/d

Adaped from Dietary Reference Intakes for energy, carbohydrates, fiber, fat, protein and amino acids (macronutrients).[22]

BIOCHEMICAL MARKERS OF EFA DEPLETION

The fatty acid eicosatrienoic acid ($C_{20:3}$ ω-9) can be synthesized by humans but is not normally present in serum. When depletion of omega-6 fatty acids occurs, the level of eicosatrienoic acid increases in serum. The ratio of trienes (C20:3 ω-9, with three double bonds) to tetraenes (C20:4 ω-6, with four double bonds) increases with deficiency of EFAs. An elevated triene-to-tetraene ratio is therefore consistant with EFA deficiency.

Healthy full-term newborns have lower serum levels of EFAs than older children, and the level of eicosatrienoic acid is slightly higher. Normal levels in preterm infants and the requirement for EFAs have not been accurately defined. However, the dietary requirements for EFAs may be higher in preterm infants than older children because of poor fat absorption and minimal stores. Full-term and preterm infants can develop fatty acid deficiency within 1 week when receiving parenteral nutrition without added lipids.[37]

The long-term effects of EFA deficiency in infants are not clear. Platelet dysfunction occurs in neonates with EFA deficiency.[38] Research in experimental animals has shown a greater susceptibility to infection in the presence of EFA deficiency. Thus, infant formulas contain at least 300 mg of linoleic acid per 100 kcal to minimize the risk of EFA deficiency, although this level may be significantly above the minimum need. The recommended intake can be attained readily in infants by the use of human milk or formula containing soy or other vegetable oils. After solid foods are introduced into the diet, the oils found in foods such as margarine, peanut butter, and cereal are good sources of omega-3 long-chain fatty acids (greater than 20 carbons). Hydrogenated coconut oil does not furnish EFAs.

In patients with steatorrhea, the provision of EFAs in the diet or by intravenous alimentation is necessary to maintain normal intake of EFAs. Medium-chain triglycerides (MCTs) are a useful source of calories in malabsorptive states, but MCTs do not provide EFAs. Infants receiving a formula with an MCT as the predominant oil may

TABLE 5.1-2 Randomized Trials of n-3 Fatty Acids and Neural-Visual Development in Term Newborns

Reference	*Study Population*	*Age at Testing*	*Results*
Agostoni et al, 1995[25]	*n* = 29 formula, *n* = 29 formula + LC-PUFA	4 mo	Infants consuming formula supplemented with LC-PUFA scored significantly higher than standard formula group
Makrides et al, 1995[26]	*n* = 14 formula, *n* = 12 formula + LC-PUFA	16, 30 wk	VEP acuity better in infants fed supplemented formula than in infants fed standard formula
Carlson et al, 1996[27]	*n* = 20 formula, *n* = 19 formula + DHA + AA	2, 4, 6, 9, 12 mo	Infants fed formula supplemented with DHA and AA had higher visual acuity scored than the standard formula group at 2 mo but not later in infancy
Agostoni et al, 1997[28]	*n* = 30 formula, *n* = 26 formula + LC-PUFA	24 mo	No difference in developmental quotient
Auestad et al, 1997[29]	*n* = 45 formula, *n* = 43 formula + DHA, *n* = 46 formula + DHA + AA	2, 4, 6, 9, 12 mo	No differences in VEP or visual acuity
Jensen et al, 1997[30]	*n* = 20 each group	4 mo	No difference in VEP Infants fed formula with n-6:n-3 ratio of 4.8 weighed less than infants fed formula with ratio of 44
Birch et al, 1998[31]	*n* = 21 formula, *n* = 20 formula + DHA, *n* = 19 formula + DHA + AA	6, 17, 26, 52 wk	Sweep VEP acuity better in infants fed supplemented formulas than in infants fed standard formula Visual acuity not different between groups
Jorgensen et al, 1998[32]	*n* = 11 formula, *n* = 12 formula + DHA, *n* = 14 formula + DHA + GLA	4 mo	No difference in VEP acuity
Scott et al, 1998[33]	*n* = 42-45 formula, *n* = 33-43 formula + DHA, *n* = 38-46 formula + DHA + AA	12 mo (Bayley), 14 mo (MacArthur)	No differences in mental and psychomotor development Vocabulary production and comprehension lower in the formula and DHA group
Lucas et al, 1999[34]	*n* = 125 formula, *n* = 125 formula + LC-PUFA	18 mo (Bayley)	No differences in mental and psychomotor development
Makrides et al, 2000[35]	*n* = 30 10:1 formula, *n* = 28 5:1 formula	16, 34 wk	No difference in VEP acuity
Makrides et al, 2000[36]	*n* = 21 formula *n* = 23 formula + DHA *n* = 24 formula + DHA + AA	16, 24 mo 12, 24 mo (Bayley)	No difference in VEP acuity or Bayley scales of mental and psychomotor development

AA = arachidonic acid; Bayley = Bayley Scales of Infant Development; DHA = docosahexaenoic acid; GLA = γ-linolenic acid; LC-PUFA = long-chain polyunsaturated fatty acids; MacArthur = MacArthur communicative development; VEP = visual evoked potential.

demonstrate signs of EFA deficiency and decreased circulating levels of AA.[39] Decreased prostaglandin levels have returned to normal in children with cystic fibrosis after supplementation with linoleic acid or calories.[40]

EFAs should provide at least 3% of energy intake for a healthy child. Ethnic differences exist for the intake of fat by children, but in the United States, mean intake of total fat is currently about 32 to 33% of energy intake. If about half of this intake comes from plant sources, the EFA requirements will be easily met. Corn oils and soybean oils both contain more than 30% linoleic acid.

GUIDELINES FOR TOTAL DIETARY FAT INTAKE IN CHILDREN OVER 2 YEARS OF AGE

Recommendations for dietary fat intake in childhood take into account the child's unique growth and developmental patterns, specific nutrient requirements, vulnerability of sentinel nutrients, factors important to the establishment of healthful eating habits, and nutritional risk factors for childhood and adult-onset diseases. The role of dietary fat as a source of calories and EFAs must be balanced with the desire to avoid excessive fat intake associated with increased risk of future chronic disease.[41]

Many health and nutrition organizations have developed dietary guidelines for children and adolescents based at least in part on the role of dietary fat (especially saturated fat) in the early development of atherosclerosis.[42–47] This rationale is strengthened by studies linking a high intake of dietary fat with some human cancers[48–50] and with obesity.[51–53] The following section summarizes (1) current guidelines for dietary fat intake in children and adolescents, (2) trends in dietary fat intake over the past several decades, and (3) the risks and benefits of these recommendations.

Dietary guidelines for children 2 to 19 years of age are summarized in Table 5.1-3. Similar to adults, it is recommended that children consume no more than 30% energy from total fat, less than 10% energy from saturated fat, no more than 300 mg of cholesterol daily, and dietary fiber.[41,54–56]

LINK BETWEEN DIETARY FAT, BLOOD LIPIDS, AND ATHEROSCLEROSIS

Recommendations to control dietary fat intake beginning in childhood primarily stem from scientific consensus on the role of dietary fat (especially saturated fat) in the early development of atherosclerosis. The National Cholesterol Education Program (NCEP) Pediatric Panel convened by the National Institutes of Health (NIH) stated in their 1992 report that "A variety of studies indicate that the process of atherosclerosis begins in childhood; that this process is

related to elevated levels of blood cholesterol; and that these levels are often predictive of elevated blood cholesterol in adults."[57–62] Autopsy studies have demonstrated that early coronary atherosclerosis or precursors of atherosclerosis often begin in childhood and adolescence. In the aorta, fatty streaks begin to develop soon after birth and are almost universal by 3 years of age. Fatty streaks in the coronary arteries lag behind by about a decade. Studies such as the PDAY (Pathological Determinants of Atherosclerosis in Youth) autopsy study in youth suggest that a critical stage of the disease process is the conversion of childhood fatty streaks into thicker raised lesions.[59] More research also needs to clarify how the conversion occurs and what risk factors influence it. Although atherosclerosis may not be totally preventable, evidence suggests that its progress can be substantially retarded and the associated cardiovascular disease deferred to much later in life.

Dietary fat (especially saturated fat) is associated with high levels of blood cholesterol, a major independent risk factor for atherosclerosis. Elevated cholesterol levels are highly prevalent in children, even in toddlers over 2 years of age.[63–67] In a study we conducted of 700 3- to 5-year-old children in New York, 26% had levels in the borderline high range (170 to 199 mg/dL) and 11% were in the high range (≥ 200 mg/dL).[68] The most recent national data on cholesterol levels in childhood are from NHANES III (National Health and Nutrition Examination Survey, 1988–1994) and indicate that, similar to adults in the United States, mean cholesterol levels in children have decreased slightly since the late 1980s (NHANES II data, 1976–1980). Regional surveys suggest that at least 10% of children are currently in the high-risk category for total cholesterol (≥ 200 mg/dL), and another 25 to 30% have borderline elevated values (170 to 199 mg/dL). These proportions are greater than the 5% and 20% reported previously from the Lipid Research Clinic (LRC) data, which formed the basis for the NCEP guidelines for interpreting pediatric lipids (eg, total cholesterol designated as "high" for children was set at ≥ 200 mg/dL, which was about the 95th percentile value for children evaluated in the LRC study).[69,70]

TABLE 5.1-3 Recommended Dietary Intake for Children ≥ 2 Years of Age

Nutrient	*Recommended Daily Intake*
Total fat	Average of no more than 30% energy and no less than 20% energy
Saturated fatty acids	Less than 10% energy
Polyunsaturated fatty acids	Up to 10% energy
Monounsaturated fatty acids	Remaining total fat calories
Cholesterol	Less than 300 mg/d
Carbohydrates	About 55% energy
Dietary fiber	Minimal: "Age +5" g/d[54]
Protein	About 15–20% energy
Calories	To promote normal growth and development and to maintain desirable body weight

Adapted from American Academy of Pediatrics, Committee on Nutrition and National Cholesterol Education Program.[42,43]

Plasma levels of total and LDL cholesterol show significant tracking from childhood to adulthood.[68–70] The Bogalusa Heart Study, for example, found that about 70% of children in the top quintile for blood cholesterol could be found in the top two quintiles 12 years later[71] and that, similarly, about 70% of children originally in the bottom quintile could later be found in the bottom two quintiles for cholesterol.[72] Obesity strengthens the tracking of both elevated cholesterol and elevated blood pressure, a factor of some importance as the pediatric population becomes more obese.[72]

Blood lipid and lipoprotein levels are correlated with dietary intake of amount and type of dietary fat in children, similar to adults. Cross-sectional studies comparing diets in different countries of children's cholesterol levels indicate a close relationship between total and LDL cholesterol levels in children, with their saturated fat intake in different countries.[73] Moreover, in studies comparing the effects of dietary changes on children's lipid levels, infants, children, and adolescents respond with similar changes in plasma total and LDL cholesterol with changes in the type of fat ingested.[74] Similarly, children decrease HDL cholesterol levels as total fat and saturated fat intake decreases and as the proportion of polyunsaturated fat in the diet increases. Dietary interventions in schools or communities are as effective in children as in adults in improving plasma lipid profiles (decreasing total and LDL cholesterol).[75]

Fasting insulin levels in children also positively correlate with degrees of adiposity, blood pressure, plasma triglyceride, LDL and very LDL cholesterol levels but inversely to HDL cholesterol levels. In addition, these traditional risk factors for coronary heart disease aggregate in children as they do in adults.[76] Of concern, in countries where adult morbidity and mortality from coronary heart disease are very high, children also have substantially higher frequencies of hyperlipidemia, obesity, and hypertension, as well as other risk factors for chronic adult diseases.[77]

Although children and adolescents as a group react to dietary changes in a way similar to adults, there are some differences between male and female adolescents. For example, the decrease in HDL cholesterol in response to increasing dietary polyunsaturated fat occurs less in female adolescents compared with males, so such a diet will have a greater tendency to decrease total cholesterol in boys. In comparing dietary responsiveness of US children from different cultural and ethnic groups, available data indicate that responses to changes in dietary total fat and saturated fat may be similar.[78]

There are interesting data from other countries on the effects of westernization of diets in children, especially the gradual increase in fat/saturated fat consumption. Demonstration of how changes in diet in children and adolescents may have substantial effects on coronary heart disease risk is evident from longitudinal data available from a number of countries. For example, total and LDL cholesterol levels in children in both Spain and Japan have rapidly increased over the last 15 to 20 years. Three decades ago, mean total cholesterol levels of children in Spain and Japan were sub-

stantially below the mean for US children. In the mid-1980s, however, mean total and LDL cholesterol levels for children from both of these countries exceeded the 75th percentile for US children.[79] This increase paralleled changes in diet, particularly dietary fat quantity and quality. In Japan over the past three decades, fat intake has increased threefold, and the saturated fat intake as represented by increased animal fat consumption has increased over eightfold.[79] In Japanese children, the increase in total caloric intake over this period has only been less than 10%, but increases in total fat are closely paralleled by two- to threefold increases in obesity prevalence. Diabetes is also becoming more prevalent in Japanese children and adolescents. In Spain, current data from Madrid schoolchildren show that dietary fat represents up to 42% of total calories, saturated fat contributing 17.5%. Of interest, although children's cholesterol levels are high in both Spain and Japan, Japanese children still ingest less total fat calories and less saturated fat than do American children. This latter observation suggests that there may be genetic differences in response to total and saturated fat in the Japanese population and in other countries that have only recently been exposed to diets high in total and saturated fat. These "country" analyses indicate that childhood populations are sensitive and responsive to dietary fat intake, in terms of plasma lipids, obesity, and diabetes—all major risk factors for premature coronary artery disease.[79,80]

GENOTYPE/PHENOTYPE–ENVIRONMENT INTERACTIONS

A number of major gene polymorphisms are clearly associated with changes in phenotype that relate to risk for disease. A specific example of the latter would include defects in the LDL receptor gene that lead to marked elevations of plasma LDL cholesterol levels and a high risk of coronary heart disease at an early age.[81] More subtle genetic polymorphisms are now being identified that have little or no effect on phenotypic expressions of specific blood parameters unless associated with differences in behavioral or environmental characteristics. Examples include genes controlling coagulation parameters such as the fibrinogen gene or perhaps blood pressure via the angiotensin-converting enzyme gene that has specific alleles associated with increased risk of coronary heart disease.[82] A specific example of environment–gene interaction is evident in subjects expressing an allele for the B-fibrinogen gene, where increases in plasma fibrinogen are much more marked in smokers compared with nonsmokers. Another example is a polymorphism in the gene for lipoprotein lipase, in which especially high increases in plasma triglyceride levels occur only in subjects with a high body mass index (BMI). Little or no knowledge is presently available as to whether specific phenotypes or haplotypes that predict dietary responsiveness in the adult population will also do so in children and adolescents. Nevertheless, it seems prudent to consider the possibility that certain children, because of a specific genetic constitution, might be at higher risk for early coronary heart disease or other chronic diseases and that specific intervention strategies could be designed for these children at particularly high risk (eg, apolipoprotein E-IV versus apolipoprotein E-III versus apolipoprotein E-II).[83] A specific example might be greater reductions in fat intake in children from families in which fibrinogen levels are particularly sensitive to higher levels of fat intake.

LINK BETWEEN DIETARY FAT AND OBESITY

There is some evidence to suggest that a high-fat diet and a sedentary lifestyle may have contributed to the current increase in obesity in the United States and other affluent countries. Fat plays a powerful physiologic role in undermining human body weight regulatory systems. This is in part because the body has the ability to increase the rate at which it oxidizes carbohydrate and protein when ingestion of these macronutrients is increased (necessary because the body has a very limited ability to store these nutrients). When large amounts of dietary fat are consumed, however, the body is unable to increase rates of oxidation to re-establish fat balance. In addition, oxidation of fat is suppressed when an excess of energy or an excess of any of the other macronutrients is consumed. Thus, the human metabolism is not designed to cope with excess fat consumption.[51–53]

Some studies also suggest that dietary fat is not particularly good at satisfying hunger, or, in other words, fat has low satiating power. This seems especially true for obese individuals. Manipulation of the fat content of diets results in reproducible spontaneous fat loss on low-fat diets and fat gain on high-fat diets. Individuals on a high-fat diet develop "passive overconsumption" because it occurs unintentionally and without consuming excess bulk. In addition, some obese individuals have a behavior preference for high-fat foods.[51,53]

Obesity in US children has been increasing over the past several decades.[84–90] Although the percentage of calories consumed as fat has declined, the total amount of calories consumed appears to have increased.[91–93] Therefore, the amount of fat consumed each day in grams may not have changed. In addition, relatively low levels of physical activity are the norm. Physical education in the schools has declined in high school, especially among older girls. In 1996, 23% of children in grades 4 to 12 had no physical education.[94,95] Thus, based on metabolic considerations, physical activity should increase and dietary energy intake decrease to achieve the synergism needed to prevent childhood obesity.

Klesges and colleagues evaluated determinants of accelerated weight gain over 3 years in a cohort of 146 preschool children.[52] Higher baseline levels of percent dietary energy from fat were associated with greater increases in BMI, as were recent increases in percent energy from fat. Total caloric intake did relate to weight gain, however, when percent energy from fat was entered into the regression equation; it explained more of the variance in weight gain than total energy intake. This suggests that for preschool children, the percent calories from total fat may be an important contributor to accelerated weight gain. Baseline aerobic

activity and increased leisure activity were also significant predictors of change in BMI. These modifiable diet/activity variables together accounted for 33% more of the variance in body mass change than the combined set of nonmodifiable variables (such as parental obesity).

It is known that the earlier the age at which adiposity rebound occurs, the more likely it is that a child will become an obese adult.[96,97] Additional studies are needed, however, to determine if the age of adiposity rebound among US children has become earlier over the past several decades and also if a high-fat diet promotes early adiposity rebound.

LINK BETWEEN DIETARY FAT IN CHILDHOOD AND CANCER IN ADULT LIFE

The National Cancer Institute, the American Cancer Society, and others feel that it is important to reduce total and saturated fat in childhood to prevent cancer later in life. Data on migrant studies of Japanese from Japan to Hawaii show an increase in colon cancer among first-generation immigrants as dietary fat increases and an increase in breast cancer in the second generation, perhaps because the effect of high dietary fat on breast cancer incidence is greatest during adolescence, when breast tissue is developing rapidly.[98–101]

Dietary fat stimulates mitotic activity and thereby promotes cancer growth after the initial mutagenic steps. Dietary fat can also lock in spontaneous mutations. For breast cancer, the n-6 fatty acids (PUFAs) have the greatest cancer-promoting effect, and n-3 (also PUFA—fish oil, flaxseed oil) fatty acids are most protective. This is not true for colon cancer. It is also speculated that the oxidation of dietary fatty acids produces free oxygen radicals that can react to and damage DNA. In this way, dietary fat may function as a mutagen.[101]

It is known that menarche occurs earlier for girls on a high-fat diet.[101] Estrogen is produced earlier, and, in turn, breast tissue is stimulated earlier and exposed to increased mitosis before differentiation is complete.[101] Menarche before age 13 is associated with a 30% greater risk of breast cancer than that for a woman with menarche at 16.[101]

LINK BETWEEN EARLY DIET BEHAVIORS AND LATER DIET BEHAVIOR

There is some evidence that dietary patterns established in childhood persist or "track" into later life. Children develop food preferences through their early eating experiences, and these may be sustained over time. The majority of studies examining dietary patterns over time have considered tracking of nutrient intake over time in cohorts of children.

In the Bogalusa Heart Study, significant correlations for 12-year tracking of macronutrient intake were found (in the 0.2 to 0.4 range), indicating a fair consistency of intake for several dietary components over a 5-year period in children from 6 months to 4 years of age. Children with higher intakes of total fat, saturated fat, and cholesterol at baseline continued to have higher intakes of these nutrients after 5 years compared with their peers. Thus, persistence of eating behaviors may begin quite early in life, in part because of parental control over food intake. Other data from the same group reported somewhat higher correlation coefficients, in the range of 0.4 to 0.5.[102] The Framingham Children's Study reported on tracking of nutrient intake in a preschool population. They reported that 40 to 57% of children in the highest quintiles for total and saturated fat intake were still in this quintile 2 to 3 years later.[103] Less is known of actual food consumption over time. That is, do young children who eat large amounts of fruits, vegetables, milk, cereal, or sweets continue to do so later in adolescence and adult life?

NUTRITIONAL ADEQUACY

Numeric guidelines for fat intake in childhood are also based on considerations of nutritional adequacy. When the dietary intake of children is examined with respect to sources of excess calories, 15% are derived from fat and 10% from sugar.[104] These calories replace the consumption of fruits, vegetables, and grains, which would result in meeting the Recommended Dietary Allowances (RDAs) for macro- and micronutrients in the diet. Thus, a moderate reduction in fat intake in childhood, if replaced by healthful fruits, vegetables, and grains, would improve the overall quality of children's diets.[104]

CURRENT GUIDELINES FOR DIETARY FAT INTAKE IN CHILDREN AND ADOLESCENTS

Current US dietary guidelines recommend no more than 30% of dietary energy from total fat, less than 10% from saturated fat, and no more than 300 mg of cholesterol daily.[41,55] These guidelines do not apply to infants and children under 2 years of age because there is consensus that a higher fat intake is needed to support the rapid growth and caloric requirements of this age (Table 5.1-4).

These guidelines were first proposed by the 1985 National Consensus Development Panel, cosponsored by the NIH and the American Heart Association (AHA).[47] They recommended numeric guidelines for dietary fat intake for all Americans > 2 years of age, with total fat intake at no more than 30% of calories and saturated fat at < 10% of calories. In 1991, these guidelines were endorsed by the NCEP report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents.[43] The AAP, which in 1983 and 1986 declined to recommend numeric fat intake guidelines for children, was represented on the NCEP Expert Panel and in 1992 also recommended "an average daily intake of 30% of total calories from fat, < 10% from saturated fat, and < 300 mg of cholesterol per day."[42] The US national health promotion and disease prevention objectives (Healthy People 2010) also recommend that Americans "reduce total dietary fat intake to an average of 30% of energy or less and saturated fat intake to less than 10% of energy among people 2 years and older."[46] Thus, at present, AAP, the AHA, NIH, US Department of Agriculture (USDA), US Food and Drug Administration, and at least 26 other health-related organizations recommend numeric limits for dietary fat intake for Americans over

age 2 years.[105] Others, however, argue against dietary fat limitations in childhood.[106,107]

The age at which to initiate a fat-controlled or prudent diet varies somewhat according to the source of the recommendation. The AHA recommends that the prudent diet be adopted after 2 years of age.[41] The NCEP considers 2 to 3 years of age as "transitional" between the high-fat diet of infancy and the fat-modified prudent diet. The USDA Dietary Guidelines (fifth edition) recommend that preschool children should gradually reduce dietary fat over a longer period of time, reaching the 30% energy from total fat at about 5 years of age.[55] There may be some rationale for establishing a preschool dietary transition period to avoid an abrupt drop in fat intake after age 2 years and a possible abrupt drop in calories, although dietary fat intake can be safely reduced to 30% of energy intake after 2 years of age without compromising growth and development.[108–113]

TRENDS IN DIETARY FAT INTAKE AMONG US CHILDREN AND ADOLESCENTS

How much dietary fat are US children eating, and how does this compare with current guidelines? There have been a number of national surveys of dietary intake in the past several decades, all of which include data on children. Although there are methodologic differences that should be taken into consideration when analyzing secular trends in dietary intake, these surveys remain the best source of data available at the present time.[92,93,114–119] National surveys of dietary intake include the NHANES I, II, and III; the National Food Consumption Surveys of 1977–78 and 1987–88; and the USDA Continuing Surveys of Food Intake of Individuals (CSFII).

A review of trends in dietary fat intake in children over 2 years of age reveals that (1) children's intake of dietary fat, saturated fat, and cholesterol tends to reflect the trend for the population as a whole; (2) the percentage of daily calories from dietary fat (%kcal) has decreased over the past decade, although the total intake of fat (grams per day) has not decreased because caloric intake has increased as well; (3) a significant proportion of children still consume amounts of total and saturated fat that are above currently recommended levels; and (4) although there are some differences in fat intake by ethnicity and poverty levels, these differences tend to be small.[92,114–118]

TRENDS IN FAT INTAKE IN CHILDHOOD

In the past 20 years since NHANES II (1976–1980), the percentage of energy consumed from total fat has decreased slightly for 3- to 5-year-old preschool children (from 34 to 33% energy) and slightly more for 6- to 11-year-old and 12- to 17-year-old children (from 36 to 34% energy). Saturated fat intake has decreased from 13 to 12% energy for 3 to 5 year olds, from 14 to 13% energy for 6 to 11 year olds, and from 14 to 12% energy for 12 to 17 year olds.[92,115–124]

The percentage of children and adolescents who meet the dietary goals for total fat and saturated fat is still quite low. Data from the CSFII (1995) found that 31 to 37% of 3 to 19 year olds met the total fat goal and 23 to 38% met the goal for saturated fat. A greater proportion of children met the goal for dietary cholesterol, ranging from 59 to 88%.[120] These estimates, however, have improved since phase I of NHANES III (1988–1991), when only 15 to 23% of 2 to 19 year olds met the total fat goal and 7 to 9% met the saturated fat goal.[117]

Total saturated fat intake was highest in both males and females between the ages of 16 and 29 years of age in the recent NHANES III survey. In addition, total and saturated fat intake was higher in non-Hispanic black compared with non-Hispanic white and Mexican American children.[124] Overall, total fat intake in US children 2 to 19 years of age is now estimated at about 33 to 34% of total calories compared with 36 to 38% over two decades ago in the late 1970s.[124] Data from the National Food Consumption Survey (1987–1988) indicate that children below the poverty level consume a greater proportion of their daily calories as fat.[120] This was greatest for children at 100 to 130% of poverty compared with those at 131% and above. Consumption of whole-milk products rather than low-fat products accounted for most of the difference in fat intake by poverty level.[91]

POTENTIAL RISKS AND BENEFITS OF A FAT-MODIFIED DIET IN CHILDHOOD

It is important to consider the potential risks and benefits of a fat-modified diet with respect to child nutrition and health. Dietary fat is a concentrated source of calories, and calories are essential for growth. Studies over the past decade have sought to determine the relative importance of caloric versus fat intake in supporting normal growth and development in childhood. The results of the most recent growth and safety studies indicate that growth is adequately supported on diets in which fat contributes approximately 25 to 30% of calories if there is adequate intake of calories, high-quality protein, and essential nutrients.[108–113]

Studies have employed computer modeling of nutrient adequacy given specific levels of dietary fat.[125] These studies indicate that the fat-modified diet need not be deficient in calories or any essential nutrients. However, care must be taken to ensure adequate intake of some nutrients, such as calcium, iron, and zinc.[91]

The STRIP Baby Project is one of the few studies in which dietary fat reduction was initiated before 2 years of age. This is an ongoing prospective randomized trial in 1,062 Finnish infants randomly assigned at 8 months of age to a usual diet (control) or to a diet with reduced total fat, saturated fat, and cholesterol. The results show that absolute energy intake, along with parental BMI and height, best predict child growth patterns and that children with a consistently low fat intake grew as well as children with a higher fat intake. In addition, intakes of vitamins, minerals, and trace elements did not differ between the intervention and control groups. All of the children in this study are under medical supervision in well-child clinics and have been followed to age 7 years.[108,126]

The SCANs (Studies of Childhood Activity and Nutrition) were observational studies that examined determinants of diet and exercise in young children. In one SCAN study, Shea and colleagues evaluated the effects of reduced fat on blood lipids and growth in a 2-year study of 215 Hispanic children (age 3 to 4 years) and found no difference in crude measurements of growth. Calcium levels were below recommended levels in the low-fat group, however, so that the need to keep up intake of low-fat milk was emphasized.[127,128]

Dietary intervention studies to lower fat intake have generally involved older children. Nicklas and colleagues, in the Bogalusa Heart Study, found that in a cross-sectional sample of 10 year olds, those with fat intake in the lowest quartile were more likely not to consistently meet the RDAs for vitamins B_6 and B_{12}, thiamin, and niacin than 10 year olds on a higher-fat diet. However, children in the lower-fat category tended to make up the missing fat calories with simple sugar rather than the recommended complex carbohydrates (160 g/day sugar in the lowest fat quartile compared with 129 g/day for the highest fat quartile).[129]

In the Child and Adolescent Trial for Cardiovascular Health (CATCH, 1991–1994), 5,000 third grade students (~ age 8 years) participating in a food service modification and education intervention reduced their total fat intake from approximately 33 to 30% of dietary energy. Growth or development was similar in both intervention and control groups after 3 years of follow-up.[112,130–135] Similarly, in the Dietary Intervention Study in Childhood (DISC), 638 8- to 10-year-old children with high LDL cholesterol followed a lower-fat Step II diet (saturated fat ~ 7% energy). After 4 years, the drop in LDL cholesterol was only 3.23 mg/dL, however, on a fat intake averaging about 27% energy from total fat, no adverse effects were observed in any of the growth variables, sexual maturation, iron stores, or psychological well-being.[74]

Recent trends also indicate that concomitant with the gradual reduction in the percentage of energy from fat in children's diets, the rate of growth retardation among vulnerable low-income preschool children has decreased steadily over the past several decades. In 1987, 16% of low-income preschool children were classified as growth retarded (prevalence of children age 5 and under who are below the 5th percentile for height based on NHANES I reference data). By 1992, however, this figure was less than 8%.[136]

Other concerns that have been raised regarding limiting fat and cholesterol intake are that such a diet could result in a lack of cholesterol for myelin formation in the nervous system and for production of steroid hormones that use cholesterol as a substrate.[106,107] However, cholesterol is not an essential nutrient. In healthy children, the body is capable of synthesizing cholesterol for all of its needs.

There is also concern that a fat-restricted diet could lead to mineral deficiencies, especially calcium, iron, and zinc if red meats are avoided.[137] With adequate consumption of low-fat dairy products, both calcium and dietary fat goals can be achieved. Fortified cereal products and inclusion of a variety of lean meats, legumes (eg, peanuts and peanut butter), whole grains, and vegetables help ensure adequate intake of zinc.

Deficiencies in EFAs may occur if dietary fat is severely restricted. EFAs should provide about 3% of energy intake in a child's diet. Generally, if about half of the child's fat intake comes from plant sources, the EFA requirements will be met. Three percent of a 1 to 3 year old's diet would be about 39 calories or 4.3 g of EFA, whereas 3% of a 4 to 6 year old's 1,800 kcal diet would be about 54 calories or 6 g EFA/day (of the total 60 g of total fat in a 30% energy from fat diet). Vegetable oils (eg, corn, soybean, etc) are good sources of EFAs; however, the *trans* isomers of linoleic acid do not have EFA activity.

BENEFITS OF A FAT-MODIFIED DIET IN CHILDHOOD

Most health authorities agree that a diet that is low in saturated fat and cholesterol during childhood reduces the development of cardiovascular disease risk factors (hyperlipidemia and obesity), which, in turn, should reduce the risk of atherosclerosis and coronary heart disease in adult life. In addition, a diet low in total fat may reduce the risk of cancer, in particular cancer of the breast, prostate, colon, and ovary. Because diets high in fat result in greater caloric density of the diet and encourage passive overconsumption of calories, high-fat diets may also foster excessive weight gain and childhood obesity. Finally, diets lower in fat (< 30% energy), along with adequate daily physical activity, may help children achieve and maintain a desirable BMI.

Dietary patterns established during childhood tend to persist over time; thus, it seems reasonable to place greater emphasis on initiation of healthful eating patterns in childhood rather than on trying to change more deeply ingrained unhealthful eating habits later in adult life. In addition, a healthful, lower-fat diet in childhood can be safely and effectively achieved through the application of a wide variety of strategies, following the principles of the USDA Dietary Guidelines and Food Guide Pyramid.[55]

FAMILY AND SCHOOL INFLUENCES ON DIETARY FAT INTAKE IN CHILDREN

Convincing evidence exists showing that chronic disease risk factors aggregate within families. Bush and colleagues found that African American mothers in the highest quartile for cardiovascular disease risk factors (including total cholesterol, blood pressure, BMI, fitness, and activity) had children who were also more likely to be in the highest quartile.[138] Therefore, it seems logical that intervention strategies that may modulate the effect of genetic factors need to be provided in the family as a whole rather than to parents or children as isolated subunits. Children, especially before adolescence, tend to follow dietary patterns set by their parents. It is clear, therefore, that, in planning strategies aimed at lowering fat intake in children, the parents' diet should also meet the Dietary Guidelines. With parents serving as role models, there is greater likelihood of successfully achieving dietary guidelines for all family members.

Schools are also influential in shaping children's nutrition and physical activity behaviors, which, in turn, pro-

mote or protect against diet-related chronic disease risk factors such as blood lipids, blood pressure, and obesity. School-based programs are unique in that they have the ability to provide classroom nutrition and other health education and then are able to extend beyond the classroom to involve food service, health service, and after-school programs. In this way, they offer a tremendous opportunity to positively influence child nutrition and health. In addition, teachers, administrators, and other school staff and peers represent an important network of role models and social supports for children and youth. The CATCH program, as noted previously, is an excellent model for effective school-based nutrition education and food service intervention in elementary schools.[113,130–135]

Preschool nutrition programs are also important in providing appropriate nutrition education as well as meals and snacks that meet state and federal guidelines. The Healthy-Start preschool nutrition and health education program is a model of an effective nutrition program in the preschool setting (<www.Healthy-Start.com>). In this program, classroom nutrition education was combined with food service intervention, teacher training, and family education and demonstrated increased nutrition knowledge, lower blood cholesterol, and decreased intake of saturated fat in children.[139–142] For as many as two-thirds of all younger children (4 to 6 year olds), it is possible to achieve dietary fat guidelines simply by switching from full-fat to 1% or fat-free milk.[143]

Tamir and colleagues performed a randomized trial of 800 first grade children in Jerusalem.[144] Experimental schools received a comprehensive educational and health promotional program (comprising 15 to 20 hours per year) and were reinforced by community activities. After 2 years of intervention, there was a decrease in both serum total cholesterol and BMI in children in the experimental compared with the control school. Similarly, other school-based health programs have shown that significant improvement in parameters relating to blood lipids and fitness can be achieved.[144]

It is important for schools to provide nutrition education for all children and adolescents from preschool through twelfth grade and to ensure that school meals and snacks are consistent with the NCEP and AHA Dietary Guidelines for Americans. The school food service should be viewed as an extension of the comprehensive health education program for the school so that children can learn about healthy nutrition in the classroom and then practice healthful food choices in the cafeteria.[145]

TABLE 5.1-4 Practical Suggestions for Achieving Pediatric Dietary Guidelines (> 2 years of age)

Eat a greater quantity and variety of fruits, vegetables, whole grains, cereals, nuts, and legumes
Eat at least 3 servings of vegetables and 2 servings of fruit daily (1 serving may be fruit juice)
Choose fat-free or low-fat (1%) dairy products and consume 2–4 servings daily
Eat moderate amounts of trimmed, lean red meat, poultry (without skin), or fish in place of choices high in saturated fat
Eat egg yolks only in moderation (less than 3 yolks per week)
Use vegetable-based oils, margarines, and shortenings that contain primarily unsaturated fatty acids instead of saturated fatty acids and that contain little or no *trans*–fatty acids
Read food labels and choose items lowest in saturated fat and cholesterol
When eating out or buying ready-made foods, select items that are low in saturated fat and cholesterol, as well as foods that were baked, boiled, or broiled without fat

SUMMARY

In summary, fat is a critical macronutrient for all children. Recommendations for dietary fat intake in childhood, however, must take into account the child's unique growth and developmental patterns, specific nutrient requirements, vulnerability of sentinel nutrients, factors important to the establishment of healthful food acceptability, preference and intake patterns, and nutritional risk factors for disease during childhood as well as later in life. All of these considerations are crucial in translating scientific findings into public policy. Numeric guidelines for fat intake in children over 2 years of age and adolescents have been recommended by the AAP and more than 25 other health-related organizations. These recommendations are based on the association of dietary fat and chronic conditions and diseases such as cardiovascular disease, cancer, and obesity, as well as on considerations of nutritional adequacy and establishment of healthful eating patterns early in life.

National surveys in the past two decades indicate that children are consuming a lower percentage of their daily energy from total and saturated fat; however, the majority still fail to meet the dietary goals. Concerns have been voiced that diets in which fat is limited to the recommended goals may have adverse effects on growth during childhood; however, a growing number of controlled trials addressing this question have demonstrated that growth is normal for children on diets in which fat contributes approximately 25 to 30% of calories if the diet also includes adequate calories, high-quality protein, and essential nutrients.

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CHAPTER 5.2

MACRONUTRIENT REQUIREMENTS FOR GROWTH: CARBOHYDRATES

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BACKGROUND

Carbohydrates are one of the three macronutrients (the others being protein and fat) that are sources of dietary energy and are present in a wide range of food. The name carbohydrate was originally given to compounds thought to be hydrates of carbon. Formally, carbohydrates are a class of substances with the formula $C_n(H_2O)_n$. This formula, however, fails for larger compounds such as oligosaccharides, polysaccharides, and sugar alcohols. Classification can be based on the number of sugar units found within a given compound.

MONOSACCHARIDES

The simplest form of carbohydrate is the monosaccharide, and as such is often referred to as the "simple sugar." These sugars have variable numbers of carbon atoms and include trioses, tetroses, pentoses, hexoses, and heptoses with 3-, 4-, 5-, 6-, and 7-carbon atoms, respectively (Table 5.2-1).

Glucose (dextrose) is a hexose and represents the most important of those sugars. It is a moderately sweet sugar and is the main form in which carbohydrates circulate throughout the body to provide fuel to various cell types. It is abundant in fruits, sweet corn, corn syrup, honey, and certain roots. Fructose (levulose) is the sugar naturally present in fruits and honey. It is the sweetest of the simple sugars, about 1.5 times the sweetness of sucrose (table sugar). Galactose, typically not found free in foods, is liberated in the hydrolysis of lactose. Other examples of monosaccharides include glycerose (triose), erythrose (tetrose), and ribose (pentose).

DISACCHARIDES

The linking of two monosaccharides forms a disaccharide. These include sucrose (glucose-fructose), lactose (glucose-galactose), and maltose (glucose-glucose). Sucrose, table sugar, is the most prevalent dietary disaccharide. It is found in cane and beet sugar, brown sugar, sorghum cane, molasses, maple syrup, pineapple, and carrots. Lactose, milk sugar, is the least sweet of the disaccharides, being one-sixth as sweet as sucrose. Maltose occurs in malt products of starch hydrolysis and in germinating cereal grains.

POLYSACCHARIDES

Oligosaccharides contain 3 to 10 sugar units and are typically the result of the digestion of polysaccharides (ie, starch and glycogen), which contain greater than 10 sugar units. Starch is the storage carbohydrate of plants, whereas glycogen is that of animals.

TABLE 5.2-1 Source and Use of Various Monosaccharides

Sugar	*Carbon Atoms*	*Natural Sources*	*Use*
Ribose	5	Metabolic processing	Formation of nucleic acids and coenzymes
Glucose	6	Fruit, hydrolysis of starch, sugar cane maltose, and lactose	Cell fuel
Fructose	6	Fruit, honey, hydrolysis of sucrose	Changed to glucose
Galactose	6	Hydrolysis of lactose	Changed to glucose, constituent of glycolipids and glycoproteins
Mannose	6	Hydrolysis of plant mannosans and gums	Component of polysaccharide of albumins, globulins, mucoproteins, and glycoproteins

Starches are composed of glucose polymers with α-(1,4) amylose (straight chain) and α-(1,6) amylopectin (branched chain) linkages. The proportion of amylose to amylopectin depends on the starch type, as do the size and shape of their storage granules. Three crystalline forms of starch are recognized: type A (ie, raw wheat, rice starch) has an open helical structure and is easily digestible; type B (ie, raw potato starch) is densely packed and thus has reduced digestibility owing to decreased access by amylases; and type C (ie, legumes) is a mixture of types A and B.[1]

The cooking of starch helps to improve the flavor as well as soften and rupture the starch cells, thus facilitating their enzymatic digestion. Starch mixtures thicken when cooked because the amylopectin that encases the starch granules has a gel-like quality.

Polyhydroxy Alcohols

The alcohol forms of sucrose, mannose, and xylose (sorbitol, mannitol, and xylitol, respectively) retain some of the sweetness of the original sugar. These sugars are more slowly absorbed from the digestive tract and thus prevent a rapid rise in blood sugar. However, this quality can also contribute to soft stools when consumed in large amounts.

The UK Department of Health originated the term intrinsic sugar to identify those sugars present within the cell walls of plants (ie, naturally occurring), as opposed to extrinsic sugars, which are typically added to foods. The US Department of Agriculture defines added sugars as sugars and syrups added to foods during processing or preparation. Major sources of added sugars include soft drinks, cakes, cookies, pies, fruit drinks, dairy desserts, and candy.

CARBOHYDRATE TYPES

Dietary carbohydrate is a major nutrient for humans and in the Western world represents approximately half of our daily energy intake. Of this ingested carbohydrate, about 60% is derived from polysaccharides, and disaccharides such as sucrose and lactose represent 30% and 10%, respectively. However, there has been an increasing trend for manufacturers to introduce monosaccharides (ie, glucose and fructose) into foods and drinks. Oligosaccharides such as raffinose and stachyose are found in small amounts in legumes.

Resistant starch (RS) is that portion that is indigestible even after prolonged incubation with α-amylase. In cereals, it comprises 0.4 to 2% of the dry matter; in potatoes, 1 to 3.5%; and in legumes, 3.5 to 5.7%. This undigested starch can be divided into three main categories: RS1 physically enclosed starches (ie, mixed grains, seeds), RS2 ungelatinized crystallite granules of the B-type x-ray pattern (ie, banana, potato), and RS3 retrograded amylose. Within the colon, the local resident bacteria ferment RS. The end products of the fermentation process are short-chain fatty acids (ie, acetate, butyrate, proprionate), carbon dioxide, hydrogen, and methane. Luminal starches stimulate the growth of colonic bacteria, and the short-chain fatty acids appear to be essential for normal colonocyte growth and function. In infants, the lower luminal pancreatic α-amylase concentrations give rise to an increased amount of RS. In infants, these RS have been associated with increased calcium, iron, and possibly zinc absorption.[2] However, RS in infancy may also contribute to diarrhea by an increase in osmotic load.

Dietary fiber includes "all plant polysaccarides and ligandin that are resistant to hydrolysis by the digestive enzymes in man."[3]

CARBOHYDRATE DIGESTION

Salivary amylase initiates the digestion of starch while in the mouth. It is detectable from 20 weeks gestation.[4] Its activity increases rapidly after birth and reaches adult levels between 6 months and 1 year. It had previously been thought that the amylase activity is inhibited within the stomach owing to the acidic milieu. However, currently, some suspect that buffering of the gastric acid by the food components allows carbohydrate hydrolysis to continue. Breast milk also contains α-amylase, which is structurally similar to salivary amylase. It is found in highest concentrations within the colostrum. Once the gastric chyle is emptied into the duodenum, pancreatic α-amylase cannot hydrolyze the one to six branching links and has little specificity for the one to four links adjacent to the branching points. Pancreatic amylase concentrations are much lower in the neonate and are not thought to reach adult levels until 5 to 12 years of age.[5] This results in the formation of large oligosaccharides (α-limit dextrans), each with an average of eight glucose units with one or more one to six links (Figure 5.2-1).

The microvilli of the small intestine support the unstirred water-layer phase within the intestinal lumen. Limit dextrans, trisaccharides, and disaccharides within this unstirred water layer are rapidly hydrolyzed by enzymes bound to the border membrane. Specifically, the α-limit dextrans are substrates for glucoamylase, which cleaves single glucose units from the nonreducing end of linear α-(1-4) glucosyl oligosaccharides.

Despite the fact that D-glucose is the major source of energy for most if not all mammalian cells, the lipid-rich cell membrane is relatively impermeable to the hydrophilic polar molecule. To this end, carrier proteins within the cell membrane are required to bind the glucose and transport it intracellularly. Two classes of such proteins have been described: facultative glucose transporters and sodium-glucose transporters (symporters). The former class includes membrane integral proteins on the surface of all cells and transports glucose down a concentration gradient via facilitative diffusion. The energy for this transfer comes from dissipation of the concentration difference of glucose. In contrast, the sodium-glucose transporters allow for uphill movement of D-glucose against the concentration gradient via active transport. The transporters are expressed in the brush border of the enterocyte and of the renal proximal tubule. Small numbers can also be found in the epithelial cells of the lung and liver.[6]

Initial movement of luminal hexoses into the enterocyte is accomplished by the action of sodium-dependent

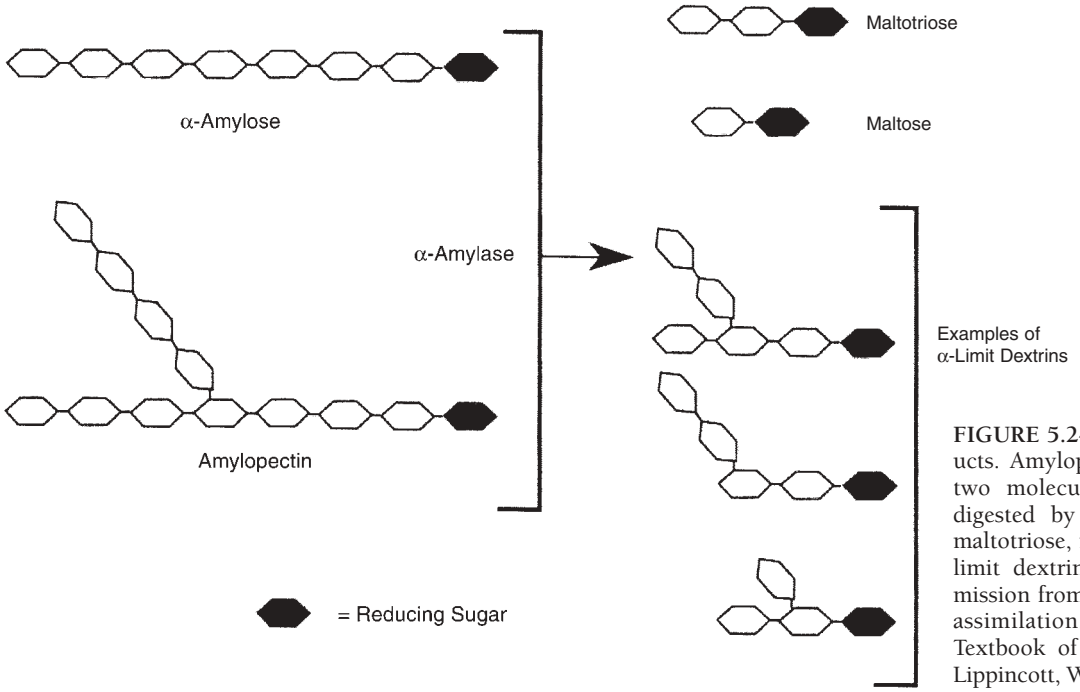

FIGURE 5.2-1 Starch digestion products. Amylopectin and α-amylose, the two molecular forms of starch, are digested by lumenal α-amylase into maltotriose, maltose, and a series of α-limit dextrins. Reproduced with permission from Traber PG. Carbohydrate assimilation. In: Yamada T, editor. Textbook of gastroenterology. 3rd ed. Lippincott, Williams and Wilkins; 1999.

glucose transporters in the brush border (SGLTs). These transporters take advantage of a sodium gradient created by the Na-K adenosine triphosphatase pump or sodium pumps on the basolateral borders of the cell. This allows for the cotransport of one molecule each of sodium and glucose. This is the physiologic basis for the design of oral rehydration solutions for the treatment of diarrhea. Glucose is then transported across the intestinal basolateral membrane by a different glucose transporter. Five major hexose transporters have been identified and cloned and are numbered GLUT 1 to GLUT 5, in order of discovery (Table 5.2-2). There are reports of possible GLUTs 6 and 7. Similar to glucose, galactose uses SGLT cotransporters and basolateral GLUT 2. In contrast, fructose does not use SGLTs but is thought to use GLUT 5, which has been demonstrated to have a high affinity for this hexose.

DIETARY REQUIREMENTS OF CARBOHYDRATES

The primary function of dietary carbohydrates in human nutrition is to provide fuel for energy (Table 5.2-3). Some cells within the body are obligatory carbohydrate users, including the brain, white blood cells, red blood cells, and the medulla of the kidney. When carbohydrates are oxidized in the body as fuel, they render 4 kcal/g.

Various cultures have evolved in which there are minimal amounts of carbohydrate in the diet for extended periods of time beyond infancy. These cultures, including the Masai, Alaska and Greenland natives, Inuit, and the people of the Pampas, exhibit no ill effects on their health or longevity. Children with intractable seizure disorders have also been shown to tolerate a ketogenic diet. Animal models on such diets have been shown to thrive. Indeed, whites who consumed an essentially carbohydrate-free diet for 1 year tolerated the diet well.[7] Azar and Bloom found that adults consuming a carbohydrate-free diet required 100 to 150 g of protein to maintain nitrogen balance.[8] The authors assumed that gluconeogenesis was supported by this protein intake and the conversion of glycerol obtained from triacylglycerol in the diet.

The brain and other parts of the central nervous system maintain an absolute requirement for glucose as an oxidizable fuel but can adapt in part to a fat-derived fuel. In the absence of carbohydrate, de novo synthesis of glucose requires amino acids derived from protein hydrolysis and/or glycerol from fat. Thus, the carbohydrate requirements are based on the composition of the remaining portion of the diet. This requirement approaches zero in infants after weaning as well as in children and adults.

The estimated average dietary requirement for carbohydrates depends on the brain's glucose use rate. The endogenous glucose production rate in a postabsorptive state (approximately 2.8 to 3.6 g/kg/day) correlates very well with the estimated size of the brain from birth to adulthood. In adults, this equates to 110 to 140 g/day.[9] However, as previously stated, there are adaptive measures during times of starvation in which liver glycogen stores are

TABLE 5.2-2 Facilitated Diffusion Glucose Transporter Family

Type	*Chromosome Location*	*Major Expression Site*
GLUT 1	1	Red blood cells, placenta, brain, kidney, colon
GLUT 2	3	Liver, B cell, kidney, small intestine
GLUT 3	12	Brain, testis
GLUT 4	17	Skeletal and heart muscle, brown and white fat
GLUT 5	1	Small intestine, sperm

TABLE 5.2-3 Carbohydrate Requirements for Children[13]

Age	*AI/EAR*	*RDA*
0–6 mo	60 g/d	
7–12 mo	95 g/d	
1–18 yr	100 g/d	130 g/d

Adapted from Institute of Medicine.[13]
AI = Adequate Intake; EAR = Estimated Average Requirement; RDA = Recommended Dietary Allowance.

depleted when "ketosis" provides keto acids as alternate fuels. In subjects fully adapted to starvation, keto acid oxidation can account for approximately 80% of the brain's energy requirements[10]; thus, only 22 to 28 g/day of glucose are required to fuel the brain.

In infants age 0 through 12 months, the brain size relative to the body size increases. The brain uses 60% of the infant's total energy intake.[11] This accounts for up to a fourfold greater turnover in glucose/kg in the infant when compared with adults. Even in the premature infant, the gluconeogenic pathway is developed enough to provide for the majority of glucose turnover. From the limited data available, the lower limit of tolerable carbohydrate intake in infants is approximately 30% of total food energy. However, it is possible that infants may grow and develop normally on a very low-carbohydrate diet. The carbohydrate in human milk is almost exclusively lactose. Lactose is readily hydrolyzed in the infant's intestine, and the resulting glucose and galactose easily pass into the portal venous system. Within the liver, the galactose yields one molecule of glucose so that the net yield from each lactose molecule is two glucose molecules. This may provide a teleologic explanation as to why lactose is the carbohydrate source in mammalian milk as the disaccharide helps to lower the osmolarity of the milk when compared with two monosaccharides. In addition, lactose has been reported to facilitate calcium absorption in the immature infant's intestine.[12] The lactose content of human milk is approximately 74 g/L. Although this does not appear to change over the nursing period, the volume consumed does decrease gradually over the first 12 months of life. For the first 6 months of life, the infant consumes approximately 0.78 L/day or 60 g of carbohydrate, representing 37% of their total food energy. For older infants (7 to 12 months), the adequate intake of carbohydrate is 91 g/day, which is the sum of that supplied from human milk (an average volume of 0.6 L/day or 44 g/day) plus that from complementary foods (estimated by the Third National Health and Nutrition Examination Survey to be 51 g/day).

In children and adolescents, the relative increase in brain size is modest. Thus, the consumption of glucose by the brain after age 1 year is rather constant and similar to that of adults. The Estimated Average Requirement (EAR) is thus determined to be 100 g/day for all children over 1 year of age.[13] The Recommended Dietary Allowance (RDA) equals the EAR plus two times the standard deviation (15% based on variation in brain glucose use). The RDA is thus 130% of the EAR or 130 g/day.

DIETARY CARBOHYDRATE SOURCES AND INTAKE

Sources of dietary carbohydrates abound in the daily diet. Since the introduction of high-fructose corn sweeteners in 1967, the amount of "free" fructose in the American diet has increased considerably.[14] These syrups are derived from cornstarch through the conversion of a portion of the glucose present in starch to fructose. The fructose content in the syrup is 42, 55, or 90%. Beverages such as soft drinks and fruit-flavored drinks are the major dietary sources of added fructose.

According to 1994–1996 US Department of Agriculture food consumption survey data, nondiet soft drinks were the leading source of added sugars in American diets, representing one-third of added sugar intake.[15] Other major sources included candies (16%), sweetened grains (13%), fruit drinks (10%), sweetened dairy (9%), and breakfast cereals (10%). All totaled, these account for 90% of added sugar intake in the American diet.

Data from the 1994–1996 and 1998 Continuing Food Survey of Intakes by Individuals revealed that the median intake of carbohydrates was 220 to 330 g/day for men and 180 to 230 g/day for women, representing approximately 50% of energy intake. Added sugar intake ranged from 40 to 120 g/day and was highest among adolescent males. The mean intake of 82 g/day represents 15.8% of total energy intake, far exceeding that recommended by the Food Guide Pyramid.

A tolerable upper intake level for sugars has not been defined. However, there are ongoing research efforts attempting to determine if increased carbohydrate ingestion can adversely affect behavior, cholesterol levels, or the risk of dental caries, type 2 diabetes, obesity, cancer, or micronutrient displacement. Indeed, a recent article by Ludwig and colleagues demonstrated a relationship between consumption of sugar-sweetened drinks and childhood obesity.[16]

FIBER

Fiber can be divided into two categories: dietary fiber is defined as nondigestible carbohydrates and lignin that are intrinsic and intact in plants; functional fiber is the nondigestible carbohydrate that has beneficial physiologic effects in humans (Table 5.2-4). Total fiber represents the sum of these two forms of fiber. By definition, these dietary fibers are not digested within the mammalian small intestine and pass relatively intact into the large intestine.

Cellulose is a polysaccharide with a high molecular weight. It is a large unbranched glucose polymer similar to starch; however, the linkage bonds are different such that humans lack the enzyme required to break the units apart. Cellulose is the principal structural material in plant cell walls. It is water insoluble but can hold water, adding bulk to the feces and reducing intracolonic pressure.

Noncellulose fiber carbohydrates include hemicellulose, pectins, gums, mucilages, and algal substances. All help to absorb water, slow gastric emptying, and bind bile acids. Lignins are a noncarbohydrate form of fiber. They

TABLE 5.2-4 Dietary Fiber

	Structure		*Sources*		
Fiber Class	*Main Chain*	*Side Branches*	*Grains*	*Fruits*	*Vegetables*
Cellulose	Glucose	None	Bran, whole wheat, whole rye	Apples, pears	Beans, peas, cabbage, roots
Hemicellulose	Glucose, mannose, xylose	Galactose, arabinose	Brans, cereals, whole grains		
Pectins	Galacturonic	Rhamnose, xylose, arabinose, fructose		Apples, citrus, berries	Green beans, carrots
Gums	Galactose, galacturonic acid-mannose, galacturonic acid-rhamnose	Xylose, galactose	Oatmeal	FPTS	Dried beans, legumes
Mucilages	Galactose-mannose, glucose-mannose, arabinose-xylose, galacturonic acid-rhamnose	Galactose		FPTS	
Algal substances	Glucose, mannose, xylose, glucuronic acid	Galactose		FPTS	
Lignin	Phenylpropane alcohols	3-D network	Whole wheat, whole rye	Peaches, pears, plums	Mature vegetables

FPTS = food products thickener, stabilizer.

are large phenylpropane polymers derived from higher alcohols and built into three-dimensional networks comprising the woody parts of plants. They form insoluble compounds with bile acids.

Fiber's effects on digestion include an ability of soluble viscous fiber to delay gastric emptying and contribute to a sense of early satiety.[17] This, in turn, results in a delay in the digestion and absorption of various nutrients. Once in the colon, the fiber is fermented by the indigenous microflora to produce carbon dioxide, methane, hydrogen, and short-chain fatty acids.

In industry, fiber is often added to foods to reduce their caloric content and replace fats or sugars. The energy value of these fibers is the center of controversy. As they are fermented, the resultant short-chain fatty acids can be used locally as an energy source (ie, butyrate for colonocytes) or enter the portal circulation and are used in the liver (ie, acetate and butyrate). A small portion of the energy from fermentation is used to promote bacterial growth and maintenance of the microflora. Some authors have suggested that fermentation of fiber may account for up to 12% of energy needs.[18–20]

Overall, functional fiber has been documented to have the effect of laxation, with an increase in fecal bulk, altering blood lipid concentrations and attenuating blood glucose responses. Ongoing research efforts are looking to determine fiber's role in preventing duodenal ulcers, diverticular disease, hyperlipidemia, hypertension, coronary artery disease, colon cancer, and breast cancer.

Because human milk is thought to be the optimal source of nourishment for infants through the first year of life and because human milk contains no dietary fiber, the adequate intake for infants age 0 to 6 months is considered zero. Between 7 and 12 months, the amount of dietary fiber increases; however, there is no basis on which to determine the adequate intake of fiber in this age group. In children over the age of 1 year, the adequate intake recommendations are based on adult data and are 14 g/1,000 kcal of energy required.[13]

According to data from the Continuing Survey of Intakes of Individuals (1994–1996), median dietary fiber intakes ranged from 16.5 to 17.4 g/day for men and 12.1 to 13.8 g/day for women. These numbers fall below the suggested adequate intake recommendations. Furthermore, there does not appear to be any significant deleterious effect of high intake of fiber if it is part of an overall healthful diet. Therefore, there is no tolerable upper intake level defined.

PREBIOTICS

Prebiotic was defined by Gibson and Roberfroid in 1995 as a "nondigestible food ingredient which beneficially affects the host by selectively stimulating the growth of and/or activating the metabolism of one or a limited number of health promoting bacteria in the intestinal tract, thus improving the host's intestinal balance."[21] Because this concept has only been recently defined, there are not as many data to support their health-promoting effects. Examples of prebiotics include the fructo-oligosaccharides (FOSs) and complex oligosaccharides in human milk.

FOSs are short and medium chains of β-D fructans in which fructosyl units are bound by a β 2-1 osidic linkage. The FOSs are classified based on the number of osyl units, which defines their degree of polymerization (DP). Accordingly, oligofructose has a DP < 9 (average 4.8), and inulin has a DP up to 60 (average 12). Inulin-producing plant species include several monocotyledonous and dicotyledonous families such as Liliaceae, Amaryllidaceae, Gramineae, and Compositae. Commercially, inulin is the

product of hot water extraction from chicory roots (*Cichorium intybus*), and oligofructose is prepared by the partial hydrolysis of inulin under controlled conditions. They are also contained in a number of common foods, including garlic, onion, artichoke, and asparagus.[21]

The β 2-1 osidic bond of FOS, including the first glucose-fructose bond, is not readily hydrolyzed by mammalian digestive systems. However, bifidobacteria possess β-fructosidases that allow them to digest these compounds.[21] The ability of prebiotics such as oligofructose to selectively stimulate the growth of bifidobacteria has been supported by numerous studies.[22] However, the effects of prebiotics appear to be limited to the time during which they are being consumed, so that when supplementation is stopped, their beneficial effect is lost.[22] Despite the effects prebiotics have in manipulating the bacterial flora, they have not been shown to have health-promoting effects to the same degree as probiotics. Some studies suggest that they may enhance mineral absorption and have a role in cancer prevention.[23]

CONCLUSION

Carbohydrates in the form of sugars and starches are common sources of energy for the various organs and cells of the human body. They are present in a wide variety of foods in various forms. Basic science has allowed an impressive understanding of the way in which these macronutrients are digested, absorbed, and transported throughout the body. Age-dependent EARs exist for both carbohydrate and fiber. Ongoing research is attempting to define potential benefits to the ingestion of various dietary forms of carbohydrates (ie, fiber, prebiotics) as well as detrimental consequences to their overconsumption (ie, obesity, cancer, diabetes).

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CHAPTER 5.3

MACRONUTRIENT REQUIREMENTS FOR GROWTH: PROTEIN AND AMINO ACIDS

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This chapter provides an overview of the current state of knowledge of protein and amino acid requirements in children. The special protein and amino acid needs of premature infants are reviewed in Chapter 28, "Nutritional Support of the Low Birth Weight Infant."

Nitrogen use, and therefore amino acids and protein, is critical in maintaining whole-body homeostasis. Loss of more than 30% of body proteins results in death.[1] Amino acids are needed for tissue formation and multiple physiologic functions.[2] Therefore, maintenance of whole-body nitrogen stores is critical to survival. Proteins are the major functional and structural component of cells, enzymes, membrane transporters, intracellular matrices, and other components, all of which are essential for life. Hence, an adequate provision of dietary protein is essential to maintaining cellular integrity and function.

Proteins are made of carbon, oxygen, and hydrogen; a smaller proportion is also made of sulfur. The chemical characteristic of proteins is their amino nitrogen group. Proteins are macromolecules consisting of a long chain of amino acid subunits. The sequence of amino acids in the chain is known as the primary structure. Proteins fold into a definite three-dimensional structure. Their exact shape depends on their function and interaction with other molecules.

After ingestion of a protein meal, proteins are denatured by the acid in the stomach, where they are also cleaved by pepsin into smaller peptides. In the small intestine the denatured proteins and peptides are hydrolyzed by a variety of pancreatic enzymes, including trypsin, chymotrypsins, elastases, and carboxypeptidases. The mixture of free amino acids and small peptides is transported into the mucosal cells by specific carrier systems. Following intracellular hydrolysis, the free amino acids are secreted into the portal blood by other specific carrier systems, or they are further metabolized within the intestine. Absorbed amino acids pass into the liver, where a fraction is taken up and used. This process is known as first-pass disappearance or splanchnic uptake. Because of this, not all of the amino acids removed from the intestinal lumen reach the systemic circulation. The amino acid fraction that disappears in the splanchnic area differs among the different amino acids. The remainder of the amino acid passes through the systemic circulation to be used in whole-body economy.[3]

The use efficiency of most dietary proteins, or capacity to integrate into body proteins, is about 90%.[4] Protein losses in the intestine account for 25% of obligatory nitrogen losses,[5] such as intestinal cell turnover and secretion of mucin and enzymes. Protein is also lost by skin, urine, and hair. There is controversy regarding the contribution of indispensable amino acids by intestinal bacteria, with conflicting data in favor of and against a significant contribution by intestinal bacteria to the amino acid pool.[6–8]

Protein synthesis and degradation are balanced during the steady state. Both increase during conditions of stress, but degradation offsets synthesis, resulting in a negative balance. Protein degradation occurs by a lysosomal- or ubiquitin-proteasome–dependent mechanism.[9]

AMINO ACIDS

The amino acids that are incorporated into mammalian protein are α-amino acids, with the exception of proline, which is an α-imino acid. This means that they have a carboxyl group, an amino nitrogen group, and a side chain attached to a central α-carbon (Figure 5.3-1). The structure of the side chains determines the functional differences among amino acids. Amino acids are provided in the diet or they can be synthesized from a carbon and nitrogen source. Amino acids are catabolized by removal of the nitrogen group through the process of transamination, which results in formation of other amino acids (alanine, pyruvate, aspartate, and glutamine) or by the process of deamination, which results in the formation of ammonia. Therefore, the nitrogen removed from any amino acid can be directed toward ammonia and aspartate, which are the

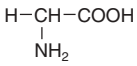
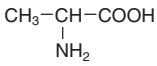
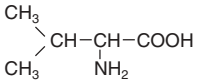
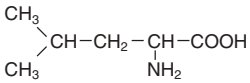
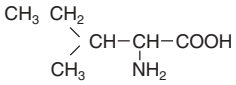
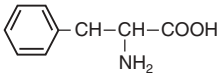
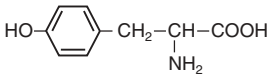
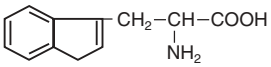
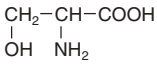
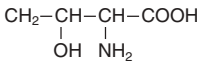
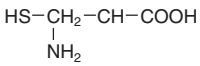
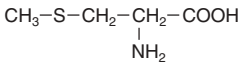
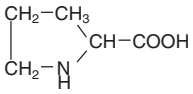
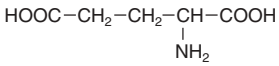
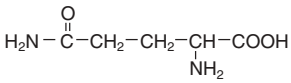
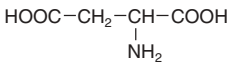
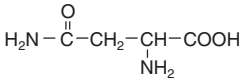
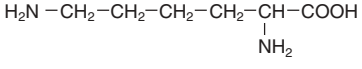
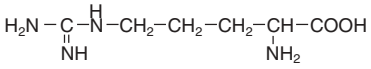
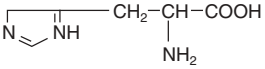
NAME	ABBREVIATION	FORMULA
Aliphatic side chains		
Glycine	Gly	
Alanine	Ala	
Valine*	Val	
Leucine*	Leu	
Isoleucine*	Ile	
Aromatic side chains		
Phenylalanine	Phe	
Tyrosine	Tyr	
Tryptophan	Trp	
Hydroxyl groups in side chains		
Serine	Ser	
Threonine	Thr	
Sulfur-containing side chains		
Cysteine†	Cys	
Methionine	Met	
Imino acids		
Proline‡	Pro	
Acidic side chains and their amides		
Glutamine acid	Glu	
Glutamine	Gln	
Aspartic acid	Asp	
Asparagine	Asn	
Basic side chains		
Lysine	Lys	
Arginine	Arg	
Histidine	His	

FIGURE 5.3-1 Amino acid structure. Reproduced from Panel on Macronutrients et al.[38] *Leucine, valine, and isoleucine are known as the branched-chain amino acids. †Cysteine is found as a dimer, linked through the sulfur atoms by oxidation. ‡Proline is strictly an imino acid rather than an amino acid.

TABLE 5.3-1 Amino Acid Classification, FAO/WHO/UNU Expert Report, 1985

Essential	*Nonessential*
Histidine	Alanine
Isoleucine	Arginine
Leucine	Aspartic acid
Lysine	Cystine
Methionine	Glutamic acid
Phenylalanine	Glycine
Threonine	Hydroxyproline
Tryptophan	Proline
Valine	Serine
	Tyrosine

precursors of urea. Urea synthesis takes place in the liver. Other organs, such as the intestine and kidney, contain an incomplete set of urea-cycle enzymes. Urea is released into the circulation by the liver and transported to the kidneys, where it is excreted in the urine. Therefore, nitrogen excretion occurs mainly as urea excretion. However, ammonium ions are also excreted, and this contributes to the maintenance of acid–base balance.

The carbon moiety of the amino acids is catabolized by oxidation through the tricarboxylic acid (TCA) pathway of glucose oxidation. Some amino acids enter the TCA cycle as keto acid analogues, and others have specific degradation pathways that produce intermediates that are metabolized in the TCA cycle. The carbon skeleton of amino acids is also available for biosynthesis of glucose and fat. If the carbon skeleton enters as acetyl coenzyme A, then fat or ketone bodies are formed. Other carbon skeletons from amino acids can be used for gluconeogenesis. Hence, amino acids are either ketogenic or glucogenic, although some amino acids can give rise to both ketones and glucose.

Classification

Classification of amino acids was initially based on the classic studies of Rose and colleagues.[10–14] These studies were based on the qualitative significance of each amino acid in human nutrition. Rose defined amino acids as essential or nonessential based on their capacity to maintain nitrogen balance in young men; the classic nutritional classification of amino acids is summarized in Table 5.3-1. Holt, Snyderman, and colleagues,[15–25] as well as Fomon,[26] extended Rose's studies to the pediatric population. In their studies, they demonstrated that only the "essential" amino acids were needed to maintain growth in infants and therefore conformed to the original definition of "essentiality of amino acids."

Through the following decades, it became evident that Rose's classification was limited and that a distinction between essential and nonessential amino acids was complex and could not be made based solely on the nutritional criteria of maintenance of nitrogen balance or growth.[27] For example, histidine, a nonessential amino acid in the rat that was considered nonessential in humans in the original Rose classification, has been proven to be essential in health and disease and was included as an essential amino acid by the Food and Agricultural Organization/World Health Organization/United Nations University (FAO/WHO/UNU) Expert Report in 1985.[28]

Over the past few decades, the concept of amino acid essentiality based on maintenance of growth or of nitrogen equilibrium has been revisited, with contributions by Mitchell,[29] Laidlaw and Kopple,[30] Young and El-Khoury,[31] Chipponi and colleagues,[32] Reeds and Biolo,[33] and Jackson.[34] Mitchell considered a more dynamic concept of "essentiality" based on the ratio of supply to demand rather than on the maintenance of nitrogen balance or growth. The term "conditionally indispensable" has been used to refer to those nonessential or dispensable amino acids that become essential or indispensable under pathophysiologic conditions.[32] Because the carbon skeleton of the amino acid is the moiety that determines its nutritional indispensability, some classifications of amino acids have been based on the ability to synthesize or aminate the carbon skeleton.[33]

In metabolic terms, the amino acids that are generally considered nutritionally essential contain specific chemical structures, the synthesis of which cannot be catalyzed by mammalian enzymes.[33] Examples include the branch aliphatic side chain of leucine, isoleucine, or valine; the primary amine of lysine; the secondary alcohol of threonine; the secondary thiol of methionine; the indol ring of tryptophan; the aromatic ring of phenylalanine; and the imidazol ring of histidine.[35] Table 5.3-2 shows an updated classification of amino acids.

It is important, however, to remember that an amino acid classification should not be based solely on nutritional (growth and maintenance), metabolic (de novo synthesis, tissue use, and catabolism), or chemical aspects of the amino acids but also, and perhaps most importantly, on the maintenance of amino acid function. Some amino acids that would be considered truly dispensable in nutritional, metabolic, and chemical terms are precursors of other amino acids that maintain important physiologic functions, such as glutamate and serine, which serve, respectively, as precursors of glutamine and cystathionine. Other dispensable

TABLE 5.3-2 Nutritional Classification of Amino Acids

Indispensable	(a) Carbon skeleton cannot be synthesized (b) Rate-limiting enzymes of catabolism regulated in relation to adequacy of intake and tissue supply
Conditionally indispensable	(a) Indispensable amino acid is a precursor (ie, phenylalanine-tyrosine) (b) Synthesis and degradation are modulated by dietary supply (ie, arginine, glycine) (c) Stressful states cause tissue depletion where rates of synthesis are insufficient to meet increased rate of metabolic demand (proline, glutamine, arginine, glycine, taurine) or match catabolic rate
Dispensable	(a) Rate of synthesis is not down-regulated by intake of amino acid; metabolism largely a function of metabolic status of major energy-yielding substrates and/or overall nutritional status (alanine, glutamate, aspartate)

Adapted from Young VR and El-Khoury AE.[31]

TABLE 5.3-3 Involvement of Amino Acids in Physiologic and Metabolic Function

System	*Function*	*Product*	*Precursor*
Intestine	Energy generation	Adenosine triphosphate	Glu, Asp, Gln
	Proliferation	Nucleic acids	Gln, Gly, Asp
	Protection	Glutathione	Cys, Glu, Gly
		Nitric oxide	Arg
		Mucins	Thr, Cys, Ser, Pro
Skeletal muscle	Energy generation	Creatine	Gly, Arg, Met
	Peroxidative protection	Taurine (?)	Cys
Nervous system	Transmitter synthesis	Adrenergic	Phe
		Serotonergic	Try
		Glutaminergic	Glu
		Glycinergic	Gly
		Nitric oxide	Arg
	Peroxidative protection	Taurine (?)	Cys
Immune system	Lymphocyte proliferation	(?)	Gln, Arg, Asp
	Peroxidative protection	Glutathione	Cys, Glu, Gly
Cardiovascular system	Blood pressure regulation	Nitric oxide	Arg
	Peroxidative protection (?)	Red cell glutathione	Cys, Glu, Gly

Adapted from Reeds PJ and Biolo G.[33]

amino acids, such as alanine and aspartate, contribute to physiologic and pathophysiologic events.[36,37] The involvement of amino acids in physiologic and metabolic functions is extensive; a partial summary is shown in Table 5.3-3.

PROTEIN AND AMINO ACID HOMEOSTASIS

The distribution of protein among the different organs varies with developmental age. Children have a proportionately larger amount of visceral (liver, kidney, brain, heart, and lung) protein than skeletal muscle protein, whereas in adults, protein constitutes about 15% of body weight.[38] During starvation or low protein intake, visceral protein is mobilized. This is called the "labile protein content." However, these "reserves" account for only 1% of total body protein.[39] During disease states, muscle is the main source of protein loss.[40]

Body proteins are in a continuous dynamic state of synthesis and catabolism (Figure 5.3-2). Under physiologic conditions, the amino acids released by protein breakdown are reused for protein synthesis. Protein turnover under these conditions is increased.

Adequate nitrogen (protein) intake is essential for growth, development, and function. However, estimating "adequate" protein or specific amino acid requirements for the pediatric population is a complex and challenging endeavor.[27,28,38,41] First, the pediatric population constitutes a dynamic group, involving different clusters of individuals from birth to adolescence. The pediatric population shows marked differences among the age groups in weight, rate of growth, hormonal milieu, activity, and other factors that can affect nutritional and metabolic status. Second, dietary recommendations for macro- and micronutrients for the different pediatric groups have been based largely on limited and inadequate data.[28,38,42–52] Because of ethical constraints that prevent the use of healthy children in invasive research studies, data in the pediatric population are based on nitrogen balance studies obtained from children recovering from malnutrition.[47,48,51] Hence, pediatric data are rather limited. Third, with new knowledge emerging on non-nutritional functions of nutrients, and based on the physiologic and pharmacologic properties of amino acids, the concept of amino acid requirement has changed from the traditional nutritional criteria based on growth or weight maintenance to a broader functional outcome, such as induction of gene expression,[52] or nutritional rescue of metabolic conditions, such as prevention of neural tube defects[53–55] or correction of hyperhomocystinemia with folic acid.[56] Therefore, "adequacy" of nutritional support is ill-defined and conditional on the goals to be achieved.

Based on this new knowledge about non-nutritional functions of amino acids,[33,35] a key question regarding nutritional adequacy is what is the objective to be achieved? Is the objective to promote growth and weight maintenance? To maintain non-nutritional functions? To prevent pathophysiologic events? To act as pharmacologic agent(s) to induce gene expression? Or for nutritional rescue? These important questions are just beginning to be explored and will be better answered in the future.

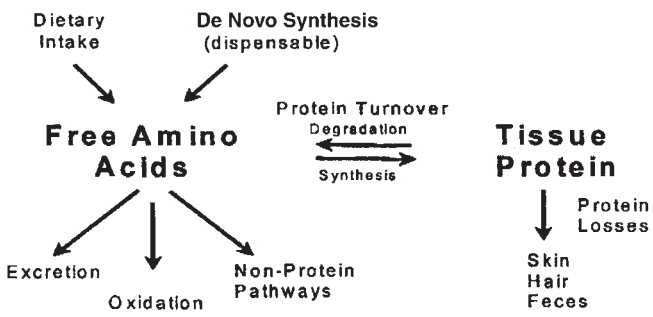


FIGURE 5.3-2 Protein and amino acid turnover. Reproduced from Panel on Macronutrients et al.[38]

ESTIMATES OF PROTEIN REQUIREMENTS

Protein requirement is defined as the "true biologic need for protein or amino acids, the lowest intake that will maintain functional needs of the individual."[38] However, because protein needs vary among individuals, the mean requirement has been taken as the starting point.[28,38] The Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, recently reviewed values for the intake of nutrients.[38] The Recommended Dietary Allowance (RDA) refers to the level of average daily dietary nutrient intake sufficient to meet the nutrient requirements of nearly all (97 to 98%) healthy individuals in a particular life stage and gender group. When the RDA cannot be estimated, "adequate" intake is recommended; this refers to the average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group of apparently healthy people, which are assumed to be adequate.[38]

The tolerable upper intake level is the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population.[38] Estimated average requirement refers to the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group.[38] The "safe level of intake" is defined as the amount that will meet or exceed the requirements of practically all individuals in a population, which is generally calculated as the mean requirement plus 2 standard deviations of the requirement.[28,41]

Dietary protein requirements involve two components: (1) total nitrogen for synthesis of the nutritionally dispensable and conditionally indispensable amino acids and for synthesis of other nitrogen-containing compounds with relevant physiologic functions and (2) to provide for the nutritionally indispensable amino acids, which cannot be synthesized by human tissues to maintain metabolic needs and therefore must be supplied by an exogenous source.[33,35]

The classic nitrogen balance studies by Rose and colleagues[10–14] and others[45,46,51] have been used for estimation of protein and amino acid requirements in older children and adults. Nitrogen balance techniques have been significantly criticized because of the difficulty in obtaining complete collections and measuring all routes of nitrogen loss (sweat, nitrate production, gaseous nitrogen). Furthermore, nitrogen balance techniques do not provide information on the dynamic status of amino acid metabolism.[51] However, although there is a great deal of criticism of using nitrogen balance studies to estimate protein requirements, currently there are no alternative data available to estimate the maintenance nitrogen needs of infants.[27,28,38,41]

Infants Up to 6 Months of Age

In 1985, the FAO/WHO/UNU considered that in early infancy (age 0 to 6 months), the protein intake of breast-fed infants constitutes the gold standard. This is based on the evolutionary assumption that breast milk is best suited to maintaining the nutritional needs of the infant.[28] This approach assumes protein efficiency (weight gain per gram of protein consumed) of 90%, given the high biologic value of the protein consumed. Therefore, the protein needs of an infant would be met if energy needs are met and the food providing the energy contains protein in quantity and quality equivalent to that of breast milk.[28,38,41]

The Food and Nutrition Board recently recommended a protein intake of 9.1 g/d^{-1} or 1.52 $g/kg^{-1}/d^{-1}$ in infants age 0 to 6 months.[38] This recommendation was based on the average volume of milk intake, which was estimated to be 0.78 L/day, and an average protein content in human milk of 11.7 g/L.

In 1996, the International Dietary Energy Consultancy Group (IDECG)[41] re-evaluated the rationale used to determine the 1985 FAO/WHO/UNU recommendations for infants and children[28] and concluded that the FAO/WHO/UNU Expert Report overestimated protein requirements during infancy by about 27 to 35%. These overestimates were felt to be attributable to a number of factors. In infants from birth to 6 months of age, the revision yielded new data estimates on the intake of breast milk, the content of protein nitrogen and nonprotein nitrogen, and the efficiency of retention of nonprotein nitrogen (which the IDECG postulated to be 46 to 61%, in comparison with the 100% assumption used by the FAO/WHO/UNU). The 1996 IDECG estimates also used body weights of breast-fed babies rather than those of formula-fed babies.[41]

Regarding estimates on the intake of breast milk, in the 1985 FAO/WHO/UNU expert report, the average intake of breast-fed infants was assumed to approximate the mean requirement, which was defined as the amount of protein needed for growth in 50% of the children.[28] However, this approach was flawed because it automatically defined half of breast-fed infants as having deficient intakes.[41] Therefore, mean intakes of breast milk do not equal "requirement." The epidemiologic probability approach indicated that at age 3 to 4 months, the nitrogen requirement is less than 170 $mg/kg^{-1}/d^{-1}$, whereas the mean intake is about 231 $mg/kg^{-1}/d^{-1}$. Likewise, milk intake in the FAO/WHO/UNU report was not corrected for insensible water loss.[28] The IDECG revision was based on more extensive data on infants exclusively breast-fed until 6 months of age, correction for insensible water loss was made, and nonprotein nitrogen was taken into account.[41]

The protein content of human milk and use of nonprotein nitrogen was also revisited by the IDECG.[41] The decline in protein content during the course of lactation was taken into account, as was the ratio of whey to casein in human milk throughout lactation. An important consideration in the assessment of the amount of protein available for tissue accretion and function (the biologic value of a protein) is the relative amount of nonprotein nitrogen. The average nonprotein nitrogen in mature human milk has been estimated to be 26% of the total nitrogen content. The major nonprotein nitrogen compounds in human milk are amino acids, creatinine, urea, creatine, and uric acid. It has been estimated that 27% of this nonprotein fraction, or about 7% of total nitrogen, is available for protein synthesis.[38,41]

The proportion of nonprotein nitrogen in human milk was considered by the 1996 IDECG revision of protein requirements.[41] Table 5.3-4 shows the revised IDECG esti-

TABLE 5.3-4 FAO/WHO/UNU Expert Report (1985) and IDECG (1996) Estimates of Average Protein Intake in Infants* to 6 Months of Age

Age (mo)	*FAO/WHO/UNU Estimate, "Crude Protein" ($g/kg^{-1}/d^{-1}$)*	*IDECG "Adjusted Protein"†* ($g/kg^{-1}/d^{-1}$)
0–1	2.46	1.95–2.04
2	1.93	1.41–1.48
3	1.74	1.19–1.25
4	1.49	1.11–1.16
6	—	1.05–1.11

Adapted from Food and Agricultural Organization et al[28] and Dewey K et al.[41]
FAO/WHO/UNU = Food and Agricultural Organization, World Health Organization, and United Nations University; IDECG = International Dietary Energy Consultancy Group.
*Exclusively breast-fed.
†Nitrogen intake includes nonprotein nitrogen (NPN). Adjusted protein intake based on milk protein concentration plus 41–61% of NPN (protein = 6.25 × nitrogen).

mates of average protein intake in breast-fed infants up to 6 months of age, compared with the estimates in the 1985 FAO/WHO/UNU expert report.[28] It is important to point out that average intake of protein in breast-fed infants does not necessarily equal the requirement. Table 5.3-4 shows that the estimated protein intake in infancy is lower than that estimated in the FAO/WHO/UNU report when adjusted by the nonprotein nitrogen fraction. It is also important to remember that protein concentration in milk decreases when the infant is between 1 and 2 months old. Decrease in milk protein concentration was not accounted for in the FAO/WHO/UNU report. Therefore, the 1996 IDECG values are 10 to 26% lower than the 1985 FAO/WHO/UNU estimates, assuming that at least 46% of the nonprotein nitrogen in human milk can be used.[28,41]

Infants, Children, and Adolescents

For infants older than 6 months and for children and adolescents, a factorial approach was used in the 1985 FAO/WHO/UNU expert report.[28] This approach takes into account (1) maintenance for obligatory losses, which is estimated by regression analysis of the relationship between nitrogen intake and nitrogen balance; (2) measurement of the rates of protein deposition, which are derived from body composition analysis; and (3) estimates of the efficiency of protein use, which is derived from the slope of the line relating intake and balance. The factorial method is summarized as follows:

> Mean dietary protein requirement = maintenance + protein accretion associated with growth × 100/utilization efficiency

Under this concept, the need for total protein and/or a particular amino acid for growth is equal to the rate of protein deposition and/or the content of that particular amino acid in the protein being deposited.[28,31,41] However, a problem with this approach is that the relationship between protein intake and nitrogen retention is not linear; thus, the efficiency of nitrogen retention is less as the zero balance point is approached.[51]

In the factorial approach used in the 1985 FAO/WHO/UNU expert report, the maintenance requirement at 6 months of age was taken to be 120 mg $N/kg^{-1}/d^{-1}$, declining to 103 mg $N/kg^{-1}/d^{-1}$ by age 18 months. A growth component was estimated and a 50% addition was made to provide a margin of safety because growth rates vary from day to day and because protein is not "stored" when there is a relative excess intake. The fractional efficiency of nitrogen use from high-quality protein sources for both maintenance and growth was taken to be 0.7 and the coefficient of variance (CV) for maintenance and growth was taken to be 12.5 and 35%, respectively, for purposes of calculating the total CV and a recommended safe protein intake level.[28] The total CV was estimated as follows:

$$\text{CV total} = \sqrt{(M \times CV_m)^2 + (G \times CV_g)^2/(M + G)}$$

Where M equals maintenance and G equals growth.

The requirements estimated by the FAO/WHO/UNU used the above data and assumptions. The data and assumptions have since been revisited, and with accrual or newer and updated information, some modifications to recommended protein intakes for children have been proposed. In 1996, the IDECG concluded that the FAO/WHO/UNU's 1985 recommendations overestimated protein requirements in childhood by 17 to 20%.[41]

For infants older than 6 months and for young children, the IDECG revisited the factorial approach used by the FAO/WHO/UNU. The maintenance requirement of nitrogen, estimated at 120 $mg/kg^{-1}/d^{-1}$ by FAO/WHO/UNU, was revised downward to 90 $mg/kg^{-1}/d^{-1}$. The IDECG estimated maintenance nitrogen needs in infants and children based on a series of nitrogen balance studies,[41,44–51] whereas the FAO/WHO/UNU had used only one study of nitrogen balance in children aged 9 to 17 months and other studies in older children, but none in children less than 12 months of age.[28] Based on these revisions, in 1996, the IDECG derived new values of estimated basal and/or maintenance nitrogen needs in infants and children, which were found to be 82 to 93 mg $N/kg^{-1}/d^{-1}$. A value of 90 mg $N/kg^{-1}/d^{-1}$ was used for the factorial model, on which the revisions of protein requirements are based.[41]

Estimated needs for growth were also revised in 1996 by the IDECG.[41] During infancy, the amount of protein required for growth is an important component of total protein needs, decreasing progressively with age. By 2 years of age, the proportion of proteins needed for growth decreases significantly, whereas the proportion needed for maintenance increases. Table 5.3-5 shows the distribution of protein needs for maintenance and growth in children. In young infants, up to 64% of protein needs are for growth, whereas after age 2 years, protein needed for growth accounts for only 11% of total protein needs. Therefore, after 2 years of age, the use of nitrogen for growth and maintenance is very similar to that in the adult population.[28,41,51]

Intraindividual day-to-day variation in the rate of growth, and therefore in the need for protein to maintain that growth, was estimated at about 50% by the FAO/WHO/UNU in 1985, based on the premise that there is no storage capacity for

TABLE 5.3-5 Protein Needs for Growth and Maintenance in Children

Age	*Protein Gain (g/kg/d)*	*Maintenance (g/kg/d)*	*Maintenance/Total (%)*	*Growth/Total (%)*
0–1 mo	1.00	0.56	36	64
1–3 mo	0.57	0.56	50	50
3–6 mo	0.30	0.56	65	35
6–12 mo	0.18	0.56	76	24
1–2 yr	0.11	0.56	89	11
1–2 yr	0.11	0.56	89	11
2–5 yr	0.07	0.56	89	11

Adapted from Dewey et al.[41]
Maintenance nitrogen assumed to be 90 mg/kg^{-1}/d^{-1}.

amino acids and therefore it would be necessary to allow for extra demand on days of rapid growth.[28] There is no evidence to support a 50% day-to-day variation in the rate of growth; therefore, the 1996 IDECG recommendations discarded the 50% augmentation.[41]

The retention efficiency value or efficiency in conversion from dietary protein to body protein was left unchanged at 0.7 in the 1996 recommendations. Based on available data, it was presumed that efficiency is the same for maintenance as for growth. Efficiency is calculated as nitrogen retained divided by nitrogen intake; obligatory losses are subtracted.[41]

The CV for the interindividual variability in the average requirement estimates for maintenance and growth in infants were also revised by the IDECG. The average requirement estimates were modified based on the extent of interindividual variability. Therefore, accurate estimation of CV is important. The 12.5% CV used by the FAO/WHO/UNU was obtained from short-term nitrogen balance studies in adults, and it was assumed to be the same in the pediatric population. Interindividual variability in growth was estimated to yield a CV of 35%. However, the CV for growth depends on the interval of measurement. The CV will be lower if the interval is longer. Although an arbitrary interval of 3 months was used by the IDECG, it yielded a more reliable CV.[41]

In summary, the 1996 IDECG revision[41] of the 1985 FAO/WHO/UNU report[28] found that (1) for infants up to 6 months of age, the estimates of protein requirement were based on breast milk intake data; intake is not equivalent to requirement, and adjustment for nonprotein nitrogen yielded a lower estimate of protein requirement; and (2) for infants older than 6 months and for children, a modified factorial approach estimating lower maintenance nitrogen needs of about 90 mg/kg^{-1}/d^{-1}, removing a 50% safety margin for intraindividual variation in growth and estimating interindividual variation in growth at a different interval, yielded lower estimates of protein requirements. It is expected that a new FAO/WHO/UNU committee will convene in the future and that the observations from the 1985 FAO/WHO/UNU report will be revisited.

The current RDAs from the Food and Nutrition Board[38] are based on the factorial approach used in the 1985 WHO/FAO/UNU report[28] and on more recent data collected over the past decade.[57–62] However, the Food and Nutrition Board stated that "the use of nitrogen balance should no longer be regarded as the gold standard for the assessment of the adequacy of protein intake, and alternative means should be sought."[38] Table 5.3-6 shows the estimated protein intake recommended by the Food and Nutrition Board.

Other Approaches to Estimating Protein Requirements in Infants

Protein requirements in infants have also been determined by a direct experimental approach, using plasma amino acid and urea nitrogen concentrations as rough indicators of the balance between intake and use.[28,38,41] Postprandial plasma amino acid concentrations are indicative of protein turnover; this is influx into the amino acid pool from protein breakdown, synthesis, and dietary intake and outflow from the plasma pool via catabolism and excretion (Figure 5.3-2). An "operational" approach involving protein-to-energy ratios has also been used to estimate protein requirements.[41] The protein requirements per unit of energy intake decrease rapidly in the first several months of life.[28,41,60] The protein-to-energy ratios for 3 to 6 months and for 6 to 9 months of age have been described as 1.5 and 1.4 g protein/100 kcal, respectively.[22,35] The use of protein-to-energy ratios requires estimating the ratio of the safe level for protein to the mean requirement for energy at each age.[38,46,63,64]

Other Factors Influencing Protein Requirements

Other factors, such as intakes of other nutrients, protein digestibility, amino acid content of proteins, and protein quality, will influence protein requirements.[28,38,41,51] Vitamin B_6 is intimately linked to protein metabolism, and high protein intakes will require higher intakes of vitamin B_6.[65]

Estimating digestibility requires measurement of dietary and fecal nitrogen loss associated with a given protein source. The derivation of the fecal index used in the estimate of "apparent protein digestibility" involves the calculation of a percentage of intake based on the subtraction of the fecal nitrogen output from the dietary nitrogen ingested. However, the input from the metabolism of endogenous proteins is not taken into account by this approach.[38,41,66,67] Hence,

$$\text{Apparent protein digestibility (\%)} = \frac{\text{N intake} - \text{fecal N output on test diet} \times 100}{\text{N intake}}$$

$$\text{True protein digestibility (\%)} = \frac{\text{N intake} - \text{fecal N output on test diet} - \text{fecal N output on nonprotein diet}}{\text{N intake}}$$

True protein digestibility has been established mainly in rat models for a variety of proteins.[38,41]

The content and metabolic availability of individual indispensable amino acids are important variables affecting the nutritional value of a protein food. If the content of a single dispensable amino acid is less than the individual's requirement, the use of other amino acids will be limited. Therefore, normal rates of protein synthesis will be affected, even if the total intake of nitrogen (protein) is adequate. The "limiting amino acid" determines the nutritional value of the total protein in the diet.[68–70] For example, a larger intake of soy protein is required to maintain balance. This difference is eliminated if sulfur amino acids are supplemented. Therefore, sulfur amino acids are the limiting amino acid in soy protein intake.[38] Lysine is the most limiting indispensable amino acid in diets based on cereal proteins.[31,69]

Protein quality refers to the amino acid pattern of food proteins that will efficiently meet both the nitrogen and indispensable amino acid requirements of the individual. The amino acid requirement, or "scoring," pattern is based on estimated average requirements for the individual indispensable amino acids and on total protein requirement. Therefore, nitrogen × 6.25 estimates the weight ratio of protein to the nitrogen content in food. It is assumed that, on average, nitrogen accounts for 16% by weight of mixed proteins. The protein-to-nitrogen ratio for whole milk is 5.62; for egg, 5.38; and for soy milk, 6.07.[38] Table 5.3-7 shows the proposed amino acid scoring pattern in infants and in children aged 1 year or older. There is no difference between preschool children and adults. Therefore, the scoring pattern remains the same after 1 year of age.[38]

The 1989 FAO/WHO expert consultation on protein quality established standards for many protein sources, such as egg (97%), soy flour (86%), and wheat (96%).[70] Animal sources of protein provide all nine indispensable amino acids and for this reason are referred to as "complete proteins," whereas "incomplete" proteins are found in plants, grains, and vegetables and tend to be deficient in one or more of the indispensable amino acids.

The protein digestibility–corrected amino acid score (PDCAAS) has been proposed for the assessment of protein quality[4,70–72] The PDCAAS is obtained by comparing the concentration of a "limiting" amino acid in the food protein source to that of a standard, such as egg protein, and multiplying by the true digestibility.[72] It is expressed as the percentage of the same limiting amino acid in the referenced amino acid pattern.[71] This assessment of protein quality is limited, however. Some investigators[71] have considered the use of ileal rather than fecal digestibility for inclusion in the scoring procedure and to determine if total dietary nitrogen digestibility represents a valid indicator of the bioavailability of the individual amino acid. It has been suggested by the same authors that the deposition of nitrogen during the prandial phase would constitute a critical factor in the deter-

TABLE 5.3-6 Mean Daily Rates of Protein Deposition and Factorial Model Calculations of Mean Protein Requirements

Age (yr)	*Girls' Protein Deposition (mg/kg/d)*	*Mean Requirement (g/kg/d)*	*Boys' Protein Deposition (mg/kg/d)*	*Mean Requirement (g/kg/d)*
0.75	232	1.09	252	1.12
1	189	1.01	160	0.96
1.5	119	0.89	114	0.88
2	83	0.83	88	0.84
3	54	0.78	57	0.78
1–3	111	0.88	105	0.87
4	48	0.77	44	0.76
5	44	0.76	40	0.76
6	48	0.77	42	0.76
7	46	0.76	46	0.76
8	42	0.76	51	0.77
4–8	46	0.76	45	0.76
9	48	0.77	55	0.78
10	36	0.74	51	0.77
11	35	0.75	48	0.77
12	39	0.75	48	0.77
13	29	0.74	41	0.76
9–13	37	0.75	49	0.77
14	23	0.73	38	0.75
15	19	0.72	34	0.74
16	8	0.70	28	0.73
17	0	0.69	19	0.72
18	0	0.69	6	0.70
14–18	10	0.71	25	0.73

Adapted from Panel on Macronutrients et al.[38]

mination of food protein quality, and this could be used to assess significant differences among dietary protein sources.

AMINO ACID REQUIREMENTS

The complexity of estimating individual amino acid requirement was described earlier. Traditionally, amino acid requirement had been based on nutritional use: growth and maintenance, with protein deposition being the predominant influence. The composition of the indispensable amino acids in body proteins of immature mammals is similar. Therefore, the composition of body protein through different species is very similar. Hence, the relative needs of each indispensable amino acid (milligrams of amino acids to grams of total amino acid) for growth will be the same across species.[28] The amino acid requirements for the support of protein deposition in humans will differ from other mammals only to the extent of the difference in growth rates between species.[41] Furthermore, even in young children, the major demand on amino acid requirement is for maintenance rather than for growth. Young and Borgonha estimated that for a 2-year-old child, maintenance accounts for 80 to 90% of the total protein requirement.[51] This is in agreement with data published by Millward, who suggested a value of 85%.[73] Given that, in humans, the obligatory amino acid needs for protein deposition are a minor fraction of the total amino acid requirement,[38,41] the greater demand for amino acid requirement will depend on amino acid use for maintenance.

Amino acid needs for maintenance have been the subject of much controversy.[8,28,31,68,73–76] It has been proposed by Reeds and Hutchens that nitrogen requirements for maintenance could depend on (1) continuous loss in the intestine, (2) maintenance of key metabolites derived from amino acids, and (3) maintenance of pathways that use amino acids involved in host defense and nucleotide synthesis.[35,76] It has been observed that amino acids are consumed in physiologic functions that are not directly related to protein metabolism,[35] and it is important now to quantify the effect of metabolic pathways on the needs for their precursor amino acids. Lyons and colleagues observed that in septic children receiving limited nutritional support, the rates of synthesis of glutathione were decreased by 60%.[77] Glutathione is an important antioxidant, and its synthesis depends on the availability of cysteine. These findings suggest that under pathophysiologic conditions, requirements for some amino acids might need to be revised based on functional rather than nutritional terms.

Specific nutritional amino acid requirements have been determined by nitrogen or amino acid carbon balance. Nitrogen balance values were obtained from the early studies of several investigators[15–26,45,47–49] and from carbon balance studies in adults and sick children performed more recently with stable isotopic techniques.[78–80]

Infants Up to 6 Months of Age

In infants from birth to 6 months of age, the requirements for indispensable amino acids were reported in 1985 in the FAO/WHO/UNU expert report.[28] These recommendations were obtained using the intakes of cow's milk or breast milk that supported satisfactory growth. These estimates are unchanged from the FAO's 1971 report.[27] In 1996, the IDECG used a factorial approach to estimate amino acid intakes in infants up to 6 months of age.[41] Amino acid needs for growth were calculated using data from Fomon and colleagues,[57] based on the daily increment in body protein of breast-fed infants and the amino acid pattern of whole-body protein.

Maintenance protein was calculated as follows: (1) by using the value of 120 mg $N/kg^{-1}/d^{-1}$ and (2) by using nitrogen requirements from balance studies but normalized to metabolic body size (0.75). The factorial approach gave lower estimates for essential amino acids in the 3 to 6 months age group. However, given the significance of the non-nutritional functions of amino acids, and because the functional implications of amino acids in breast milk have not been fully understood, it appeared safer to continue to support the 1971 estimates, and no revision was proposed by the IDECG in 1996.[41]

The recommended adequate intakes for infants up to age 6 months estimated by the Food and Nutrition Board are based on the methods used in 1985 by the FAO/WHO/UNU,[28] using an average volume of milk intake of 0.78 L/day and the mean indispensable amino acid content of human milk. The recommended values are similar to those recommended by the FAO/WHO/UNU in 1985. Table 5.3-8 shows the estimated average requirement and RDA for amino acids at different ages recommended by the Food and Nutrition Board.

TABLE 5.3-7 Food and Nutrition Board Amino Acid Scoring Pattern in Infants and Children

	*Infants**	*All Other Age Groups†*	
Amino Acid	*mg/g Protein*	*mg/g Protein*	*mg/g N*
Histidine	23	18	114
Isoleucine	57	25	156
Leucine	101	55	341
Lysine	69	51	320
Methionine + cysteine	38	25	156
Phenylalanine + tyrosine	87	47	291
Threonine	47	27	170
Tryptophan	18	7	43
Valine	56	32	199

Adapted from Panel on Macronutrients et al.[38]
*Pattern based on amino acid composition of breast milk.
†Pattern derived from estimated average requirement for amino acid divided by estimated amino acid requirement for protein according to age.

Children and Adolescents

For preschool children, amino acid requirements are based on nitrogen balance studies conducted at the Institute of Nutrition for Central America and Panama, in Guatemala.[28,38,41,51] The data were presented only in summary form at a conference.[51] For older children, the requirements from the 1971 FAO/WHO report were upheld. These data were obtained from studies conducted by Nakagawa and colleagues in the 1960s in Japan[49] but were re-examined by the National Research Council and the National Academy of Sciences in Washington.[50] Because of significant methodologic limitations, the data from the

TABLE 5.3-8 Estimated Average Requirement (EAR) and Recommended Dietary Allowance (RDA) for Amino Acids

Amino Acid	*Maintenance (mg/kg/d)*	*Amino Acid Deposition (mg/kg/d)*	*Total EAR (mg/kg/d)*	*RDA (mg/kg/d)*
Boys and girls aged 7–12 mo				
Histidine	11	7	22	32
Isoleucine	15	9	30	43
Leucine	34	18	65	93
Lysine	31	18	62	89
Methionine + cysteine	15	9	30	43
Phenylalanine + tyrosine	27	18	58	84
Threonine	16	10	34	49
Tryptophan	4	3	9	13
Valine	19	12	39	58
Boys and girls aged 1–3 yr				
Histidine	11	3	16	21
Isoleucine	15	4	12	28
Leucine	34	8	48	63
Lysine	31	8	45	58
Methionine + cysteine	15	4	22	28
Phenylalanine + tyrosine	27	8	41	54
Threonine	16	5	24	32
Tryptophan	4	1	6	8
Valine	19	5	28	37
Boys and girls aged 4–8 yr				
Histidine	11	1	13	16
Isoleucine	15	2	18	22
Leucine	34	4	40	49
Lysine	31	3	37	46
Methionine + cysteine	15	2	18	22
Phenylalanine + tyrosine	27	3	33	41
Threonine	16	2	19	24
Tryptophan	4	1	5	6
Valine	19	2	23	28
Boys aged 9–13 yr				
Histidine	11	1	13	17
Isoleucine	15	2	18	22
Leucine	34	4	40	49
Lysine	31	4	37	46
Methionine + cysteine	15	2	18	22
Phenylalanine + tyrosine	27	4	33	41
Threonine	16	2	19	24
Tryptophan	4	1	5	6
Valine	19	2	23	28
Girls aged 9–13 yr				
Histidine	11	1	12	15
Isoleucine	15	1	17	21
Leucine	34	2	38	47
Lysine	31	2	35	43
Methionine + cysteine	15	1	17	21
Phenylalanine + tyrosine	27	2	31	38
Threonine	16	1	18	22
Tryptophan	4	< 0.5	5	6
Valine	19	2	22	27
Boys aged 14–18 yr				
Histidine	11	1	12	15
Isoleucine	15	1	17	21
Leucine	34	2	38	47
Lysine	31	2	35	43
Methionine + cysteine	15	1	17	21
Phenylalanine + tyrosine	27	2	31	38
Threonine	16	1	18	22
Tryptophan	4	< 0.5	5	6
Valine	19	1	22	27
Girls aged 14–18 yr				
Histidine	11	< 0.5	12	14
Isoleucine	15	< 0.5	16	19
Leucine	34	1	35	44
Lysine	31	1	32	40
Methionine + cysteine	15	< 0.5	16	19
Phenylalanine + tyrosine	27	1	28	35
Threonine	16	< 0.5	17	21
Tryptophan	4	< 0.5	4	5
Valine	19	1	20	24

Adapted from Panel on Macronutrients et al.[38]

nitrogen balance studies were not used to determine requirements of indispensable amino acids in children aged 7 months through 18 years. Instead, the factorial approach has been used by the IDECG,[41] Millward,[73] Young and Borgonha,[51] and the Food and Nutrition Board[38] to estimate indispensable amino acid requirements. The values obtained are similar to, but slightly lower than, the estimates of the 1985 FAO/WHO/UNU expert report.[28]

The recommendations from the Food and Nutrition Board for amino acid scoring patterns for use in children older than 1 year of age are shown in Table 5.3-7. These data are based in part on the 1985 FAO/WHO/UNU expert report and on more recent data. There is great need for further studies on the protein and amino acid requirements of children, for both nutritional and functional outcomes.

Other Methods for Estimating Individual Amino Acid Requirements

Isotopic studies for quantitative estimates of amino acid requirements and for determination of the efficiency of dietary protein use in meeting these requirements are based on bolus or continuous infusion of amino acid tracers or ingestion of single amino acid–labeled protein or uniformly labeled protein.[38,80]

Indicator Amino Acid Balance In the indicator amino acid balance method, the amino acid test of interest is given at graded levels, and measurements of the carbon oxidation of single indispensable amino acids are taken as indicators of the adequacy of the test amino acid.[81] This method is based on the idea that the nutritional indispensability of an amino acid is attributable to the inability to synthesize its carbon skeleton. Therefore, if the test amino acid is labeled with ^{13}C, the production of $^{13}CO_2$ in breath is assumed to accurately reflect the irreversible oxidative loss of the test amino acid. When this method is used at progressively lower levels of test amino acid intake, a minimum level, or "break point," in the relationship between carbon catabolism, as estimated from the $^{13}CO_2$ in breath, and test amino acid intake can be established. It is assumed that below intake requirement, the test amino acid will be conserved and the rates of oxidation will be low and constant, but once the requirement is exceeded, the oxidation of the test amino acid will increase. Therefore, nutritional requirement will be established at the break point level.[81]

Indicator Amino Acid Oxidation This method is based on the measurement of the oxidation of an indicator amino acid (^{13}C phenylalanine or ^{13}C lysine), which falls to a break point when the amino acid test requirement is achieved.

24-Hour Amino Acid Balance Amino acid balance studies carried out over 24 hours have been obtained for leucine,[82] phenylalanine and tyrosine,[83] lysine,[84] and threonine.[85] This approach provides a more accurate estimate of amino acid needs. However, the intake of tracer over the 24-hour period has been considered a drawback. Twenty-four-hour balance studies have not been conducted in children.

All of these methods have drawbacks and strengths. To date, these are the most reliable data on quantitative estimates of amino acid requirement in adults.

AMINO ACID SUPPLEMENTATION

It has been proposed that supplementation with some amino acids could improve specific physiologic or pathophysiologic conditions.[86–90] However, there have been no dose-response human studies, and only a few controlled, randomized trials have been conducted. Because of the lack of evidence, the value of dietary supplementation with a particular amino acid for improvement of a functional outcome remains to be established.

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CHAPTER 6

TRACE ELEMENTS

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More than 99.7% of the body weight is accounted for by 11 elements, termed the major elements (Table 6-1). The remainder of the body weight consists of approximately 25 trace elements, each of which contributes less than 0.01% to the body weight. Of these, a mammalian nutritional requirement has been established for iron, iodine, zinc, copper, chromium, selenium, molybdenum, manganese, cobalt, nickel, vanadium, silicon, arsenic, boron, and fluoride. 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. Although it is reasonable to assume that the trace elements required by humans are similar to those required by other mammalian species, currently, a human nutritional requirement is 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.

BIOLOGIC ROLES

Many enzyme systems depend on one or more specific trace elements, either as key components of metalloenzymes or as catalysts of metal ion–activated enzymes. The roles of metal ions in metalloenzymes may be structural, that is, maintaining the conformation of the protein, catalytic, or both. Iron, copper, zinc, molybdenum, selenium, and manganese have been identified as constituents of specific enzymes. Certain trace elements are of fundamental importance in the structure or metabolic activity of other compounds, including hemoglobin (iron), nucleic acids (multiple trace elements), transcription factor proteins (zinc), and vitamin B_{12} (cobalt). The roles of iodine in thyroxine (T_4) and triiodothyronine (T_3), zinc in steroid hormone receptors, and chromium in facilitating the action of insulin are examples of the importance of trace elements in the activity of certain hormones. The dependence of many vital metabolic processes on trace elements confers a physiologic importance on these micronutrients that is analogous to that of vitamins and is out of proportion to their small contribution to body weight. Although considerable progress has been achieved in determining the functions of several trace elements, little is yet known about the biochemistry of others.

TABLE 6-1 Elements with a Role in Human Physiology

	Trace Elements	
Major 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^-)	Cobalt (Co)	
Calcium (Ca)	Fluoride (F^-)	
Magnesium (Mg)		

DOSE RESPONSE

An elementary but important concept is that the biologic effect of any trace element depends on the dose or, more specifically, on the level of intake and on tissue concentrations (Figure 6-1). For each element, there is an optimal range of intake, the magnitude of which varies considerably between different elements and depends on a number of factors, including the efficiency of homeostatic mechanisms. Obviously, if intakes are sufficiently high, any element will prove toxic. In the case of nonessential elements (eg, mercury), harmful effects can result only from toxic levels of intake. However, in the case of the "essential" trace elements, problems may result from intakes that are too low as well as too high. In animal husbandry, the economic importance of trace deficiency states has been recognized for many years.[1] However, in human nutrition, only iron and iodine deficiencies were recognized prior to the 1960s, and it is only more recently that a broader concept of trace element nutrition has started to develop with the recognition of zinc, copper, chromium, selenium, molybdenum, and possibly manganese deficiency states in humans.

ETIOLOGY OF HUMAN TRACE DEFICIENCY STATES

The last several decades have been notable not only for the number of new trace elements implicated in deficiency disease but, perhaps more surprisingly, for the wide variety of

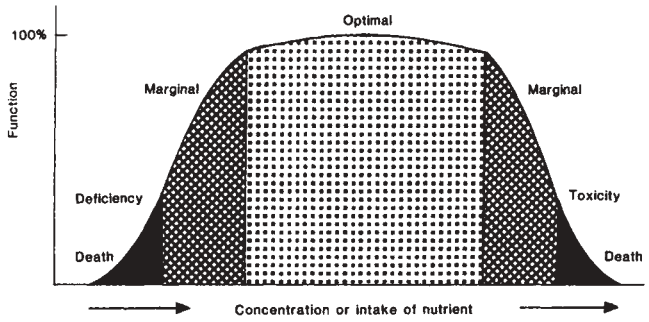

FIGURE 6-1 Dependence of biologic function on tissue concentration or intake of a nutrient. Reproduced from Mertz W. The essential trace elements. Science 1981; 213:1330.

different factors that have been discovered to play a role in the etiology of these deficiency states (Table 6-2). These include inherited or acquired alterations in metabolism and other special circumstances leading to increased nutritional requirements as well as factors that contribute to inadequate intakes of one or more of the trace elements.

Clinically, the most notable examples of the former are provided by inborn errors of trace element metabolism.[2,3] Although these entities are rare and not strictly nutritional deficiency diseases, some of them are important in a nutritional context because of the insight they provide into the clinical and metabolic effects of severe nutritional deficiencies. Moreover, in some instances, manipulation of dietary intake has remarkable therapeutic benefits. Both of these points are well illustrated by acrodermatitis enteropathica, which is discussed below. Although unresponsive to dietary supplements, Menkes' steely-hair syndrome (MSHS) is attributable in part to a de facto deficiency of copper in certain tissues and subcellular sites, resulting from deranged copper transport. An inborn error of molybdenum metabolism has also been described, the clinical features of which suggest a severe molybdenum deficiency state.

TABLE 6-2 Etiology of Trace Deficiencies

Etiology	*Trace Elements**
Inadequate Intake	
No special circumstances required but risk increased during infancy and pregnancy	Fe, Zn
Losses during food processing, including preparation of "humanized" infant milk formulas	Zn, Cr, Cu, Se
Poor bioavailability	Fe, Zn
Local deficiencies in geochemical environment	I,Se
In association with protein-energy malnutrition	Zn, Cu, Cr
Synthetic diets, including intravenous feeding	Zn, Cu, Cr, Se, Mo
Other Circumstances	
Prematurity	Fe, Cu, Zn
Diseases and other unusual circumstances causing impaired intestinal absorption or excessive losses of trace elements	Zn, Cu, Cr
Inborn errors of trace element metabolism	Zn, Cu, Mo

*Elements given are notable examples, but not necessarily a complete list.

Diseases that cause intestinal malabsorption of fat and other nutrients may also lead to trace element deficiencies.[4] Excessive losses of trace elements occur in certain diseases through the kidneys, gastrointestinal tract, sweat, exudates, or hemorrhage. Low blood plasma concentrations of specific trace elements can occur in certain disease states in association with the redistribution of these elements within the body. For example, movement of zinc and iron from the plasma to the liver occurs in stress situations, including infectious diseases. Correction of hypozincemia in these circumstances may be contraindicated, although the host response may depend on the specific cause of the stress.

The premature infant with very low birth weight provides a unique nutritional challenge that includes the provision of adequate trace elements.[5] Some elements, notably copper, iron, and possibly zinc, are stored extensively by the fetus during the last trimester. These stores, which are available to the term infant in early postnatal life, are diminished in the premature infant. Immaturity of intestinal absorption mechanisms and relatively high losses of endogenous zinc have been reported. These problems are aggravated further by the high nutritional requirements that are imposed by the rapid growth of the premature infant after the early postnatal period. Nutritional requirements may also be relatively high during periods of rapid growth in the term infant and in later childhood, as well as during pregnancy and lactation.

Although nutritional requirements for trace elements are small and these nutrients are ubiquitous in the environment, the quantities present in food and water are usually correspondingly low. Hence, contrary to earlier concepts, it is not surprising that humans are at risk from nutritional deficiencies of the trace elements. Iron deficiency, although outside the scope of this chapter, remains one of the most common human nutritional disorders. Other trace deficiencies occur in more restricted geographic locations owing to localized deficiencies in soils, plants, or water. The classic example of a geographic deficiency is that of endemic goiter. The body content of selenium is relatively low in some countries, including New Zealand, and selenium depletion is even more marked in large areas of China. Diets deficient in other nutrients may also contain inadequate quantities of trace elements. Thus, deficiencies of zinc, copper, and chromium have been documented in association with protein-energy malnutrition.

In North America, there is evidence that diets may frequently be marginal or deficient in zinc. Losses during food processing have been implicated as at least a contributory cause. For example, it has been estimated that the milling of grain removes more than three-quarters of the zinc and manganese normally present with substantial losses of other elements, including copper and molybdenum. Refining of sugar also causes losses of trace elements, including chromium. A process that is of special concern for pediatricians is the humanizing of cow's milk in the production of infant formulas. All infant formulas in the United States are now supplemented with variable quantities of iron, zinc, and copper, and, more recently, with sele-

nium. Overall, there remain substantial variations in trace element concentrations in different formulas on a worldwide basis.

Variations in bioavailability are a major factor in determining the adequacy of dietary intake of some of the trace elements. This also applies especially to the infant because of its dependence on one major food staple. Thus, if the milk or milk substitute that provides most or all of the nutrients consumed by the infant is low in available trace elements, there is no chance that this deficit will be compensated for by a more favorable supply in other food items. Although our understanding of this complex subject is far from complete, it is known that human milk confers important advantages with respect to the bioavailability of iron and zinc. Although not proven, it seems probable that this may also be true of other trace elements. As a corollary, the trace element concentrations in breast milk should be considered a minimum guideline for corresponding concentrations in infant milk formulas, and higher concentrations of at least some elements, including iron and zinc, are necessary in the latter. However, indiscriminate supplementation may have adverse consequences, especially through undesirable interactions with other trace elements. Additional research directed at mineral–mineral interactions is needed to determine optimal fortification levels in foods and formulas.

The increasing use of synthetic diets in medical practice, including those used in intravenous feeding, has provided some of the most dramatic examples of acquired trace-deficient states. The development of this area of specialized nutritional support illustrates the extent of our continuing ignorance, not only of the quantities of trace elements required, both orally and intravenously, but also of which micronutrients are desirable additions to synthetic diets. Deficiencies of zinc, copper, chromium, molybdenum, and probably selenium have been documented in association with long-term intravenous feeding.

NUTRITIONAL REQUIREMENTS

The evolving nutritional importance of trace elements has been recognized by the publication of guidelines, including those of the Food and Nutrition Board of the National Academy of Sciences (see Appendix 2).[6] A formal Recommended Dietary Allowance (RDA) has been established for copper, iodine, iron, molybdenum, selenium, and zinc. An Adequate Intake (AI) has been set for chromium and manganese, which reflects the more limited data available on which to base an Estimated Average Requirement (EAR).[6] Information is limited on the quantities of some of these elements in individual food items, which limits the application of these guidelines by nutritionists and other health professionals. There are theoretic advantages to defining recommendations for such elements as zinc according to the bioavailability from different diets, as has been done by the World Health Organization (WHO),[7] but caution is warranted when currently available data are not adequate to support precise tailoring of such recommendations. A specific point that merits emphasis is that intakes below the recommended levels are not necessarily inadequate. In particular, it is wrong to conclude that human milk is deficient in a specific trace element because it provides relatively low quantities of that element.

Guidelines have also been published for intravenous administration of trace elements to children who have to be maintained with total intravenous nutrition (Table 6-3).[8] Intravenous requirements for zinc vary according to the extent of ongoing losses, especially from the gastrointestinal tract. Hence, it is desirable to monitor zinc status at regular intervals.

LABORATORY ANALYSES AND THE DETECTION OF TRACE ELEMENT DEFICIENCY STATES

Fundamental advances in analytic instrumentation, especially the advent and progressive refinement of atomic absorption spectrophotometry, have facilitated the quantitative measurement of trace elements that are present in the parts-per-billion as well as parts-per-million concentration ranges. Yet formidable analytic difficulties remain. For example, accurate measurement of chromium, which now appears to be present in blood plasma, urine, and milk in only parts-per-trillion concentrations, is extraordinarily difficult. Even for relatively simple measurements, such as those of zinc in plasma or serum, substantial interlaboratory differences in analytic results continue to be evident, and it is necessary for each laboratory to establish its own normal range. Even when analytic data are accurate, interpretation is frequently problematic. Plasma concentrations of zinc, for example, may be depressed for reasons other than a deficiency of these elements and frequently fail to provide a sufficiently sensitive or reliable guide to body status. Established physiologic indices, such as the measurement of the activity of an enzyme that depends on a specific trace element, are generally unavailable. The depression of glutathione peroxidase activity in selenium deficiency states is one exception, but the clinical significance of this observation remains uncertain. Overall, laboratory indices for detection of "newer" trace element deficiencies are not as dependable as those available for the detection of iron deficiency. Hence, for research purposes, more cumbersome approaches are necessary to confirm the suspicion of a specific deficiency, including especially the effects of supplementation on specific physiologic parameters under carefully controlled conditions. Meanwhile, the health professional needs to be aware of the circumstances in

TABLE 6-3 Guidelines for Maintenance Intravenous Administration of Trace Elements during Parenteral Nutrition

Trace Element	*Maintenance Requirement (μg/kg/day)*
Zinc	100*
Copper	20
Chromium	0.2
Manganese	1
Selenium	2
Iodine	1

*Requirements for zinc may be much greater in patients who continue to excrete excessive quantities of zinc; also, in premature infants, 300 μg/kg/day should be administered.

which there is a risk of specific trace deficiencies and of the clinical features that may be attributable to such a deficiency.

Hair analyses merit special mention because of their widespread misuse and the unsubstantiated claims for this diagnostic tool. Currently, the value of chemical analyses of hair in clinical practice is extremely limited.[9] Moreover, because of the inherent difficulties in interpretation of analytic data, it is unlikely that future research will lead to more than very limited clinical applications of hair analyses.

ZINC

A nutritional requirement for zinc was first recognized in microorganisms in 1869, in plants in 1914, and in mammals in 1934.[1] In 1954, zinc deficiency was shown to be the cause of porcine parakeratosis. The first of the zinc metalloenzymes to be identified was carbonic anhydrase in 1940.[1] Subsequently, over 100 zinc metalloenzymes have been identified, including at least one in every major enzyme classification. Appreciation of the role of zinc in nucleic acid metabolism, mitosis, and protein synthesis developed in the 1960s and was extended in the 1970s. Understanding of the role of zinc in cell growth and differentiation took a major step forward with recognition of "zinc fingers" as the most frequent deoxyribonucleic acid (DNA) binding motif for transcription factor proteins.[10] Studies of human zinc status were very limited prior to 1960 but included the first documentation of altered zinc metabolism in alcoholic cirrhosis.[11] The first reports of human zinc deficiency attributable to dietary factors emerged in the Middle East in the early 1960s in relation to the syndrome of adolescent nutritional dwarfism.[12] The 1970s were a time of rapid growth in knowledge about the extent, causes, and effects of human zinc deficiency states.[13] In the 1990s, the importance of zinc deficiency on childhood morbidity and mortality in the developing world was documented by a number of carefully conducted, large-scale, randomized, controlled supplementation trials in vulnerable populations.

Clinical Features of Zinc Deficiency

The clinical features of human zinc deficiency range from a life-threatening disease state, characterized by acro-orificial skin rashes, diarrhea, growth arrest, anorexia, depressed mood, and increased susceptibility to infection, to a mild impairment of growth velocity, often accompanied by other problems, including poor appetite and possibly impaired taste perception (Table 6-4). In addition to the severity of the zinc depletion, the clinical sequelae appear to depend on other factors, including the speed of onset and associated clinical and dietary factors such as protein-energy malnutrition.

Decreased growth velocity or growth arrest is a consistent and early result of even mild zinc deficiency in young experimental animals and in infants, children, and adolescents. In severe acute zinc deficiency states (eg, acrodermatitis enteropathica), there is an abrupt cessation of weight gain when the skin rash becomes manifest, and "catch-up" growth occurs when adequate zinc supplements are administered.[14]

Randomized, double-blind, controlled studies in young formula-fed infants, older infants and toddlers, and young children in Colorado have demonstrated increases in weight and/or linear velocity in association with the daily administration of a small dietary zinc supplement for 6 to 12 months duration.[15–18] During the 1990s, the results of more than 20 randomized, controlled zinc supplementation trials were reported from five continents, from developed and developing countries. A meta-analysis of trials in prepubertal children that met strict criteria indicated that supplementation was associated with significant responses in both height and weight increments. Responses were strongest in those initially underweight and in children > 6 months of age with evidence of stunting.[19] These collective results suggest that zinc deficiency is a common cause of retarded growth velocity in the developing world. The first reports of human zinc deficiency concerned severely growth-retarded adolescents in the Middle East,[12] and the need for adequate zinc for optimal weight gain during recovery from protein-energy malnutrition has been reported from Jamaica.[20] Zinc deficiency has also been linked to poor growth in association with certain diseases, including regional enteritis and sickle cell anemia.[21,22]

One large-scale, randomized, controlled study of maternal dietary zinc supplementation during the second and third trimesters of pregnancy showed a beneficial effect on fetal growth and resulted in significantly greater birth weight and head circumference in the offspring of zinc-supplemented mothers, owing in part to a significantly lower incidence of prematurity.[23] Other studies of maternal zinc supplementation have demonstrated mixed results with respect to maternal, fetal, and infant outcomes. Additional well-designed studies in populations in developing countries are warranted before universal fortification or supplementation programs can be recommended.[24]

Anorexia is an early manifestation of zinc deficiency in experimental animals. Although this has long been recognized as a feature of acrodermatitis enteropathica and is also noted in association with milder zinc deficiency syndromes, it has been difficult to acquire objective evidence of a direct cause-and-effect relationship in humans. However, a significant effect of zinc supplementation on food intake has been observed in a double-blind, controlled study.[25]

TABLE 6-4 Clinical Features of Zinc Deficiency*

Decrease in growth velocity
Impaired appetite and decreased food intake
Diarrhea
Increased susceptibility to infection with associated abnormalities of the immune system
Acro-orificial skin lesions; other epithelial lesions, including glossitis, alopecia, nail dystrophy, and hair loss
Behavioral abnormalities, including impairment of hedonic tone
Delayed sexual maturation and impotence
Eye lesions, including photophobia and lack of dark adaptation
Delayed healing of wounds, burns, and decubitus ulcers
Hypogeusia or dysgeusia
Low birth weight
Prematurity

*Features are dependent on severity of deficiency and other factors.

Appetite may not be impaired in zinc-deficient children who are also protein depleted.[20] In addition to decreased food intake, zinc deficiency may be one cause of pica.[26]

Diarrhea is one of the hallmark features of the early descriptions of acrodermatitis enteropathica and occurs in a high percentage of cases. There is growing evidence that zinc deficiency contributes to the incidence, severity, and duration of acute infectious and persistent diarrhea in infants and young children in the developing world. On the basis of pooled analysis of zinc supplementation trials, a 42% reduction in the rate of treatment failure or death in children given zinc supplements has been estimated.[27,28] Diarrhea can itself also contribute to zinc deficiency because of the losses of endogenous zinc in diarrheal fluids.[29] Requirements for zinc are likely to be greater in the presence of diarrhea.

The skin lesions of severe acute zinc deficiency syndromes have a characteristic distribution, primarily at the extremities and adjacent to the body orifices (Figure 6-2). However, lesions do occur elsewhere and may become generalized. Most commonly, the rashes are erythematous, vesiculobullous, and pustular. Secondary infection is common, especially with staphylococci or *Candida*. Hyperkeratotic plaques may develop when severe zinc deficiency persists, and chronic skin lesions have also been reported in moderate zinc deficiency complicating chelation therapy.[1] In acrodermatitis enteropathica, the skin lesions typically occur in early infancy, although they are usually delayed until after weaning if the infant is breast-fed. Similar lesions occur in severe acquired zinc deficiency states, including patients fed intravenously without zinc supplements,[30] and in premature infants, especially those whose mothers have an inability to secrete normal quantities of zinc into their milk.[31] Other epidermal lesions include gingivitis, dermatitis, glossitis, conjunctivitis, blepharitis, alopecia, and, in chronic cases, nail dystrophies. The open skin sores that occur characteristically in kwashiorkor have been reported to respond specifically to topical zinc applications and appear to be caused or at least aggravated by a concurrent zinc deficiency,[32] which is not necessarily as severe as that responsible for the typical acrodermatitis rash. A dry hyperkeratotic skin and acne have been reported in some cases of more moderate zinc deficiency states.

Behavioral abnormalities are a notable feature of severe zinc deficiency states. Irritability, lethargy, and depression occur typically in conjunction with the skin rash of severe zinc deficiency. Hedonic tone and motivation to engage in the environment[33] improve dramatically after the commencement of zinc therapy.[26] Cognitive development is impaired in young zinc-deficient animals, and there is growing evidence that the same applies in the human.[34]

Frequent bacterial and monilial infections, associated with abnormalities of the immune system, contribute to the progressive and often fatal course that characterizes untreated acrodermatitis enteropathica. Abnormalities of the immune system also occur in less severe zinc deficiency states. Compared with studies of zinc and diarrhea, there are fewer trials examining the effects of zinc on the incidence of pneumonia, but the results of a pooled analysis suggest a 41% lower rate of pneumonia in zinc-supplemented children.[27,28] Zinc supplementation may also have a positive impact on clinical attacks of malaria, although the results of controlled trials have been somewhat mixed.[28] Chronic zinc deficiency in adolescents may cause prolonged delay of sexual maturation.[12] Some cases of impotence complicating chronic renal disease have responded to zinc supplementation. Eye lesions that may occur in severe chronic zinc deficiency states include severe photophobia and keratopathies.[1] Visual adaptation to the dark may also be impaired.

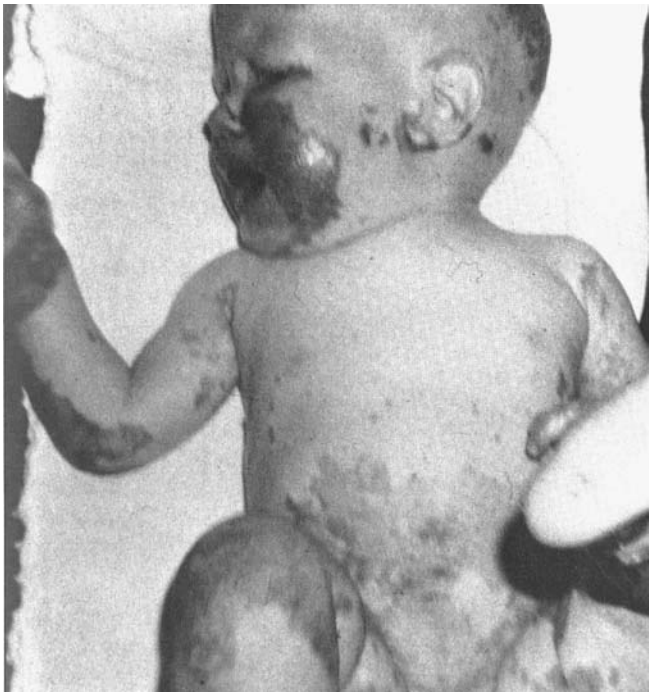

FIGURE 6-2 The acute skin lesions of acrodermatitis enteropathica are demonstrated in this 10-month-old infant. Reproduced from Hambidge KM, Nichols PL Jr, editors. Zinc and copper in clinical medicine. Jamaica (NY): Spectrum Publications; 1978.

Another feature of zinc deficiency that has been more definitively studied in animals than in humans is the delayed healing of wounds. However, there is substantial evidence that zinc deficiency can delay the healing of surgical wounds, burns, and decubitus ulcers in humans.[4]

Biochemical Correlates

Although there is now extensive knowledge about the biochemistry of zinc, especially its role in a wide range of enzyme systems, the biochemical correlates of the clinical features of human zinc deficiency remain poorly defined. Many of the features of zinc deficiency, including growth retardation, poor wound healing, and abnormalities of fetal development and the immune system, are thought to be attributable, at least in part, to disturbances in nucleic acid metabolism and protein synthesis. Its role as a stabilizer of the molecular structure of subcellular constituents and membranes is exemplified by the observation of altered membrane signaling and postreceptor events that coordinate the response to insulin-like growth factor 1 when zinc availability is limited.[35] Such observations provide another

plausible link to the growth retardation and impaired immune function during zinc deficiency. The so-called zinc fingers are the most common motif for the repetitive sites on transcription proteins that bind with DNA to initiate transcription.[10] Through this mechanism, which can be compromised by zinc restriction, zinc has an extraordinarily important role in gene expression. Similar zinc finger motifs are involved at the receptor sites of some steroid hormones,[36] including those for testosterone and in nuclear receptors for vitamins A and D. Several of the enzymes involved in nucleic acid synthesis are zinc dependent, including DNA and ribonucleic acid (RNA) polymerases, reverse transcriptase, and thymidine kinase, the activity of which is known to be reduced in human zinc deficiency.[37]

Zinc is critical for normal immune function and interacts with several components of the immune system, ranging from the skin and its barrier function to aspects of both cellular and humeral immunity. In vitro studies emphasize the responsiveness of some components to zinc concentrations, with both deficiency and supraphysiologic levels leading to impaired immune function. As a highly proliferative organ, the immune system strongly depends on an adequate zinc supply. Recent reviews address in vitro and in vivo studies of the role of zinc in normal immune function and the impact of zinc deficiency.[38,39] Controlled supplementation trials in humans that examine specific markers of immune function are limited. Zinc supplementation of malnourished preschool-aged children was associated with a significant reduction in anergic/hypoergic children and a significantly greater rise in lymphocyte subsets.[40] Positive effects have also been observed with zinc therapy in acrodermatitis enteropathica,[41] Down syndrome,[4] and generalized malnutrition.[42] In Jamaica, improvement in delayed cutaneous hypersensitivity and an increase in thymic size in undernourished infants have resulted from topical and oral zinc therapy, respectively.[42,43] In acrodermatitis enteropathica, impairment of monocyte and neutrophil chemotaxis has been corrected by zinc therapy in vivo and by incubation with zinc in vitro.[44]

Abnormalities of essential fatty acid metabolism and of prostaglandin synthesis may result from zinc depletion.[45] It is possible that some of the features of zinc deficiency, including dysfunctional uterine labor patterns and postpartum hemorrhage, are mediated through these abnormalities. Currently, this remains a poorly clarified but potentially interesting area of research in zinc metabolism. Membrane sodium transport is affected by zinc deficiency, and the diarrhea characteristic of zinc deficiency may be attributable to altered membrane permeability. Other proposed mechanisms include induction during zinc deficiency of specific gene products that alter fluid balance in the intestine.[4,46]

Although the activity of so many enzymes is zinc dependent, there have been very few direct links between clinical features of disease and impaired activity of specific zinc-dependent enzymes. Some of the effects of zinc deficiency may be mediated through effects on hormones. For example, testosterone secretion is decreased in experimental zinc deficiency, and increases in circulating insulin with concurrent decreases of blood glucose have been observed in the treatment of human zinc deficiency.[47] In the same study, zinc supplementation was associated with improved nitrogen balance. The importance of zinc to normal function of the central nervous system, including as a prominent neurosecretory product in the cerebrocortex, has recently been reviewed.[48]

Etiologic Factors in Zinc Deficiency

The prototype of the severest forms of human zinc deficiency is provided by acrodermatitis enteropathica, a rare autosomal recessively inherited disorder. The phenotypic expression of this disease is attributable entirely to a severe zinc-deficiency state.[2] The zinc deficiency results from a partial block in the intestinal absorption of this trace metal. A candidate gene has been proposed that codes for a transmembrane histidine-rich protein that functions as a zinc-uptake protein.[49] Although total body zinc is not greatly reduced, plasma zinc concentrations are typically extremely low. Before the beneficial effects of zinc therapy were recognized, this was a severe, progressive, and often fatal disease. Similar clinical syndromes result from severe acquired zinc deficiency and have been observed frequently in pediatric and adult patients who are fed intravenously. The most important etiologic factor is failure to add zinc supplements to the intravenous infusate. Contributory factors may include excessive urine losses of zinc liganded to amino acids and, in some cases, extraordinary gastrointestinal losses attributable to the gastrointestinal pathology for which intravenous nutrition was administered.[47]

There have been numerous reports of similar severe zinc deficiency states in a few breast-fed infants, especially those delivered prematurely. Several of these cases have been attributable to an inability of the mother's mammary gland to secrete normal quantities of zinc into the milk despite an otherwise apparently normal maternal zinc status.[31] A mutation of one of the recently identified zinc transporters, ZnT-4, whose expression has been localized primarily to the mammary gland, has been proposed to be responsible for the lethal milk mutation in mice.[50] This mutation is characterized by markedly low serum zinc concentrations in the dam and in the milk, which lead to severe zinc deficiency in suckling pups within approximately the first week of life. Death follows shortly thereafter if supplemental zinc or alternative feeding is not initiated. Current understanding suggests that the abnormal zinc concentrations in human milk, with resulting severe deficiency in the breast-fed infants, may be analogous to the lethal milk mutation seen in mice and represent another inherited defect in human zinc metabolism.

Zinc deficiency has been well documented in premature and low birth weight infants. Contributory factors may include immaturity of the gastrointestinal homeostatic processes, including both absorption of exogenous zinc and conservation of endogenous zinc, relatively high urine losses, and relatively high zinc requirements when rapid postnatal growth commences. Fortification of human milk and use of fortified formulas designed to meet the needs of premature infants have been associated with positive net absorption and

retention of zinc.[51] The results of zinc supplementation trials in low birth weight infants in developing countries have resulted in a striking reduction in morbidity and mortality, illustrating the apparent vulnerability of these infants without a generous dietary intake to zinc deficiency.[52]

A wide variety of etiologic factors may contribute to more moderate and mild zinc deficiency states. An "absolute" dietary deficiency is rare, although it may occur with the use of synthetic diets lacking zinc or in other exceptional circumstances. Usually, however, the diet is deficient in zinc because of special needs for rapid growth, excessive losses of endogenous zinc (intestinal and urine), and/or dietary factors that have an unfavorable effect on zinc bioavailability. Older breast-fed infants are susceptible to zinc deficiency because of the low zinc concentrations in human milk by 6 months. Deficiency has been documented in infants in impoverished conditions, in whom both a combination of complementary foods with low zinc content and/or bioavailability and a high infectious burden may contribute to the risk of deficiency.[53,54] Poor bioavailability of zinc, attributed to high levels of dietary phytate and fiber, coupled with low animal protein intakes, was considered to be the major etiologic factor in the syndrome of adolescent nutritional dwarfism in Egypt and Iran.[12] As phytate intakes are high in many developing countries owing to dependence on plant staples such as maize, wheat, or legumes, there is special concern about the adequacy of zinc intake in children in the developing world. Zinc deficiency in malnourished Jamaican infants was most pronounced in infants who were rehabilitated with a soy protein formula, probably because of the adverse effect of phytate on zinc absorption. Another important factor in this instance was the high zinc requirement necessary to meet the needs of rapid growth during the recovery phase.

The subject of zinc bioavailability is also of special importance in infant feeding because of the infant's dependence on one food. Bioavailability of zinc from human milk is considerably more favorable than that from cow's milk or infant formulas.[55,56] "Humanized" cow's milk formulas require supplementation with zinc to prevent limitation of infant growth by an inadequate zinc intake.[16] Excessive iron may inhibit zinc absorption, and iron-fortified formulas require additional zinc. The potential for interaction among trace elements at the level of gastrointestinal absorption adds to the complexity of determining optimal quantities of trace elements in infant formulas.

The risk of zinc deficiency is enhanced in certain disease states owing to malabsorption of zinc or excessive losses.[4] Fat malabsorption or intestinal inflammation may impair zinc absorption and enhance losses of intestinal endogenous zinc, as in regional enteritis,[21] celiac disease, and cystic fibrosis.[57,58] Excessive urinary losses of zinc occur in liver disease,[59] diabetes mellitus, sickle cell disease,[22] nephrosis, and catabolic conditions.[4] A number of chelating agents, diuretics, and other drugs can also cause excessive zinc excretion. More extensive data are needed to determine whether such clinical conditions pose a significant risk to zinc status.

Diagnosis of Zinc Deficiency

The characteristic distribution of the skin lesions facilitates the clinical diagnosis of severe zinc deficiency states. Unfortunately, however, the clinical features of more moderate and mild zinc-deficient states are nonspecific. Currently, laboratory parameters are of only limited value in the confirmation of zinc deficiency. Plasma zinc concentrations are markedly depressed (< 40 μg/dL) in the severest deficiency states, and moderate hypozincemia (40 to 60 μg/dL) occurs in more moderate zinc deficiency states. However, plasma zinc levels may be depressed to this extent in other circumstances as well, including the physiologic decline that occurs in pregnancy and that attributable to the effects of various stresses, including infections, in redistributing body zinc. Hypozincemia is not a consistent feature of mild chronic zinc deficiency states. Interlaboratory differences in normal ranges make it necessary to use local normal ranges for reference purposes. Serum zinc levels have been reported to be higher than plasma zinc levels; this is attributable to a delay in separation from red cells.[60] Erythrocyte zinc is little affected by zinc deficiency and is not a sensitive index, although zinc is primarily an intracellular cation. Leukocyte zinc concentrations as an index of status have not withstood the test of time. Hair zinc levels may be markedly depressed in mild zinc deficiency states but are normal in severe zinc deficiency when hair growth is arrested. Difficulties in interpretation severely limit the value of hair analyses, especially in infants and very young children. Urine excretion rates are diminished in marked zinc deficiency, but this is not a sufficiently sensitive assay. Unfortunately, no blood zinc fraction has been identified that will provide a good measure of zinc status or that is comparable to serum ferritin levels in the assessment of iron status. Initial comparisons of lymphocyte metallothioneine messenger RNA levels in conditions of zinc restriction and supplementation appear promising but require more corroboration.[61,62] Serum alkaline phosphatase activity is depressed in severe zinc deficiency states and increases with zinc supplementation in cases of more moderate zinc deficiency. However, this assay is not a sufficiently specific diagnostic tool used alone, and no other assays of zinc-dependent enzymes have yet proved satisfactory. Because of the limitations of currently available laboratory indices in the detection of mild zinc deficiency states, the most reliable approach remains the demonstration of the effects of zinc supplementation under adequately controlled conditions.

Treatment of Zinc Deficiency

Acrodermatitis enteropathica can be treated effectively with 40 to 50 mg/day of elemental zinc administered as the sulfate, gluconate, or other salt. One milligram of elemental zinc is equivalent to 4.4 mg of $ZnSO_4$ $7H_2O$, 7 mg of zinc gluconate, and 2.8 mg of zinc acetate (anhydrous). This dose is not dependent on body weight, but requirements in infants and toddlers with acrodermatitis enteropathica may be considerably less (ie, zinc, 20 to 30 mg/day). In severe zinc deficiency in premature breast-fed infants, temporary zinc supplements are necessary until other sources of zinc are added to the diet. Most other milder cases of zinc defi-

ciency can be treated effectively with zinc, 1 mg/kg body weight/day, up to a maximum of 20 to 30 mg zinc/day. Somewhat larger quantities may be required in the presence of excessive ongoing losses or malabsorption.

Maintenance intravenous requirements in adults are approximately 2 mg and in infants 100 μg/kg body weight/day. In premature infants, 300 μg/kg body weight/day have been recommended.[8] Ongoing losses through the gastrointestinal tract owing, for example, to intractable diarrhea may increase the intravenous requirement 10-fold.[47] For intravenous administration, zinc chloride is frequently used; 1 mg zinc is equivalent to 2.1 mg $ZnCl_2$.

Toxicity

Acute toxicity is rare but can occur, for example, from the ingestion of large quantities of pharmacologic preparations of zinc or from the consumption of acidic drinks from galvanized cans. Symptoms are usually limited to diarrhea and vomiting, but there may be severe lethargy. Toxicity has also resulted from storage of dialysis water in a galvanized tank. Administration of zinc in quantities of 50 mg/day to adults can cause anemia owing to copper deficiency and may depress plasma high-density lipoprotein cholesterol levels. Even lower doses may impair copper balance.

Absorption and Metabolism

Fractional absorption of zinc averages about 60% when ingested in solution in water but is usually only in the range of 20 to 40% from composite meals or infant formulas. Fractional absorption of zinc from human milk and some synthetic formulas approaches that of zinc absorption when taken with water alone.[55,56] On the other hand, fractional absorption is depressed by certain dietary constituents, notably phytate (inositol hexaphosphate; see next section). Total absorption of zinc is considerably greater than net (apparent) absorption owing to the substantial intestinal excretion of endogenous zinc. The postprandial secretion of endogenous zinc into the intestinal lumen, mainly via the pancreas and the small intestinal mucosa, is greater than fecal excretion of endogenous zinc, and reabsorption of some of this secreted zinc is likely to be necessary if balance is to be maintained.[4] Even with reabsorption, the intestine is the major route for excretion of endogenous zinc. Approximately 0.5 mg/day of zinc is excreted by adults in the urine, and in temperate climates, a similar quantity is lost in the sweat. The intestine has a major role in the maintenance of zinc homeostasis. Higher zinc intake will be accompanied by diminished fractional absorption, but when dietary zinc is limited, intestinal conservation of endogenous zinc appears to have the greatest role in maintaining or restoring zinc balance.[4,63] The ability of the intestine to conserve endogenous zinc may be impaired by a high intake of phytate from vegetable foods and by malabsorption, including cystic fibrosis.[58,64]

Absorption of zinc occurs by a saturable mechanism that is consistent with a carrier-mediated or enzyme-dependent process. There is a rapid initial phase followed by a slower phase that probably involves two different mechanisms. Data from studies in humans suggest that absorption occurs primarily in the proximal small bowel.[4] Mechanisms of absorption of exogenous dietary zinc and of secretion and reabsorption of endogenous zinc at a molecular level remain to be elucidated.[65,66] The metabolism of zinc is complex. About 10% of total body zinc, 100 to 200 mg, intermixes with circulating plasma zinc within 2 days.[67] This zinc is thought to be of special physiologic importance to many of the zinc-dependent metabolic processes in the body, and it is also this zinc that is vulnerable to dietary zinc restriction. This is likely to explain why symptoms of zinc deficiency occur with very little change in total body zinc. It has been found that the quantity of readily exchangeable zinc has a strong positive correlation with dietary zinc and an even stronger correlation with quantity of zinc absorbed.[4,63] A substantial part of this rapidly exchanging zinc, which is thought to be important for many zinc-dependent processes, is located in the liver. Humoral factors that may increase liver uptake include cytokines (interleukin-6), corticosteroids, and glucagon. Interleukin-6 and other cytokines are responsible for the decline in plasma zinc associated with infections.

In the systemic circulation, approximately 75% of the plasma zinc is loosely bound to albumin, and most of the remainder is bound to α_2-macroglobulin. A small fraction is bound to amino acids. The normal zinc concentration in plasma averages about 0.85 μg/mL (13 μmol/L), with a range from 0.70 to 1.00 μg/mL. The zinc concentration in erythrocytes, most of which is incorporated in carbonic anhydrase, is approximately 12 μg/g wet weight. Leukocyte zinc concentrations are higher, with mean literature values of about 100 μg/10^{10} cells. The highest known zinc concentrations are in certain regions of the eye, including the retina. Bone, prostate, and hair all have concentrations near 100 μg/g or even greater. Muscle, liver, and kidney contain about 50 μg/g, whereas the value for heart and intestinal mucosa is 20 to 30 μg/g. The total body zinc content of an adult has been calculated to be about 2 g.[1]

Dietary Requirements

The results of recent studies of breast-fed and formula-fed infants using zinc stable isotope techniques allow reasonably accurate factorial estimates of zinc requirements. The major route of endogenous zinc excretion is via the intestine. In fully breast-fed infants receiving mature human milk, conservation of endogenous zinc is critical to maintaining positive net absorption and averages approximately 50 μg zinc/kg body weight/day.[55] Because the amount of endogenous fecal zinc is positively correlated with dietary zinc intake and absorbed zinc, this figure is considerably higher in formula-fed infants receiving zinc-fortified formulas.[56,68] Allowing 10 μg zinc/kg body weight/day for urine, sweat, and integumental losses, total calculated minimal endogenous losses are 60 μg zinc/kg body weight/day. With an average fractional absorption of approximately 0.5, this figure translates into a dietary zinc requirement of approximately 150 μg zinc/kg/day. Actual zinc intake of breast-fed infants varies considerably over the first 3 months of life as milk zinc concentrations decline. Mean intakes at 5 months of age have been found to be close to

this projected dietary requirement.[69] Retention required for normal growth is approximately 20 μg zinc/g new tissue. In the young infant, the growth requirement may therefore reach 600 μg zinc (ie, approximately 150 μg zinc/kg body weight/day) or more per day, but part of this may be met by hepatic stores acquired in utero.[70] In the older infant and toddler, retention required for normal growth will have declined to approximately 300 μg zinc/day or approximately 30 μg zinc/kg/day. Factorial estimations are higher for rapidly growing premature infants, for malnourished infants during the "catch-up" growth phase, and to compensate for unusual endogenous losses that occur, for example, with diarrhea and malabsorption.

The AI of 2 mg zinc/day for 0 to 6 months is based on the zinc intake of exclusively breast-fed infants at approximately 2 months of age (Appendix 2). This does not imply that lower zinc intakes of exclusively breast-fed infants at 4 to 6 months are inadequate. EARs and RDAs for older infants and children have been calculated by extrapolation from factorial data for infants, as described above, or adults. These RDAs are substantially lower than those in the tenth edition of the RDAs and, in contrast, are based on calculations of requirements that are substantially higher than those published by WHO.[7] Although further research is necessary, they are the best available figures that may well be subject to only minor refinements in the future. In contrast, the Tolerable Upper Intake Levels (Uls) have simply failed to take into account the fact that the majority of North American infants and young children who are not exclusively breast-fed consume substantially more zinc than the Uls, with no detectable evidence of any harm. It is assumed that these aberrant levels will be revised at the first opportunity and, meanwhile, should not alone influence food fortification or zinc supplementation decisions.

Zinc in Foods

The highest concentrations of zinc are found generally in animal products, especially meats; whole grains, nuts, and legumes also contain substantial quantities of zinc, but this is less likely to be bioavailable.[71] The zinc content and bioavailability of typical complementary foods for the older breast-fed infant vary widely.[54] The choices available will strongly influence the risk of deficiency to the older infant.[72] Several ready-to-eat breakfast cereals and some infant cereals are now fortified with zinc as well as iron and other micronutrients. The zinc content of human milk declines by several-fold from colostrum to mature milk. Concentrations are not influenced by maternal zinc intake when dietary intake is generous. Whether this is also true in populations with marginal intake or less favorable bioavailability remains uncertain.[73] Infant formulas and a wide range of special formulas are now routinely zinc supplemented/fortified. An overview of the zinc and copper content of major food items is given in Table 6-5.

COPPER

Copper-dependent redox reactions developed very early in the evolutionary process. Because the earth's atmosphere changed from a reducing to an oxidizing environment, copper, together with iron, has been involved at the active sites of respiratory proteins. A mammalian nutritional requirement for copper was first demonstrated in 1928, and subsequent studies revealed numerous copper-dependent mammalian enzymes. During the 1920s, several reports suggested that copper supplements may have a role in the treatment of some cases of hypochromic anemia in infants and adults, but the occurrence of human copper deficiency failed to achieve recognition until 1964.[74] Since then, copper deficiency has been identified in several special circumstances, but its frequency and the extent of its clinical importance in some conditions remain unclear, for example, in the very low birth weight premature infant.

Although beyond the scope of this chapter, an introduction to copper would not be complete without reference to two inborn errors of copper metabolism, which have attracted more clinical interest than has human copper deficiency. The central role of copper in the pathophysiology of Wilson's disease was recognized in 1945 and of MSHS in 1962. The research stimulated by these inborn errors of copper metabolism has led to a clearer understanding of normal human copper metabolism. It is now recognized that these two conditions represent disruption of copper transport across cell membranes. The two homologous cation-transporting P-type adenosine triphosphatases (ATPases), the Menkes P-type ATPase (MNK) and Wilson ATPase (WND), are the gene products primarily responsible for cellular copper homeostasis. The MNK functions in copper, trafficking to the secretory pathway for efflux from cells, including enterocytes. In Menkes' syndrome, there is reduced copper absorption and placental copper transport. Although the pathophysiology of MSHS is complex, at least some of the principal clinical features can be attributed to a de facto severe copper deficiency state, at least in certain tissues, including the brain. The WND P-type ATPase also functions in copper trafficking to secrete excess copper into the biliary canalicular system. In Wilson's disease, mutations of the WND ATPase result in copper accumulation.[75,76] Hence, recognition of the role of disordered copper metabolism in these diseases has helped to improve our understanding of the effects of severe human copper deficiency and of copper toxicity.[77]

Clinical Features of Copper Deficiency

The principal features of copper deficiency are hypocupremia, a hypochromic, normocytic anemia that is unresponsive to iron therapy, neutropenia, and osteoporosis. The bone marrow shows megaloblastic changes and vacuolization of the erythroid series. Iron deposits may be seen by electron microscopy in mitochondria and in some of the cytoplasmic vacuoles in red blood cell precursors. Maturation arrest of the granulocytic series may be evident. Iron stores in the intestinal mucosa, reticuloendothelial system, and liver cells are increased. The anemia is initially hypoferremic but later becomes hyperferremic because of the decreased uptake of transferrin-bound iron by the developing erythrocytes.

TABLE 6-5 Trace Element Content of Common Foods

Item	*Zinc (mg/100 g)*	*Copper (mg/100 g)*
Meat group		
Regular ground beef	4.4	0.06
Round steak	5.8	0.05
Beef liver	5.1	4.6
Chicken—drumstick, fried	2.7	0.01
Pork chop	2.4	0.01
Bologna, all meat	1.8	0.02
Hot dog, all meat	1.6	0.08
Fish group		
Oyster, raw, Atlantic	74.7	3.62
Perch fillet	1.0	0.21
Tuna—in oil, drained, solids	1.1	0.01
Dairy and egg group		
Whole milk	0.4	0.005
Cheddar cheese	3.1	0.11
American cheese	3.0	0.11
Ice cream, vanilla	1.06	0.005
Eggs, hard-boiled	1.0	0.05
Infant formula	0.5	0.06
Nuts and legumes		
Common beans, cooked (red, kidney, pinto)	0.6	0.25
Peanut butter	2.9	0.61
Roasted peanuts	3.0	0.43
Bread and cereal group		
Whole wheat bread	1.0	0.17
Graham crackers	1.1	0.04
Corn flakes	0.3	0.02
Oatmeal, cooked	0.5	0.02
Macaroni, cooked	0.5	0.02
Rice	0.4	0.02
Vegetable and fruit group		
Green beans, canned	0.3	0.02–0.04
Potatoes, boiled	0.3	0.10
Potato chips	0.8	0.29
Lettuce	0.4	0.04
Apple	0.05	0.01
Banana	0.2	0.11
Orange juice	0.02	0.008

Early radiologic findings are osteoporosis of the metaphyses and epiphyses and retarded bone age. Typical findings in the established case are increased density of the provisional zone of calcification and cupping with sickle-shaped spurs in the metaphyseal region.[78] Other skeletal abnormalities include periosteal layering and submetaphyseal and rib fractures.

Other clinical findings have been observed in association with copper deficiency, especially in premature infants.[79,80] These are pallor, decreased pigmentation of skin and hair, prominent superficial veins, skin lesions similar to those of seborrheic dermatitis, failure to thrive, diarrhea, and hepatosplenomegaly. Features suggestive of central nervous system involvement are hypotonia, lack of interest in outside surroundings, psychomotor retardation, apparent lack of visual responses, and apneic episodes. In MSHS, there is severe and eventually fatal central nervous system involvement owing to disordered copper metabolism within the brain cells, which probably results in localized intracellular deficiencies at physiologically important subcellular sites. Other features attributable to copper deficiency in this complex entity include the hair changes, which are reminiscent of the wool of copper-deficient sheep and which led to the initial recognition of the role of disordered copper metabolism; hypothermia; and evidence of defective elastin and collagen formation.

Copper-deficient animals exhibit a number of characteristics similar to those seen in human ischemic heart disease, for example, hypercholesterolemia, decreased high-density lipoprotein cholesterol, hypercoagulability, and cardiac arrhythmias.[81] Premature ventricular contractions have been linked to copper intake in humans,[82] but this has not been supported by other trials of copper depletion.[83,84] Thus, an association between copper deficiency and ischemic heart disease remains an unproven hypothesis.

Biochemistry and Biochemical Correlates

Copper is an essential component of several oxidase enzymes, the decreased activity of which can explain many of the features of copper deficiency. Cytochrome oxidase is the terminal enzyme in the electron transport chain and catalyzes the oxidation of reduced cytochrome-*c* by molecular oxygen, which is itself reduced to water. This enzyme, which is necessary for normal cellular respiration, has been shown to be markedly reduced in the brains of copper-deficient lambs suffering from swayback. Reduced activity of this enzyme may be responsible for certain other features of copper deficiency, for example, the hypothermia that occurs in MSHS.

More than 90% of the circulating copper in plasma is tightly and specifically bound to ceruloplasmin, a glycoprotein that contains six copper atoms per molecule. The functions of this protein, which was first identified in 1948, have been and continue to be the focus of considerable interest and controversy. Roles in copper metabolism include copper transport, mobilization of iron for transfer in the plasma, and regulation of the biogenic amines.[84] Ceruloplasmin (ferroxidase I) exhibits enzymatic ferroxidase activity and is necessary for the oxidation of ferrous iron stored in the liver and bone marrow to ferric iron. This is an essential step in the release of iron from body stores and its attachment to transferrin for transport to developing erythrocytes in the bone marrow.[85] Aceruloplasminemia, an autosomal recessive condition in humans, does not produce obvious disordered copper metabolism but results in iron accumulation in tissues.[75] There is a second copper-containing enzyme in the circulation, designated ferroxidase II, which may have a role in preventing anemia in Wilson's disease when ceruloplasmin levels are low. Depressed activity of the ferroxidase role of ceruloplasmin is likely to be related to the hypoferremic, hypochromic anemia of copper deficiency. However, there are, in addition, abnormalities of iron metabolism within the erythroid cell line, and it appears that intracellular transport of iron is defective, so that, despite an abnormal accumulation of iron, there is a lack of iron available for normal heme synthesis in the

mitochondria. The pathologic mechanisms for the neutropenia remain unexplained.

The bone lesions of copper deficiency are attributable, at least in part, to a lack of copper-dependent amino oxidases or, more specifically, lysyl oxidase, which is required in the cross-linking of collagen. Similar oxidases are necessary for this cross-linking of elastin, defects that are responsible for the gross structural defects seen in arteries and veins in copper-deficient animals and in MSHS. Lysyl oxidase catalyzes the oxidative deamination of ε-amino groups of lysine, which are necessary for the synthesis of desmosine, which, in turn, is essential for the cross-linking bonding of elastin.

Among other copper-containing oxidases is tyrosinase, which catalyzes the first two steps in the oxidation of tyrosine to melanin. Lack of pigmentation is a prominent feature of copper deficiency in some species but is only mild in human copper deficiency. Superoxide dismutase contains two copper atoms and two zinc atoms. Copper proteins previously given other names such as cerebrocuprein, hepatocuprein, and erythrocuprein are now known to be superoxide dismutase, which catalyzes the dismutation of superoxide-free radical ions:

$$O_2^- + O_2 + 2\ H^+ \rightarrow O_2 + H_2O_2$$

Detoxification of dangerous free radicals within the cell is of the greatest importance, but little is known about the activity of this enzyme in human copper deficiency states and what role decreased activity may play in the pathophysiology of copper deficiency.

Etiologic Factors in Copper Deficiency

The first cases of human copper deficiency were reported in infants and children in Peru who were recovering from protein-energy malnutrition.[86] Prior to their initial hospitalization, the infants had long histories of inadequate nutrition, which consisted mainly of diluted milk. Cow's milk is a relatively poor dietary source of copper, and copper deficiency has been reported in otherwise healthy infants whose diets have consisted primarily of unmodified cow's milk.[87] Frequent episodes of diarrhea were thought to contribute to the copper loss in the malnourished infants, although the diarrhea may have resulted in part from the copper deficiency state. Symptoms of copper deficiency did not usually appear until late infancy, when the child was recuperating from the protein-energy malnutrition but receiving a milk-based diet relatively low in copper. Neonatal stores of copper would have been dissipated by this age. In a retrospective analysis of these data, it was concluded that about one-third of the malnourished infants were copper deficient, including 25% who were deficient on admission.[86] Copper deficiency in association with malnutrition is not limited to Peru and is probably not uncommon. For example, copper supplementation was associated with improved growth rates in copper-deficient Chilean infants recovering from malnutrition.[88]

The term infant accumulates substantial hepatic stores of copper, which is attached to metallothioneine during the last 3 months of gestation. These stores are released postnatally and are thought to ensure protection of the young infant against copper deficiency. Very low birth weight infants born prematurely do not have the benefit of these stores and have very little copper at birth.[89] Although premature infants are at risk for copper deficiency, positive copper balance is apparently achieved in early postnatal life in premature infants with current fortification of human milk and formulas, although the adequacy of retention is not yet clear.[51,90] Symptomatic copper deficiency was documented in formula-fed premature infants in the early 1970s, a time when cow's milk formulas in the United States were not supplemented with copper, at least to the extent that is customary today.[79,80,90] The copper content of unmodified cow's milk is usually lower than that of human milk, and levels may be further decreased during processing. The incidence of copper deficiency in very low birth weight infants has been substantially reduced by the routine use of copper-fortified premature infant formulas.[91] The extent to which a mild deficiency contributes to osteoporosis, anemia, and to otherwise unexplained neutropenia in this population is unknown.[90]

Copper deficiency has been observed during intravenous feeding in both infants[92] and adults. Other causes of human copper deficiency include intestinal malabsorption syndromes, chronic diarrhea, and chelation therapy. Symptomatic copper deficiency has also been reported in normal infants who were fed primarily unmodified cow's milk and who developed severe anemia, neutropenia, and bone changes at the age of 6 months.[87] High intakes of zinc and possibly iron can precipitate a deficiency of copper.[90,93] Human copper deficiency has been documented in an infant and in adults who have received high doses of zinc therapy.

Diagnosis of Copper Deficiency

Both plasma copper and ceruloplasmin levels are depressed in copper-deficiency states. Unfortunately, these parameters are also influenced by other factors, some of which are likely to be operative when the possibility of copper deficiency is considered. Ceruloplasmin synthesis is limited in the liver of the term neonate, and neither serum copper nor ceruloplasmin concentrations reach adult levels until at least 1 month of age. In the very low birth weight infant, copper concentrations are even lower, averaging about 0.30 to 0.40 μg/mL, and do not start to increase until 41 weeks of gestational age.[94] It has been suggested that concentrations lower than 0.25 μg/mL may be abnormal in the young preterm infant and may be associated with neutropenia.[90,94a] However, the interpretation and value of the data on serum copper levels prior to 40 to 44 weeks of gestational age remain uncertain. By 6 months of postnatal age, serum copper and ceruloplasmin concentrations are similar to, or higher than, adult levels.[95,96]

Ceruloplasmin synthesis in the liver may be reduced in protein-energy malnutrition, and protein-losing enteropathy is associated with losses of ceruloplasmin, both situations leading to low circulating levels of ceruloplasmin and copper in clinical circumstances requiring assessment of copper status. Hypocupremia is also a feature of both Wilson's disease and MSHS.

Copper deficiency can also be difficult to confirm by laboratory assays when there is an increase in synthesis of ceruloplasmin. Ceruloplasmin is regarded as an acute-phase reactant and is elevated in stress situations and in response to inflammatory stimuli. Hence, hypercupremia occurs, for example, in association with infections, in the postoperative period, and in patients with neoplasms. Several hormones cause hypercupremia, most notably estrogens, and levels are increased substantially throughout pregnancy and for several weeks postpartum. Hypercupremia also occurs in obstructive liver disease owing to failure of the normal biliary excretory mechanisms.

Erythrocyte superoxide dismutase (ESOD) has been investigated as an index of copper status and has been reported to be an early indicator of disturbed copper metabolism. Its activity seems to be stable across age and sex categories and with hormonal therapy.[82] In infants recovering from protein-energy malnutrition, copper supplementation was associated with a significant rise in ESOD as well as plasma copper and ceruloplasmin concentrations.[97] Significantly lower ESOD activities were reported in preterm infants supplemented with iron from approximately 4 weeks through 20 weeks postnatal age, but there was no effect on plasma copper or zinc concentrations, hematologic indices, or growth parameters.[93]

Radiologically, separation of the epiphyses, an absence of metaphyseal fraying, and the increased density of the provisional zone of calcification may all help to distinguish copper deficiency from rickets. In contrast to scurvy, copper deficiency does not produce either a lucent line beneath the increased density of the provisional zone of calcification or a "corner sign," nor does it cause hemorrhages.

The diagnosis of copper deficiency should be considered in the presence of suggestive etiologic circumstances, particularly when there is a hypochromic anemia unresponsive to iron therapy. If the anemia is accompanied by neutropenia and osteoporosis, together with low ceruloplasmin or plasma copper levels, the diagnosis becomes likely. Confirmation will be provided by a prompt response to copper therapy with a reticulocytosis and increases in circulating neutrophils and in ceruloplasmin or plasma copper levels.

Treatment of Copper Deficiency

Nutritional copper deficiency in infants has been treated successfully with 2 to 3 mg/day of copper sulfate as a 1% solution, which provides 400 to 600 μg of copper. Maintenance requirements for copper during intravenous nutrition are 0.5 to 1.0 mg/day for adults; as little as 20 μg/kg/day appears to be adequate for infants.[8] Although higher quantities may be required to achieve a positive balance, there is concern that the immature liver of the premature infant may be prone to cholestasis and thus to hepatotoxicity from intravenous copper.

Toxicity

Copper toxicity has resulted from the accidental or deliberate ingestion of excess copper, hemodialysis with copper-contaminated solutions, and absorption of topically administered copper salts. Acute poisoning by the oral route causes a metallic taste, nausea, epigastric pain, green-blue vomitus, and diarrhea. Jaundice and hepatomegaly may occur 2 to 3 days later. Laboratory parameters are indicative of hepatic injury, and there is histologic evidence of centrilobular necrosis and biliary stasis. Jaundice may also result from intravascular hemolysis caused by free copper ions, which also cause hematuria and a direct renal tubular toxic effect, leading to oliguria and anuria. Copper salts may have a cardiotoxic effect, which is responsible for the hypotonia and coma seen in severe cases. Chronic copper poisoning is a rare entity that has been associated with drinking water with a high copper content. Indian childhood cirrhosis, a liver disorder associated with greatly increased hepatic copper concentration, has been attributed, in some instances, to copper contamination of animal milk that was introduced at an early age—milk that had been in contact with brass vessels.[98–100] Acrodynia and cirrhosis have both been attributed to chronic copper poisoning. A concentration of 2 mg/L in potable water has been recommended as safe for infants without causing gastrointestinal symptoms,[101] and this level has been provisionally endorsed by WHO.[102] However, higher levels (8 mg/L) in drinking water have not been associated with apparent toxicity, suggesting that copper intake may be only one of several factors for the expression of these diseases.[103]

Absorption and Metabolism

Approximately 35% of ingested copper is absorbed in the stomach and upper small intestine. The percentage of absorption is inversely related to the quantity ingested and is increased in copper deficiency states. The percentage of absorption also depends on the dietary form and on other dietary constituents. Absorption from human milk is favorable compared with that from cow's milk or from cow's milk–based or soy-based infant formulas. Studies using stable isotopes demonstrated a 40% absorption of copper in formula-fed premature infants, whereas absorption from human milk was approximately 70%. Studies in animal models have reported a range of copper absorption from infant formula, from 25 to 70%.[90] The wide range likely reflects the technical difficulty of accurate determinations with isotope techniques for copper.[90] Zinc, iron, cadmium, calcium, sulfate, and molybdenum will interfere with copper absorption if given in sufficient quantities. In contrast to other trace elements, cellulose and phytate have not been found to have marked effects on copper absorption.[104]

Absorbed copper passes through the portal circulation attached to albumin and is taken up by the hepatocytes. Copper may then be used by the hepatocytes for the synthesis of cuproproteins, especially ceruloplasmin, which is released 3 days later into the systemic circulation. Excess copper is excreted by the bile. Ceruloplasmin copper accounts for 90 to 95% of the circulating copper in plasma. The possible functions of this controversial cuproprotein have been discussed above. The remainder of the copper in plasma is bound to albumin and to amino acids. Copper bound to amino acids is thought to be important for uptake by cells in other organs, but ceruloplasmin copper may also be available for this purpose. The highest copper

concentrations are found in the liver, brain, heart, and kidneys. Because of their large mass, bone and muscle contain 50% of the body copper, whereas the liver contains only 10%. The liver of full-term infants contains 200 to 400 μg of copper/g of dry weight, which is 10 to 20 times the adult concentration (12 to 48 μg/g dry weight). Forty percent of neonatal hepatic copper occurs in the lysosomes attached to metallothioneine. In contrast to liver copper, brain copper increases twofold from birth to adulthood. The highest concentrations are in the locus ceruleus of the brainstem and in the cortical gray matter. In erythrocytes, the copper concentration is similar to that of normal plasma (75 to 120 μg/dL). This copper concentration remains stable; 60% is associated with superoxide dismutase. The total copper content of an adult man is approximately 75 mg.

Dietary Requirements

Earlier, minimal estimates of copper requirements for older children and adults were 2 mg/day, and most diets were thought to contain at least this quantity. The most recent EAR, based on studies in normal adults under experimental depletion conditions, was set at 700 μg/day for adult men and women. The RDA was set at 900 μg/day. Most recent national survey data indicate that median copper intakes for men and women are 1.0 to 1.6 mg/day. Six RDAs were established for children by extrapolation from the adult EAR; these are given in Appendix 2.

The young term infant is protected from copper deficiency by hepatic stores accumulated in utero. Moreover, the term infant usually achieves a positive copper balance by 1 week of age or a little later. The Food and Nutrition Board has recommended a daily copper intake of 200 μg/day (30 μg/kg/day) for infants 0 to 6 months of age and 220 μg/day (24 μg/kg/day) for infants 7 to 12 months.[6] The estimated dietary requirement of the very low birth weight premature infant is approximately 100 μg/kg/day of copper.[90]

Food Sources

The richest sources of copper are oysters, followed by nuts, liver, kidney, corn oil, margarine, and dry legumes. The contribution of drinking water to the total copper intake varies with the type of piping and the hardness of the water. Information on the copper content of food items remains inadequate for optimal calculations of dietary intakes.

Infant formulas in North America now contain a minimum of 60 μg/100 kcal of copper, and those designed specifically for the premature infant contain substantially higher quantities, with a recommended range of 100 to 250 μg/100 kcal.[90] However, on a worldwide basis, there is still considerable variation in the copper content of infant formulas, and some contain higher quantities. Unprocessed cow's milk contains about 150 μg/L of copper, which is lower than that usually found in human milk (200 to 600 μg/L of copper) at any stage of lactation.[95,105]

SELENIUM

Interest in the toxicity of selenium in mammals developed in the 1930s with the discovery of both acute and chronic forms of selenosis among grazing animals in Nebraska and Wyoming. The proved toxicity of selenium in animal husbandry in "natural" circumstances (in seleniferous areas) has resulted in extreme and only partially justified caution in adding selenium supplements to diets that are low in selenium. A beneficial role for selenium was not demonstrated until 1957, when selenium supplements were found to protect against liver necrosis in rats fed certain diets. The following year, selenium deficiency was shown to cause naturally occurring muscular dystrophy in lambs and calves, a problem that occurs in many areas of the world. The early nutritional studies indicated that there was a close association between selenium and vitamin E. In 1973, selenium was shown to be an integral component of glutathione peroxidase, an enzyme that destroys peroxides.[106] Although other selenoproteins have been identified, it is only recently that the metabolic role of a second selenoprotein has been identified. This is type 1 iodothyronine 5′ deiodinase enzyme, which is partially responsible for conversion of T_4 to T_3 in the liver.[107] Experimentally, selenium restriction has been shown to cause hypothyroidism.

Although low selenium states have been recognized in certain populations, notably in New Zealand,[107a] for many years, it was not until the 1970s, when a geochemical deficiency of selenium in a large area of China was recognized as the major etiologic factor in Keshan disease (KD), that the clinical importance of human selenium deficiency was unequivocally demonstrated. Similar individual cases, as well as skeletal myopathies, have since been identified in North America and elsewhere, although less well-characterized milder selenium deficiency syndromes have also been reported. An RDA for selenium was included for the first time in the tenth edition of the RDAs published by the National Academy of Sciences, and this has recently been revised.[6]

Clinical Features and Etiology of Selenium Deficiency

KD is an endemic cardiomyopathy affecting children and women of childbearing age. The disease, named for a county in northeastern China, has a clear-cut geographic distribution in a broad area of China from the northeast to the southwest, an area in which the selenium content of food staples has been shown to be exceptionally low.[108] A series of controlled selenium supplementation studies was associated with an 80% reduction in the incidence of KD, whereas the mortality of identified cases was only 1% of that of untreated children.[109] Some of the etiologic circumstances of KD have not been explained clearly. The seasonal and annual fluctuations in KD have raised the possibility of an interaction between nutritional state and an infectious etiology. The recognition that selenium deficiency increases the cardiovirulence of coxsackievirus in animal models by changing the viral genome sequence is particularly intriguing.[110] Further supportive evidence is the isolation of coxsackievirus from patients with KD in the selenium-deficient area of China, although not all serotypes are equally pathogenic.[111] More studies will be required to determine whether the observations in animal

models are relevant to humans with KD. However, the primary role of selenium deficiency and the public health benefits of selenium supplementation in prevention of KD have been established convincingly.

The main pathologic feature of KD consists of multiple focal areas of myocardial necrosis. Presentation may be acute, with heart failure, arrhythmias, and cardiogenic shock, or chronic, with cardiomegaly with or without congestive failure. Electrocardiographic features include low-voltage ST-T wave changes, right bundle branch block, or complete atrioventricular block. Serum selenium levels in KD are extremely low, typically less than 10 μg/L. Other laboratory indices are correspondingly low.[112]

Long-term total parenteral nutrition devoid of selenium supplements can also cause severe selenium deficiency with cardiomyopathy or skeletal myopathy.[112–114] Some of these and other case reports have involved children.[115]

Kashin-Bek disease (KBD), a degenerative osteoarthropathy named for two investigators who studied patients in Siberia in the nineteenth century, has a geographic distribution similar to that of KD within China. KBD is an endemic osteoarthropathy involving children aged 5 to 13 years. The disease is characterized pathologically by degeneration and necrosis of multiple articular cartilages and growth plates, causing enlargement especially of fingers, toes, and knees and shortened extremities. Disabilities are typically permanent. Millions of people are likely to be affected with KBD. The relationship between selenium deficiency and KBD is unclear, but evidence from epidemiologic studies suggests that selenium and iodine deficiencies may interact to cause the condition. Deficiencies of both of these trace elements often coexist in geographic regions, including China and central Africa. In Tibet, a comparison of those with and without KBD showed selenium deficiency in both groups, but iodine deficiency was more severe in those with KBD.[116]

Although our current understanding of the changes in thyroid hormone metabolism with selenium deficiency has resulted principally from animal studies, observations in human populations are accumulating. For example, in goitrous children, the severity of selenium deficiency predicted the response to iodine supplementation, both with respect to reduction in thyroid size and to improved biochemical measures of thyroid function.[117] Limited data from observational studies suggest a possible sex difference in the interaction of selenium and iodine on thyroid function, but this clearly requires additional testing under controlled conditions. Impaired T_4 conversion to T_3 and low regulation of T_3 production have been reported in children with phenylketonuria (PKU) who were fed a phenylalanine-restricted diet that was also low in selenium,[118] but this has not been found consistently in children with PKU, even those with evidence of selenium deficiency and compromised antioxidant status.[119]

Moderately depressed levels of erythrocyte glutathione peroxidase activity, hair selenium, serum selenium, or blood selenium have been found in association with protein-energy malnutrition in developing countries and in low birth weight infants.[120] One report found significantly lower selenium levels in Malawian children with kwashiorkor who had congestive heart failure compared with those who did not develop this complication.[121] The clinical significance of these low selenium states remains unresolved. Milder degrees of selenium depletion, notably those associated with low dietary levels in New Zealand and certain other geographic areas, do not appear to be associated with any adverse clinical consequences. However, subtle chronic effects cannot be entirely ruled out at this time. For example, there have been case reports of children on long-term parenteral nutrition[122] or synthetic oral diets[123] without selenium supplements who had macrocytosis and loss of hair pigment, both of which normalized following selenium supplementation.

Interest in selenium in adult and pediatric patients with human immunodeficiency virus (HIV) has been prompted by observations suggesting an ameliorating role in the pathophysiologic processes of this infection. The effects seem to be mediated by its antioxidant effects as well as inhibition of viral replication.[124] In HIV-positive pediatric patients, low plasma selenium levels were an independent predictor of mortality and faster disease progression.[125]

Biochemistry and Metabolism

Several selenium proteins have been identified, but only two of these have an established physiologic role: glutathione peroxidase and iodothyronine deiodinase (ID). Selenium is an essential component of cellular glutathione peroxidase (GPx), its plasma homologue, and the membrane-bound phospholipid-hydroperoxide GPx. Glutathione peroxidase uses two molecules of reduced glutathione to reduce hydrogen peroxide and convert it to two molecules of water. This enzyme also catalyzes the reduction of fatty acid hydroperoxides to hydroxy acids in the tissues and thus helps to protect the lipids in cell membranes from peroxidation. GPx is present in a wide variety of tissues and accounts for 90% of the selenium in erythrocytes. Messenger RNA levels of liver GPx decrease with dietary selenium restriction.[126]

ID I has been identified as a selenoenzyme. This enzyme catalyzes the conversion of T_4 to T_3 in the liver and other tissues. Selenium, as selenocysteine, is an integral component of ID, and its expression is influenced by dietary selenium. This enzyme provides the link between iodine and selenium because both are involved in thyroid hormone production.

Absorption of selenium depends to some extent on its chemical form. Selenomethionine is better absorbed than inorganic forms of selenium. Intestinal absorption of food selenium is as high as 80%. Selenium homeostasis in the rat is controlled by the kidney, and the principal route of excretion in humans is the urine. The total body selenium content is estimated to be about 6 mg in the New Zealand adult but is probably higher in areas with higher environmental levels.[127] The highest concentrations are found in liver, tooth enamel, and nails. In the body, selenium is intimately associated with specific proteins, especially as selenocysteine. More than 80% of the selenium in the rat is present as selenocysteine.

Diagnosis and Treatment of Selenium Deficiency

Selenium depletion is associated with low levels of selenium in whole blood, plasma, and hair and low erythrocyte GPx activity.[128] Care must be taken, however, to distinguish between selenium-dependent and -independent activity. A strong positive correlation between erythrocyte GPx activity and whole blood selenium levels has been found in some populations. However, it is not yet clear how well these indicators may correlate with clinical features of selenium deficiency. Remarkably, low blood selenium levels in New Zealand are not associated with any apparent deficiency symptoms.[127]

The optimal treatment for selenium deficiency has not been determined. Currently, there are no clear-cut indications for oral selenium therapy apart from the prevention of KD, for which a weekly supplement of 500 μg in younger children and 1,000 μg in older children appears to suffice. On a daily basis, these quantities are somewhat above the RDA recommended by the Food and Nutrition Board.[6]

Selenium supplements should be added routinely to intravenous infusates, at least for those patients who receive a substantial portion of their nutrient intakes by the intravenous route for more than 2 weeks. The dose recommended is 2 μg/kg body weight/day.[8]

Toxicity

Although excess selenium can cause undesirable consequences in agriculture, chronic selenium toxicity does not appear to be a problem in humans. Blood selenium levels are elevated in children living in seleniferous areas of Venezuela, but the only clinical findings were the somewhat poorly defined ones of nausea and pathologic nails.[129] Loss of hair, brittleness of fingernails, garlic odor, a higher incidence of dental caries, and increased fatigue and irritability were reported to be signs of selenosis in an early survey of residents of South Dakota, where selenium toxicity occurred in farm animals. Urinary selenium excretion was elevated in these people.

Acute selenium poisoning is rare in humans but has been reported as a result of self-administration of selenium supplements. The outcome of acute toxicity appears to depend on both the amount ingested and the type of selenium compound. Acute ingestion of sodium selenite caused garlic odor on the breath and diarrhea in several cases. Evidence of mild, temporary liver damage and cardiac abnormality was seen in one case,[130] but there were no permanent sequelae.

The highest selenium concentration observed in human milk in the United States, 60 μg/L, was used as the basis for the "no observed adverse effect level" in the 2000 DRIs,[6] and the DRI upper limit was set at 45 μg/day (7 μg/kg) for term infants 0 to 6 months. This amount was used parenterally in a supplementation trial of very low birth weight infants until the infants advanced to enteral feeds, at which time they received ~ 5 μg/kg until 36 weeks postmenstrual age, with no apparent adverse effects.[131]

Dietary Requirements

Dietary surveys of selenium intake in endemic and adjacent nonendemic KD areas have led to the conclusion that selenium requirements for adult Chinese men and women are 19 and 13 μg/day, respectively.[132] This is the quantity calculated to be necessary to prevent KD. RDAs in this country have been set at 55 μg selenium/day for adult men and women.[133]

An AI was established for infants in 2000, recommending 15 μg/day (2.1 μg/kg/day) for infants up to 6 months of age, based on a mean selenium concentration of 18 μg/L in human milk and an average intake of 780 mL/day. The AI for older infants and young children (7 to 36 months) is 20 μg/day, for older children (4 to 8 years) 30 μg/day, and for adolescents 40 to 55 μg/day.[6] These recommendations have been extrapolated for adults with a generous addition for growth; actual requirements are substantially less. The intake of formula-fed infants prior to weaning has generally been 4 to 5 μg selenium/day in this country. Although higher intakes are desirable, there is no evidence that any harmful effects have resulted from this relatively low selenium intake.

Food Sources

The selenium content of human milk depends on maternal dietary selenium intake. Extremely low values, that is, less than 3 μg selenium/L, have been reported from areas where KD is endemic.[90] Concentrations between 5 and 10 μg selenium/L have been reported from other countries where maternal selenium intake is relatively low (eg, New Zealand, Finland, and Poland).[134,135] In the United States, the mean value for the selenium content of human milk is approximately 18 μg selenium/L.[90]

The selenium content of cow's milk is generally lower than that of human milk in this country. The selenium content is reduced in the preparation of cow's milk–based infant formulas. The minimum for standard infant formulas was recommended to be 1.5 μg/100 kcal.[136] Whether the low plasma selenium and GPx levels in low birth weight infants are increased by providing generous selenium supplementation of formulas has been controversial,[137] and feeding regimens that have provided amounts adequate to increase biochemical markers of selenium status in low birth weight infants have not demonstrated clear clinical benefit. Nevertheless, premature infants are born with strikingly low serum selenium levels and GSPx, and, without supplementation, these levels decline further.[131] An expert panel recently recommended a minimum concentration in formulas for preterm infants of 1.8 μg/100 kcal and a maximum of 5.0 μg/100 kcal, while acknowledging that it was unknown whether the lower amount would be adequate or optimal for preterm low birth weight infants.[90]

Concentrations of selenium in foods vary with geographic region and soil content.[138] Generally, seafoods (approximately 0.5 μg/g), kidney, liver, and meats (approximately 0.2 μg/g) are the best sources of selenium.[139] Whole grains are also generally good sources of selenium provided that the soils in which they are grown are not low in selenium. Vegetables and fruits, with the exception of garlic, provide little. Daily intake in North America has been reported to range from 60 to 220 μg/day,[138] but in New Zealand, intake is only 6 to 35 μg/day.

CHROMIUM

A role for chromium in mammalian physiology was indicated first in 1959, when it was reported that trace amounts of this element are necessary for normal glucose tolerance in the rat. Subsequent research suggested that chromium acted as a cofactor for insulin.[140] These observations stimulated considerable interest in a possible role for chromium deficiency in the high incidence of impaired glucose tolerance in industrialized societies. Progress has been hampered, however, by a lack of laboratory indices of chromium status that would be of the greatest value in identifying appropriate subjects to include in clinical trials of chromium supplementation.

Clinical Features and Etiology of Chromium Deficiency

Experimental chromium deficiency in several animal species has been reported to result in impaired glucose tolerance in the presence of normal concentrations of circulating insulin. Features of chromium deficiency have been reported to include impaired glucose tolerance with relative insulin resistance and peripheral and/or central neuropathy. Weight loss and poor childhood growth have also been reported.

In the pediatric age range, chromium supplementation studies have been undertaken in infants and young children suffering from protein-energy malnutrition. The results of these studies, which involved the use of a single oral dose of 250 μg trivalent chromium, suggested that chromium deficiency may be one factor responsible for the impaired glucose tolerance that occurs in association with severe generalized malnutrition. Chromium deficiency appears to complicate protein-energy malnutrition in some but not all geographic areas. Turkey is notable among countries in which studies have been performed.[141] Chromium deficiency has also been reported to limit weight gain during recovery from malnutrition in Turkish infants.[142] Lack of controls in some studies and limited subject numbers hamper definitive interpretation of these data.

Several trials of chromium supplementation have been reported in adults, including elderly subjects.[143] Most of these trials have been small. Subjects have included non–insulin-dependent diabetic patients and otherwise normal subjects with evidence of impaired glucose tolerance. Supplements have always been trivalent chromium, on some occasions as an inorganic salt and on others as brewer's yeast or in other forms that are thought to have favorable absorption. In several studies, chromium supplementation has been associated with improved glucose tolerance in more than 50% of the chromium-supplemented subjects. Other apparent effects noted in some studies include a decrease in insulin response to an oral glucose load, a decrease in total blood lipids, and an increase in high-density lipoprotein cholesterol. A meta-analysis of chromium supplementation trials reported for healthy individuals and in those with glucose intolerance or type 2 diabetes found no effect of chromium on glucose or insulin concentrations in nondiabetic subjects, whereas the results from trials in diabetic subjects were inconclusive.[144]

Chromium deficiency has also been reported in patients receiving long-term parenteral nutrition.[145] Clinical features attributed to the chromium deficiency were weight loss, peripheral neuropathy, and encephalopathy. An abnormally low removal rate of intravenous glucose and an abnormally low respiratory quotient indicating difficulty in metabolizing glucose for energy, dependence on exogenous insulin, and abnormalities of nitrogen and lipid metabolism all responded rapidly to intravenous chromium.[145]

Biochemical Correlates

Although chromium may have several physiologic roles, for example, in nucleic acid metabolism, the role that has received most attention is its action as a cofactor for insulin. Experimental evidence is consistent with the hypothesis that chromium acts as a cofactor for insulin at the site of peripheral insulin receptors. Specifically, it has been hypothesized that a low molecular weight chromium-binding substance facilitates the initial attachment of insulin to its receptors both at the cell membrane and intracellularly.[146] Chromium may have to be in the form of a biologically active organic compound, termed glucose tolerance factor (GTF), to exert this physiologic effect or at least to exert an optimal effect. GTF is thought to be a nicotinic acid, amino acid, chromium compound. The biologic role of chromium as a cofactor for insulin requires further clarification and confirmation.

Diagnosis of Chromium Deficiency

The lack of established laboratory assays is especially evident for chromium, and deficiency states can be confirmed currently only by means of careful monitoring of the effects of chromium supplementation under controlled conditions. Normal values in such samples as blood plasma and urine have had a disconcerting tendency to fall as analytic techniques improve so that they remain near the detection limits of the equipment available at any particular time. Currently, normal levels for plasma chromium, for example, are considered to be only about 0.1 parts per billion (100 pg/mL). This means that it continues to be extraordinarily difficult to measure low values accurately. An additional difficulty in interpretation results from uncertainties about the physiologic meaning of low chromium levels. For example, it is thought that solitary plasma chromium levels do not reflect body chromium status but only recent intake. However, low plasma chromium levels have been reported in chromium-deficient subjects,[145] in pregnant women,[147] and in association with experimental infections that cause impaired glucose tolerance.[148] There have been conflicting reports about a measurable increase in plasma chromium in response to a glucose load. At best, this is a tedious and difficult test for assessing chromium status. Absence of a detectable plasma chromium "response" has been reported in some diabetic patients, including gestational diabetic patients, and in some elderly people. An inverse correlation has been reported between the postprandial increase in plasma chromium and fasting blood glucose. Hair analyses provide only a crude index of chromium status. Theoretically, urine

chromium levels, perhaps including measurement of the increase in urine excretion following a glucose load, should provide a useful index of chromium status. To date, however, this approach has not proved to have any conclusive value. Excessive urine chromium losses have been noted in diabetic patients, and it has been suggested that the low chromium content of adult American tissues could result from excessive urine losses triggered by a diet high in sucrose. Confirmation of excessive chromium losses during the consumption of such diets is lacking. In summary, chromium measurements in tissue and body fluids are of no proven value in the diagnosis of chromium deficiency even if adequate laboratory facilities are available.

Treatment of Chromium Deficiency

Suspected chromium deficiency states can be treated with 200 μg of trivalent chromium daily for several weeks or months in adults. In malnourished children, a single dose of Cr^{3+} 250 μg has been effective. Current recommendations for chromium during parenteral nutrition are 10 to 15 μg/day for adults or 0.1 to 0.2 μg/kg body weight/day for infants and young children. Levels considerably lower than this are probably adequate and may be preferable.

Toxicity

Trivalent chromium has a low toxicity, and there are no reports of toxicity from oral administration. The minimum lethal dose of intravenous chromium as chromic chloride in mice is 800 mg/kg. Hexavalent chromium is more toxic, but 100 parts per million in drinking water can be tolerated by animals for many years. Chromate is a local irritant and is a cause of acute and chronic disease of the respiratory system, including bronchogenic carcinoma in workers in the chromate industry.

Plasma chromium concentrations have been reported to be elevated in patients receiving total parenteral nutrition, including standard quantities of intravenous chromium, who develop evidence of renal disease.[149] Chronic interstitial nephritis has been associated with ingestion of chromium picolinate as a dietary supplement.[150,151] It has been suggested that the renal disease is a result of chromium toxicity, although animal studies have not confirmed such toxicity.[152] It is also possible that the elevated plasma chromium levels are secondary to impaired chromium excretion via the kidneys. It appears prudent to reduce or withhold intravenous chromium supplements in the presence of renal disease.

Absorption/Metabolism

Inorganic trivalent chromium is absorbed poorly. Absorption of ^{51}Cr-labeled chromium chloride is limited to approximately 0.5%. A larger percentage of chromium is thought to be absorbed from organic chromium complexes found, for example, in brewer's yeast. Chromium picolinate has been marketed aggressively with claims that it is well absorbed and has some special beneficial metabolic effects, but documentation of these claims is poor. It is thought that the liver may be the site of a specific pool of biologically active chromium and that GTF chromium is released from this pool in response to a glucose load. This response may be mediated by the response of endogenous insulin. GTF has been reported to be the only form in which chromium can cross the placenta to the fetus. The major excretory route for chromium is through the kidney, and the urine contains at least 80% of excreted chromium. The total body chromium content of adults has been estimated to be about 6 mg.

Dietary Requirements and Food Sources

Dietary chromium intakes for adults in the United States range from 25 μg/day for women to 50 μg chromium/day for men. The estimated AI for dietary chromium intake for adults set by the Food and Nutrition Board is 35 μg/day for men and 25 μg/day for women.[6] The AI recommended for infants 0 to 6 months is 0.2 μg/day and 5.5 μg/day for infants 7 to 12 months. The large increase in the second half of the first year of life reflects the contribution of complementary foods. The AIs for children and adolescents range from 11 to 35 μg/day.[6]

The mean chromium concentration of breast milk is approximately 0.25 μg/L.[153] Hence, the intake of the breast-fed infant would be about 0.2 μg/day. The bioavailability of this chromium may be high by comparison with that of other trace elements, but this has not been determined. Concentrations of chromium in cow's milk and infant formulas have been reported to be higher than those in human milk.[154]

Spices, brewer's yeast, liver, and kidney are especially good sources of chromium, but only small quantities are present in fish, vegetables, and fruit. Major losses of chromium have been reported during milling of wheat and refining of sugar, but stainless steel cooking containers may add to the chromium intake. Calculations of chromium in food have undoubtedly varied, depending on methods of sample preparation and analyses. Moreover, absolute quantities may not be as important as the form in which the chromium is present in foods.

MOLYBDENUM

The first evidence of a biologic role for molybdenum was obtained in 1930, when it was shown to be necessary for the growth of a microorganism. In 1938, the drastic scouring disease of cattle known as "teart" was traced to molybdenum poisoning. A physiologic role for molybdenum in mammals was demonstrated in 1953, when xanthine oxidase was discovered to be a molybdenum-containing metalloenzyme.[6] Experimental molybdenum deficiency in animals is difficult to achieve but has been reported in goats and lambs. Because of the difficulties of deliberately inducing molybdenum deficiency experimentally, human deficiency of this trace element was thought to be unlikely.

Clinical Features and Biochemical Correlates of Molybdenum Deficiency

The features of human molybdenum deficiency can be correlated with the known biochemical functions of this trace element. Four molybdoenzymes have been identified in

animals. The role of molybdenum in the activity of these enzymes is linked to the fact that molybdenum readily changes its oxidation states and can thus act as an electron transfer agent in redox reactions. Xanthine oxidase is best known for its role in purine metabolism, oxidizing hypoxanthine to xanthine and xanthine to uric acid. Xanthine dehydrogenase is nearly identical in structure and function except that it uses nicotinamide-adenine dinucleotide as a hydrogen acceptor, whereas xanthine oxidase uses molecular oxygen. Apparently, there is interconversion between these two molecules. Sulfite oxidase oxidizes reduced sulfur to $(SO_4)^{2-}$. Relatively little is yet known about the fourth molybdoenzyme, aldehyde oxidase.

One case of human molybdenum deficiency has been described in a patient receiving prolonged intravenous nutrition.[155] This patient was intolerant of intravenous amino acids, especially L-methionine. Clinical features include tachycardia, tachypnea, central scotomata, night blindness, and irritability leading to coma. The symptoms disappeared when intravenous amino acids were withheld. The same symptoms could be elicited by infusion of sodium bisulfite, a preservative used in the amino acid solution, but amino acid infusates without bisulfite as a preservative produced similar features. The clinical features of the disease were associated with high plasma methionine levels, low urinary inorganic sulfate, and a high level of thiosulfate in the urine. Low serum uric acid and hypouricosuria were also observed. There was rapid clinical and biochemical improvement following the addition of ammonium molybdate (300 μg/day) to the intravenous infusate.

Apart from this one case of acquired human molybdenum deficiency, there have been case reports of individuals, including children, with congenital deficiencies in both sulfite and xanthine oxidase activity.[156] Molybdenum levels in the blood were normal, but there was no detectable molybdenum in the liver. More than 50% of molybdenum in the liver is in the form of a nonprotein cofactor containing "active" molybdenum, which has to be bound to the apoprotein of xanthine or sulfite oxidase before these enzymes are active. These children, who had severe neurologic abnormalities, appeared to have an inability to synthesize active molybdenum cofactor.

Metabolism and Diagnosis of Molybdenum Deficiency

Molybdenum absorption in the rat occurs in both the stomach and the small intestine, although there are conflicting reports about the main site within the small intestine. The mechanisms of absorption have not been clearly defined. At high luminal concentrations, molybdenum may move mainly by diffusion, whereas at low luminal concentrations, active transport may provide a major pathway of absorption. Sulfur, copper, and tungsten may interfere with molybdenum absorption if their luminal concentrations are sufficiently high, and molybdenum absorption with meals appears to be much less than that of the nutrient taken alone. After an oral tracer dose, blood levels rise and fall quickly, and molybdenum moves in and out of tissues rapidly, suggesting passive transport. Liver levels fall only a little and maintain a plateau, whereas kidney levels remain relatively high. The total body content of adults has been calculated to be about 10 mg. Most of the absorbed molybdenum is excreted rapidly in the urine. There is little excretion of endogenous molybdenum through the feces.

Because of the rapid temporary effects of dietary molybdenum on blood and urine levels, these levels must be interpreted with caution in assessing molybdenum status. The combination of reduced activity of both xanthine oxidase and sulfite oxidase is strongly suggestive of molybdenum deficiency.

Toxicity

Because excess molybdenum is excreted rapidly through the kidneys, accumulation is limited, and greatly elevated levels of intake are necessary in nonruminant animals to produce toxicity. However, there is some concern that chronic moderately excessive intake can produce deleterious subclinical effects in humans. For example, villagers in areas of Russian Armenia with high molybdenum content in the soil and a daily intake of molybdenum as high as 10 to 15 mg had elevated xanthine oxidase activity, hyperuricemia, and a high incidence of gout. Similar symptoms have been reported in Russia as a result of industrial exposure. Copper metabolism appears to be mildly affected by industrial exposure to molybdenum in Colorado.[157] Serum uric acid, although normal, was higher than in controls.

Dietary Requirements and Food Sources

Daily average intakes of molybdenum for adults in the United States have been calculated as 180 μg, but there is a wide individual range.[6] Drinking water is usually a minor source, with water supplies containing 0.20 μg/L. However, molybdenum levels in drinking water are raised by mining effluents to as high as 400 μg/g in parts of Colorado. Foods highest in molybdenum are dried legumes, grains, cereal products, and organ meats. Average concentration in human milk is 2 μg/L.[6]

Recent stable isotope studies of molybdenum metabolism at different levels of molybdenum intake indicate that the minimum requirement for young adult men is 25 μg molybdenum/day.[158] The Food and Nutrition Board has established an RDA for molybdenum of 45 μg/day for adults and 2 to 3 μg/day for infants.[6] The risk of subclinical toxicity appears to be greater than that of deficiency. Naturally occurring molybdenum deficiency, uncomplicated by molybdenum antagonists, has not been documented in animals, and it is extremely unlikely that humans are at risk of molybdenum deficiency except in the most unusual circumstances, such as the prolonged use of a synthetic diet.

MANGANESE

A nutritional requirement for manganese has been established in a wide variety of organisms and was first shown to be "essential" for animals in 1931. Interest was stimulated by the discovery in the 1930s that two economically important diseases of poultry, perosis and chondrodystrophy,

were caused by manganese deficiency. There are now extensive data on animal requirements, but knowledge of human manganese requirements and status is much more limited.[6]

One probable case of human manganese deficiency has been reported in a subject who was receiving an experimental synthetic diet that was retrospectively found to be low in manganese, providing only 350 μg/day of manganese for 3 months.[159] Features attributed to manganese deficiency were hypercholesterolemia, depressed levels of clotting proteins in the plasma, weight loss, and slow growth of hair and nails. Low serum manganese levels have been reported in some diabetic and in epileptic children, and a negative manganese balance has been observed in children with pancreatic insufficiency. The clinical significance of any of these observations remains obscure. Opinions differ on the likelihood of manganese deficiency occurring in free-living human populations, although, in general, it is thought to be unlikely.[6] Experimental manganese depletion in animal models affects cartilage and bone structure and neurologic function and is associated with stunted growth and ataxia in newborns. Deficiency was also associated with lipid accumulation in liver and kidney and with hypercholesterolemia, a finding also observed in humans.[160]

The low manganese concentrations found in blood plasma (approximately 1 ng/mL) and, until recently, the difficulty of obtaining accurate analyses have hindered progress in our understanding of manganese status in humans. Erythrocyte, plasma, and serum manganese concentrations demonstrate an age-dependent pattern, with the highest levels observed in young infants. Blood concentrations increase during pregnancy, which apparently result in high manganese concentrations in the fetus. Infants born prematurely have higher blood levels than term infants, and these relatively high levels persist for several weeks postnatally.[90]

Biochemically, manganese is required for the synthesis of mucopolysaccharides through the manganese-dependent enzymes polymerase and galactotransferase. Reduced activity of these enzymes, resulting in impaired mucopolysaccharide synthesis, accounts for the extensive skeletal abnormalities and the ataxia owing to impaired otolith synthesis that are seen in animals with manganese deficiency. Pyruvate carboxylase is a manganese metalloenzyme, and manganese is a potent, although not necessarily specific, promoter of oxidative phosphorylation. Peptidases, manganese superoxide dismutase, succinic dehydrogenase, and arginase appear to be manganese-dependent enzymes.

Adults absorb less than 5% of an ingested dose of ^{54}Mn.[90] Only half of this amount is retained 10 days later, but retention of the ingested dose at 10 days is 8% in the newborn and 16% in the premature infant. Breast-fed infants maintain positive balance on much lower manganese intakes than formula-fed infants. The higher retention of infants, especially those born prematurely, may reflect higher absorption efficiency but may also reflect less efficient excretory mechanisms. Manganese absorption is enhanced by iron deficiency, but the long-term effects on retention are less clear. Neither the effects in infants of feeding iron-fortified formula on achieving optimal manganese status nor of iron deficiency on predisposing to manganese toxicity are well understood.[90] The emerging understanding of shared transport of manganese and iron in the brain and the potential for neurotoxicity highlight the potential importance of the interaction between these elements.[161] Manganese is excreted almost entirely through the bile, and urine losses are small.

Chronic manganese toxicity, owing principally to inhalation from occupational exposure, causes extrapyramidal neurologic disease similar to Parkinson's disease, Alzheimer's disease, and Huntington's disease. Such neurologic symptoms are associated with neuronal death in the globus pallidus.[162] Experimental manganese overload in rodents can cause cholestatic liver disease. Likewise, cholestatic liver disease, including that associated with total parenteral nutrition,[163] has been associated with manganese accumulation in the liver[164] and brain. Manganese, as well as copper, should be reduced or withheld from parenteral nutrition patients with cholestatic liver disease, and iron deficiency should also be avoided if possible.[161]

Adults are in positive manganese balance with an intake of 2.5 mg/day, but intakes of 0.7 mg/day result in negative balance. Human milk contains only 3 to 4 μg/L of manganese.[90,105] Hence, it appears that the requirements of young infants are extremely small. The Daily Recommended Intake (DRI) AI level for healthy 0- to 6-month-old infants was set at 3 μg/day (0.4 μg/kg), based on the mean manganese intake of exclusively breast-fed infants.[6] Formula-fed infants ingest much more manganese than breast-fed infants. Fortunately, the toxicity of manganese administered by the oral route appears to be low, and a wide range of intakes is tolerated without any apparent clinical problems. Nuts and unrefined grain are rich sources of manganese. Vegetables and fruits contain moderate amounts, whereas animal products and seafood are relatively low in this trace element.

FLUORIDE

Fluoride has both beneficial (prevention of dental caries) and toxic (fluorosis) effects on teeth, with a small margin between intakes that are beneficial and those that are toxic.

Fluoride has proved to have beneficial cariostatic properties during tooth development and, for this reason, is generally accepted as a necessary micronutrient. Other beneficial properties, for example, in ameliorating osteoporosis and protecting against arterial calcification, have not been substantiated convincingly.

Prevention of Dental Caries

Fluoride is, without question, effective in preventing dental caries.[165] The principal means by which this protection is conferred is via a local effect at the tooth surface. Fluoride decreases demineralization of the enamel when the pH of the dental plaque is low owing to the action of oral bacteria on fermentable carbohydrates. Fluoride also accelerates remineralization when the pH rises.[166] In addition, fluoride appears to decrease production of organic acids

from fermentable carbohydrates on the teeth. The fluoride concentration in saliva and in dental plaque fluid necessary to achieve effects is only 0.1 part per million.[167] The systemic effect of fluoride on teeth prior to eruption appears to be small,[168] although some protection may be conferred by incorporation of fluoride into enamel crystals during tooth development.[169]

Prior to the widespread use of fluoridated dentifrices, lifelong use of a water supply containing 1 part per million fluoride resulted in a 50 to 60% decrease in the prevalence of dental caries in permanent teeth. The beneficial effect on primary teeth was only slightly less. With the current widespread use of fluoridated dentifrices, the benefits of a fluoridated water supply have dropped to about a 25% decrease in prevalence of dental caries.[170]

Near-maximal protective effect is achieved with a fluoride concentration of 1 part per million in the drinking water. The beneficial effects are likely to be greatest among children from low-income families, whose use of fluoridated dentifrices is more restricted.

Fluorosis

Dental fluorosis is characterized by undermineralization of the surface and subsurface enamel, resulting in increased porosity. This is a developmental abnormality affecting both primary and permanent teeth.[171,172] Although the mechanism is not fully understood, fluoride appears to damage the ameloblasts that produce the enamel. The enamel appears opaque. Visible changes range from barely discernible fine white lines across the teeth to entirely chalky-white teeth. The outer enamel may break apart, and the exposed subsurface then becomes discolored.

The incidence of fluorosis has a linear relationship to calculated fluoride intake per unit body weight.[168] This relationship is evident even at levels of fluoride intake that approach zero. The infant is thought to be especially susceptible to the effects of fluoride, with fluorosis resulting once the fluoride intake has reached a level of 40 to 100 μg/kg/day. The incidence of fluorosis appears to have increased recently in communities with and without fluoridated water.[173] The teeth of greatest cosmetic concern are the permanent incisors and cuspids. Enamel formation in these teeth begins at 3 months and is completed by 7 years.

Intake of Fluoride by Infants

The fluoride content of breast milk is uniformly low whatever the maternal intake of this trace element.[174] Remarkably, the incidence of dental caries is relatively low in children who have been breast-fed as infants. Fluorosis is uncommon in children who have been breast-fed as infants. The intake of fluoride from unmodified cow's milk is also low, although not as low as from human milk. Fluoride concentrations approximate 40 and 60 μg/L, respectively.[168] The fluoride intake from formula tends to be higher and potentially in a range that can cause fluorosis, even though the fluoride content of water used in the manufacture of infant formulas has been restricted since 1978 and even when dried formulas are made up with water of relatively low fluoride content. For example, the calculated intake of fluoride of a young infant receiving 150 mL formula/kg body weight/day, prepared by mixing powdered milk–based formula (fluoride content = 690 μg/L) with water containing only 200 μg fluoride/L, is 41 μg/kg/day.[168] If a concentrated liquid milk–based formula is used, fluoride intake would be a little lower, and if isolated soy protein formula is used, the fluoride intake would be a little more. Ready-to-feed formulas contain ≤ 20 μg fluoride/L.[90] The fluoride content of bottled distilled water is low, but this does not apply to all bottled waters. Weaning foods may also provide significant quantities of fluoride, especially fruit juices, cereals, and poultry products.

Overall, the fluoride intake of young infants is less than it was two decades ago because of a decrease in fluoride content of formulas and because of the increased incidence of breast-feeding. On the other hand, the intake of older infants tends to be higher because of the progressive substitution of infant formulas for whole cow's milk at this age. Older infants may also start to use fluoridated dentifrices. Small children ingest most of this dentifrice, and the fluoride is subsequently absorbed. The AI for 0 to 6 months is 10 μg/day (1.4 μg/kg/day).[175] The American Academy of Pediatric Dentistry and the American Academy of Pediatrics recommend no fluoride supplementation for infants under 6 months of age. For older infants and children from 6 months to 3 years for whom the community water supply is less than 0.3 parts per million, a supplement of 250 μg/day is recommended. These recommendations and a broad discussion of use of fluoride to prevent and control dental caries has recently been published.[176]

It is recommended that fluoride supplements be withheld from infants because of the risk of fluorosis and the limited benefits of ingested fluoride. Fluoridated water can, with advantage, be given several times a day to infants who are feeding on a milk/formula with a fluoride content of less than 0.3 μg/L.[168]

IODINE

The clinical importance of adequate iodine intake has, like that of iron, been recognized for many years. Iodine was used in the treatment of goiter in the early years of the nineteenth century, and the major role of iodine deficiency in the etiology of endemic goiter was confirmed early in this century when the prophylactic value of iodine was demonstrated in Ohio schools. The early recognition of the nutritional role of this trace element can be attributed to the specific nature of the clinical features of iodine deficiency, the relative simplicity of measuring iodine in foods and other biologic samples, and the high concentration of iodine in one specific organ, the thyroid gland. Sixty percent of T_4 by weight is iodine, and the biologic importance of iodine is related entirely to its role in the thyroid hormones.[177]

Iodine deficiency disorders remain a global problem, despite aggressive prophylactic measures, and are the most prevalent cause of brain damage. WHO estimates that there are 740 million people affected by iodine deficiency disorders, and as much as one-third of the world's population is

at risk. Endemic goiter now occurs mainly in developing countries, typically mountainous areas such as the Andes and Himalayas and the mountainous chain extending through Southeast Asia and the South Pacific. Iodine deficiency also remains a problem in certain parts of Africa. Endemic goiter also persists in the Alps and in several Western and mid-European countries.[177]

There are two clinical types of endemic cretinism, the neurologic and the myxedematous, both of which exhibit severe mental retardation. The neurologic type prevails in most regions and is characterized by severe mental retardation, deaf mutism, spastic diplegia, and strabismus. The cretin appears normal at birth but is obviously retarded by 6 months of age. There is a characteristic vacant face with a large protruding tongue. The head appears large, and a lordosis is usually prominent. Clinical evidence of hypothyroidism is usually absent. The neurologic damage does not appear to be attributable to maternal or fetal hypothyroidism; there has been speculation that it may be owing to the direct effects of fetal iodine deficiency or to an imbalance between serum T_4 and T_3. In iodine deficiency, T_4 decreases, but T_3 remains normal or even elevated. The myxedematous type of cretin predominantly has the signs of congenital hypothyroidism but typically has only modest enlargement of the thyroid gland. This type, which may result from a combination of a dietary goitrogen and iodine deficiency, predominates in some Central African countries. Endemic cretinism is not a distinct entity in a region of endemic goiter but rather the severe end of a spectrum of neurologic damage.[177]

In mildly iodine-deficient areas, goiters may not occur until adolescence or during pregnancy. These goiters disappear in adult males, but in women they become large. Degenerative changes then occur, and myxedema or, paradoxically, sometimes thyrotoxicosis, may follow. Milder cognitive and neuromuscular impairment owing to chronic iodine deficiency is much more common.

Earlier this century, prophylaxis with iodized salt proved to be highly effective in North America. Although sporadic goiters still occur, these are apparently attributable primarily to unidentified goitrogens. Bread, water, milk, and chocolate are other vehicles that have been used to provide supplemental iodine. In areas of endemic goiter, intramuscular depot injections of 5 mL of iodized oil, providing 400 μg/mL of iodine, have also been used extensively. With the relatively high iodide concentrations now found in foods, especially milk, and the nationwide food distribution system in the United States, iodized salt is no longer needed.[178] In contrast, WHO and other international agencies have spearheaded national salt iodization programs in developing countries to eliminate the full spectrum of iodine deficiency disorders. In the 1990s, the number of countries with iodization programs doubled from 46 to 93, and there has been an accompanying improvement in the iodine status of these populations.

Measurement of iodide excretion in casual or spot urine samples provides an excellent index of recent iodide intake and is a useful assay for assessing community iodide status. Once iodide deficiency is established, T_4 levels will be decreased (normal range equals 0.8 to 2.4 ng/dL). Thyroid size and thyroid-stimulating hormone and thyroglobulin concentrations reflect chronic iodine deficiency disorders.

With the increasing levels of iodide in the US food supply, the risk of iodide toxicity is currently of greater concern than that of iodide deficiency. More cases of goiter in this country are currently attributable to excess rather than to a lack of iodide. The effects of excessive iodide intake include thyroiditis, goiter, hypothyroidism, and hyperthyroidism.[179] Intake of more than 1,000 μg iodide/day (14 μg/kg) in adults may cause toxicity, especially in those who have previously had chronic iodine deficiency.[177] The corresponding figure in young children is uncertain.

Cow's milk is a major dietary source of iodide in the United States, one that has increased in recent years. This has resulted not only from use of iodized salt in the dairy industry but also from the use of iodates as sanitizers, especially in teat dips. A 1984 report of a survey of farms in New York State indicated that milk iodide concentrations were greater than 500 μg/L from 10% of farms and between 200 and 500 μg iodide/L from another 28% of farms.[180,181] Iodide concentrations in human milk are also relatively high in this country (ie, 140 to 180 μg iodide/L), much higher than the concentration in other countries.[182–184] The recommended range for term infant formulas is 53 to 230 μg iodide/L[136]; the comparable recommendation for preterm formulas is 48 to 280 μg iodide/L.[90] Fish is notable among other foods as naturally rich in iodide. Iodide in water does not usually contribute more than 10% of intake.

The adult EAR of iodide is 95 μg/day or approximately 1 μg iodide/kg body weight/day; the RDA is 150 μg/day.[6] AIs for infants are 110 μg/day before the age of 6 months and 130 μg/day in older infants.[6] These recommendations are generous. Some centers do not add iodide to intravenous nutrition because of that already present as contamination, including that derived from iodates used to clean tube connections. We recommend providing 1 μg iodide/kg body weight/day in case these alternative sources are not always effective. This low dose carries no risk of toxicity.

CONCLUSION

Recognition of the practical importance of the trace elements in human nutrition has progressed substantially within the past few years. Concurrently, there have been exciting advances in understanding of the biology, especially the molecular/subcellular biology of these micronutrients. Recent advances have been most notable for zinc, both in terms of basic biology and global public health. Identification of "new" biologic roles for selenium and increasing respect for its importance for human health serve as a reminder that knowledge of less prominent trace elements is likely far from complete. Although, globally, issues of trace element deficiencies pose major public health challenges, there are also issues of overabundance owing especially to food fortification programs. The latter tend to underscore the importance of both vigilance toward and further research on interactions and other possible adverse effects.

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CHAPTER 7

VITAMINS

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Since ancient times, diet has been used to prevent and treat ailments such as night blindness, pellagra, scurvy, and rickets. However, it was not until the end of the nineteenth century that specific compounds in foodstuffs, beyond the three major sources of energy and building units (carbohydrates, fats, and proteins), began to be identified as responsible for vital functions in animals. The term "vitamine" was coined by Casimir Funk in 1911 to describe an antineuritic water-soluble compound discovered in rice bran that was initially believed to consist of an "amine" structure.[1] This compound, thiamin, would later be identified as a "vitamin," together with other vital compounds of varied chemical structures that were discovered in the early twentieth century.

Traditionally, vitamins have been classified according to their hydrophilic potential as fat soluble (hydrophobic) (A, D, E, and K) or water soluble (C, thiamin [B_1], riboflavin [B_2], niacin, pyridoxine [B_6], folate, cobalamin [B_{12}], biotin, and pantothenic acid). This chapter presents a succinct discussion on each vitamin, emphasizing the basic chemistry, physiology, and current epidemiologic knowledge, with special focus on issues pertaining to child health. The reader is referred to the Appendix to a list of the Recommended Dietary Allowances (RDAs); Table 7-1 lists the tolerable upper intake levels (ULs) of the vitamins discussed, and Table 7-2 provides a summary of sources and functions of vitamins and their assessment.

VITAMIN A

Structure and Metabolism

The importance of a substance present in certain foods for the treatment of night blindness was already known in ancient Egypt. The Greek physician Hippocrates (460–327 BC) recommended the intake of "raw beef liver, soaked in honey, once or twice by mouth" for the treatment of "nyktalopia," or the total inability to see in darkness.[2] However, it was only in the late nineteenth and early twentieth centuries that the biochemistry of this compound was clarified. In 1881, Nicholai Lunin reported that mice could not survive on a purified diet of fats, carbohydrates, proteins, and salts alone, but survival was more likely when whole milk was added.[3] Similar findings led Sir Frederick Gowland Hopkins to postulate in 1906 the existence of "unsuspected dietetic factors" that were necessary for life and growth.[4] For this he was awarded the Nobel Prize in 1929. A fat-soluble factor was isolated from egg yolk in 1909 by Wilhelm Stepp[5]; the same factor isolated from alfalfa leaves, liver, kidney, or butter fat was independently shown to promote growth in rats by Elmer V. McCollum[6,7] and Thomas Osborne and Lafayette Mendel[8,9] in 1913 and was dubbed "fat-soluble factor A." The factor was finally named vitamin A in 1920.[10] Before the discovery of vitamin A, various carotenoid pigments had been described in the nineteenth century. They were later found to be precursors of vitamin A,[11] and the structure of betacarotene, the major provitamin A carotenoid, was disclosed by Paul Karrer in 1930.[12] He won the Nobel Prize in 1937.

The term vitamin A groups a number of retinoid compounds with the biologic activity of all-*trans* retinol. Retinoids usually consist of four isoprenoid units with five conjugated carbon-carbon double bonds.[13] 11-*Cis* retinal is the oxidation product of retinol primarily involved in visual functions. Retinal can be further oxidized to retinoic acid, which possesses growth but not visual or reproductive functions. Retinyl palmitate, an ester, is the principal storage form of vitamin A. More than 600 carotenoids have been identified in nature, but only about 50 have the unsubstituted β-ionone ring that guarantees vitamin A activity. As opposed to retinol, most carotenoids have antioxidant properties owing to their long chain of conjugated double bonds.

Vitamin A is usually ingested as retinyl palmitate from animal sources and as carotenoids from plants and animal tissue. In the stomach, preformed vitamin A and carotenoids are released from protein by proteolysis; they then aggregate with other lipids and pass into the upper part of the small intestine. Bile salts stimulate pancreatic lipase and other esterases that hydrolyze retinyl esters to retinol in enterocytes. Retinol subsequently binds to the cellular retinol–binding protein (CRBP) II. Carotenoids, on the other hand, pass into the mucosal cells unaltered and are cleaved by a 15-15-oxygenase into retinal, which also binds to CRBP II. Retinal reductase and lecithin-retinol acyltransferase (LRAT) recognize the CRBP II complexes and synthesize retinol, which is then packed into chylomicra before entering the circulation via the lymphatic system.[14] Triacylglycerol is hydrolyzed from circu-

TABLE 7-1 Tolerable Upper Intake Levels (ULs)*

Age (yr)	*Thiamin (mg/d)*	*Riboflavin (mg/d)*	*Niacin (mg NEs†/d)*	*Biotin (µg/d)*	*Pantothenic Acid (mg/d)*	*Vitamin B_6 (mg/d)*	*Folate (µg DFEs‡/d)*	*Vitamin B_{12} (µg/d)*	*Vitamin C (mg/d)*	*Vitamin A (µg RE/d)*	*Vitamin D (µg/d)§*	*Vitamin E (mg α-TE/d)*	*Vitamin K (µg/d)‖*
Infants													
0–0.5	—	—	NP‖	—	—	NP‖	NP‖	—	NP‖	600	25	NP‖	—
0.5–1	—	—	—	—	—	—	—	—	—	600	25	—	—
Children													
1–3	—	—	10	—	—	30	300	—	400	600	50	200	—
4–8	—	—	15	—	—	40	400	—	650	900	50	300	—
9–13	—	—	20	—	—	60	600	—	1,200	1,700	50	600	—
14–18	—	—	30	—	—	80	800	—	1,800	2,800	50	800	—

Adapted from Food and Nutrition Board. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline. Washington (DC): National Academy Press; 1998, and from references 22, 88, and 99.

DFE = dietary folate equivalent; NE = niacin equivalent; RE = retinol equivalent; TE = tocopherol equivalent.

'—' denotes no evidence of adverse effects.

*Upper intake levels (ULs) represent the highest level of nutrient intake that is likely to pose no risk of adverse health effects.

†For both niacin and folate, ULs apply to intakes of synthetic forms obtained from fortified foods, supplements, or both.

‡Applies to preformed vitamin A only.

§Applies to any form of supplemental α-tocopherol, fortified foods, or both.

‖Not possible to establish. Source of intake should be from formula and food only.

TABLE 7-2 Sources and Functions of Vitamins and Their Assessment

Nutrient	*Sources*	*Major Functions*	*Deficiency Symptoms*	*Status Assessment**
Vitamin A	Preformed vitamin A: liver, fish liver oils, eggs, dairy products Provitamin A: dark green leafy vegetables, deep orange fruits, vegetables	Vision, immunity, maintenance and differentiation of cells, growth	Night blindness, xerophthalmia, hyperkeratosis, anemia, suppressed immunity	Plasma retinol (HPLC), plasma retinol-binding protein
Vitamin D	Skin synthesis, vitamin D–fortified foods (milk, margarine, butter), fish oils	Homeostasis of calcium and phosphate, mineralization of bones	Signs of rickets or osteomalacia	Plasma 25-hydroxycholecalciferol (HPLC), serum alkaline phosphatase, bone densitometry
Vitamin E	Vegetable oils, wheat germ, nuts, green leafy vegetables	Antioxidant defense	Hemolytic anemia in newborns (esp. premature), increased risk of erythrocyte hemolysis, neurologic alterations	Plasma tocopherol (HPLC), adjusted for blood lipids, detection of malonaldehyde
Vitamin K	Colonic bacterial synthesis, vegetables (esp. green leafy), milk, liver	Carboxylation of blood clotting and bone proteins	Hemorrhaging, skeletal weakness	Prolonged prothrombin time, plasma phylloquinone levels, presence of undercarboxylated proteins (PIVKAs)
Vitamin C	Citrus fruits, broccoli, bell peppers, tomatoes, brussels sprouts, many berries	Antioxidant defense, collagen synthesis, fatty acid metabolism, immunity	Scurvy, impaired wound healing, petechiae, anemia	Plasma levels (HPLC/enzyme assay), leukocyte levels, urinary levels
Thiamin	Pork, whole grains, fortified grain products, yeast	Part of TPP (thiamine pyrophosphate in energy metabolism), synthesis of neurotransmitters	Beriberi, cardiac failure, peripheral neuropathy, confusion, anorexia, weakness	Erythrocyte transketolase activity, with and without added TPP
Vitamin B_6	Poultry, fish, liver, eggs, whole-grain products, vegetables	As part of cofactors PLP (pyridoxal phosphate) and PMP (pyridoxamine phosphate) used in amino acid and fatty acid metabolism	Hypochromic and microcytic anemia, convulsions, abnormal encephalograms, weight loss, vomiting	Erythrocyte aminotransferase activity, plasma PLP (HPLC), urinary levels of 4-pyridoxic acid
Folate	Green leafy vegetables, legumes, orange juice, fortified grain products	In the form of tetrahydrofolate (THF), functions in 1-C transfer and DNA synthesis	Megaloblastic anemia, hypersegmented neutrophils, glossitis, stomatitis, neural tube defects during pregnancy, elevated blood homocysteine levels	Serum/erythrocyte folate concentrations (microbial/competitive binding assays)
Vitamin B_{12}	Animal foods (meat, poultry, milk, fish)	As part of methylcobalamin and 5-deoxyadenosylcobalamin, required for formation of erythrocytes, nerve sheaths; folate metabolism; amino acid and fatty acid metabolism	Pernicious anemia, megaloblastic anemia	Saturation of serum transcobalamin II, plasma levels (microbial/radioimmunologic assay), Schilling test for absorption, urinary methylmalonic acid levels (HPLC)
Biotin	Egg yolk, organ meats, fish, certain vegetables, colonic bacterial synthesis	As part of cofactors, used in energy metabolism, fatty acid synthesis, amino acid metabolism, glycogen metabolism	Nausea, vomiting, depresssion, lethargy, hair loss, dry, scaly dermatitis	Plasma levels (microbiologic assay)
Pantothenic acid	Widespread in foods; high levels in organ meats, chicken, beef	As part of coenzyme A, used in energy metabolism; as part of 4-phosphopantetheine (Ppant), used in fatty acid synthesis	Extremely rare; mild neurologic symptoms, vomiting, abdominal cramps	Urinary excretion, whole blood levels (radioimmunologic/microbiologic assay)

HPLC = high-performance liquid chromatography.
*For further information, see Gibson RS. Principles of nutritional assessment. New York: Oxford University Press; 1990.

lating chylomicra by plasma lipoprotein lipase to form chylomicron remnants. These remnants deliver retinol to the liver, where it is taken up by hepatocytes through high-affinity receptors of apolipoproteins E and B-48. In hepatic lysosomes, an acidic hydrolase releases retinol to bind with apo-CRBP. At least three pathways could follow after this CRBP-retinol complex is formed: (1) synthesis of CRBP-retinal through retinol dehydrogenase and later retinal through retinal dehydrogenase, (2) retinol esterification mediated by LRAT, and (3) rapid mobilization of retinol catalyzed by the bile salt–independent reductase.[14]

From the hepatocyte, vitamin A can be locally transported to fat-storing stellate cells or released to the systemic circulation. For the latter, all-*trans* retinol binds to retinol-binding protein (apo-RBP), which is produced by the hepatic parenchymal cells. RBP is a single-chain polypeptide with a unique binding site for retinol. It protects circulating retinol from oxidation and destruction. Plasma concentration of RBP in children ranges from 1 to 1.5 μmol/L (20 to 30 μg/mL) and reaches adult levels (2 to 2.5 μmol/L) at puberty.[15] Under repletion conditions, RBP is 90% saturated with retinol. Both plasma vitamin A and RBP may be elevated during chronic renal failure and diminished in protein-energy malnutrition. The holo-RBP complex is secreted in plasma together with transthyretin, a tetramer that minimizes the loss of RBP in urine. The complex is then distributed to peripheral tissues or recycled back to the liver in a tightly regulated system that allows retinol molecules to recirculate more than seven times before final excretion. In the retina, holo-RBP binds to membrane receptors for internalization by endocytosis. These receptors have also been found in skin, placenta, and the blood-testes and blood-brain barriers.[16] However, they are not present in lung, kidney, or muscle. It is possible that in these and other organs, retinol is taken up directly by lipid membranes on a receptor-independent fashion.

Bioconversion of carotenoids is inversely regulated by vitamin A status[17]; this offers a potential explanation to the lack of toxic effects even at an extremely elevated intake of carotenoids. The bioavailability of vitamin A and carotenoids is influenced by the integrity of the intestinal mucosa and the intake of other nutrients.[18] Factors that increase bioavailability include the presence of fat, protein, vitamin E, zinc, and possibly iron; cooking; and processing. Dietary fiber from highly methoxylated pectins reduces absorption of carotenoids.[19] During the first 6 months of life, the most important sources of vitamin A for the infant are breast milk and vitamin A available from the infant's own liver stores. The concentration of vitamin A in breast milk is dependent on the mother's vitamin A status, so that the infant's vitamin A status may be compromised if the mother's vitamin A status is inadequate.[20] After 6 months of age, complementary foods increase in importance to meet the infant's vitamin A requirements. Among American children age 2 to 18 years, ready-to-eat cereals and milk supply more than 40% of vitamin A intakes.[21] Excessive amounts of vitamin A lead to symptoms of toxicity in infants and children such as anorexia, bulging fontanels, increased intracranial pressure, occipital edema, and bone and liver damage. Women of childbearing age in particular should be advised against consumption of vitamin A levels in excess of 2,800 to 3,000 μg of preformed vitamin A owing to increased risk of teratogenicity.[22]

Functions

Vitamin A exhibits an overarching function in gene expression that affects various physiologic processes. In the form of its metabolite, all-*trans* retinoic acid, vitamin A is a ligand for a family of nuclear receptors known as retinoic acid receptors (RARs), whereas another metabolite, 9-*cis* retinoic acid, activates two families: RARs and retinoid X receptors (RXRs). These receptors form heterodimers and bind to genes in regulatory regions known as retinoic acid response elements. The regulation of gene induction by retinoic acid can be further modulated by a large number of transcriptional mediators and repressors that include hormonal receptors. Metabolites of the retroretinoid family may also have a role in gene transcription.

Specific physiologic functions exhibited by vitamin A include vision, immunity, cell differentiation, and growth. The visual role of vitamin A occurs in the rod cells of the eye and enables sight in dim-light conditions. In this biochemical process, all-*trans* retinol undergoes isomerization and oxidation to yield the light-sensitive molecule 11-*cis* retinal. The 11-*cis* retinal molecule binds to opsin to form rhodopsin. As rhodopsin absorbs light, 11-*cis* retinal changes to all-*trans* retinal, causing it to dissociate from opsin. As all-*trans* retinal is released, opsin undergoes a confirmational change, which induces an alteration in permeability to cations, increased polarization of the membrane, and generation of a nerve impulse. Rhodopsin can be regenerated, which completes the vitamin A–dependent visual cycle (Figure 7-1).[23]

The role of vitamin A in immunity has been recently reviewed.[24] The immune effects of vitamin A seem to be mediated mainly through the acid metabolites of the vitamin, all-*trans* retinoic acid, and 9-*cis* retinoic acid. The immune response elements that are potentially associated with retinoid regulation have been reviewed.[25] At the level of mucosal immunity, vitamin A deficiency (VAD) is related to alterations in the integrity of ocular, respiratory, gastrointestinal, and genitourinary epithelia. These alterations include replacement of normal ciliated and mucus-producing cells by keratinized epithelium. Keratinization and mucin production may be additionally regulated by vitamin A at the transcriptional level. Local secretion of specific and unspecific humoral immune factors (secretory immunoglobulin [Ig]A, lactoferrin) may also be impaired by VAD.

Retinoids influence the differentiation of white cell lines in the bone marrow, as well as the function of circulating immune cells. Phagocytosis, chemotaxis, and production of free radicals carried out by neutrophils are altered in vitamin A–deficient animals, as well as the number and cytotoxic activity of natural killer cells. Retinoic acid enhances various functions of mononuclear cells in vitro, such as phagocytic activity of macrophages and release of tumor necrosis factor-α, interleukin-1 (IL-1), transforming growth factor-β, and expression of Ig recep-

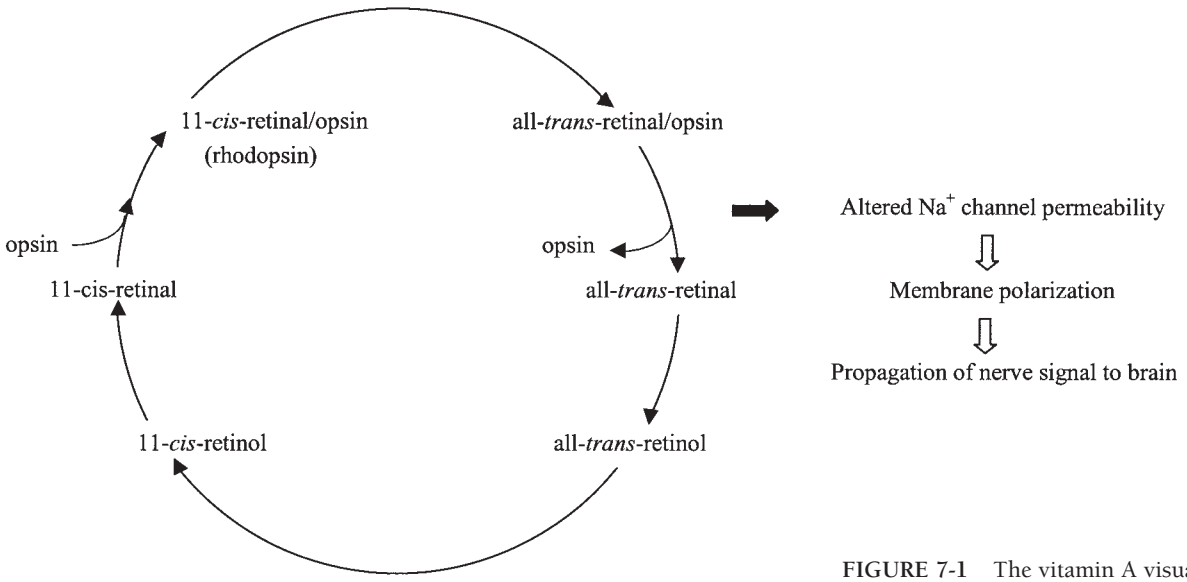

FIGURE 7-1 The vitamin A visual cycle.

tors by monocytes that modulate proliferation of B lymphocytes. It also increases the capacity of Langerhans' cells to present antigens to T lymphocytes in the skin.

Vitamin A appears to influence the antigen-specific proliferation of T lymphocytes. In animals, VAD impairs cytotoxic T-lymphocyte activity. Growth and differentiation of B lymphocytes into Ig-producing cells also requires retinol, possibly through the induction of cytokine secretion by T helper lymphocytes. The antibody response against T cell–dependent antigens is usually impaired by VAD in animals, particularly during infections that would normally induce a T helper type 2–like response. In this case, instead of high production of IgG, IL-4, IL-5, and IL-10, a T helper type 1 response seems to be favored with low antibody production and increased levels of IL-2 and interferon (IFN)-γ. During infections that predominantly stimulate a T helper type 1 immune response, it has also been suggested that VAD further up-regulates such a response. Only a few studies have directly addressed the impact of vitamin A supplementation to humans on indicators of the immune function. The protective effect of vitamin A supplementation against infant morbidity and mortality is attributed to the vitamin's vital role in sustaining and enhancing the immune response at various levels.

A range of trials has examined the effect of vitamin A supplementation on mortality among children older than 6 months who live in developing countries. In two trials, vitamin A supplements had no effect on mortality, whereas a beneficial effect ranging from 19 to 54% was observed in the remaining studies. The pooled effect from eight clinical trials was estimated to be around 30%.[26] The effect varied with the dosage and frequency of administration; small weekly or daily doses were associated with a 42% mortality reduction, whereas large spaced doses (every 4 to 6 months) were associated with a 19% risk decline. The effect also seemed greater among children ≤ 1 year old and was more strongly protective against death from diarrheal disease. More recent studies suggest that vitamin A supplements could be particularly protective against death associated with other infectious diseases such as human immunodeficiency virus (HIV) (in the absence of antiretroviral therapy).[27] The effect of supplementation of infants < 6 months is not clear. Administration of vitamin A to newborns resulted in a 64% mortality reduction in only one of three trials.[28–30] There does not appear to be a positive effect of vitamin A on respiratory infections–specific mortality in this age group.[31] Variation in the effect of vitamin A supplements across populations can be attributed to setting-specific conditions such as the presence of concomitant nutrient deficiencies that affect the absorption and use of vitamin A, the prevalence of infectious diseases, and the underlying severity of vitamin A deficiency in the population.

The effect of vitamin A on the incidence and severity of infections has been assessed in several community- and hospital-based trials. There is a clear benefit of vitamin A supplementation among children hospitalized with measles; the average mortality risk reduction is estimated to be 60%.[26] The effect is larger in children with measles-pneumonia and among infants compared with older children. Also, vitamin A reduces the risk of acquiring pneumonia in children with uncomplicated measles.[32] Children with measles and diarrhea who received vitamin A recovered more rapidly from the diarrheal episode.[33] Vitamin A also appears to have a beneficial effect on the incidence and severity of certain types of diarrhea. Several community-based studies demonstrated reductions in diarrhea-specific mortality[34] and the number of severe diarrheal episodes,[35,36] including acute watery diarrhea.[37] Among hospitalized children in Bangladesh, vitamin A supplementation reduced diarrheal symptoms caused by shigellosis[38] but not symptoms related to rotavirus and enterotoxigenic *Escherichia coli* infections.[39] The varying efficacy of vitamin A supplements between the two studies may reflect differences in the pathogenesis of diarrhea attributable to the etiologic factors involved. A few studies have shown that vitamin A supplements may increase the occurrence of cough and other signs of respiratory infection.[40,41]

It is not clear whether this is the result of an improved inflammatory response associated with vitamin A therapy. Some data suggest that vitamin A supplementation may reduce the occurrence and severity of malaria in children.[42] In observational studies on the role of vitamin A in mother-to-child transmission of HIV, protective associations were noted suggesting that vitamin A supplementation may be beneficial. However, evidence from clinical trials showed either no effect of vitamin A supplements or a detrimental effect.

Vitamin A was discovered as a growth-promoting factor[6,7]; in the 1930s, growth arrest, particularly on weight gain, was demonstrated in vitamin A–depleted rats.[43] However, the role of vitamin A in growth and body composition of humans is less clear. Positive relationships between vitamin A status and growth have been reported from observational studies, particularly in malnourished populations. Children with ocular signs of severe VAD, including night blindness and xerophthalmia, are usually stunted[44]; however, at subclinical stages of vitamin A deficiency, other determinants of poor linear growth might be important.[45] High dietary betacarotene and total vitamin A intake have been positively related to linear growth in children 2 to 19 years[46] and 6 to 72 months,[47] respectively. However, these observational studies are limited by potential confounding by other nutrient deficiencies and infection. In Asia and Africa, various randomized clinical trials of vitamin A supplementation to children showed an overall lack of effect on weight or height gains.[48–53] However, when the effect was examined in subgroups of children, vitamin A supplements were found to selectively improve the growth pattern of children at higher risk of VAD as reflected in their age above 2 years,[54,55] poor breast-feeding status,[52–56] low seasonal availability of vitamin A–rich foods,[57] and low serum vitamin A levels.[56,57] Lately, vitamin A supplementation has been related to large improvements in growth among children suffering from debilitating infectious diseases including HIV, malaria, and persistent diarrhea.[58]

Vitamin A functions in the normal metabolism of iron, and research indicates that vitamin A deficiency is a risk factor for iron deficiency anemia.[59,60] Vitamin A enhances the growth and differentiation of erythrocyte progenitor cells, aids in the mobilization of iron stores from tissues, and improves resistance to infections, all of which prevent the development of anemia.[61] The trace element zinc plays a role in the absorption, transport, and use of vitamin A.[62] Zinc supplements have been shown to restore vision under dim-light conditions, which suggests an interaction between zinc status and vitamin A–related functions.[63] However, more research is needed on the synergy between zinc and vitamin A, particularly with regard to other end points.

VITAMIN D

Structure and Metabolism

Rickets, a disorder caused by vitamin D deficiency, has afflicted humanity since Neanderthal times some 200,000 years ago; however, it was described scientifically only in the seventeenth century and was linked to a nutritional deficit in 1919 by Sir Edward Mellanby. He induced rickets in dogs fed with a synthetic diet and showed that it could be prevented with the administration of cod liver or butter.[64] This led him to propose that the dietary factor responsible for rickets was vitamin A. In 1922, McCollum distinguished the antirachitic from the antixerophthalmic factors in diet because the former did not lose its properties after intense heating and aeration and called it vitamin D.[65] Also in 1919, Huldschinsky had shown that rickets could be cured with exposure to ultraviolet (UV) rays, but the realization that there was a relationship between the UV and dietary actions against rickets only occurred later, when Goldblatt and Soames demonstrated that irradiation of food could also cure rickets[66] and when Hess and Weinstock showed that UV irradiation induced the formation of an antirachitic factor in the skin.[67]

Vitamin D designates a group of compounds derived from the cyclopentanoperhydrophenanthrene molecule, which have antirachitic activity.[68] All of these substances have a conjugated triene system of double bonds. The two most abundant forms of the vitamin are D_3 and D_2. Vitamin D_3 is also called cholecalciferol and is produced in the skin from 7-dehydrocholesterol by solar radiation. Vitamin D_2, or ergocalciferol, is derived industrially from ergosterol, a plant steroid. Given that vitamin D can be produced by the human body, there is no dietary requirement for the vitamin as long as access to sunlight is available. For these reasons, vitamin D does not strictly fulfill the definition of a vitamin, and based on its various metabolic functions, it is currently classified as a steroid hormone.[69]

Absorption of vitamin D from the diet is relatively low, with around 50% of it being absorbed. The major source of the vitamin in humans is from photochemical conversion of 7-dehydrocholesterol to previtamin D in the skin and posterior isomerization to vitamin D (Figure 7-2). Vitamin D then passes to the systemic circulation bound to its transporter, the vitamin D–binding protein (DBP).[70] DBP carries most biologic forms and metabolites of the vitamin. It is taken up rapidly by the liver but is not preferentially stored there.[68] The highest concentrations of vitamin D are found in blood, although adipose and muscle tissue in humans are also major storage sites for vitamin D.[71] During deprivation, turnover from these sites is slow, and the supply of vitamin D to peripheral organs can be sustained for a period of time.

Vitamin D_3 does not have known biologic functions[69]; first, it must be hydroxylated to 25-hydroxycholecalciferol ($25(OH)D_3$) in the liver. $25(OH)D_3$ is the most abundant circulating form of the vitamin and is considered a good proxy of vitamin D_3 status. It is transported to the proximal tubules of the kidney, where a 1-hydroxylase converts it into $1\alpha,25(OH)_2D_3$. This hydroxylase is considered the most important regulatory mechanism of the vitamin D endocrine system,[68] and its activity is regulated by the concentration of $1\alpha,25(OH)_2D_3$, parathyroid hormone (PTH), calcium, and phosphate. The second hydroxylated metabolite of D_3 produced in the kidney is $24R,25(OH)_2D_3$. Although this metabolite may play unique roles in vitamin D functions such as regulation of PTH and bone mineral-

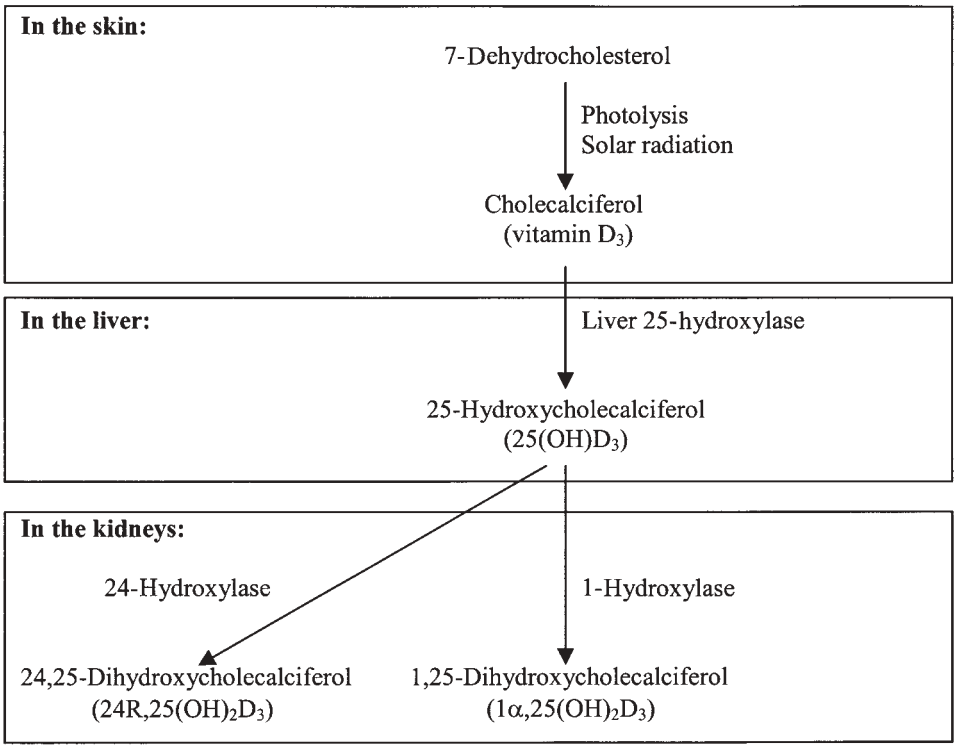

FIGURE 7-2 Vitamin D metabolism.

ization, it is likely that both $25(OH)_2D_3$ and $24R,25(OH)_2D_3$ may be required. Vitamin D metabolites are excreted mostly in the feces via the bile through catabolic pathways that are not yet well understood. Glucuronide forms are also excreted in urine.[72]

Functions

In target organs, $1\alpha,25(OH)_2D_3$ binds to its nuclear receptor, VDR_{nuc}, which has domains also found in other steroid hormone receptors. After binding, VDR forms a heterodimer with RXR, and later, the complex interacts with the vitamin D response element in the transcription control region of target genes. These activated promoter genes may also bind to coactivator proteins such as TATA, TBP, and TFIIB, and the resulting transcriptional complex is then able to modulate deoxyribonucleic acid (DNA) transcription.[73]

In addition to the nuclear receptor–mediated responses to vitamin D, there are also rapid physiologic responses triggered by the interaction of $1\alpha,25(OH)_2D_3$ with the membrane receptor VDR_{mem} in target cells.[74] These functions include the stimulation of Ca^{2+} absorption in the intestine (transcaltachia), opening of Ca^{2+} and Cl^- channels, activation of protein kinase C and mitogen-activated kinase, Ca^{2+} entry in skeletal muscle cells, and uptake of Ca^{2+} by osteoblasts.[69]

Of the more than 50 genes regulated by $1\alpha,25(OH)_2D_3$, the gene linked to the induction of the calcium-binding protein calbindin D is one of the most important ones as it is directly related to many of the known physiologic functions of vitamin D.[68] Regulation of mineral homeostasis is the classic function attributed to vitamin D. This process occurs at various target organs. In the intestine, $1\alpha,25(OH)_2D_3$ induces the transport of calcium and phosphate from lumen to plasma, possibly by activating calbindin and also through changes in the membrane composition of the brush border cells.[75] In the kidney, the major known role of $1\alpha,25(OH)_2D_3$ is the down-regulation of $25(OH)D_3$-1α-hydroxylase, thus controlling its own production.[76] It also stimulates the activity of $25(OH)D_3$-24-hydroxylase. In bone, vitamin D stimulates bone resorption that results in increased blood concentrations of calcium and phosphorus.[77] Increased serum calcium stimulates the secretion of PTH, which induces the production of $1\alpha,25(OH)_2D_3$ in kidney. However, steadily high concentrations of $1\alpha,25(OH)_2D_3$ may shut down PTH production through direct suppression of the prepro-PTH gene or via increased circulating calcium. These mechanisms are crucial in maintaining constant serum calcium concentrations independently of calcium intake. $1\alpha,25(OH)_2D_3$ may promote bone growth and mineralization through its effect on increasing intestinal calcium absorption and perhaps also by promoting differentiation of growth plate cells via chondrocyte membrane receptors[78] and augmenting the proliferation of osteoblasts and calcium uptake. Other actions of $1\alpha,25(OH)_2D_3$ on the osteoblasts include a decrease in type I collagen production and an increase in alkaline phosphatase, osteocalcin, and matrix G_{la} protein syntheses. Osteoclasts do not possess nuclear receptors for vitamin D; therefore, increased osteoclast proliferation in the presence of $1\alpha,25(OH)_2D_3$ may indicate an effect on progenitor cells or a nongenomic effect.

Vitamin D nuclear receptors have been found in other tissues, and some of their functions are being clarified. In skeletal muscle, vitamin D may be an important stimulant of calcium release during hypocalcemia. Myopathy frequently

accompanies bone diseases related to vitamin D deficiency. In the skin, $1\alpha,25(OH)_2D_3$ appears to foster differentiation of keratinocytes and protects them from UV stress.[79] Some types of psoriasis can improve with the topical application of vitamin D analogues.[80] Pancreatic beta cells respond to vitamin D with insulin secretion, and vitamin D deficiency is accompanied by impaired insulin production.[81] Some studies suggest that high doses of vitamin D may decrease the risk of type 1 diabetes in children.[82]

Various actions of vitamin D on the immune system have been reported. It induces differentiation of promyelocytic leukemia cells to macrophages or monocytes and decreases the expression of surface antigens in mononuclear cells that are involved in autoimmunity disorders. Vitamin D also inhibits the activation of B and T lymphocytes, the proliferation of activated lymphocytes, and the production of antibodies by activated B lymphocytes. T-cell suppressor lines may be enhanced by $1\alpha,25(OH)_2D_3$, whereas the activity of natural killer and T cytotoxic cells may be down-regulated. Decreased secretion of both T helper types 1 and 2 cytokines (IL-2, -4, -10, -12, and IL-13; IFN-γ; and granulocyte-macrophage colony-stimulating factor) is also related to vitamin D activity.[83,84] This has been associated with the potential development of allergies in children who are exposed to vitamin D early in life. In spite of these apparent immunosuppressing actions, $1\alpha,25(OH)_2D_3$ does not appear to induce systemic, generalized immunosuppression. Therefore, many of these findings may represent a local, vitamin D–dependent autocrine or paracrine regulation of the immune function.

Newborn vitamin D status is heavily dependent on maternal status. If a woman is deficient in vitamin D during pregnancy, her infant will accumulate insufficient vitamin D stores during intrauterine life and display low plasma concentrations of the vitamin.[85] The infant's vitamin D status is further compromised by low availability of vitamin D in the breast milk of vitamin D–deficient mothers. However, regular small exposure to sunlight can offset low dietary intakes of vitamin D. Dark-skinned individuals are at an increased risk for vitamin D deficiency at least partly owing to decreased skin synthesis of vitamin D.[86,87] Establishing dietary reference intakes for vitamin D has proven difficult owing to the major contribution of endogenously derived vitamin D to vitamin D status. Current guidelines for vitamin D are conservative in proposing levels that are adequate for children with insufficient exposure to sunshine to synthesize vitamin D.[88]

VITAMIN E

Structure and Metabolism

Vitamin E was discovered in 1922 as a fat-soluble compound in wheat and lettuce that was necessary to avoid fetal death in rats.[89] Its essentiality in humans was only recognized in the late 1960s in connection with the occurrence of hemolytic anemia among premature infants who were vitamin E deficient.[90] The potential protective role of vitamin E as an antioxidant against chronic and degenerative illness is currently an active field of research.

The term vitamin E groups all chemical compounds with the biologic activity of α-tocopherol. Tocopherols are molecules consisting of a 6-chromanol ring or head and a phytyl chain or tail. Eight naturally occurring compounds comprise the tocopherol family: α-, β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols.[91] The antioxidant potency of tocopherols depends on their ability to donate phenolic hydrogens to free radicals such as molecular oxygen, superoxide radicals, and peroxyl radicals and to inhibit auto-oxidation of fats. It is generally accepted that α-tocopherol (prefixed "*RRR*-," as a single steroisomer) has the highest antioxidant activity in vivo.[90] Synthetic forms of vitamin E are mainly esters and consist of a mixture of eight steroisomers (prefixed "*all-rac*-," as all racemic). These forms are less susceptible to oxidation and less biologically potent than α-tocopherol according to the fetal resorption test in rats.[92]

After ingestion, tocopherols are emulsified with bile salts in the intestinal lumen and absorbed by the enterocytes in the upper half of the small intestine through passive diffusion.[93] Absorption is inversely related to intake and reduced by long-chain polyunsaturated fatty acids. It is increased by medium-chain triglycerides.[90] At the enterocyte, tocopherols are incorporated into chylomicrons and absorbed mostly via the lymph ductus. Some chylomicron-bound α-tocopherol is transported to peripheral tissues after catabolism by lipoprotein lipase; the rest is taken up by the liver as chylomicron remnants. In the liver, α-tocopherol is reincorporated into nascent very low-density lipoproteins (VLDLs) by α-tocopherol transfer protein and recirculated through the body.[94] The precise nature and function of tocopherol-associated proteins are unclear.[95] Parenchymal cells of extrahepatic organs including adipose, muscle, and brain take up α-tocopherol from all lipoproteins, particularly low-density lipoprotein (LDL) and high-density lipoprotein (HDL), through a number of mechanisms that can be receptor dependent or receptor independent.[96] At the cell level, tocopherol is mostly localized in the membranes. In human tissues, the predominant form of vitamin E is α-tocopherol.[97] Excess tocopherol is excreted into the bile and then into the feces. The metabolic products of α-tocopherol after oxidation are dimers and trimers, as well as tocopheryl chromanoxy radicals that can be reverted to tocopherol by reducing agents such as vitamin C and glutathione. Subsequent oxidation of the tocopheroxyl radical produces tocopheryl quinone, which, after reduction, can be excreted in the feces or converted into tocopheronic acid by side chain oxidation and excreted in urine as glucuronate conjugates.[90] Other nonoxidation metabolites of tocopherol's phytyl tail are excreted in urine. These include 2,5,7,8-tetramethyl-2-(2′-carboxyethyl)-6-hydroxychroman, or α-CEHC,[98] and γ-CEHC.

Functions

Vitamin E deficiency is associated with a large number of manifestations in animals, the most common of which is necrotizing myopathy. Encephalomalacia and exudative diathesis have also been described, in addition to embryonic degeneration. Vitamin E deficiency syndromes seem

to be specific to the animal species and also appear to depend on the status of other nutrients, such as selenium and some amino acids.[90] Most recent dietary recommendations are based exclusively on α-tocopherol, recognizing that the other naturally occurring forms of vitamin E (β-, γ-, and δ-tocopherol and tocotrienols) do not have vitamin E activity.[99] In humans, vitamin E deficiency is associated with neurologic alterations,[100] as reported in patients suffering from familial isolated vitamin E deficiency and pathologies causing malabsorption such as abetalipoproteinemia, cystic fibrosis, and cholestatic disease. Erythrocyte hemolysis occurs at a plasma concentration below 5 μg/mL (11.6 μmol/L).[101]

The specific mechanisms of vitamin E deficiency syndromes are not clearly understood. However, it is accepted that the most important function of vitamin E is protection against tissue damage caused by lipid peroxidation.[102] Primordial free radicals (eg, superoxide) can be originated in normal metabolism and through the effect of toxins. These free radicals may contribute to the formation of lipid free radicals when conjugated with polyunsaturated fatty acids (PUFAs). The lipid radicals undergo a propagation sequence whose final products are lipid hydroperoxides (LOOHs). LOOHs enter an auto-oxidative chain sequence until two radicals combine in a two-electron bond. Vitamin E prevents auto-oxidation in at least two steps: (1) it traps peroxyl radicals; thus, a stable LOOH molecule is formed with a vitamin E radical subproduct; and (2) this vitamin E radical can still bind to another lipid radical. It is estimated that one tocopherol molecule is enough to protect 100 PUFA molecules from auto-oxidation.[101] Some functions of vitamin E are strongly dependent on interactions with other nutrients. The antioxidant efficacy of tocopherol is enhanced by the presence of other antioxidant systems. The glutathione peroxidase system is selenium dependent and may explain the fact that selenium reduces the severity of vitamin E deficiency and that both may act synergistically against oxidative stress.[103] Ascorbic acid (vitamin C) appears to reduce the vitamin E requirement possibly owing to the role of vitamin C in tocopherol regeneration after it has been oxidized.[104] Betacarotene also may be a coadjuvant of vitamin E in its membrane antioxidant functions; on the other hand, vitamin E increases the lymphatic uptake of betacarotene and its conversion to retinol.[105] Iron and amino acids containing sulfur may also interact with vitamin E activities.[90]

Vitamin E appears to have other functions not necessarily related to its antioxidant role. Tocopherol may be an important structural part of cell membranes that contributes to stability and permeability.[106] It regulates the synthesis of xanthine oxidase, an important enzyme in the conversion of purine bases to uric acid,[107] and modulates the activity of microsomal oxidases, protein kinases, and proliferation of smooth muscle[108] and endothelial[109] cells. α-Tocopherol decreases the genetic expression of important regulatory receptors, the collagenase and scavenger receptor (SR-A and CD36), and up-regulates the expression of connective tissue growth factor.[110] Vitamin E has positive effects on the immune function at various levels. It inhibits the activity of cyclooxygenase in macrophages, thus decreasing the production of proinflammatory prostaglandins like prostaglandin E_2[111]; it also increases the mitogenic activity of T cells and the production of IL-2[112] and IFN-γ.[113] Vitamin E has anti-DNA mutagenic damage properties[114] and down-regulates the generation of hydrogen peroxide in the mitochondria.[115] These mechanisms could help explain the protective effects of vitamin E against degenerative pathologies in humans, such as certain cancers,[116] cardiovascular disease,[117,118] and Alzheimer's disease.[119]

VITAMIN K

Structure and Metabolism

Vitamin K was discovered by Henrik Dam in 1935 as a fat-soluble compound that prevented hemorrhagic disease in chicks.[120] Almost simultaneously, Almquist and Stokstad demonstrated the antihemorrhagic properties of an ether-soluble compound from alfalfa.[121] They also suggested that microbial activity in bran and fish preparations was related to antihemorrhagic activity. Later, Dam and colleagues demonstrated that prothrombin activity was diminished in vitamin K–deficient chicks,[122] and a few years later it would be shown that other coagulation factors were also dependent on vitamin K. Dam and Karrer's groups isolated the vitamin from alfalfa, and it was characterized and synthesized as a quinone by Doisy's group in 1939.[123] The same group discovered a form of the vitamin in putrified fish meal, and, in 1958, Martius and Esser showed that vitamin K could be formed in animals from the parent compound, menadione.[124] In the 1970s, vitamin K was shown to participate in the synthesis of γ-carboxyglutamic acid (Gla).[125]

Vitamin K describes all compounds with a 2-methyl-1,4-naphthoquinone ring (menadione or vitamin K_3) that have antihemorrhagic properties in animals fed a vitamin K–deficient diet. Two natural forms of the vitamin have been described: phylloquinone or vitamin K_1, which possesses a phytyl group in the –3 carbon and is the main dietary source of vitamin K from plants, and menaquinones or vitamin K_2, which is produced by bacteria and has an unsaturated isoprenyl side chain at position –3.[126]

Vitamin K is absorbed from the first half of the small intestine in micelles that form with the presence of pancreatic enzymes and bile salts. Absorption of pharmacologic preparations of phylloquinone in adult humans is about 80%, but it is significantly lower from food sources.[127] Whereas cooking and preparation do not appear to affect the bioavailability of vitamin K, addition of fat may increase its absorption by a factor of three.[128] After lymphatic absorption, phylloquinone circulates with lipoproteins, mostly VLDL, at low concentrations (0.3 to 2.7 μmol/L),[129] and is taken up by the liver from chylomicron remnants through apolipoprotein E receptors. The main storage organ for vitamin K is the liver, although it is also found at relatively high concentrations in trabecular and cortical bone, as well as in heart, pancreas, brain, and kidney.[126] The functional significance of the menaquinones

produced in the gut is not well understood. Dietary restriction of vitamin K has been related to deficiency in healthy humans, suggesting that the bioavailability of bacteria-produced menaquinones may be low[130] and not enough to avoid deficiency. The total pool of vitamin K is smaller compared with other vitamins and is rapidly exhausted under conditions of restricted intake.[131] Phylloquinone is excreted in the feces via the bile and the urine.

Functions

Vitamin K is fundamental for the carboxylation of a large number of proteins in vertebrates and invertebrates. Undercarboxylation of these proteins decreases their affinity for calcium and may render them nonfunctional. The process of carboxylation consists of transferring a carboxyl group from glutamic acid residues in proteins to form γ-Gla, in the presence of vitamin K–dependent carboxylase, hydroquinone, carbon dioxide, and oxygen.[132] This reaction occurs at the luminal surface of the endoplasmic reticulum. After carboxylation, vitamin K is oxidized to vitamin K 2,3-epoxide, which can be successively recycled to quinone and hydroquinone in reactions catalyzed by dithiol-dependent reductases. These reductases can be inhibited by coumarinic drugs such as warfarin, which explains their anticoagulant effects. There is an alternative pathway for reducing quinone into hydroquinone, which is catalyzed by a reduced form of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme and is therefore unaffected by coumarinics. It is possible to use this enzyme pharmacologically in the treatment of coumarin intoxication. Undercarboxylated proteins, also referred to as proteins induced by vitamin K absence (PIVKAs), can be used to assess vitamin K status (PIVKA-II or prothrombin and PIVKA-osteocalcin).[133]

Vitamin K–dependent proteins have been found mainly in blood and bone, although the newly discovered Gas6 protein has been found in vascular smooth muscle cell and the nervous system.[134] Blood proteins include prothrombin (factor II); factors VII, IX, and X; and proteins C, S, and Z.[135] All are synthesized in the liver and contain 12 Gla residues that facilitate calcium-mediated binding to membrane phospholipids in platelets and endothelial cells in the process of forming a clot. During the coagulation cascade, factors VII and IX activate factor X through the extrinsic and intrinsic pathways, respectively. Factor X activates the synthesis of prothrombin from thrombin. Proteins C and S are anticoagulants. The first one inhibits factors V and VII, and both increase fibrinolysis.

Bone vitamin K–dependent proteins are osteocalcin (bone Gla protein), matrix Gla protein, and protein S. Osteocalcin is produced by osteoblasts and odontoblasts and binds to hydroxyapatite crystals through its three Gla residues. Although the specific functions of osteocalcin remain unclear, it has been suggested that this protein may promote the differentiation of osteoclasts and induce bone resorption as well as closure of the growth plate. Osteoporosis has been associated with low plasmatic concentrations of vitamin K,[136] and vitamin K supplementation results in decreased undercarboxylated osteocalcin and increased bone density.[137] Supplementation is also related to lower incidence of osteoporosis and fractures[138]; however, it is suggested that these effects may be independent of the carboxylation function of vitamin K. Matrix Gla protein (MGP) appears to be an inhibitor of cartilage calcification. In animal studies, MGP depletion leads to calcification of arteries and heart valves, whereas low vitamin K intake among women is associated with calcification of the abdominal aorta.[139] This suggests a potential role for vitamin K in cardiovascular health. The role of protein S in bone is unknown; however, evidence from studies among protein S–deficient children suggests that it may be important in bone mineralization. Other recently discovered vitamin K–dependent proteins include nephrocalcin, atherocalcin (plaque Gla protein), and praline-rich Gla proteins 1 and 2.[126] Their function has not been established yet. Vitamin K appears to play a role also in the synthesis of some sphingolipids, possibly as a cofactor in phosphorylation reactions.

Deficiency of vitamin K is uncommon in adults. It may occur among patients with fat malabsorption from any cause. Some agents have been implicated in precipitating vitamin K deficiency states; these include antibiotics that inhibit the epoxide reductase (cephalosporin, cefamandole, moxalactam) and megadoses of vitamins A and E.[126] Newborns are at risk of hemorrhage during the first weeks after birth (hemorrhagic disease of the newborn), in association with vitamin K deficiency. This occurs because of limited transfer of the vitamin through placenta and breast milk and as a consequence of insufficient production of clotting factors in the liver. Prophylaxis is carried out by administering 0.5 to 1 mg phylloquinone intramuscularly or 2 mg orally within 6 hours of birth.[140] Analyses conducted by researchers in the United Kingdom in the early 1990s associated intramuscular vitamin K with an increased risk of childhood cancer, especially leukemia.[141,142] However, various subsequent studies with rigorous epidemiologic designs did not replicate these findings. Furthermore, no strong biologic evidence can support the purported association. Modification of existing recommendations supporting the use of an intramuscular dose to the infant after birth is therefore not warranted.[140] An additional motivation to administer an intramuscular dose of vitamin K to the newborn is that there is currently no licensed form of oral vitamin K available in the United States, that is, the parenteral form is given orally when needed. Some studies suggest that oral forms of vitamin K are less effective at reducing the risk of hemorrhagic disease of the newborn, yet new oral forms with greater reliability of absorption promise to be equally as efficacious as intramuscular vitamin K.[143,144] In least developed countries, stand-alone prophylactic programs of vitamin K are not recommended owing to the complicated delivery of the prophylaxis in the presence of a high percentage of at-home deliveries and constrained health budgets that should favor more cost-effective public health measures, such as prevention and treatment of infectious diseases. Vitamin K prophylaxis has been recommended for middle-income and industrialized countries given its demonstrated public health benefit.[145]

VITAMIN C

Structure and Metabolism

Medical writings from ancient Egyptians, Greeks, and Romans described a syndrome that was probably scurvy, the disease associated with vitamin C deficiency. The first modern accounts of scurvy appear in the sailing logs of the Portuguese and Spanish marine expeditions of the early sixteenth century.[146] During Vasco da Gama's expedition to the Cape of Good Hope, intake of oranges was associated with relief from the symptoms of scurvy. However, this practice did not become popular knowledge, and it was only in 1747, when James Lind conducted his famous clinical trial on board the British vessel *Salisbury*, that the dietary origin of scurvy was completely proven. It took the British navy another 50 years to routinely provide lemon juice to its sailors.[147] Zilva isolated a compound with antiscorbutic properties in 1915, and the name vitamin C was proposed because factors A and B had already been postulated. In the early 1930s, Szent-Gyorgyi, Haworth, and King isolated vitamin C and showed its antiscorbutic activity.[148] For this, Szent-Gyorgyi and Haworth received the Nobel Prize in 1937.

Vitamin C has been defined as a redox system composed of L-ascorbic acid, monodehydro-L-ascorbic acid (a free radical), and oxidized ascorbate (dehydro-L-ascorbic acid [DHA]).[149] Chemically, ascorbic acid is composed of a 6-carbon γ-lactone. Except in guinea pigs, bats, and primates, including humans, most animals can synthesize ascorbic acid from glucose via the hexuronic acid pathway. Humans lack L-gluconolactone oxidase, an enzyme necessary for the synthesis of ascorbic acid, and depend completely on the diet for the supply of vitamin C.[149] After ingestion, ascorbic acid is absorbed in the small intestine, preferentially in the distal segment, through a sodium-dependent mechanism that can be inhibited by glucose.[150] It then moves to the systemic circulation via facilitated diffusion and is oxidized to DHA, which enters the cells on glucose transporters 1, 2, or 4 by facilitated diffusion.[149] Once in the cell, it is reduced again to ascorbate by glutathione-dependent mechanisms. If this recycling reduction does not occur, DHA is degraded to oxalic acid and excreted in urine. Unmetabolized ascorbic acid is also excreted in direct proportion to intake, reaching 100% excretion after about 500 mg of an injected dose.[151] The recycling mechanism of ascorbic acid may be compromised in diabetics,[152] smokers,[153] and patients with the glucose transporter protein syndrome.[154]

Functions

Ascorbic acid maintains metal ions in a reduced state, which allows the proper function of some mixed-function oxidases in the synthesis of important molecules. Vitamin C deficiency affects collagen synthesis by impeding the hydroxylation of lysine and proline residues in precursor polypeptide chains, which become unable to fold into their final triple helical structure. The accumulation of immature collagen molecules is reflected in weakness of collagen-rich tissues and explains many of the symptoms of scurvy, including gum bleeding, bruising, and inadequate repair of damaged tissue. Vitamin C supplementation is effective in improving collagen synthesis among patients with the Ehlers-Danlos syndrome, who suffer from genetic abnormalities of lysyl hydroxylase. Vitamin C also plays an important role as a cofactor of hydroxylase enzymes involved in the synthesis of carnitine, a molecule that is necessary for the incorporation of long-chain fatty acids into the mitochondria. Carnitine deficiency and decreased oxidation of fatty acids in muscle may also be responsible for the muscular weakness characteristic of scurvy. Vitamin C is a cofactor of dopamine-β hydroxylase in the synthesis of norepinephrine from dopamine. The activation of other neutrotransmitters and hormones through α-amidation is also likely to depend on vitamin C.

Ascorbic acid possesses strong antioxidant properties. It acts as a scavenger of reactive oxygen and nitrogen radicals. In combination with vitamin E, ascorbic acid delays the formation of peroxyl radicals in LDL.[155] Vitamin C supplementation is associated with decreased concentration of oxidated DNA bases in human sperm[156]; however, a direct antioxidant effect of ascorbic acid in the nucleus has not yet been demonstrated. Some proteins may also be protected from oxidation by vitamin C. Ascorbic acid positively interacts with the glutathione system (GSH) as a scavenger of reactive oxygen radicals.

There is evidence to suggest that vitamin C is related to several aspects of the immune function. Ascorbic acid supplementation improves neutrophil chemotaxis. However, it does not appear to enhance bactericidal activity or lymphocyte proliferation. Vitamin C destroys histamine, and it has been suggested that this antihistaminic effect may be responsible for the reduction in the severity of cold symptoms that is observed among supplemented patients. In vitro assays indicate a possible antiviral role of the vitamin. It inhibits intracellular replication of HIV in chronically infected lymphocytes and inhibits the reverse transcriptase enzyme.[157] In humans, local application of ascorbic acid on herpes simplex lesions reduces viral shedding and accelerates the disappearance of the lesions.[158]

The antioxidant properties of ascorbic acid suggest that the vitamin could have protective properties against degenerative diseases such as atherosclerosis and cancer. Large supplemental doses of vitamin C have been related to decreased LDL peroxidation and improved vasomotor function in humans.[159,160] However, a protective effect of vitamin C against mortality from coronary heart disease or the incidence of cancers of the digestive tract has yet to be demonstrated in clinical trials. The potential effect of vitamin C against *Helicobacter pylori* infection is under investigation.

It is very likely that the effects of nutrients in vivo depend on interactions with each other rather than on the properties of a single nutrient. For example, the short-term absorption of nonheme iron is augmented by more than 100% by vitamin C, possibly because ascorbic acid increases the reduction of ferric iron to ferrous iron, which is less likely of chelation by phytates.[149] The benefit from this interaction in increasing the iron reserves among people consuming mainly nonheme iron seems to be lower.

THIAMIN

Structure and Metabolism

Descriptions of beriberi or *kakke*, the disease caused by thiamin deficiency, appeared in Chinese medical manuscripts more than four millennia ago. The prevalence of this polyneuritic paralysis had been traditionally higher in Far East societies with a high consumption of rice than in the rest of the world. However, it increased in Europe during the nineteenth century, with the advent of highly efficient polishing rice mills that remove the aleurone layer of thiamin-rich cells between the germ and the endosperm.[161] The first reference to a potential nutritional cause of beriberi appeared in 1884 when a Japanese surgeon, Takaki, showed that the prevalence of the disease in the navy could be reduced by feeding sailors meat, wheat, and milk instead of their usual diet, which consisted of polished rice and dried fish.[162] In 1890, a Dutch physician working in Java, Christian Eijkman, documented polyneuritis in chicken caused by a diet of polished rice and proposed that an antitoxin should be present in the bran. In 1901, Gerrit Grijns found that the antineuritic factor in rice bran was water soluble, and Casimir Funk coined the term "vitamine" in 1911 to refer to this compound.[1] Frazier and Stanton successfully used extracts of rice polishing to cure beriberi in humans in 1909 to 1915, and Roger Williams elucidated the structure of the vitamin in 1936.

Thiamin, also called vitamin B_1, vitamin F, and aneurine, is composed of a pyrimidine ring with an amino group and a thiazole ring with a sulfur group, linked by a methylene bridge. The natural form of the vitamin is a base, and the commercial form is usually a chloride hydrochloride salt. In addition to rice bran and wheat germ, thiamin is also abundant in yeast extract, pork meat and ham, animal liver and kidney, and vegetables, including peas, asparagus, and okra. The thiamin content of foods can be decreased by sodium bicarbonate, residual chlorine, excess water, sulfites, intense heating, alcohol, and irradiation with x-, gamma, and UV rays. There are also known antithiamin factors in foods, including thiaminase I, found in raw fish and fern, and thiaminase II, found in various microorganisms.[163] Some polyhydroxyphenols such as caffeic acid, chlorogenic acid, and tannins can also exhibit antithiamin properties. In humans, tea and coffee drinking may induce thiamin depletion, whereas ascorbic acid intake enhances thiamin status. After ingestion, thiamin is absorbed preferentially in the jejunum and ileum by an active, saturable, energy-dependent transport or by passive diffusion when the concentration is high. In the gut cells, phosphate esters are formed. Absorption can be inhibited by alcohol and folate deficiency.[164] Thiamin is transported from the general circulation to the liver mainly as thiamin pyrophosphate, which is the most abundant form of the vitamin. Although a specific thiamin-binding protein has been identified, its specific role is still unclear. The uptake mechanism by peripheral tissues varies and may consist of facilitated diffusion (as in erythrocytes) or active transport. High concentrations of the vitamin are found in skeletal muscle, heart, liver, kidney, and brain. Tissue depletion of thiamin occurs relatively rapidly under low dietary intake, and this is the reason why thiamin deficiency is one of the first to appear during nutritional emergencies.

Functions

Thiamin pyrophosphate (TPP) acts in conjunction with Mg^{2+} as a coenzyme in biochemical reactions involving active aldehyde transfers. These reactions can be grouped into (1) oxidative decarboxylation of α-keto acids and (2) transketolase reaction.[163]

Oxidative decarboxylation of α-keto acids includes (1) oxidative decarboxylation of pyruvic acid, the first step in the conversion of pyruvate to acetyl coenzyme A (CoA) in the mitochondria; (2) oxidation decarboxylation of α-ketoglutaric acid, a step within the tricarboxylic acid cycle in which α-ketoglutarate is converted into succinyl CoA; and (3) oxidative decarboxylation of branched-chain α-keto acids: α-ketoisocaproate, α-keto-β-methylvalerate, and α-ketoisovalerate, to produce isovaleryl CoA, α-methylbutyryl CoA, and isobutyryl CoA, respectively, in high energy–generating pathways. The transketolase reaction catalyzed by TPP occurs in the cytosol as part of the pentose phosphate pathway, whose primary purpose is to generate NADPH, an electron and hydrogen donor in the biosynthesis of fatty acids and pentoses.

Studies in animals suggest that thiamin may be necessary in the synthesis of neurotransmitters, including acetylcholine, catecholamines, serotonin, and amino acids with neurotransmitter functions that are produced through the oxidative metabolism of glucose such as γ-aminobutyric acid, glutamate, and aspartate. Thiamin also appears to play a role in nerve conduction, possibly mediated through the control of sodium channel proteins in axons.

Thiamin deficiency may be caused by suboptimal dietary intake, absorption, transport, or metabolism and by increased requirement or losses. In adults, beriberi can occur as a consequence of low intake of thiamin accompanied with high intake of carbohydrate from milled rice. Thiamin depletion is also related to fermented raw fish consumption, chewing betel nuts or fermented tea leaves, and chronic alcoholism. In the 1990s, nationwide shortages of intravenous multivitamins used in US hospitals and home health care agencies led to the development of acute thiamin deficiency among several patients receiving total parenteral nutrition.[165,166] The chief deficiency symptom in these patients was severe lactic acidosis, based on an impairment in the oxidation of α-keto acids. Patients who received treatment with parenteral thiamin showed rapid clinical improvements.

Infantile beriberi may be found in children 2 to 3 months of age whose mothers have low thiamin concentrations in breast milk. It may be manifested in any of at least four syndromes.[163] The cardiac or acute fulminating form is characterized by the rapid appearance of beriberi signs such as loud piercing cry, cyanosis, dyspnea, vomiting, tachycardia, and cardiomegaly; the prognosis is fatal unless thiamin is administered. The aphonic form is characterized by the child's voice tone, which may vary from hoarseness to total aphonia owing to paralysis of phona-

tion nerves. The pseudomeningitic form presents with neurologic abnormalities that may include vomiting, nystagmus, purposeless movement of the extremities, and convulsion with normal cerebrospinal fluid. In the mixed form, any combination of the cardiac, aphonic, or pseudomeningitic forms can be present.[163]

In adults, thiamin deficiency may be manifested as dry beriberi, wet beriberi, or the Wernicke-Korsakoff syndrome. Dry beriberi is usually characterized by peripheral neuropathy with sensory, motor, and autonomic compromises, predominantly of the distal segments of the limbs. Wet beriberi courses with signs of congestive heart failure. Wernicke's disease is an encephalopathy of acute onset characterized by ataxia of gait and paralysis of eye movements, usually accompanied by the Korsakoff psychosis, which consists of amnesia and other mental alterations. Alcoholism is a major factor in the etiology of Wernicke-Korsakoff syndrome.

Beriberi responds to the intravenous or intramuscular administration of large daily doses (50 to 100 mg) for 1 to 2 weeks, followed by daily oral doses of 10 mg.

RIBOFLAVIN

Structure and Metabolism

Riboflavin, or vitamin B_2, was discovered as a fluorescent "yellow growth factor" in the heat-stable fraction of antipellagra extracts found by McCollum and collaborators. It was synthesized by Kuhn and Karrer in 1935, and its structure was elucidated by Warburg and Christian in 1938.[167]

All riboflavin-related compounds possess an isoalloxazine ring. Riboflavin does not have significant physiologic functions, but it is the substrate for two major coenzymes: flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The former contains a phosphate group, and the latter is formed by a combination of FMN with adenosine triphosphate (ATP) in the presence of FAD pyrophosphorylase. FAD can be further metabolized and bound covalently to proteins. Riboflavin is very sensitive to UV radiation[168] and can be destroyed during phototherapy of neonatal jaundice. After ingestion, riboflavin coenzyme derivatives are hydrolyzed and absorbed in the small intestine by saturable, active transport. Alcohol and antacids decrease the absorption of the vitamin, whereas dietary fiber increases it. In blood, riboflavin is transported bound to albumin or Igs.[169] Riboflavin-binding proteins have been found in sera of pregnant women[170] that may have special functions in carrying the vitamin to the fetus or facilitating conversion to FAD, acting as enzymes. Excretion of riboflavin is mainly urinary as the precursor molecule; it is increased by boric acid and chlorpromazine.[171]

Functions

Riboflavin plays a key role in the production of energy through the coenzymatic activity of FAD in the respiratory chain. Many other reactions that involve oxidation and reduction are also catalyzed by flavin coenzymes. Regeneration of glutathione in the glutathione peroxidase antioxidant system requires FAD; thus, antioxidant defense against free radicals may be compromised during riboflavin deficiency. Results from observational and supplementation studies suggest that riboflavin deficiency may be protective against malaria.[172] Given that FAD is a coenzyme for the methyltetrahydrofolate reductase enzyme, it has been postulated that riboflavin status may play a role in homocysteine metabolism and is therefore related to the pathophysiology of cardiovascular disease.[167] No epidemiologic evidence is available to support this hypothesis.

Several signs and symptoms have been related to riboflavin deficiency in humans, including stomatitis, glossitis, dermatitis, keratitis, anemia, and neurologic dysfunction. However, there is not one specific clinical syndrome characteristic of deficiency as it occurs usually in the context of multiple nutrient deficiencies. In addition to suboptimal dietary intake, riboflavin deficiency may also be the consequence of thyroid or adrenal insufficiency or negative interactions with alcohol and some psychotropic, chemotherapeutic, and antimalarial medications. These drugs include chlorpromazine, imipramine, amitriptyline, doxorubicin, and quinacrine. Deficiency of vitamin B_2 may impair the absorption of iron and the conversion of vitamin B_6 to its active coenzymatic metabolite.

NIACIN

Structure and Metabolism

Pellagra, the manifestation of niacin deficiency in humans, was first described in 1735 in Spain as a disease primarily affecting the very poor. The disorder was soon recognized throughout southern and eastern Europe as well as Egypt, where corn became the major food crop. The disease was also common in the United States in the early twentieth century, where it affected hundreds of thousands of people, with up to 7,000 reported deaths annually.[173] Nicotinic acid, one chemical form of niacin, was first isolated in 1867, but it was not until the work by Goldberger starting in 1914 that pointed to pellagra being a nutritional deficiency disease. In 1937, nicotinic acid was shown to cure the manifestation of pellagra in dogs and humans.[174]

The term niacin refers to nicotinic acid (pyridine-3-carboxylic acid), nicotinamide (nicotinic acid amide), and functional derivatives of nicotinamide. The two coenzyme forms of niacin, nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), participate in the catalysis of oxidation and reduction (redox) reactions. In addition, NAD exhibits several nonredox functions.

Absorption of nicotinic acid and nicotinamide in the stomach and intestine occurs via facilitated diffusion at low niacin concentrations and passive diffusion at higher concentrations. The major food forms of niacin, NAD and NADP, are converted by enzymatic action in the gut mucosa to nicotinamide. Nicotinamide constitutes the major form of niacin in the blood and serves in the tissue synthesis of NAD when needed. However, both NAD and NADP can be synthesized in all tissues of the body from nicotinic acid or nicotinamide. Excess niacin is excreted in the urine, mainly in the forms of N^1-methylnicotinamide and 2-pyridone. Measurement of these two urinary metabolites serves to assess niacin status.

Niacin is unique among the B vitamins in that it can be synthesized from a precursor molecule. The essential amino acid tryptophan can be converted to NAD via the formation of quinolinic acid and nicotinic acid ribonucleotide. An average conversion ratio of 60 mg tryptophan to 1 mg niacin has been proposed, but such a summary figure fails to account for variation introduced by other nutritional and hormonal factors (see below).

Functions

The metabolically active forms of niacin are NAD and NADP. These active forms participate in a wealth of redox reactions in which they serve as coenzymes for oxidoreductase enzymes. The niacin coenzymes transfer two electrons at a time without the formation of one-electron intermediates. NAD cycles between the oxidized form NAD+ and the reduced form NADH + H^+. Similarly, NADP cycles between $NADP^+$ and NADPH + H^+. The coenzyme function of niacin is a key component of a variety of metabolic pathways affecting carbohydrate, lipid, and amino acid metabolism.

NAD generally functions as an electron acceptor in catabolic reactions that produce energy (eg, the citric acid cycle). NADP tends to participate in biosynthetic pathways such as fatty acid synthesis, cholesterol synthesis, and the pentose phosphate pathway. NAD also participates as a substrate for enzymes in nonredox pathways that catalyze the transfer of adenosine diphosphate (ADP)-ribose moieties.[175] The enzymes mono-ADP-ribosyltransferases and poly-ADP-ribose polymerase (PARP) catalyze the donation of ADP-ribose to acceptor proteins and the enzyme ADP-ribosyl cyclase catalyzes the synthesis of cyclic ADP-ribose.[176] In prokaryotic cells, mono-ADP-ribosyltransferases produce substances acting as toxins (eg, diphtheria and cholera toxins), whereas in eukaryotic cells, they are thought to participate in signal transduction by modulating G protein activity.[177] PARP activity is augmented during cell growth and differentiation and was shown to control the repair of DNA in human cell extracts.[178] However, more research is needed to determine the role of PARP in the prevention of carcinogenesis. Via the synthesis of cyclic ADP-ribose, ADP-ribosyl cyclase triggers the release of calcium ions from an internal storage site, which is important in cell signaling.[176]

The classic symptoms of the niacin deficiency disease pellagra can be summarized as dermatitis, diarrhea, dementia, and potentially death (often called "the four Ds"). Pellagra develops when dietary niacin and tryptophan are insufficient to meet niacin requirements. Human experiments indicate that pellagra develops after 50 to 60 days on a corn diet, which is low in both bioavailable niacin and tryptophan.[177] Other dietary factors may contribute to the development of pellagra by inhibiting the conversion of tryptophan to niacin. They are excessive intake of the amino acid leucine and inadequate intakes of iron, riboflavin, or vitamin B_6. Pellagra-like symptoms in humans have also been reported after prolonged isoniazid treatment, during malignant carcinoid syndrome, and in Hartnup disease. On the other hand, there is evidence that the conversion of tryptophan to niacin is augmented considerably among pregnant women and women taking oral contraceptives.[179]

Pharmacologic doses of nicotinic acid (but not nicotinamide) in the range of 1.5 to 4 g/day have proven effective at reducing the risk of atherosclerotic heart disease.[180] This risk reduction is brought about by an improvement in the blood lipid profiles of at-risk patients, such as reduction of total cholesterol, LDLs, and triglycerides and increases in HDLs.[180]

VITAMIN B6

Structure and Metabolism

The term vitamin B_6 encompasses a group of compounds that are metabolically interchangeable and that in their free form are named pyridoxine (an alcohol), pyridoxal (an aldehyde), and pyridoxamine (an amine). The vitamin also exists in phosphorylated versions of these forms, namely as pyridoxine phosphate, pyridoxal phosphate (PLP), and pyridoxamine phosphate (PMP). Vitamin B_6 was discovered in 1934 while investigating the etiology of the niacin deficiency disease pellagra, and its structure was determined in 1939.

The major forms of the vitamin B_6 in foods are pyridoxine, PLP, and PMP. Pyridoxine is the form used in vitamin supplements. Vitamin B_6 is absorbed by passive diffusion in the small intestine. Because only free forms of the vitamin can enter the intestinal mucosa, the phosphate ester forms of the vitamin first have to be hydrolyzed to yield the free absorbable forms. PLP is the major form of the vitamin in plasma and is the major coenzyme expressing vitamin B_6 activity. The formation of PLP requires the riboflavin-dependent coenzyme FMN.[181] Phosphorylation of free forms of the vitamin to yield functional PLP occurs in most tissues of the body but to the greatest degree in the liver. About three-quarters of the body's vitamin B_6 pool are present in muscle. This pool is resistant to depletion even after prolonged intake of a vitamin B_6–deficient diet, which indicates that muscle vitamin B_6 is not a storage form of the vitamin that can be drawn on in times of inadequate vitamin B_6 intakes.[182] Catabolism of vitamin B_6 occurs mostly in the liver and excretion of the vitamin occurs in the urine, predominantly as pyridoxic acid.[183]

Functions

Vitamin B_6, via its main cofactor form PLP, features prominently in the metabolism of amino acids. PLP facilitates the transfer of amino groups and is thus critical for the production of nonessential amino acids. For example, PLP is a cofactor for the enzyme glutamate-oxaloacetate aminotransferase, which catalyzes the formation of aspartic acid from glutamate. PLP acts as a cofactor in the conversion of the amino acid tryptophan to active niacin and to the neurotransmitter serotonin. It is also involved in the synthesis of other neurotransmitters, such as epinephrine, norepinephrine, and γ-aminobutyrate. In the transsulfuration pathway from homocysteine to cysteine, PLP acts in concert with cystathione synthase to convert homocysteine to cystathione. In the breakdown of glycogen, PLP aids to liberate glucose-1-phosphate and is also part of nucleic acid biosynthesis stimulating 1-carbon metabolism. Other functions include the synthesis of carnitine and the production of compounds necessary for phospholipid biosynthesis.

Vitamin B_6 deficiency is first evidenced by decreases in plasma PLP levels and lowered amounts of the excretory product 4-pyridoxic acid in the urine. Continued vitamin B_6 deficiency leads to seborrheic dermatitis and decreased synthesis of neurotransmitters, resulting in depression, confusion, and abnormal brain wave patterns as indicated by abnormal electroencephalograms. Infants fed vitamin B_6–deficient formula are also at risk of developing convulsions.[184] Hematologic features of vitamin B_6 deficiency may include microcytic anemia, decreased lymphocyte levels, and impaired blood clotting. Levels of vitamin B_6 in breast milk are dependent on maternal intakes of the vitamin, and there is evidence that lactating mothers who consume inadequate levels of vitamin B_6 pass on deficient amounts of the vitamin to the infant.[185]

Vitamin B_6 deficiency in humans most commonly occurs in the elderly, alcoholics, individuals consuming vitamin B_6 antagonists such as penicillamine, and several inborn errors in vitamin B_6 function. Impairments resulting from genetic conditions have been shown to respond to high doses of supplemental vitamin B_6.[186]

FOLATE

Structure and Metabolism

Folate is a generic term for a family of compounds that have nutritional properties of the simplest form of the vitamin, folic acid. Clinical folate deficiency was first described in 1931 as a tropical "macrocytic anemia" that was distinct from the signs of pernicious anemia, which is an autoimmune disease leading to vitamin B_{12} deficiency.[187] The structure of folic acid was elucidated in 1945, and the understanding of its biochemical functions has rapidly grown since then. In recent years, folate has received considerable attention in the prevention of cardiovascular disease, cancer, and neural tube defects.[188]

Folic acid (pteroylglutamic acid) consists of a pteridine bicyclic ring system linked to p-aminobenzoic acid, which is connected by a peptide bond to glutamic acid. Folic acid is the chemical form used in synthetic folate supplements but does not occur in appreciable amounts in foods. Rather, most folates in nature occur as polyglutamates, with five to eight glutamate residues joined to the first glutamate. Next to modifications of the length of the glutamate chain, the vitamin may be modified by reduction of the pteridine ring system to generate dihydrofolic acid and tetrahydrofolic acid (THF). The N-5 and N-10 positions of THF, either individually or in concert, can carry 1-C units, including methyl (–CH3), formyl (–HCO), methylene (–CH2), formyl (–CH = O), or formimino (–CH = NH) groups. THF is the biologically active coenzyme and accounts for the 1-C transfer characteristic of folate-requiring reactions.

Naturally occurring folylpolyglutamates need to undergo hydrolysis for efficient absorption of dietary folate to occur. In the enterocyte, the membrane-bound enzyme γ-glutamylhydrolase catalyzes the hydrolysis of folylpolyglutamates to folylmonoglutamates. Transport across the brush border membrane of folylmonoglutamates occurs by a pH-dependent carrier-mediated mechanism.[189] At high intraluminal concentrations (> 10 μmol/L), a nonsaturable ion-mediated transport mechanism dominates folate absorption.[190] In the bloodstream, the predominant form of the vitamin is 5-methyl-THF-monoglutamate. After cellular uptake, folylmonoglutamates are converted back to folylpolyglutamates to retain the vitamin in the cell, strengthen the binding of the vitamin to folate-dependent enzymes, and allow for channeling reactions to occur.[191] Excess folate is excreted in the form of cleavage products in the urine. Fecal losses of folate occur as well but are difficult to quantify.

Functions

Folate, in the form of its primary coenzyme form THF, functions in the transfer of 1-C compounds needed in the metabolism of amino acids, purine and pyrimidine synthesis, and the *S*-adenosylmethionine (SAM) (Figure 7-3). In the metabolism of amino acids, serine can transfer a methylene group to THF to form glycine and 5-10-methylene-THF. The latter can be reduced to 5-methyl-THF, which functions in the methylation of the amino acid homocysteine to methionine using vitamin B_{12} as a cofactor.

5-10-Methylene-THF can also donate a methyl group for the formation of the pyrimidine thymidylate, a necessary precursor of DNA synthesis and erythrocyte formation. Action of the enzyme C1-THF synthetase converts 5-10-methylene THF to 10-formyl THF, which is necessary for the de novo synthesis of the purines adenine and guanine. Folate donates a methyl group to methionine to generate the methyl donor SAM, whose methyl donation is involved in more than 100 physiologic reactions. Examples include the methylation of DNA, ribonucleic acid, and membrane phospholipids.

The first manifestation of folate deficiency is a decline in serum folate levels, occurring approximately after 2 weeks of consumption of a folate-deficient diet. Hyperpigmentation of neutrophils and a rise in homocysteine levels can be noted, and abnormally nucleated erythrocytes start to appear in the bone marrow. If folate deficiency continues, megaloblastic anemia can occur. It should be noted that such hematologic changes can also be induced by diseases other than folate deficiency. Owing to the rapidly dividing nature of cells lining the gastrointestinal tract and the unmet need for folate for DNA synthesis, gastrointestinal symptoms are common in folate deficiency. Elevated plasma homocysteine concentrations, as occurring during folate deficiency, have been associated with increased risk of atherosclerotic vascular disease in adult life.[192,193] Folate supplementation has been shown to reduce homocysteine levels, and research is under way to examine the effect of folate supplementation on cardiovascular disease.[194] Poor folate status has also been associated with increased risk of cancer, especially colon cancer. This may be explained by folate's role in normal synthesis and methylation of DNA.[195]

Adequate folate status early in pregnancy greatly decreases the risk of neural tube defects, the most common major congenital abnormality in many countries.[196]

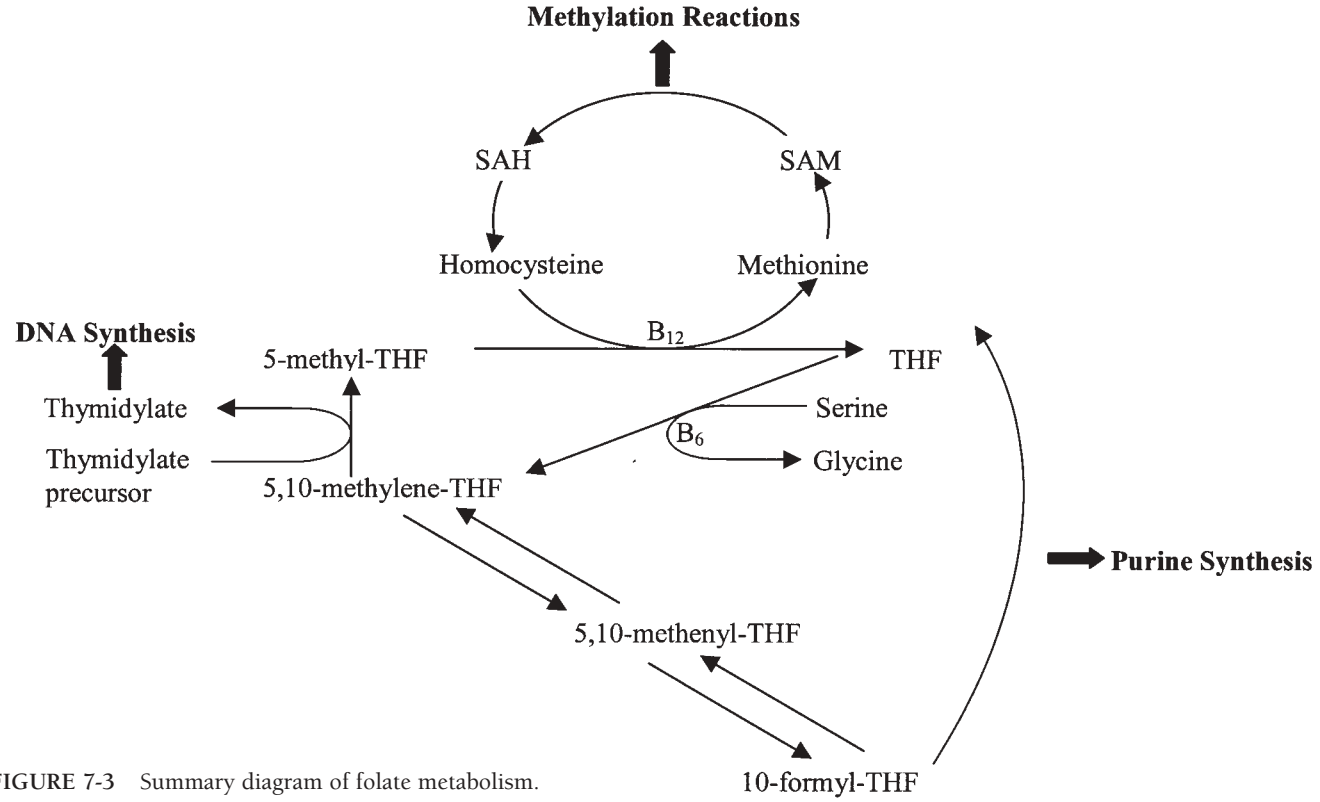

FIGURE 7-3 Summary diagram of folate metabolism.

For this reason, folic acid has been added to enriched grains and mixed food items containing these grains in the United States since 1998 at levels of 0.14 mg/100 g flour.[197] Fortified grains have thus become a good source of folate, and there is evidence that the folate status of the general population has increased as a result of this fortification program. Benefits of this fortification program are possible for disorders other than neural tube defects, such as cardiovascular disease.[198]

Folate requirements increase during pregnancy owing to the requirements of the growing fetus and related tissues. Folate secreted in milk also increases requirements during lactation. Folate deficiency during infancy may result from inadequate intakes of the vitamin, such as in infants fed on goat's milk, which is a poor source of folate. Deficiencies may also occur owing to impaired absorption of the vitamin and after intake of a range of medications, including methotrexate, anticonvulsants, and anticancer drugs that have antifolate activity.

VITAMIN B_{12}

Structure and Metabolism

The symptoms of the vitamin B_{12} deficiency disorder pernicious anemia were first described in the mid-nineteenth century. In 1926, large quantities of liver were shown to normalize the hematologic symptoms of pernicious anemia. Vitamin B_{12} was first successfully isolated in 1948 and chemically synthesized in 1973.

Vitamin B_{12} is a large molecule similar to porphyrin that has a complex ring structure (corrin ring). At its center, it possesses a cobalt molecule. Its chemical name is cobalamin, and it is solely synthesized by microorganisms. Animals consuming the vitamin conserve it in the liver in the chemical forms methylcobalamin, adenosylcobalamin, and hydroxocobalamin. Supplemental forms of vitamin B_{12} are generally in the form of cyanocobalamin, but hydroxocobalamin has also been used as a supplemental form.

In vitamin B_{12} absorption, parietal cells of the gastric mucosa secrete intrinsic factor, which is a highly specific glycoprotein for the vitamin. Absorption of the vitamin takes place at receptor sites in the distal ileum. The main serum transport protein for vitamin B_{12} is transcobalamin II (TCII). However, the vitamin B_{12} bound to TCII accounts for only 20% of the vitamin in serum. Cellular uptake of the TCII-B_{12} complex proceeds via receptor-mediated endocytosis, and cyanocobalamin is subsequently released in the lysosome. Cyanocobalamin is readily converted in the body to the two active coenzyme forms methylcobalamin and 5-deoxyadenosylcobalamin. Vitamin B_{12} is stored in the liver bound to TCI. Liver storage makes vitamin B_{12} unique among the water-soluble vitamins. Vitamin B_{12} is continuously secreted into bile, yet the majority of the secreted vitamin is reabsorbed in the process of enterohepatic circulation. Excess vitamin B_{12} is excreted in the urine, and losses also occur by the fecal route.

Functions

Vitamin B_{12} is required by all DNA-synthesizing cells, including those of the hematopoietic and nervous system. Its function is closely tied with that of folate in methyl

transfer reactions and synthesis of purines and DNA. Vitamin B_{12}, in its methylated form methylcobalamin, is required by methionine synthase for the methyl transfer from 5-methyl-THF to homocysteine to yield the end products methionine and THF (see Figure 7-3). In the absence of vitamin B_{12}, folate becomes trapped in its inactive form, 5-methyl-THF, DNA synthesis is impaired, and megaloblastic anemia develops. This type of anemia is indistinguishable to that induced by folate deficiency. Vitamin B_{12} is also a cofactor for leucine aminomutase, yet this enzyme is not vitally important in metabolism.[191–199]

In the form of its second active coenzyme form 5-adenosylcobalamin, vitamin B_{12} is required for the enzyme L-methylmalonyl-CoA mutase to convert L-methylmalonyl-CoA to succinyl-CoA in an isomerization reaction. Lack of production of succinyl-CoA by this pathway in the presence of vitamin B_{12} deficiency is unlikely to have serious metabolic consequences as succinyl-CoA is abundantly derived from fats and carbohydrates. However, accumulation of L-methylmalonyl-CoA in the cell can lead to increased production of odd-chain and branched-chain fatty acids through a sequence of reactions. Such fatty acids may be abnormally incorporated into nerve cell membranes, and it is hypothesized that they may account for neurologic symptoms owing to degeneration of myelin nerve sheaths.[191] Such neurologic symptoms may include tingling and numbness sensations in the extremities, motor disturbances, and cognitive changes such as loss of concentration and dementia. In extreme cases, the degeneration of peripheral nerves may progress to irreversible paralysis. Neurologic complications may in some cases present without hematologic symptoms. In fact, there is evidence of an inverse association between the prominence of neurologic complications and the severity of anemia, that is, more prominent neurologic complications tend to occur in individuals who are less anemic.[200,201] It should be noted that folate deficiency cannot induce neurologic complications.

Vitamin B_{12} deficiency is commonly attributable to poor absorption and less as a result of inadequate intake. Infants and children with diseases or resection of the terminal ileum (eg, Crohn's disease, short-bowel syndrome) are at risk of vitamin B_{12} deficiency. Malabsorption can also be attributable to pernicious anemia, a chronic atrophic gastritis that is characterized by the presence of autoantibodies to parietal cells, which causes loss of these intrinsic factor–producing cells. Autoantibodies to intrinsic factor have also been demonstrated.[202] Pernicious anemia in children is generally the result of a genetically determined defect in secretion of intrinsic factor or the secretion of a defective intrinsic factor.[203,204] The vitamin deficiency can be corrected by large monthly injections of vitamin B_{12}.

Vegan mothers, who are at risk of vitamin B_{12} deficiency and who may have depressed vitamin B_{12} in their breast milk, are advised to supplement their infants with vitamin B_{12} supplements from birth. Vitamin B_{12} can be effectively diagnosed by a variety of tests (see Table 7-2).

BIOTIN

Structure and Metabolism

Biotin was first isolated in 1935 from dried egg yolk, and its structure was established in 1942.[205,206] The total synthesis of the vitamin was achieved shortly thereafter. Biotin is an imidazole derivative widely distributed in foods, where it is mostly bound to proteins. Digestion of dietary protein releases biotinyl peptides, and intestinal biotinidases further hydrolyze biotinyl peptides to biotin. At low luminal biotin concentrations, the vitamin is absorbed by a sodium-dependent saturable process, whereas a nonsaturable process dominates at higher luminal biotin concentrations. Intestinal transport of biotin is faster in the jejunum than in the ileum and is very low in the colon. Biotin-producing microorganisms exist in the colon and may contribute to biotin requirements. Information on the transport mechanism of biotin to the liver and other tissues is scarce, but it is known that the liver contains significant amounts of the vitamin. Urinary losses are the major excretory route, but some losses also occur through the biliary route.

Functions

Biotin acts as a component of four ATP-dependent multisubunit enzymes that catalyze carboxylase reactions needed in energy metabolism, fatty acid synthesis, and amino acid metabolism. As a cofactor for pyruvate carboxylase, biotin aids in gluconeogenesis and replenishment of oxaloacetate for the citric acid cycle. As part of propionyl-CoA carboxylase, it helps convert propionate to succinate, which also participates in the citric acid cycle. The biotin-dependent enzyme acetyl-CoA carboxylase catalyzes the production of malonyl-CoA necessary for fatty acid synthesis, and with biotin as a cofactor, β-methylcrotonyl-CoA carboxylase metabolizes the amino acid leucine.

Human biotin deficiency is extremely rare. First, symptoms of biotin deficiency are depressed levels of the vitamin in urine, and other deficiency symptoms include nausea, vomiting, depression, dry, scaly dermatitis, glossitis, and hair loss. The egg protein avidin binds biotin tightly and prevents absorption of the vitamin; however, avidin is heat labile, and biotin deficiency can occur only in people who eat large amounts of raw eggs over many months.[191] The vitamin is synthesized by the intestinal microflora and colonic absorption occurs; controversy persists, however, over how much synthesized biotin can contribute to meet human requirements.[207]

Several genetic defects can induce potent biotin deficiency. Infants with a genetic defect in the enzyme biotidinase fail to recycle biotin and lose large amounts of biotin metabolites in the urine. Symptoms generally occur after the first week of life but before age 1 year and include poor feeding; vomiting; rash around the eyes, nose, and mouth; and neurologic symptoms such as muscle pain, lethargy, and numbness. Biotidinase deficiency is rare, with an incidence of about 1 in 120,000.[208] Genetic defects may also induce deficiencies in individual and multiple carboxy-

lases, which cause biotin deficiency symptoms and accumulation of substrates. Pharmacologic doses of oral biotin restore normal function.[209]

PANTOTHENIC ACID

Structure and Metabolism

Pantothenic acid was discovered in the 1930s as a growth factor for yeast. The structure of the vitamin was established in 1938, and its essentiality for human nutrition was first reported in 1954.[210] Pantothenic acid is formed by combination of pantoic acid and β-alanine. In food, the vitamin is present as CoA or as 4′-phosphopantetheine (Ppant). Hydrolysis of CoA and Ppant in the intestinal lumen renders the vitamin readily absorbable. After absorption, the vitamin is transported in the bloodstream to various tissues, where synthesis of CoA occurs from pantothenic acid, ATP, and cysteine. Pantothenic acid is not directly involved in the synthesis of the cofactor Ppant as the reaction proceeds from CoA as substrate. Excretion of the vitamin occurs in the urine, primarily as pantothenic acid.

Functions

As a constituent of CoA, pantothenic acid plays a key role in the metabolism of carbohydrates, proteins, and fats. CoA functions in the transfer of an acetyl group in many vital reactions, such as in the citric acid cycle, the synthesis of cholesterol, hormones, neurotransmitters, phospholipids, and antibodies. CoA is also involved in the metabolism of drugs, such as sulfonamides. Ppant is a cofactor of fatty acid synthase, to which it is covalently bound.

Pantothenic acid deficiency in humans is rare. Historically, it has been implicated in the "burning feet" syndrome, a condition noted among malnourished prisoners of war during World War II. Experimental states of pantothenic acid deficiency have been created by feeding synthetic diets devoid of pantothenic acid or by administering pantothenic acid antagonists.[211,212] Manifestations of deficiency may include neurologic symptoms such as listlessness, fatigue, headaches, tingling sensations in arms and legs, and gastrointestinal symptoms such as vomiting, abdominal cramps, and flatulence.

CONCLUSION

This chapter highlighted the main functions of vitamins and stressed the importance that adequate vitamin status plays in the well-being of infants and children. Our understanding of the functions of individual vitamins has grown considerably in the last five decades. However, a lot remains to be learned about interactions between vitamins and other nutrients. A heightened awareness of such interactions is likely to translate into improved pediatric care because deficient and excess intakes of nutrients generally occur in concert and because the metabolic pathways of many nutrients are interrelated. More research is also needed to accommodate the special needs of infants born prematurely or with low birth weight, those receiving parenteral nutrition, and those suffering from infections. During adolescence, vitamin malnutrition is still a problem in the United States and deserves particular attention. Data from US national surveys indicate that a significant proportion of adolescents consume inadequate amounts (< 75% RDA) of vitamins A, B_6, C, and E.[213] The high prevalence of inadequate intakes was present despite reported supplement intakes in one-third of the adolescents surveyed, which may indicate that those at nutritional risk are less likely to consume supplemental doses.[210] Vitamin nutrition needs to be improved on a scientific level, that is, to establish recommendations taking into consideration possible nutrient interactions and particular physiologic and disease states, as well as on a policy and programmatic level, to help children attain existing levels of recommended intakes.

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CHAPTER 8

THE PRUDENT DIET: PREVENTIVE NUTRITION

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CONCERNS FOR LEVELS OF BLOOD CHOLESTEROL IN CHILDREN AND ADOLESCENTS

Atherosclerosis begins in childhood and progresses into adulthood, at which time it leads frequently to coronary heart disease (CHD), the major cause of death in the United States.[1,2] The disease is responsible for more than 500,000 deaths annually. Estimates of the annual cost of CHD range less than $74 billion.[3] Hospital discharges for acute CHD are often for premature disease (ie, in patients under 55 years of age) because of familial factors. Many of these adults have children who may have CHD risk factors needing treatment.

Elevated cholesterol levels early in life play a role in the development of adult atherosclerosis; eating patterns and genetics affect blood cholesterol levels and CHD risk.[3] Risk factors for atherosclerosis and CHD may originate early in life and should be addressed. Specifically, cigarette smoking should be discouraged, hypertension should be identified and treated, obesity should be avoided or reduced, regular aerobic exercise should be encouraged, and diabetes mellitus should be diagnosed and treated.

Diet, Blood Cholesterol, and Coronary Heart Disease

Research provides evidence linking diet, blood cholesterol levels, and CHD. Most human studies have been conducted in adults because overt, clinical CHD does not usually occur until adulthood. However, data now available support the view that atherosclerosis begins in childhood and is related to cholesterol levels and thus to nutritional factors.

Lipoprotein Metabolism

Lipoproteins play a distinctive role in cholesterol transport and apparently in atherogenesis. Research shows that low-density lipoproteins (LDLs) are atherogenic, whereas high-density lipoproteins (HDLs) may provide protection against atherosclerosis.[3–8]

Studies in laboratory animals demonstrate that high blood cholesterol levels promote atherosclerosis.[9] Diets that raise total cholesterol and LDL cholesterol levels result in atherosclerosis in many species. Hypercholesterolemic animals develop intimal lesions that progress from fatty streaks to complicated ulcerated plaques.[10,11] Studies in adolescent, nonhuman primates show that they also develop fatty streaks and fibrous plaques after a diet high in cholesterol and saturated fatty acid (SFA), similar to but less extensive than adults in that study.[12,13] Severe atherosclerosis in monkeys regresses when blood cholesterol is lowered substantially for an extended period by diet or drugs.[9,14,15] These studies support the view that there is a causal relationship between LDL cholesterol and atherosclerosis and suggest that atherosclerosis may be reversible.

Several human genetic dyslipidemias have in common raised concentrations of cholesterol-rich lipoproteins, resulting from specific gene mutations. These disorders are characterized by severe atherosclerosis and often by the occurrence of CHD at a young age. The most striking example is familial hypercholesterolemia, either in its more common heterozygous form (prevalence 1 in 500) or in its rare but much more severe homozygous form (prevalence 1 in 1 million).[3] Other examples are familial dysbetalipoproteinemia[16] and familial combined hyperlipidemia.[17]

Many epidemiologic studies target LDL cholesterol levels as one of several major risk factors for CHD in men and women. The Framingham Heart Study, the Honolulu Heart Program, the British Regional Heart Study, and studies of men screened for the Multiple Risk Factor Intervention Trial (MRFIT) show that blood cholesterol levels are a powerful and independent predictor of CHD; on average, each 1% rise in cholesterol is associated with an approximate 2% increase in CHD risk.[18–24] Recently, Davis and colleagues suggested that this relationship was underestimated because of failure to take into account intraindividual variations in cholesterol levels.[25] In fact, each 1% rise in blood cholesterol is associated with an approximate 3% increase in risk. The level of HDL cholesterol, in contrast, is inversely and independently related to CHD in both sexes and at all ages (Table 8-1).[26]

In countries where CHD mortality is highest, children's cholesterol levels are higher than in countries where CHD mortality is lower.

Recommendations for a comprehensive program of blood cholesterol lowering are based on clinical trial evidence that cholesterol lowering is effective and safe in reducing CHD risk in adults.

Clinical trials in adults show that cholesterol lowering reduces coronary risk. In the Coronary Primary Prevention Trial (CPPT), cholestyramine-induced cholesterol lowering in hypercholesterolemic middle-aged men produced an average 19% reduction in definite fatal and/or nonfatal myocardial infarction over 7 years. Men who took the full dose of resin lowered their cholesterol levels by more than 25% and reduced their risk of CHD by half.[27,28] The Helsinki Heart Study compared gemfibrozil therapy with use of a placebo in hypercholesterolemic, middle-aged men, producing a moderate reduction in LDL and a moderate increase in HDL, with a reduction of 34% in fatal and nonfatal myocardial infarction.[29] A follow-up of patients with a prior history of myocardial infarction, who had received nicotinic acid for 5 years in the Coronary Drug Project, resulted in reduced total and cardiovascular mortality in the nicotinic acid group when compared with the control group.[30] Both the Stockholm Ischaemic Heart Disease Secondary Prevention Study and the Oslo Study Diet and Antismoking Trial reported beneficial outcomes, including reduced total mortality, with reduction of cholesterol levels.[31,32] Follow-up of the MRFIT showed that lowering blood cholesterol level, drug treatment of hypertension, and counseling to achieve smoking cessation in high-risk men resulted, 10.5 years later, in a 10.6% reduction in deaths from acute myocardial infarction and a 7.7% reduction in total mortality compared with a control group.[24] Aggregate analysis of these and many other clinical trials shows that cholesterol lowering, whether induced by diet or by various drugs, in the context of either primary or secondary prevention, reduces fatal and nonfatal myocardial infarction.[33]

Initially, there had been some controversy about the cholesterol hypothesis because a number of these trials did not find a significant reduction in total mortality following cholesterol-lowering treatment.[9] These findings may be related, in part, to relatively small sample sizes or trials of relatively short duration. A number of studies (Coronary Drug Project, Stockholm Ischaemic Heart Disease Secondary Prevention Study, and Oslo Study Diet and Antismoking Trial) have demonstrated clear reductions in total mortality as well as CHD mortality, and a fourth, the Program on the Surgical Control of the Hyperlipidemias (POSCH), showed a trend in this direction.[30–32,34,35]

Several angiographic studies report the beneficial effects of lowering cholesterol. Following the National Heart, Lung, and Blood Institute (NHLBI) type II trial, the results suggested that lesions can be stabilized and progression can be slowed.[36] The 1987 results of the Cholesterol Lowering Atherosclerosis Study further indicated that regression of existing lesions can be obtained in a proportion of patients.[37] Other studies show more regression in the treated groups than in control groups, and the conclusion now seems inescapable that definite regression can be expected in 16 to 47% of patients provided that large decreases in LDL cholesterol (of the order of 34 to 48%) are induced for a period of 2 to 5 years.[35,38–40]

In summary, many studies demonstrate that lowering elevated blood cholesterol levels in adults by diet or drug treatment, or both, favorably affects development, progression, and even regression of atherosclerotic plaques. No studies provide direct proof that lowering blood cholesterol levels in children and adolescents will reduce their risk of CHD in adulthood. Such studies may never be possible because they would involve large numbers of children over several decades. Because no available evidence exists in children's diet, the available adult evidence strongly suggests that the benefit of reducing cholesterol levels in childhood will be realized in adulthood, and conclusions drawn from adult studies support the belief that long-term benefit can be expected from lowering cholesterol levels in childhood. The safety, efficacy, and acceptability of a lower total fat, saturated fat, and cholesterol dietary intake have been shown in the Dietary Intervention Study in Children (DISC) and the STRIP Baby Project.[41–43]

TABLE 8-1 Dietary Saturated Fat and Cholesterol Intake, and Serum Total Cholesterol in Boys Ages 7–9 in Six Countries

	Dietary Intake		*Serum Total Cholesterol*
Country	*Saturated Fat (% of energy)*	*Cholesterol (mg/1,000 calories)*	*(mg/dL)*
Philippines	9.3	97	147
Italy	10.4	159	159
Ghana	10.5	48	128
United States	13.5	151	167
Netherlands	15.1	142	174
Finland	17.7	157	190

Adapted from Knuiman JT et al[86] and from United States dietary data from NHANES-II[87] and serum cholesterol data from NHANES-I.[88]

Pathology of Atherosclerosis in Young People

The arterial lesions of atherosclerosis have their origin in childhood. In the aorta, fatty streaks occur in early childhood regardless of ethnic background, gender, or geographic location. In the coronary arteries, fatty streaks occur in many individuals during the second decade of life, and fibrous plaques, the lesions that begin to narrow the arteries, appear in the coronary arteries of some young persons in the United States as early as the second decade. After age 20, fibrous plaques occur in significant numbers of people.[44]

Enos and colleagues and Strong described the high frequency of advanced coronary artery lesions in young American soldiers killed in the Korean War.[45,46] Similar evidence is provided by a study of soldiers in the Vietnam War.[47] Also, investigators in the United States and abroad have documented the importance of the early development of atherosclerosis, particularly in the aorta.[48–52]

Holman and colleagues emphasized and documented the childhood origin of atherosclerosis.[53] In this study, all individuals 3 years of age and older had at least minimal fatty streaks in the aorta, and the extent of intimal surface

involved with fatty streaks progressed dramatically in the second decade of life. Strong and McGill assessed the prevalence and extent of atherosclerotic lesions in the coronary arteries of deceased subjects ages 1 to 69 years in New Orleans.[54] They showed important differences in the prevalence and extent of coronary artery lesions in population subgroups developed early in life and at least 20 years before the onset of manifest clinical disease.

The International Atherosclerosis Project (IAP) undertook an extensive study of the geographic pathology of atherosclerosis in over 23,000 sets of aortas and coronary arteries collected from autopsies in 14 countries and systematically evaluated by a group of cooperative pathologists.[55] Reports from the IAP strongly support the view that fatty streaks progress to fibrous plaques and more complicated atherosclerotic lesions based on topographic and microscopic studies.[56,57]

Strong and McGill investigated aortic and coronary lesions in 4,737 younger subjects included in the IAP, ranging in age from 10 to 39 years and belonging to six geographic-ethnic groups.[44] By age 10, most aortas from all groups had aortic fatty streaks. Coronary fatty streaks, although not as frequent as aortic fatty streaks, occurred in some cases from each geographic-ethnic location group, even in the 10- to 14-year age group. Fatty streaks were present in the coronary arteries of all persons over age 20 in New Orleans and of approximately 90% of persons in the other groups by age 30.

To assess the earliest microscopic changes of atherosclerosis, Stary systematically studied, by light and electron microscopy, unopened, pressure perfusion–fixed, left coronary arteries of 691 male and female subjects dying between full-term birth and 39 years of age.[58,59] More than 50% of children aged 10 to 14 years had lesions characterized by accumulations of macrophage foam cells, lipid-containing smooth muscle cells, and thinly scattered extracellular lipid, these changes representing the microscopic counterpart of fatty streaks. Approximately 8% of subjects 10 to 14 years of age had more advanced lesions with larger accumulations of extracellular lipid, representing lesions that either were in transition or had features of atherosclerotic plaques associated with clinical disease in adults. These microscopic studies clearly indicate a progression from fatty streaks through intermediate or transitional lesions to atheromatous lesions (comparable to fibrous plaques by gross classification) in a defined segment of the left anterior coronary artery predisposed to clinically significant lesions.

The Bogalusa Heart Study showed a significant relationship between LDL cholesterol and coronary artery fatty streaks, with significant relationships between LDL cholesterol levels and the prevalence of both aortic and coronary fibrous plaques.[60] The PDAY Study (Pathobiological Determinants of Atherosclerosis in Youth) has shown a relationship between the earliest lesions and the postmortem levels of LDL, very LDL, and HDL cholesterol and serum thiocyanate concentrations.[2] These data highlight the origin of atherosclerosis in young persons and its relationship to circulating lipids and lipoproteins and to smoking behavior.

Childhood and Adolescent Levels of Lipids

Several studies provide distributions of lipid and lipoprotein levels in American children and adolescents.[61–66] The National Cholesterol Education Program has suggested the acceptable borderline and high levels of total, LDL, and HDL cholesterol levels (Table 8-2).

Tracking

Several studies show that childhood rank order of cholesterol is maintained over time ("tracking"), although not as consistently as rank order of height and weight is maintained.[67–71]

Studies relate childhood cholesterol levels to later young adult levels.[71–73] One study examined data on children 5 to 18 years of age whose cholesterol levels were greater than the 90th percentile at a single measurement.[73] At 20 to 30 years of age, 43% of these individuals had levels greater than the 90th percentile (about four times the percentage expected), 62% greater than the 75th percentile (about two to three times the percentage expected), and 81% greater than the 50th percentile (about 1.5 times the percentage expected).[73] Of children whose cholesterol levels were greater than the 90th percentile on two occasions, 75% had higher than desirable levels (> 200 mg/dL) and 25% had desirable levels (< 200 mg/dL) at ages 20 to 25 years.[74] Because 200 mg/dL is approximately the 75th percentile for adults in their twenties, this percentage of individuals with levels at or above 200 mg/dL is about three times the percentage expected for the general population.

THE PRUDENT DIET

An approach to lowering cholesterol levels in children and adolescents is the population approach, which aims to lower the average population levels of blood cholesterol by encouraging the adoption of a low-SFA, low-cholesterol eating pattern. Even though this approach results in a relatively small reduction in mean total and LDL cholesterol levels in children and adolescents, if carried into adulthood, it could substantially decrease the incidence of CHD. It would also reduce the number of adults who have high-risk cholesterol levels.[62,75]

In the population approach, the nutrition recommendations are to lower average population levels of blood cholesterol in children and adolescents to reduce the incidence of adult CHD. These recommendations, generally to

TABLE 8-2 Classification of Total and LDL Cholesterol Levels in Children and Adolescents from Families with Hypercholesterolemia or Premature Cardiovascular Disease

Category	*Total Cholesterol (mg/dL)*	*LDL-Cholesterol (mg/dL)*	*HDL-Cholesterol (mg/dL)*
Acceptable	< 170	< 110	≥ 35
Borderline	170–199	110–129	
High	≥ 200	≥ 130	
Low			< 35

Adapted from National Cholesterol Education Program.[3]

improve health, were defined for all children and adolescents by the Expert Panel on Blood Cholesterol Levels in Children and Adolescents of the National Cholesterol Education Program.[3]

The following nutrient intakes are for healthy children and adolescents. With the introduction of solid foods in infants who have no history of allergies, fruits and vegetables can be introduced with first solids. This may induce preferences in later life for these foods. As toddlers over 2 years of age begin to eat with the family, they may safely make the transition to this eating pattern over a period of 3 to 4 years. Because food intake varies from day to day, these recommendations are meant to represent an average of nutrient intake over several days:

1. Nutritional adequacy should be achieved by eating a wide variety of foods.
2. Energy (calories) should be adequate to support growth and development and to reach or maintain desirable body weight.
3. The following pattern of nutrient intake is recommended:
   a. Saturated fatty acids—less than 10% of total calories
   b. Total fat—an average of no more than 30% of total calories
   c. Dietary cholesterol—less than 300 mg per day

No single food item provides all of the essential nutrients in the amounts needed. Choosing a wide variety of foods from all of the food groups is the best way to ensure an adequate diet.

Adequate Energy (Calories)

Children require sufficient calories for growth as well as maintenance of body functions, and their energy needs depend on height, weight, rate of growth, and level of physical activity. Younger children require a higher caloric intake per unit of body weight than older children and adolescents. Some children and adolescents may need more calories than indicated by the Recommended Dietary Allowances, particularly adolescents who participate in athletic activities.[76] An eating pattern that contains about 30% of calories from fat can readily provide adequate calories for children over 2 years of age. Excessive calories can lead to obesity and should be avoided.

Saturated Fatty Acid

SFA raises blood cholesterol levels[4]; therefore, a major dietary emphasis should be on reducing SFA intake. Thus, it has been recommended that less than 10% of calories from SFA should be consumed.

Total Fat

The percentage of calories from total fat intake, independent of the relative content of the individual fatty acids, does not affect the level of blood cholesterol. A sufficiently low SFA intake can be achieved with a fat intake of about 30% of calories. A lower fat intake is usually not necessary and, for some children and adolescents, may make it difficult to provide enough calories and minerals for optimal growth and development. The recommended target of no more than 30% of calories from fat is a practical approach to controlling SFA intake yet provides sufficient fat for essential fatty acids and absorption of fat-soluble vitamins and contributes calories for normal growth and development.

Unsaturated fatty acids do not increase blood cholesterol levels. The two major types of unsaturated fatty acids are polyunsaturated and monounsaturated. The panel recommends that up to 10% of total calories come from polyunsaturated fatty acids; this includes omega-6 and omega-3 fatty acids (largely derived from vegetable oils and fish, respectively). Monounsaturated fatty acids should provide the remaining 10 to 15% of calories from fat.

Dietary Cholesterol

It has been estimated that, with a 2,500-calorie diet, blood cholesterol will decrease by about 4 mg/dL for every 100 mg/day decrease in dietary cholesterol.[77] This response holds even at low intakes of cholesterol; thus, the lower the dietary cholesterol, the lower the blood cholesterol on the average. There appears to be considerable interindividual variability in the response of blood cholesterol to dietary cholesterol.

Carbohydrate

With the reduction in fat intake, consumption of complex carbohydrates can be increased. This level can be achieved primarily by increasing foods high in carbohydrates, such as pastas, potatoes, many vegetables, legumes, and cereals and breads, especially whole grain. These foods, as well as fruits, which are sources of simple carbohydrates, are generally low in fat and are good sources of dietary fiber, vitamins, and minerals.

Protein

Protein is vital to growth and development. Given the above recommendations for fat and carbohydrate, protein should provide about 15 to 20% of caloric intake. Protein from low-fat animal sources (meat, poultry, fish, eggs, and many dairy products) contains all of the essential amino acids in proportions needed for human growth and tissue repair. Plant proteins (from legumes, bread, cereal, pasta, and grain products) are typically low in one or more of the essential amino acids. Incomplete protein foods can be combined (eg, brown beans with rice) to achieve a balanced mixture of essential amino acids. These combinations of plant proteins are quite low in SFA and total fat.

Fiber

Foods naturally high in fiber provide energy and a variety of nutrients and are low in SFA, total fat, and cholesterol. These foods—such as fruits, vegetables, and grains, including oat and wheat cereals—are not a panacea for high blood cholesterol but are nutritious and useful components of a low-SFA, low-fat, and low-cholesterol eating pattern.

Vitamin E

Vitamin E was once widely advocated for prevention and treatment of CHD.[78] Early studies supporting these claims were marred by a lack of controls and doubtful diagnosis of CHD, and subsequent studies have failed to confirm the results.[79] Children who eat a wide variety of foods do not require supplemental vitamins.[80,81]

Eating Patterns

To meet the recommendations for nutrient intake for healthy children and adolescents, families should adopt eating patterns that include lower amounts of SFA, total fat, and cholesterol. To accomplish this, the following nutritional changes have been recommended:

1. Maximize the quantity and variety of fruits, vegetables, grains, breads, cereals, and legumes.
2. Substitute low-fat dairy products such as skim or low-fat milk and skim or low-fat milk products for those high in fat.
3. Eat moderate amounts of trimmed, lean red meat, poultry without skin, or fish in place of choices high in SFA.
4. Eat egg yolks only in moderation.
5. Use oils, margarines, and shortenings with vegetable oils containing primarily unsaturated fatty acids instead of SFA.
6. Choose prepared baked goods that have been made with unsaturated vegetable oils and, at most, small amounts of egg yolk.
7. Choose "convenience foods" that are low in SFA, total fat, and cholesterol.
8. In fast-food and other restaurants, select menu items that are low in SFA, total fat, and cholesterol as well as cooked foods that are baked, boiled, or broiled without fat.

An option is to use a system of monitoring grams of saturated fat. This system eliminates rules forbidding certain foods and focuses on personal preferences and saturated fat "budgeting."

Figure A-24 in Appendix 2 shows the US Department of Agriculture (USDA) Food Guide Pyramid for children.[82] Five major food groups replace the former USDA recommendations for a well-balanced diet.

If a vegetarian diet is chosen, consultation with a registered dietitian or other qualified nutrition professional can be helpful. Well-planned vegetarian diets have potential nutritional and health benefits, according to the American Dietetic Association.[83,84] Individuals following vegetarian plans have been shown to have lower average serum cholesterol levels and blood pressures than nonvegetarians. These findings may be related to the reductions in dietary fat and SFA and lower body weights in vegetarians rather than vegetarianism per se.[85]

Vegetarian diets for children and adolescents require careful attention. Diets must be planned to include adequate calories, protein, iron, calcium, and vitamins B_{12} and D.[83,84] Inadequate intakes of calories and nutrients from poorly planned vegetarian diets have caused growth retardation, rickets, vitamin B_{12} deficiencies, and hypocalcemia.[85] Dietary deficiencies are most common in vegan diets, which do not include dairy products or eggs. Lactovegetarian and lacto-ovovegetarian diets provide greater opportunities to include calories, protein, and other nutrients needed for growth.

Safety of the Prudent Diet

The DISC provides evidence that cholesterol-lowering diets in children are safe.[41] This study's objective is to assess the efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol to decrease LDL cholesterol levels in children.

This study was a six-center randomized controlled clinical trial with prepubertal boys (n = 362) and girls (n = 301), age 8 to 10 years, with LDL cholesterol ≥ 80th and < 98th percentiles for age and sex. They were randomized into an intervention group (n = 334) and a usual care group (n = 329). Intervention involved behavioral change to promote adherence to a diet providing 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75 mg/1,000 kcal per day of cholesterol (not to exceed 150 mg/day).

Main outcome measures involved a mean LDL cholesterol at 3 years with primary safety measures of mean height and serum ferritin levels at 3 years. Secondary efficacy outcomes were mean LDL cholesterol at 1 year and mean total cholesterol at 1 and 3 years. Secondary safety outcomes included red blood cell folate; serum zinc, retinol, and albumin; serum HDL cholesterol, LDL-to-HDL cholesterol ratio, total triglycerides; sexual maturation; and psychosocial health.

At 3 years, dietary total fat (28.6% kcal), saturated fat (10.2% kcal), and cholesterol (95 mg/1,000 kcal) decreased significantly in the intervention compared with the usual care group. LDL cholesterol fell to a greater degree ($p < .001$) in the intervention group (–15.3 mg/dL) compared with the usual care group (–11.9 mg/dL). There were no significant differences between the groups in adjusted mean height or serum ferritin ($p > .05$) or other safety outcomes.

The DISC showed that dietary intervention is effective in achieving modest lowering of LDL cholesterol over 3 years while maintaining adequate growth, iron stores, nutritional adequacy, and psychological well-being during the critical growth period of adolescence. An important public health message from this study is that current dietary recommendations for healthy children, which are less restricted in total fat than the DISC diet, can be prescribed safely with surveillance of growth and development on a consistent basis.

CONCLUSIONS

Dietary changes in children are effective in lowering LDL cholesterol levels while maintaining nutritional adequacy, iron stores, and psychological well-being. Although diet changes result in modest LDL lowering, when these

changes occur in large numbers of children, they have the potential to result in a large public benefit by impeding the atherosclerotic process.

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CHAPTER 9.1

COMMUNITY NUTRITION AND ITS IMPACT ON CHILDREN: DEVELOPED COUNTRIES

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If the future of a society is to be shaped by its children, then a strong national commitment is needed to develop their bodies, minds, and spirits. Good nutrition plays a role in growth, development and later health, prevention, control and treatment of disease, and improvement of quality of life. Community efforts are key to making this happen.

REASONS FOR CONCERN

Nutrition is an important component of health care for infants, children, and adolescents. Infants grow rapidly and have requirements for protein, energy, and other essential nutrients that are higher per unit of body weight than at any other time in childhood, making them vulnerable to dietary deficiencies and growth failure. Dietary habits of toddlers and preschoolers are important in shaping their later health and may play a role in increasing or decreasing obesity, high blood pressure, high serum cholesterol, and dental caries later in life. Adolescence, a time of emotional, physical, social, biologic, and educational transitions, is a period with particular susceptibility to weight concerns, eating disorders, alcohol abuse, and other poor dietary habits. Children with special health care needs at all ages, because of a variety of disabilities, handicaps, and chronic illnesses and conditions they may have, often need special complex and involved care and require particular attention to enable them to achieve their maximum potential.

Eating patterns begin to develop early in childhood and can profoundly affect health throughout life. In childhood, the immediate effects of improper diet are most apparent in such conditions as failure to thrive, obesity, the dietary deficiency diseases, and fetal alcohol effects. Later, chronic degenerative disease risks increase. The leading causes of death and disability for adults today include cancer, heart disease, stroke, osteoporosis, and alcoholism. Each involves risks associated with dietary patterns, as well as other preventable factors. Programs for the family and community must be designed to accommodate all of these diet-related problems.

COMMUNITY NUTRITION AND CHILDREN TODAY

The current status of some key national indicators of child well-being in the United States today has recently been summarized.[1] In the year 2000, there were 70.4 million children under age 18 in the United States, about 25% of the population. America's children are racially and ethnically diverse. In 2000, 65% of US children were white non-Hispanic, 16% were white Hispanic, 15% were black non-Hispanic, 4% were Asian or Pacific Islanders, and 1% were American Indians and Native Americans. From birth to kindergarten age, fully 61% of children received child care on a regular basis from a caretaker who was not their parent.

For many socioeconomic and health indicators, gains have been impressive over the past decade. For example, with respect to poverty, the rate for children living with their families is now 16%, which is lower than it has been for decades. In 2000, 0.8% of children lived in households reporting child hunger and 18% lived in households reporting any level of food insecurity, rates that were lower than in prior years. But problems still exist. For example, children in families below the poverty line were nearly three times more likely to experience food insecurity and hunger than their peers in families above the poverty line. According to the Healthy Eating Index, 27% of children 2 to 5 years have "good" scores, whereas only about 15% of those 6 to 9 years of age do. Children in families living in poverty were less likely than those from higher-income families to have a dietary pattern rated as "good." They also tend to be in poorer health than their more affluent counterparts. Therefore, many health and nutritional problems remain. Ways of ameliorating them by community-wide interventions are the focus of this chapter.

As a nation, we have made great strides in nutrition over the past century. The situation today differs dramatically from that in 1900, when dietary deficiency disease and undernutrition were the major problems.[2] Then

undernutrition and food insecurity were major societal problems. Now there are still some individuals who suffer from these problems. But today there are new faces to malnutrition. Overnutrition and obesity are increasing. Sometimes they coexist in the same individuals who suffer from deficiencies in other respects. Although malnutrition, starvation, and nutritional deficiency diseases will probably continue to be problems in some areas in the United States in the future, more prevalent nutrition problems involving overconsumption and imbalances in the types and amounts of food consumed and excesses of certain nutrients are also challenges.[2] Social and economic changes, such as altered family structures with more single parents, increasing ethnic diversity, a predominantly urban maternal and child population, high rates of poverty among children and their families, and more eating outside of the home, are some key variables in explaining the new forms of malnutrition we see today.[3,4]

THE FUTURE

There will be more children and a greater percentage of children in the population by the year 2010 than there are today.[1] For this reason alone, continued efforts to improve child health at the community level are necessary. Whether America's children will be healthier than ever before in the future will depend on sustained efforts on the part of parents and caretakers as well as the larger community. Systems for tracking health promotion and disease prevention objectives that include nutrition and other aspects of child and family health are now available that permit us to monitor our progress and to make corrections to improve health when they are necessary.

DEFINITIONS

Public Health

Public health is "the science and art of preventing disease, prolonging life, and promoting health and efficiency through organized community effort, so organizing these benefits as to enable every citizen to realize his birthright of health and longevity."[5] The goal of public health is to attain the highest level of physical, mental, and social well-being and longevity consistent with available knowledge and resources at a given time and place.[6] It accomplishes these objectives by focusing on the community or on large population groups rather than on individuals, on planning and monitoring rather than on delivering services.

Community Nutrition

Communities are groups of individuals or families living in a defined geographic area who live and work together, hold similar values, are influenced by the same environment, and share a number of common concerns. An understanding of the influences of society and of the community is necessary for planning effective nutrition interventions. Community nutrition applies scientific knowledge in food, nutrition, and health to a specific group of people to improve their health and welfare. To be successful, it must take into consideration the wide range of societal influences and constraints.

The community nutritionist must take into account an individual's cultural eating habits, ethnic background, income, health history, clinical assessment, dietary intake, and use of community nutrition programs to screen, assess needs, and intervene effectively.

The objectives of community nutrition are to promote health; prevent nutrient deficiencies, excesses, and imbalances; prevent diet-related diseases or conditions; and rehabilitate those suffering from nutrition-related problems. This is done by promoting healthful eating habits, ensuring access to food, and integrating nutrition into primary, secondary, and tertiary health care services.[2] Thus, it represents the traditional public health concerns (such as mass prevention and intervention measures) as well as a personal health services focus to ensure that high-risk, high-priority children especially receive health and other services they need. In this respect, community nutrition represents a fusion of both the personal health service's focus on individuals and the public health focus on the entire population.

GOALS OF COMMUNITY NUTRITION

The US Department of Health and Human Services' (DHHS) Healthy People 2010 plan singles out nutrition as essential to promote optimal health and prevent disease and provides nutrition goals for children and adolescents, which are listed in Table 9.1-1.[7] This chapter focuses on needs and meeting these goals at the community level.

The goals of child nutrition programs are to optimize growth and decrease the risk of all diet-related diseases. Strategies to accomplish the goals in the community must include consideration of the child's family; the efforts of the child, the family, and many members of the health care team; and contributions by institutions as well as economic resources in the health, food, education, and welfare sectors of the community. A supportive physical environment is also important.

In the community setting, strategies should focus on health promotion, early intervention, and prevention of diet-related diseases in groups of children and their families. In addition, community-level efforts must focus on ensuring that preventive and curative health services are in place.

Federal and state governments have been committed to promoting child health since early in this century.[8] However, the many programs they have instituted are useless unless communities make them available and families take advantage of them. Both states and communities exhibit considerable variation in the extent to which they provide supportive services and extra funds for reaching nutrition objectives. Detailed advice is available for discovering and mobilizing community nutrition resources.[9]

In the clinical setting, community nutrition–related strategies should focus on providing anticipatory guidance, preventive activities, and control of clinical problems

TABLE 9.1-1 Healthy People 2010 Nutrition-Related Goals for Children and Adolescents

- Increase abstinence from alcohol use by pregnant women.
- Increase to at least 80% those women of childbearing age who take a vitamin with the recommended 0.4 mg folic acid daily.
- Reduce low birth weight to no more than 5% of live births and very low birth weight to 1% or less.
- Increase to 75% mothers who breast-feed their babies in the early postpartum period, to at least 50% those who breast-feed until their infants are 6 months old, and to at least 25% those who breast-feed until their infants are 1 year old.
- Reduce growth retardation among low-income children aged 5 and younger to 5% or less.
- Reduce to 5% or less the prevalence of overweight and obesity (defined as at or above the sex- and age-specific 95th percentile of BMI from the NCHS/CDC growth charts) in children aged 6–11 and adolescents 12–19 years.
- In those 2 years of age and older, increase to at least
  - 75% those who meet the Dietary Guidelines' average daily goal of no more than 30% of calories from fat
  - 75% those who meet the Dietary Guidelines' average daily goal of less than 10% of calories from saturated fat
  - 75% those who meet the Dietary Guidelines' minimum average daily goal of at least five servings of vegetables and fruits
  - 80% those who meet the Dietary Guidelines' minimum average daily goal of at least 6 servings of grain products
  - 90% those who meet dietary recommendations for calcium
  - 65% those who meet the Daily Value of 2,400 mg or less of sodium consistent with the Dietary Guidelines
- Reduce iron deficiency to 5% or less among children 1–2 years, to less than 1% among children 3–4 years.
- Increase the proportion of children and adolescents 6–19 years whose intake of meals and snacks at school from all sources contributes proportionally to good overall dietary quality.
- Increase the proportion of the nation's public and private elementary schools that teach all essential nutrition education topics to their students in at least 3 different grades and the proportion of middle/junior high and high schools that teach all essential nutrition education topics in at least one required course.
- Increase the prevalence of food security among US households to at least 94% of all households.

Adapted from US Department of Health and Human Services.
BMI = body mass index; CDC = Centers for Disease Control and Prevention; NCHS = National Center for Health Statistics.

involving both primary and secondary malnutrition in all children but particularly in high-risk children.

All health care team members need to understand the importance of community nutrition, know what programs are (or should be) available, know how to obtain them for patients and clients, and know how to advocate their extension. Otherwise, those who provide direct care to children may fail to meet all of their nutrition needs.

HISTORY OF COMMUNITY NUTRITION AND HEALTH

Only in the twentieth century did the federal government begin to play a role in ensuring and safeguarding the health of American children. The Children's Bureau was established in the Department of Labor in 1912 to "investigate and report…upon all matters pertaining to the welfare of children and child life among all classes of our people."[8] It was the forerunner of efforts now centered in the Maternal and Child Health Bureau (MCHB) of the DHHS. The first federal grants-in-aid to the states for planning to improve infant and maternal health were authorized by the Sheppard-Towner Act of 1921. This legislation was first administered by the Children's Bureau in the Labor Department, but since the 1960s, the US Public Health Service in the DHHS has administered such programs.

Title V of the Social Security Act of 1935 initiated the federal and state partnership for maternal and child health that served as the major impetus for the development of public health nutrition services for mothers and children. The states used these federal funds for planning and developing a wide range of programs to improve the health of mothers and children. In 1981, Title V changed with the creation of the Maternal and Child Health Service Block Grant, which provided monies with fewer specific requirements and more state discretion within the general realm of maternal and child health needs. Fifty-nine states and jurisdictions now receive funding. The federal government also provides small amounts of federal set-aside funds to support special projects of regional or national significance. Other categorical programs for specific purposes are funded from the DHHS, the US Department of Agriculture (USDA), and other branches of government. With these funds and their own matching resources, the states provide a variety of services. However, access to health care remains an unresolved issue today.[10,11] Lack of access to medical nutrition therapy and other health services is a major problem for children who have health problems that cannot be solved by community nutrition or public health efforts. Community efforts supplement, but are not substitutes for, individual health services.[12]

Today more than 2,000 public health nutritionists are employed in federal, state, and local public health agencies. They also serve as members of health care teams, where they have the responsibility of assessing community nutrition needs as well as planning and directing programs of nutrition services for individuals. Many other health professionals, including over 60,000 registered dietitians, devote some of their time and effort beyond the scope of individual counseling to community programs and also play a role in ensuring that community nutrition needs are met.

NUTRITION SCREENING, ASSESSMENT, AND INTERVENTION

Nutrition screening, assessment, and intervention are important at both the level of the individual patient and that of population groups. A systematic approach and an integrated structure for screening, assessing, and intervening are needed to deal with nutrition problems in both health and social service settings.[13] The approach is summarized in Table 9.1-2. Details on how nutrition screening and assessment apply to individuals are provided elsewhere in this book.

The first step in developing an appropriate care plan for a community is nutrition screening of the entire maternal and child population to identify major problems. This may

involve examination of relevant statistics and resources of actual surveys. Next, the specific subpopulation of interest must be considered. Screening aims both to increase nutrition awareness among communities, families, and health professionals and to identify factors increasing nutritional risks in target groups. In the community nutrition context, the screening process might involve review of health indicators, such as the prevalence of low birth weight, with further delineation of high-risk groups using income, ethnicity, age, and other characteristics of parents or infants. Those groups who are found to be at risk are then further assessed.

The second step in care planning is a comprehensive nutritional assessment of the community in which the children live. Nutrition screening and assessment should be used in an effort to find groups at especially high nutritional risk. Some nutritional issues can be easily assessed and remedied by the health and social service systems. Others require further medical or social assessment before the causes of the malnutrition can be assessed. The process of setting priorities for intervention among the groups found to be in need of services and allocating resources appropriately to these efforts depends on the individual initiative and political will of the group's providers.

The final step in care planning is intervention, which may be at either the individual or the community level. This may involve nutritional measures such as food or counseling or other interventions that improve nutritional status more indirectly, such as oral health, pharmacy, social, and mental health services. The ultimate goal is to prevent, control, or ameliorate nutrition-related problems. The end result should always be to improve or ameliorate children's health.

TABLE 9.1-2 Pediatric Nutrition Screening, Assessment, and Intervention in the Community

Screen for Risk: Identify individuals and groups in the community needing further assessment for potential health problems with nutritional implications.	Look for the following "*DETERMINE*" risk factors: • *D*isease • *E*ating disorders • *T*ooth decay • *E*conomic hardship • *R*educed nutrition education • *M*ulticultural issues • *I*nadequate food intake • *N*utrient deficiencies • *E*levated or reduced body weight
Screen and Assess Community Resources	Determine whether nutrition resources are adequate, which groups are at high risk, and extent to which community nutrition needs are being met by existing programs. Tools include demographics, socioeconomic stratification, health statistics, local health resources, cultural factors, housing, food supply, child nutrition programs, social welfare programs, education, occupational data, etc.
Assess Child: Confirm that diet-related problems are present and whether growth and nutrition are inadequate owing to dietary deficiency, excess, or imbalance or secondary to disease.	Follow the *ABCDEF*s of assessing nutritional status: • *A*nthropometrics: height, weight, triceps skinfold, arm circumference • *B*iochemical: hemoglobin/hematocrit, albumin, transferrin • *C*linical: skin, tongue, hair • *D*ietary intake: by 24-h recall, food frequency, food record • *E*mpathy • *F*unctional status at all levels: physical, mental, emotional
Intervene at Individual and Community Levels	Identify and use community and individual health care resources, using the mnemonic SOMe Meds and Nutrition: • *S*ocial services • *O*ral health • *M*ental health • *Med*ical care and medications • *Nutrition* counseling, education, and support

Adapted from Gallagher-Allred C[13] and Dwyer JT. Strategies to detect and prevent malnutrition in the elderly: The Nutrition Screening Initiative. Prepared for Lugano Forum; 1994.

NUTRITIONAL MONITORING AND SURVEILLANCE AT THE STATE AND NATIONAL LEVELS

Monitoring and surveillance are analogous to repeated screening and evaluation efforts at the individual level. Monitoring is the periodic measurement of factors that indicate that changes in nutritional status have occurred. It applies to specific individuals, communities, and the general population. Surveillance is the continuous and regular collection of data that are compiled to detect warning signs of problems at the community level early enough to provide feedback for health care team members.

The purpose of monitoring and surveillance is to provide continuous, reliable information on a community's nutritional status and the factors that influence it to find ways to improve it.

National nutrition monitoring involves measurement of health status, food supply, food consumption and composition, and dietary knowledge and attitudes.[14] At the federal level today, nutrition monitoring and surveillance are conducted by several different government agencies. Within the DHHS, the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC) conducts the National Health and Nutrition Examination Survey (NHANES). NHANES is a periodic, population-based survey providing national data on specific health status measures, including dietary intake, eating habits, and biochemical and anthropometric indices related to nutrition. NHANESs are now continuously in the field. The NHANES data provide useful benchmarks for the health of these groups. However, the number of children and adolescents surveyed is small, and not all relevant problems can be examined in each survey. Therefore, occasionally, special surveys have been conducted that oversample these groups.

In 1999, the USDA's CSFII (Continuous Survey of Food Intake of Individuals) was merged with the NHANES. Both the USDA and the CDC's National Center for Health Statistics now partner on the dietary portion of the survey, which

is called "What We Eat in America." The combined survey is now in the field, and the results should be available in 2004.

The USDA monitors food security in the United States through an annual survey of 40,000 US households conducted as a supplement to the US Census Bureau's nationally representative Current Population Survey. The most recent food security survey revealed that 89.5% of US households were food secure. The remaining 10.5% were food insecure; at some time during the prior year, these households were uncertain about having or were unable to acquire enough food to meet the basic needs of all household members because they had insufficient money or other resources.[14] Single mothers with children had the highest levels of food stress. Minority group black and Hispanic households also had rates of food insecurity and hunger above the national average.

The USDA also provides funds for grants and contracts to universities and nonprofit organizations to perform analysis and research in support of improving food consumption practices. These include rating food intakes of various portions of the population from national survey data using a new tool, the Healthy Eating Index,[15] and program-specific analyses, such as studies of the National School Lunch and Breakfast Programs.[16]

The CDC of the DHHS conducts ongoing state-based nutritional monitoring activities. The database consists of data collected on children and pregnant women enrolled in health department clinics, the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), and the Head Start programs at the state and local levels. Programs include the Pediatric Nutrition Surveillance System (PedNSS), the Pregnancy Surveillance System (PNSS), and the Severe Pediatric Undernutrition Surveillance Systems (SPUN). These surveys are not necessarily representative of the entire population but provide much useful data on groups at special risk.[17]

DIVISION OF LABOR: MANAGEMENT OF COMMUNITY NUTRITION SERVICES

The management process consists of planning, organizing, implementing, directing, controlling, and monitoring. The dynamic aspects of the process of community nutrition service management are illustrated in Figure 9.1-1 and occur on two levels. First, there is program management at the indirect service level, which includes macrolevel planning, administration, supervision, consultation, and training, as well as screening and assessment of problems at the community level. Program management and evaluation efforts generally occur at this level. Second, direct service delivery may be provided to both groups and individuals, and this includes screening, assessment, intervention, and follow-up. Both levels must focus on the child and his/her family if the programs are ultimately to be effective.

Planning

Planning is a process of devising a course of action to reduce uncertainty and to anticipate and initiate change. Community nutrition planning involves analyzing subjective and objective data, writing mission statements, setting goals and objectives, and activating means of achieving objectives. Nutrition planning is influenced by the internal culture and capabilities of each organization involved, as well as by the public agenda, state of scientific knowledge, wants and needs of the families, and advocacy of experts, parents, and professional groups.

Community nutritionists should participate in the planning processes of the agency, study the agency or community health plans, know those who participate in the planning group, get involved, and involve others. Planning goes beyond administrators, leaders, and program managers and should include those who will be responsible for implementation and those who will be recipients of services.[18]

Planning for high-priority nutrition problems can be aided by forming alliances with related constituencies in the service network. Some examples are collaborative planning by nutrition service providers, advocates, and patients. This sort of collaboration may build political support and bridge organizational and ideologic boundaries, identify mutual goals, and build cohesion and capacity to act together if potential adversaries are approached, coopted, and included in the process. In some instances, it may assist in making difficult decisions about using limited resources.

Implementing

Planning identifies what to do. Implementation begins the process of doing. Effective community nutrition program implementation requires administrative support (budget, staff, space, equipment); commitment of staff to program goals, objectives, and interventions; and support and respect of a target population who is also convinced of the benefits of the program and willing to commit time and effort to participate.

Screening and assessment at the community level are the responsibilities of the community nutritionist, who ensures that systems are in place in community programs and encourages their institution in personal health services. Nutrition screening and assessment also occur at the direct service delivery level, where they are usually administered by health or social welfare care team members such as dietitians, physicians, nurses, social workers, and physical therapists.

The role of the community nutritionist in implementing programs varies. Depending on the health and nutritional problems found, children and/or families are referred to different community and personal health services for interventions including nutritional counseling, food, welfare education, and health programs or to private physicians.

Monitoring and Evaluation

Community nutrition program implementation must be systematically monitored by the collection and analysis of appropriate data to provide the continuous feedback needed to assess performance. Evaluation involves the systematic measurement of results by comparing the data collected with pre-established standards or controls to decide whether to continue, expand, redesign, or terminate the program.

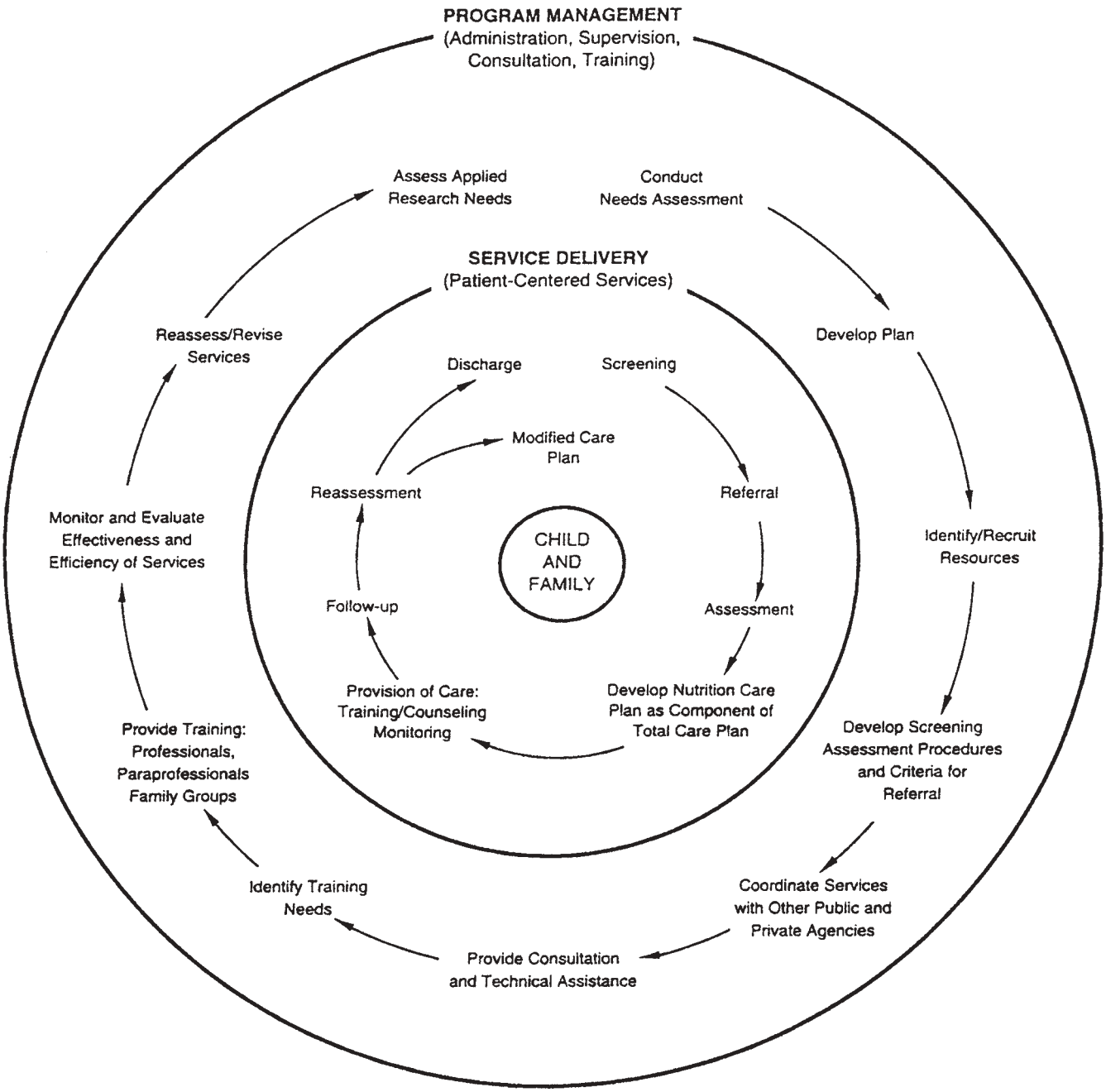

FIGURE 9.1-1 System for nutrition services. Adapted from Baer MT, editor. Nutrition services for children with handicaps: a manual for state Title V programs. Los Angeles: University Affiliated Program, Center for Child Development and Developmental Disorders; 1982.

Monitoring must also be accomplished at both direct and indirect service levels. At the direct personal health service delivery level, the health care team evaluates program impact on a population or community by observing improvements in health. At the indirect level, the management of the community nutrition program may also evaluate effectiveness, efficiency, and cost through cost-effectiveness analysis to determine whether the program's benefits are sufficient to offset its cost. One current effort of this type is the Preventive Health Services Task Force. Its publications on health services that are viewed as effective are increasingly being used as a guide for services.[19] Another key document for monitoring progress at the community level is the tracking system for the Healthy People 2010 objectives.[20]

CURRENT NUTRITIONAL STATUS OF INFANTS, CHILDREN, AND ADOLESCENTS

This section summarizes the major problems of different age groups today and some diet-related risk factors. It provides recommendations needing incorporation in both community nutrition programs and personal health and social services for children.

Some nutrition problems such as iron deficiency anemia, growth retardation, dental caries, obesity, and possibly diet-related decreased resistance to infection affect some children at all ages and are matters of concern across the entire developmental period.[21] Others, as described below, affect specific age groups.

Pregnant Women and Infants

Community concern about good nutrition should start before birth. Nutritional needs in pregnancy and lactation at both the individual and community levels have recently been summarized.[21–23] High-risk women who are poor need to be enrolled in the WIC and provided with nutrition counseling, food education, and other specialized health services.

Adequate nutrition is vital for premature, small-for-date, and other low birth weight infants who are at risk of developmental disadvantage. (See other chapters in this volume for more details.) Early intervention programs to encourage and promote good nutrition among those infants most in need are of particular concern.

The March of Dimes recently published a report that summarizes interventions that are needed to deal with the new faces of nutritional problems that confront Americans today, particularly those that affect those in the childbearing years.[24] These include not only undernutrition and food insecurity but also nutritional imbalances and excesses. The report emphasizes prevention, not only in one-on-one health visits but also by social marketing and health communications to create healthier environments in the larger community. The importance of prevention particularly targeting childhood and preconceptional females is highlighted. Some of the key recommendations of the report that have implications for community nutrition include the following:

1. *Early nutrition matters*. Attending to early nutrition of infants and children under 2 years is critical. Steps include promoting and supporting exclusive breast-feeding for 6 months and continued breast-feeding with complementary foods up to 12 months of age or longer. The special needs of nutritionally at-risk infants, including preterm and/or low birth weight infants, must be ensured. Promotion and support of programs to ensure adequate intakes in pregnant and lactating mothers and the introduction of safe, nutritionally adequate, and developmentally appropriate complementary foods are needed.
2. *Healthy weight matters*. It is important to increase awareness of healthy weight throughout the life cycle to improve health, including good pregnancy outcomes. Those who are at risk of pregnancy with body mass indices under 18.5 or over 25 should reduce them to more healthful levels. Increasing the average age at first pregnancy will permit full maturation before childbearing. Women who are pregnant need assistance to gain a healthful amount of weight during pregnancy and also may need help in achieving a healthy weight after birth.
3. *Nutritious, safe food and diet quality matter.* Food-based dietary guidelines must address the nutritional requirements of periconceptional, pregnant, and lactating women and very young children. When it is not possible to meet all of their needs through available food sources, including fortified foods, appropriate specific vitamin and mineral supplements for women of childbearing age, infants, and young children should be provided.

Nutrition is especially critical in the first year of life.[25] Nutrient needs are high because growth and development are more rapid in infancy than at any other time after birth. Weight usually triples and height doubles in the first year. Approximately a third of calories consumed is used for growth during the first 4 months. This rapid growth in the healthy term infant during the first 4 months of life requires more energy, protein, and other essential nutrients per unit of body weight than at any other time in infancy or childhood. Feeding nourishing foods to infants promotes adequate growth and good health.

The gastrointestinal tract of the newborn infant is well developed but immature. All of the secretions of the digestive tract contain enzymes especially suited to the digestion of human milk. The ability to handle foods other than human milk or formula depends on the physiologic development of the infant. Thus, it is important to encourage breast-feeding and to feed infants age-appropriate foods selected on the basis of their developmental readiness.[25] Not only will this help to prevent complications, it will also help to build positive attitudes about food and eating.

Attention to feeding the appropriate type and amount of food is essential. All parents and caretakers need appropriate advice and guidance. For the poor at high risk, WIC, which provides food, health services, and education, may be in order. For the ill, Title V and Medicaid-supported health services, as well as special services for those with especially severe handicapping conditions, may be in order.

Some of the common nutritional and health problems and related risk factors in infants that need attention by community nutritionists are summarized in Table 9.1-3. Table 9.1-4 provides recommendations for promoting good nutritional status during this period.

Preschool and School-Aged Children

Table 9.1-5 outlines some of the current nutritional concerns and Table 9.1-6 provides recommendations on promoting good nutrition after infancy in the preschool and school years.

In late infancy, children begin to learn to feed themselves independently. They progress from eating with their hands to using utensils. Children need to be independent and able to try new skills to help them develop positive attitudes about food and eating.

Children's growth rates slow considerably after the first year of age, resulting in decreased appetite and food intake. This normal phenomenon is often mistaken for poor appetite, although it is not. In spite of the slower growth rates, appropriate nutrition is vital to provide needed nutrients and energy to maintain resistance to infections, materials needed to build new tissues as growth proceeds, and adequate nutrient stores.

TABLE 9.1-3 Current Nutritional Issues and Recommendations for Infants

Current Health Problems	*Related Nutrition Risk Factors*
Growth retardation, underweight	Dietary inadequacies, low birth weight, inappropriate introduction of foods
Dental caries	Excessive, frequent consumption of sweets that are retained in the mouth, baby bottle tooth decay, lack of fluoride
Iron deficiency anemia	Early introduction of cow's milk, malnutrition, inadequate dietary iron intake
Other nutrient deficiencies	Inadequate intake of certain nutrients, lack of appropriate supplements
Infections	Malnutrition, lack of breast-feeding

What Needs to Be Done?

- Improve nutrition training of health professionals
- Increase nutrition counseling and education of parents and caretakers
- Strengthen breast-feeding support
- Develop nutrition and feeding guidelines for agencies responsible for the administration of health, social welfare, and related program services
- Enhance the research base for current issues in infant nutrition
- Prevent or treat inappropriate weight gain

TABLE 9.1-4 Recommendations for Enhancing the Nutritional Status of Infants

Early infancy (0–6 mo)

- Breast-feed until 4–6 mo of age
- If breast milk is not provided, feed with a hygienic, nutritionally adequate source of heat-treated formula until 4–6 mo of age
- Supplement with vitamin D and iron if the infant is solely breast-fed for the first 6 mo of life or if these are not provided in formula
- Supplement with fluoride if the water or formula is devoid in the nutrient
- Avoid unsuitable feedings (solids, cow's milk, and skim milk) under 6 mo of age and encourage breast-feeding and adequate supplementation
- Ensure that the infant receives enough food by monitoring growth
- Use proper feeding techniques to avoid gas, aspiration, and other problems
- Delay introduction of solid foods until age 5–6 mo, when the infant is developmentally ready to deal with them
- Avoid foods commonly causing allergies, intolerances, or hypersensitivities
- Ensure that water intakes are adequate
- If family resources are inadequate, obtain assistance from federally sponsored food programs for infants and children
- Obtain relevant anticipatory guidance on feeding and health

Later infancy (6–12 mo)

- Use iron-fortified formulas, iron supplements, and iron-fortified cereals
- Ensure a gradual transition to family diets rather than attempting to wean suddenly
- Introduce solid foods sequentially after 4 to 6 mo when the child is developmentally ready and needs supplementary feedings
- Take common problems in stride. Temporary refusals of solid foods at weaning and failures to switch over from pureed or baby foods to foods that must be chewed are normal setbacks
- Consult health providers if feeding problems persist
- Health and encourage self-feeding
- Realize that some decrease in appetite in late infancy is to be expected as growth slows and that it is no cause for alarm
- Avoid struggles and battles of will with the child about food
- Keep environments safe (especially with respect to lead and common household chemicals, which are poisonous) and begin to teach child to shun mouthing and eating nonfood objects
- Begin oral hygiene measures

Good nutrition is important to sustain growth and permit development. It is especially important in the weaning period to prevent the risks of iron deficiency anemia, dental caries, and obesity and diet-related risks that may contribute to later hyperlipidemia and hypertension.

Obesity is increasing in Americans, with estimates of obesity in 10 to 30% of school-aged children.[26,27] Therefore, attention to nutrition must not be neglected in the preschool, primary, and middle school years. The US Surgeon General recently called for immediate action on obesity, particularly in children and adolescents.[28] His report concluded that in 1999, approximately 61% of American adults were overweight, along with 13% of children and adolescents. Overweight among adolescents has tripled since 1980, and obesity among adults has doubled. Also, associated conditions such as asthma and type 2 diabetes are rising among children, and diet-related chronic disease risks linked to obesity are also on the rise. Minorities and low-income families often are particularly afflicted. Therefore, there is a need for immediate action. Strategies that communities can use in helping to address overweight and obesity especially in children and adolescents involve "CARE": communication of the problem and steps to correct it, actions, research, and evaluation. These action options include the following:

1. *Physical activity.* Require daily, quality physical education at all school grades. Currently, the only state requiring physical education for kindergarten to grade 12 is Illinois. Today only about one in four teenagers nationwide take part in some form of physical education. It is also important to provide safe and accessible facilities for the recreation of people of all ages. Community facilities should be available for physical activity for all people, including on the weekends, and there should be more opportunities for physical activity at work sites. At the same time, it is important to reduce the time people spend in watching television and in other sedentary behaviors. In 1999, 43% of high school students reported watching 2 or more hours of television a day.
2. *Food options.* Ensure the availability of more food options that are low in fat and calories, as well as fruits, vegetables, whole grains, and low-fat or nonfat dairy products, on school campuses and at school events. It is important to enforce existing USDA regulations that prohibit serving foods of minimal nutritional value during mealtimes in school food-service areas, including vending machines.
3. *Communications.* Change the perception of obesity so that health, and not simply personal appearance, becomes the chief concern. This means providing

TABLE 9.1-5 Current Nutritional Issues and Recommendations for Children

Current Health Problems	*Related Nutrition Risk Factors*
Obesity	Caloric consumption exceeds caloric need
Failure to thrive	Dietary inadequacies
Iron deficiency anemia	Malnutrition, inadequate dietary iron intake
Dental caries	Excessive, frequent consumption of foods high in sugar and starch with poor oral hygiene
High blood pressure	Overweight, high sodium intake
High blood cholesterol	Excessive intakes of saturated fat and cholesterol

What Needs to Be Done?

- Achieve adequate nutrition services in daycare programs and early childhood education (Head Start)
- Increase participation in and coverage of child nutrition programs (School Lunch and Breakfast)
- Increase parent and community nutrition education
- Improve nutrition training of health professionals
- Enhance the research base to answer existing questions in child nutrition
- Change policy to integrate nutrition services into all aspects of child health care

TABLE 9.1-6 Recommendations for Enhancing Nutritional Status in Children

Preschool years

- Ensure that levels of physical activity and rest suffice to maintain normal growth and development and a good appetite
- Provide nutritious food in the home and in other settings in which the child eats to encourage good food choices
- Teach the child to choose and eat nutritious foods for meals and snacks
- Avoid sugary starchy snacks that are retained in the mouth and encourage oral hygiene practices to promote good dental health
- Foster appropriate eating behaviors by providing suitable role models, by permitting the child to choose food portions, by giving some latitude in food preferences, by exposing him/her to new foods, by fostering table manners appropriate to his/her developmental level, and by keeping meals as times for social interchange
- Recognize and deal with feeding problems early before they become well established
- Handle struggles over food reasonably to avoid the development of feeding problems
- Feed and hydrate children appropriately during illness
- Help the child grow out of fatness by encouraging physical activity
- Ensure that iron needs are met by wise food choices
- Ensure that the child learns to distinguish food and nonfood objects

School years

- Monitor growth in height to ensure that nutritional status is satisfactory
- Provide good examples and guidance to instill healthful habits and attitudes about foods and eating
- Establish consistent guidelines and follow them to ensure that the child's diet is nutritionally adequate
- Promote eating and physical activity habits that will foster normal body fatness
- If excessive fatness is a problem, encourage child to increase physical activity and help him/her to cut energy intakes slightly so that the child can grow out of his/her fatness
- Ensure that diet-related risks of dental caries are minimized
- Help the child to distinguish between reliable sources of information on food choices and promotional messages, which may be unreliable
- Ensure dietary moderation with respect to dietary fat, cholesterol, sugar, and sodium
- Ensure that diets are adequate in fiber
- Ensure that iron needs are met by wise food choices

appropriate education in schools and communities and in the training of health professionals about healthful eating habits and regular physical activity, based on the Dietary Guidelines for Americans, for people of all ages.

4. *Growth monitoring.* New growth charts are now available for children and adolescents to evaluate their size and growth.[28,29] They need to be used on a continuing basis.

Adolescents

Puberty is a unique and complex developmental period marking the transition from childhood to adulthood. It is accompanied by a series of physical, physiologic, biochemical, hormonal, social, and psychological changes. Adolescence is a nutritionally vulnerable period for several reasons. A dramatic increase in physical growth occurs during puberty. The growth spurt is highly sensitive to nutrient deprivation. Inadequate nutrition during this time may delay or stunt linear growth.[30] Alterations in body composition in puberty and during the consolidation that occurs in later adolescence, as maturity is reached, increase nutrient and energy needs. During the second decade of life, children gain about 20% of their adult height and 50% of their adult weight.[31] After puberty, although linear growth ceases, changes continue until maturity is reached.

The larger body requires increased amounts of nutrients. Calcium is a nutrient of particular concern because bone growth and bone mass accumulate rapidly during this time of life. Osteoporosis is a disease that afflicts mostly the elderly, but just as is the case with atherosclerosis, its seeds are sown in childhood. One of the most effective ways to prevent osteoporosis is to build a strong, dense skeleton during the growing years to act as a reserve later in life. Moreover, changes in individual behaviors and lifestyle preferences in younger children may last through adolescence and into adulthood, again contributing a lifetime of optimal bone health. Increasing attention is being paid to school programs that will increase bone accretion and muscular strength in children starting in early elementary school, aged 5 to 7 years of age, and continuing into adolescence. The interventions now being tested include weight-loading physical activity and calcium-rich snacks for children as well as age-appropriate, behaviorally focused active learning to promote skill building and self-competence while building bone quality and bone strength.

Growing independence, the need for peer acceptability, concern with appearance, and active lifestyles of adolescents often affect eating habits, food choices, nutrient intake, and thus nutrition status. Adolescents are seeking to establish their identity and are susceptible to peer pressure and mass media. They are also preoccupied with physical appearance and body shape and size. Desires to be lean and to have an attractive body, societal pressures, and an abundance of food in the environment can lead to inappropriate weight reduc-

tion, dietary aberrations, and nutrient deficiencies.[32] Chronic dieters are at high risk for inadequate diets. In adolescent females, such behavior may lead to eating disorders, such as anorexia nervosa and bulimia nervosa.[33,34]

Common nutritional problems in adolescents are provided in Table 9.1-7. They include obesity, hyperlipidemia, dental caries, and hypertension.[35,36] These problems of dietary imbalance and excesses may coexist with undernutrition with respect to iron, energy, and other nutrients in some individuals. Dietary factors increasing the later risk for chronic diseases such as osteoporosis (inadequate intakes of calcium and vitamin D), heart disease (excessive intake of saturated fat and cholesterol, low intake of fiber), and some types of cancer may be present.[36] Table 9.1-8 provides recommendations to enhance nutritional status during adolescence.

Pregnancy and lactation in adolescence also increase nutrition risk because the young female needs a supply of nutrients to support her own growth as well as the growth of the fetus and nutrition of the suckling infant.[37] Nutritional needs of pregnancy and lactation are discussed elsewhere in this book.

TABLE 9.1-7 Current Nutritional Issues and Recommendations for Adolescents

Current Health Problems	*Related Nutrition Risk Factors*
Hypertension	Overweight, excessive sodium intake, low potassium intake
Underweight	Undernutrition, anorexia nervosa, bulimia nervosa
Obesity	Caloric consumption exceeds caloric need, sedentary lifestyle
Dental caries	Excessive, frequent consumption of sugary starchy foods that are retained in the mouth, lack of oral hygiene
Iron deficiency anemia	Malnutrition, inadequate dietary iron intake, pregnancy without iron supplementation
Elevated serum cholesterol	Excessive saturated fat and cholesterol intake
Nutrient deficiencies	Inadequate nutrient intakes, extended periods of dieting
Eating disorders	Societal pressure to be thin, peer pressure, diet fads
Alcohol abuse	Underage alcohol use

What Needs to Be Done?

- Include nutrition in comprehensive health education in schools
- Develop national guidelines for school-based nutrition education programs
- Increase nutrition education to parents and communities
- Increase School Lunch and Breakfast participation
- Improve training and continuing education for all health care providers in the area of nutrition
- Integrate nutrition screening, education, and intervention services into health services aimed at teenagers
- Expand school-based health clinics especially for teenagers who have no primary physician
- Expand research on nutritional needs of adolescents

NUTRITION FOR CHILDREN WITH SPECIAL NEEDS

Some of the most common nutritional issues of children with special needs are outlined in Table 9.1-9. Children with special health care needs make up approximately 10 to 20% of the pediatric population, depending on the definition used.[38] The term special needs describes a group of infants, children, and youth with or at risk for physical or developmental disability or with a chronic medical condition caused by or associated with genetic/metabolic disorders, birth defects, prematurity, trauma, or infection (including human immunodeficiency virus [HIV] infection). They present a particular challenge to community nutritionists today because many special needs children who were formerly institutionalized now dwell with their families in the community.

Table 9.1-10 provides some recommendations for enhancing the nutritional status of special needs children. Some of the nutrition needs of children with special health care needs are unique (eg, the child with a metabolic disorder controllable only by diet), but in most aspects, their nutritional needs are similar to those of other children. The "special needs" child in the family is first of all a child who has the same nutrient needs for optimal health, growth, and development as any other child. Superimposed on these needs, however, may be multiple risks, ranging from social/environmental factors, such as decreased access to food because of limited finances, to factors involving disorders, such as feeding problems or the need for chronic medication.[39] These factors may place a child at risk for inadequate nutrient intake, impaired nutrient absorption or use, or increased nutrient excretion. Such insults, if they are severe and/or prolonged, and especially if they occur early in life, can have lasting effects on the child's growth and cognitive development. Various handicapping conditions have different nutrition-related problems and needs.[40]

TABLE 9.1-8 Recommendations for Enhancing Nutritional Status in Adolescents

- Maintain desirable weights. Avoid obesity and eating disorders by developing healthful attitudes toward food, appropriate energy intakes, and a physically active lifestyle, including both aerobic and strength-building exercise
- Abstain from self-induced vomiting, bulimia, and laxative abuse
- Eat a variety of foods to ensure dietary sufficiency of protective nutrients, including protein, vitamin, minerals, and fiber
- Avoid dietary imbalances, stressing moderation with respect to fat, saturated fat, cholesterol, sugars, and salt by moderation in intakes of foods high in these and low in protective nutrients
- Find ways to eat that fulfill the teenager's individual needs, philosophies, wants, and schedules without doing violence to nutritional status
- Identify and alter eating habits that are not conducive to good nutrition, including long-standing poor dietary intakes, irregular or unplanned food intakes, and excessive intakes of fat, cholesterol, sodium, sugar, and alcohol
- Avoid alcohol use
- Provide assistance for special problems such as teenage pregnancy, diets for competitive athletes, diets for those with allergies and disease
- Ensure adequate intakes of calcium and vitamin D to maximize bone density

TABLE 9.1-9 Current Nutritional Issues and Recommendations for Children with Special Needs

Current Health Problems	*Related Nutrition Risk Factors*
Growth retardation, underweight	Increased needs; inadequate intake caused by mechanical difficulties with chewing, swallowing, or feeding oneself; malabsorption
Obesity	Reduced resting metabolism, decreased energy expenditure, excessive calorie intake
Gastrointestinal complications	Diet not adequate in fiber and water
Nutrient deficiencies	Inadequate intake of certain nutrients, lack of supplementation, increased needs, drug–nutrient interactions
Infections	Malnutrition

What Needs to Be Done?

- Ensure that community programs for special needs children are in place to screen and assess nutrition problems
- Implement use of standardized screening and referral tools for service providers
- Improve nutrition training of health professionals
- Increase nutrition counseling and education for families
- Develop nutrition and feeding guidelines for agencies responsible for the administration of health, social welfare, and related program services
- Enhance the research base for current issues in nutrition for children with special needs

TABLE 9.1-10 Recommendations for Enhancing Nutritional Status in Children with Special Needs

- Recognize that expectations for growth may be different; use appropriate standards when available
- Provide adequate nutrition to achieve optimal growth potential
- Consider the extra or lessened energy needs owing to the child's condition and adjust intake accordingly
- Use vitamin and mineral supplements if directed by physician
- Frequently evaluate adequacy of child's diet
- Ensure adequate intake of fluid and fiber
- Consult an interdisciplinary team and develop a care plan that includes realistic expectations regarding the child's potential, understanding of feeding skill progression and recognition of developmental readiness for next steps, and enrolment in early intervention programs as needed
- If warranted, adjust feign positioning to allow for adequate food intake, use appropriate nipples and feeding devices for children unable to use standard equipment, and adjust pace of feeding appropriately
- Determine family's need for food assistance, support with home and money management, diet information, and emotional support

These are represented schematically in Figure 9.1-2 and are discussed in more detail in another chapter.

An amendment (PL 99-457) to the Federal Education for the Handicapped Act gives nutrition professionals the opportunity to have a voice in establishing nutrition policy and standards of care for young handicapped and high-risk children. Preventive services now extend to children as young as 3 years of age, and Part H of the law provides financial incentives for states to provide services to children with special health care needs from birth to 2 years of age. Nutrition should be included in these services.

EXISTING PROGRAMS

Federal Programs

Either the USDA or the DHHS administers most federally funded food and/or nutrition programs for mothers and children. The programs are administered on the state level by the Department of Welfare, Department of Education, or Department of Health depending on their particular focus. One type of federal support is through benefits or cash assistance that goes directly to eligible recipients (such as the Food Stamp program, which provides food vouchers, or the School Lunch program, which provides inexpensive or free meals). Another type is in-kind services (such as the USDA's Expanded Food and Nutrition Education Program [EFNEP], which provides nutrition education to low-income families).

Means-tested programs require assessment of means or income before one qualifies for them. They are special cash or in-kind services targeted to provide a safety net to protect children in low-income families. Eligibility for such programs, such as Food Stamps, Medicaid, general relief payments, funded child health services, or free school lunch and breakfast, is assessed by review of family incomes. These programs are valuable contributions for maintaining or improving the nutritional status of low-income families. Such families may have limited access or resources available to buy food, and those who are particularly vulnerable from the physiologic standpoint include infants, young children, and pregnant and lactating women.

Community nutrition services for families and children are also available as part of other health and social services, such as intensive infant care programs, services for handicapped children, dental health programs, family planning service, school health, and teenage pregnancy/parenting programs.

The federal government also provides grants for planning and service provisions to states for program development to provide food assistance, nutrition education, and counseling to eligible families at the local level through health centers, school systems, and community action agencies.

Health care providers need to know about the many food and nutrition programs available in their local areas and how and when to refer their patients to them.

USDA Programs The USDA provides various public health programs at the community level. These include Food Stamps, School Lunch and Breakfast, Special Milk Program for Children, Child Care Food Program, Summer Food Service Program for Children, WIC, EFNEP, and Commodity Supplemental Food Program (CSFP). These programs served an estimated one in six Americans at some point during 2001.[41] Food pantries and soup kitchens are also available for some families that lack food. Surplus foods, both dry and perishable, are distributed to food pantries and soup kitchens. Table 9.1-11 presents a summary of current expenditures on these programs.

DISORDER	PREVALENCE ESTIMATES PER 1,000 (AND RANGE)	EXAMPLE OF NUTRITION PROBLEMS AND FACTORS CONTRIBUTING TO HIGH NUTRITIONAL RISK: Child-related: Altered nutrient needs	Altered energy needs/intake	Problems with oral cavity	Nutrient deficiencies	Constipation/diarrhea	Poor appetite	Delayed feeding skills	Malabsorption	Nutrient-drug interactions	Maladaptive behaviors	Lack of knowledge	Caregiver-related: Difficulty understanding diet	Does not limit intake	Inappropriate feeding practices
Asthma	38 (20–53)		●		●		●			●					
Moderate to Severe	10 (8–15)														
Visual Impairment	30 (20–35)														
Impaired Visual Acuity	20							●			●				
Blind	0.6 (0.5–1)														
Mental Retardation	25 (20–30)		●	●		●		●			●				●
Hearing Impairment	16														
Deafness	0.1 (0.6–1.5)														
Congenital Heart Disease	7 (2–7)	●	●		●		●		●	●		●			
Severe Congenital Disease	0.5														
Seizure Disorder	3.5 (2.6–4.6)	●								●		●			
Cerebral Palsy	2.5 (1.4-5.1)		●	●	●	●	●	●		●		●		●	●
Arthritis	2.2 (1–3)	●	●									●			
Paralysis	2.1 (2–2.3)		●			●		●			●	●		●	
Diabetes Mellitus	1.8 (1.2–2.0)											●	●	●	
Cleft Lip/Palate	1.5 (1.3–2.0)		●	●				●				●			●
Down Syndrome	1.1		●	●		●		●			●	●		●	●
Sickle Cell Disease	< 1.0	●			●										
Neural Tube Defect	< 1.0		●			●				●				●	
Autism	< 1.0						●			●	●				●
Cystic Fibrosis	< 1.0	●	●		●	●	●		●	●		●	●	●	●
Hemophilia	< 1.0														
Acute Lymphocytic Leukemia	< 1.0	●	●		●	●	●			●					
Phenylketonuria	< 1.0	●			●							●	●	●	
Chronic Renal Failure	< 1.0	●	●		●	●	●			●		●	●		
Bronchopulmonary Dysplasia	< 1.0	●	●		●			●		●					
AIDS	< 1.0	●	●	●	●	●	●	●	●	●		●			
Gastrointestinal Disorders	< 1.0	●			●	●	●		●						

FIGURE 9.1-2 Prevalence of certain chronic conditions with associated nutrition-related problems.

Food Stamp Program ***What It Is.*** This is the largest and most far-reaching food assistance program for low-income families in the United States to help them buy the food they need for a nutritionally adequate diet. The amount provided is based on the USDA's Thrifty Food Plan, a market basket of suggested amounts of food that make up a nutritious diet and that can be purchased at a relatively low cost. The federal government pays for all benefits issued through the program and shares administrative costs with the states. Puerto Rico, American Samoa, and the Marianas receive cash grants instead under the Nutrition Assistance Program that permits them to provide food assistance programs for their low-income residents. Food Stamps is a means-tested entitlement program; any household that meets program eligibility requirements may receive them. Households participating in the program actually receive their benefits by an electronic benefits transfer card system rather than by stamps or coupons, as in days gone by. Benefits can be used to buy food but not alcohol, tobacco, or nonfood items such as soap or paper supplies. Nationally, the majority of all Food Stamp recipients are children, and the preponderance of Food Stamp benefits is paid to families with children.

Who Qualifies. For families with children, the principal eligibility requirement is that gross household income is below 130% of the federal poverty level and that net income, after various deductions, is at or below 100% of the poverty level. The value of a household's assets (eg, cash on hand, checking or savings accounts, stocks and bonds, recreational boats and vehicles, some cars, and land that is owned but not inhabited by the household) is also accounted for in determining eligibility.

How to Enrol. Contact the state or local welfare office and obtain an application.

Child Care Food Program ***What It Is.*** This program provides cash reimbursement and/or commodities for the provision of meals and snacks to institutions such as child care centers and family and group daycare homes providing nonresidential child care to children from low-income families. This program funds the meals provided in Head Start. This is not an entitlement program. Subsidies are

TABLE 9.1-11 Food Assistance Program Expenditures, USDA, 2001

Food Assistance Program	*Program Costs, 2001 (Million Dollars)*
Food Stamp–related programs	19,009.5
Food Stamp Program	17,702.2
Nutrition assistance programs	1,279.4
Child nutrition programs	9,918.6
National School Lunch Program	6,454.8
School Breakfast Program	1,441.4
Child and Adult Care Food Program	1,733.6
Summer Food Service Program	272.3
Special Milk Program	15.5
Supplemental Food Programs	4,235.1
WIC	4,133.2
Commodity Supplement Food Program	102.0
Food donation programs	596.8
Food distribution on Indian reservations	68.6
Disaster Feeding Program	0.4
The Emergency Food Assistance Program	370.0
Charitable institutions and summer camps	6.0

Adapted from USDA Food and Nutrition Service, Keydata, September 2001.
WIC = Special Supplemental Nutrition Program for Women, Infants, and Children.

provided for two meals and one snack per day for children less than 12 years old. Meals must meet USDA-specified requirements. Family or group daycare homes are paid a fixed reimbursement, depending on the type of meals served. Daycare centers are reimbursed for meals at rates depending on the type of meal and eligibility of children for free, reduced-price, or paid meals.

Who Qualifies. Institutions eligible to participate include child care centers, settlement houses, neighborhood and Head Start centers, and institutions providing day care for the handicapped and their families or group daycare homes. Private daycare centers can participate only when at least 25% of their enrolled children are from low-income families receiving benefits through Title XX of the Social Services Act.

How to Enrol. Contact the local school authority or child care center.

School Lunch and School Breakfast Programs ***What They Are.*** Over 90% of all schools in the United States participate in the National School Lunch Program. They receive cash assistance to help purchase food and pay labor costs as well as direct donations of agricultural food commodities. Participating schools must agree to serve meals at a reduced price or free to children who are unable to pay the locally established full price. The federal reimbursement level is such that all meals fed to children receive some subsidies, but they are largest for the poorest children, who receive meals free. To receive a free or reduced-price meal, means tests are required. Each year, the Secretary of Agriculture issues uniform national standards for free and reduced-price eligibility based on national poverty guidelines.

To ensure that the nutrition goals of the program are met, minimum meal pattern requirements are specified, and the USDA periodically updates these. The lunch is designed to provide about one-third of the Recommended Dietary Allowances (RDAs) for age and the breakfast about one-fourth. Recent regulatory changes have provided for more flexibility in the quantities and types of foods offered in the meal pattern; for example, skimmed milk, unflavored low-fat milk, flavored whole milk, or buttermilk can be offered as a choice for those who do not wish regular whole milk. Children can now choose three of the five meal components for lunch, and the school will still be reimbursed for the whole price of the meal. This provision of offering instead of simply serving all meal components is designed to cut down on waste.

Who Qualifies. Any public or nonprofit private school of high school grade or under is eligible. Public and licensed nonprofit private residential child care institutions such as orphanages, homes for retarded children, juvenile detention centers, and temporary shelters for runaway children also are eligible.

How to Enrol. Contact the local school authority.

Special Milk Program for Children ***What It Is.*** This program reduces the cost of each half-pint of milk served to children by providing for cash reimbursement at an annually adjusted rate to public and nonprofit schools, child care centers, summer camps, and similar institutions that do not participate in any other federally assisted nutrition program. Participants can choose to provide milk free or at low cost to all children or may elect to serve free milk to children whose families are below 130% of poverty.

Who Qualifies. This program is available only to institutions that do not participate in the National School Lunch, School Breakfast, or Commodity Programs.

How to Enrol. Contact the local school authority.

Summer Food Service Program for Children ***What It Is.*** This program provides nutritious meals for preschool and school-aged children under 18 years of age in recreation centers or summer camps, during vacations in areas operating under a continuous school calendar, or in areas with poor economic conditions. Meals are served free and must meet the minimum standards established by the USDA.

Who Qualifies. Sponsors of the program must be public or private-nonprofit school food authorities; state, local municipal, or county governments; or public, private-nonprofit residential summer camps. The programs must be in areas where at least half of the children are from households with incomes at or below 185% of federal poverty guidelines; there is no income test for eligibility in these low-income areas, and any child in the program may participate. Other programs that contain at least half of children from families at or below 185% of the federal poverty guidelines may also provide food to all children in the program. Individual children in these programs may participate without regard to their family's income, and they may receive as many as two meals and two snacks per day. The USDA reimburses sponsors of the program.

How to Enrol. Contact the local school authority.

WIC ***What It Is.*** Since its inception in 1972, the WIC program has grown from $20 million to more than $4.1

billion yearly in authorized funds. The USDA provides annual cash grants to state health departments or comparable agencies on the basis of a formula that considers food costs and administrative costs. The program is very large, but it is not an entitlement program; rather, it is a grant program with funding limits that are set annually. Participation is an option for states and localities, but today it is available in virtually all parts of the country.

The WIC program differs from all other federal food assistance programs in its close association with health care services and inclusion of food, health, and nutrition education services together.[42,43] These services are defined as ongoing, routine pediatric and obstetric care. Health care itself, other than screening and limited assessment and care provided by WIC, must be supported by state, local public and private-nonprofit health or human service agencies as well as the private sector. The amount and kind of health services provided to WIC recipients vary from state to state and locally.

The benefits of the program include vouchers for the purchase of specific foods tailored to the dietary needs of infants, children, and pregnant or postpartum women. Physicians or health professionals may also prescribe special infant formulas and certain medical foods for WIC participants with special medical conditions. In addition to food, WIC also provides referrals to health and social services, including prenatal care, and nutrition counseling and education sessions. In addition, many pregnant women gain initial access to prenatal care via their WIC screening. Efforts are made to adapt the education activities to the individual participant's nutritional needs, cultural preferences, and education levels. Approximately 75% of the current participants are children ranging in age from newborn to 5 years.

Who Qualifies. Low-income pregnant and postpartum women, lactating mothers, infants, and children up to 5 years old who are determined to be at nutritional risk by a health professional are eligible if they fall below 185% of federal poverty guidelines. The criteria for nutritional risk include dietary risk, anthropometric risk (eg, overweight, underweight), biochemical risk (eg, low hematocrit), and medical risk (eg, diabetes mellitus) and other factors such as homelessness. A priority system is in place that categorizes participants on the basis of severity of potential effects and outcomes so that those at highest risk are served first. Participants must be recertified every 6 months to continue receiving benefits.

How to Enrol. To obtain WIC benefits, an individual must apply at a WIC clinic.

Commodity Supplemental Food Program ***What It Is.*** This program provides nutritious supplemental foods at no cost to infants and children up to their sixth birthday and to pregnant and postpartum women who are at or below 185% of the federal poverty level who are not served by WIC. The program provides food packages that are tailored to the needs of participants.

Who Qualifies. Those below 185% of federal poverty levels who are not served by WIC qualify. States can require that participants be nutritionally at risk to qualify for the program. It operates in parts of 18 states and the District of Columbia.

EFNEP ***What It Is.*** This program provides instruction in basic food and nutrition-related topics to low-income families and individuals and is operated through the state Cooperative Extension service. It is not an entitlement program. Its aim is to develop understanding and awareness through a variety of methods, including direct teaching by nutrition assistants in existing groups (such as employment and training programs and shelters for homeless families), cluster groups consisting of two to five participants, one-on-one home visits, mailings, telephone, and mass media efforts.

EFNEP teaches participants how to plan for daily food needs; prepare nutritious, low-cost meals that meet the daily RDAs of nutrients; select and buy food economically; and effectively use other supplemental programs available, such as Food Stamps, WIC, School Meal Programs, and CSFP.

Who Qualifies. Families with children under 19 years of age, pregnant women, and individuals who are responsible for purchasing and preparing foods (such as special needs adults, teens living independently) are eligible. To qualify, applicants must have income at or below 185% of federal poverty guidelines and be at nutritional risk as determined by an EFNEP nutritionist.

How to Enrol. Call the national EFNEP office at 202-720-8855. A coordinator will refer the applicant to an EFNEP office in his/her area.

CSFP ***What It Is.*** This in-kind program provides food and is available at local option in several states. Providing commodity supplemental foods and nutrition education to participants, the CSFP is designed to supplement their diets with nutritious foods. The foods supplied by CSFP are different from WIC foods in their variety (ie, they consist of canned meat or poultry and canned vegetables). CSFP distributes food rather than vouchers for redemption at the grocery store. Also, the provision of health care to recipients is encouraged but not mandated, unless it was already in existence prior to 1978. Simultaneous participation in WIC and CSFP is prohibited. The supplemental foods (usually surplus agricultural commodities) are distributed to state agencies, Indian tribes, or groups responsible for administering the program. Each state selects local, private, nonprofit agencies to administer the program at the local level. Local agencies determine the eligibility of applicants, distribute the supplemental foods, and provide nutrition education. Federal funds provide for some of the administrative costs such as outreach, warehousing of food, and transportation to obtain food if necessary.

Who Qualifies. Low-income pregnant, lactating, and postpartum women, infants, and children to age 6 years are eligible.

How to Enrol. Contact state or local public or private-nonprofit health agencies.

Food Distribution Program on Indian Reservations ***What It Is.*** This program provides commodities to low-

income households on participating reservations and to Native American families living in designated areas near reservations. This is an alternative to the Food Stamp program for American Indians who do not have easy access to food stores. Participants receive a monthly food package containing a variety of foods to meet their health needs and preferences.

Who Qualifies. Program eligibility is based on a person's household income, assets, and residence on or near a reservation.

The Emergency Food Assistance Program (TEFAP) ***What It Is.*** First started as a way to reduce inventories and storage costs of surplus commodities by distributing them to needy households, it now also includes funds appropriated by Congress to purchase additional commodities. The USDA buys the food, processes and packages it, and ships it to the states based on a formula that takes into account the number of people below the poverty level and the number unemployed.

Who Qualifies. States set their own eligibility criteria and select emergency feeding organizations such as soup kitchens, food recovery organizations, and food banks to distribute the food.

Charitable Institutions and Summer Camp Food Distribution Program ***What It Is.*** The USDA donates food to nonprofit charitable institutions serving meals on a regular basis to summer camps for children, orphanages, soup kitchens, temporary shelters, and church-operated community kitchens for the homeless. The amount of food donated depends on the amount of surplus and price support commodities that are available.

Who Qualifies. Institutions participating in the Summer Food Service Program are not eligible.

DHHS The DHHS provides a wide variety of public health programs at the community level, as well as payments for health services. The public health programs include the Head Start and Early Intervention (EI) programs and the Aid to Families with Dependent Children (AFDC) program. In addition, limited monies are provided for nutrition services such as assessment and counseling. Title V of the Social Security Act of 1935 authorized grants to states to plan for provision of comprehensive health services to mothers and children. In subsequent years, funding of categorical programs provided monies for planning and provision of special services, such as lead poisoning prevention, services for handicapped children, and family planning. Monies for planning such programs are provided from federal funds by the DHHS. Demonstration grant funds have also been available on an increasingly limited basis over the past few decades for high-risk communities and groups. The comprehensive services include medical and dental care, nursing, nutrition, and social work.

Head Start ***What It Is.*** This program is particularly well known for its multifaceted approach to child health and development, including social and educational development. Administered by DHHS and funded directly to local agencies, Head Start provides low-income preschoolers and their families with day care, access to medical care and social services, and nutrition services, including meals, nutrition education, and staff training.[44]

Head Start programs are funded through grants from the Administration for Children, Youth and Families regional offices and the Native American Migrant Program branches. These grants are awarded to a variety of local public agencies, private-nonprofit organizations, and public school systems. The program is very large but not an entitlement. It is at the discretion of states and localities and serves primarily children from poor families.

Head Start programs serve a multiracial, multiethnic group of low-income children and families. Each program must offer four major components: education, social services, parent involvement, and health services. With the goal of meeting each child's individual needs, the program offers a wide variety of learning experiences aimed at fostering intellectual, social, and emotional growth. Head Start also aims to meet the ethnic and cultural characteristics of the communities served.

Head Start's nutrition program is part of the health component offered and provides nutritious meals from the Child Care Food Program, as well as nutrition education for children, staff, and parents.

Who Qualifies. To be eligible for Head Start, a child must be between 3 and 5 years of age and come from a low-income family whose total annual income does not exceed 100% of the federal poverty guideline or who is receiving public assistance from programs such as AFDC or SSI.

How to Enrol. Contact the Head Start Bureau, which is located in the Administration for Children, Youth and Families, Office of Human Development Services, DHHS.

Head Start for Children with Special Needs ***What It Is.*** Head Start is the largest provider in this country of services for preschool children with handicapping conditions.

Who Qualifies. It is mandated to serve preschool children who have a broad range of handicaps. Children with severe or multiple handicaps present additional challenges to Head Start staff in the planning and provision of individual services. Program requirements call for individualized plans for special education, treatment, and related services for all handicapped children served by Head Start. These plans must be based on the child's specific handicapping conditions, as well as the unique needs arising from those conditions.

How to Enrol. Contact the Head Start Bureau, which is located in the Administration for Children, Youth and Families, Office of Human Development Services, DHHS.

EI Programs and Services ***What It Is and Who Qualifies.*** EI programs and services for infants, toddlers, and their families have existed in many areas of the United States for more than 25 years. These services are organized to address the developmental needs of young children between birth and 3 years of age who may be at risk for

poor developmental outcome because of an identified disability or because of biologic or environmental risk factors.[45,46] Although all of these programs share the common goal of optimal infant development, they approach it in different ways. That is why collaboration is essential in the development of an Individual Family Service Plan (IFSP), which addresses all of the child's needs that must be met for the child's potential to be reached. Some EI programs are home-based models, others are center-based models, and others are a combination of those two approaches. Intervention programs also differ with respect to their program philosophy and goals, the population that is served, team composition, program content, and program evaluation. Services are generally multidisciplinary, in recognition of the interrelationship of development in various domains, and may include input by developmental educators, occupational and physical therapists, speech pathologists, psychologists, nurses, dietitians, and social workers.

Federal law significantly influences the development of EI programs. The most applicable law, enacted in 1986, is Title I, Part H, Handicapped Infants and Toddlers, of PL 99-457, Education of the Handicapped Amendments of 1986. That law extends public education to children 3 years old and older and provides incentives to states to serve children with special needs from birth onward. It includes nutrition as one of eight disciplines to be included on the team providing services to these handicapped infants and their families.

Part H of PL 99-457 requires that services designed for children from birth through 36 months meet their developmental needs. It mandates psychological services, parent and family training and counseling, transition services, diagnostic medical services, case management, and health services that will enable the child to benefit from other early interventions. The eight disciplines specified by PL 99-457 include special education, nursing, nutrition, psychology, physical therapy, occupational therapy, speech-language pathology, and social work. This law provides great opportunities for nutrition intervention in preschool children with handicapping conditions and their families. To date, however, most states have done little to develop community-wide networks to provide EI services that include nutrition.

How to Enrol. Contact the state Maternal and Child Health Department.

Personal Responsibility and Work Opportunity Reconciliation Act ***What It Is.*** In 1996, under the Personal Responsibility and Work Opportunity Reconciliation Act, the basic cash assistance program AFDC was eliminated and replaced with Temporary Assistance for Needy Families (TANF).[47] The 1996 welfare legislation provides block grants to states for time-limited cash assistance and made other program changes (Food Stamps, SSI for children and others). How these programs develop will have a profound effect on families living in poverty in the United States and the potential to significantly impact the nutritional status of children. The overall effects of welfare reform on child health and nutrition need to be closely monitored.

Who Qualifies. States have much more control over the money block granted including time limits, sanctions, and categorical restrictions. Although there are advantages to this (flexibility), there are no assurances that the funds will be spent where most needed, and the program may lack focus.

How to Enrol. Contact the local Department of Public Health.

State and Local Programs

There is a great deal of variability between states and localities in the extent to which they supplement federal nutrition funds or provide additional in-kind resources, such as health services. These variations make it essential for community nutritionists to know the specifics of state and local programs in their areas..

WEB-BASED RESOURCES FOR COMMUNITY NUTRITION

The DHHS has developed a number of Web-based resources that may be helpful in planning community nutrition efforts. Many nutrition resources not specified below are listed at this Web site: <http://www.nutrition.gov>. The gateway to reliable consumer health information on the Internet is provided at <http://www.healthfinder.gov>. Healthy People 2010–related materials include a general description of the initiative at <http://www.health.gov/healthypeople>, a community-planning guide using Healthy People 2010, entitled *Healthy People in Healthy Communities*, at <http://www.health.gov/healthypeople/publications/HealthyCommunities2001>. Information on TANF is available at http://www.neighborhoodlaw.org/aprimer.htm. A "toolkit" for planning at the state level is at this Web site: <http://www.health.gov/healthypeople/state/toolkit>. The CDC's planned approach to community health (PATCH) is provided at <http://www.cdc.gov/nccdphp/patch/index.htm>.

Several Web sites focus on physical activity and health. These include the Surgeon General's report on this topic at <http://www.cdc.gov/nccdphp/sgr/sgr.htm>. The President's Council on Physical Fitness and Sports is available at <http://www.fitness.gov>. Tips for promoting better health for young people through physical activity and sports are provided at <http://www.cdc.gov/nccdphp/dash/presphysactrpt/index.htm>.

The USDA provides several Web sites to improve access to food stamp and food program–related nutrition resources for assisting community nutrition efforts.

All USDA Web sites are available at the National Agricultural Library's homepage: <http:/www.nal.usda.gov>. Some specific Web sites include the following:

- The Food and Nutrition Information Center is a large, Web-based information center backed up with trained nutritionists who can help in locating information and borrowing additional resources from the collection of the National Agricultural Library. Access it at <http://www.nal.usda.gov/fnic>.

- The Food Stamp Nutrition Connection has a training center with a collection of social marketing and programming resources on food stamps, a resource library providing ready-to-use educational materials, information on hot topics, contacts at the state and national levels, and program facts. These are available at <http://www.nal.usda.gov/foodstamp>.
- The WIC program has a Web site that summarizes recent studies on WIC and provides other educational materials. It is located at <http://www.fns.usda.gov/oae/menu/published/wic/wic.htm>.
- A special Web site for child care nutrition resources focuses on food programs for children in child care. It is located at <www.nal.usda.gov/childcare>.
- The Healthy School Meals Resource System is a searchable Web site that provides information to persons working in USDA's child nutrition programs. It includes materials to assist nutrition educators both in the classroom and in the school cafeteria. Access it at <http://www.schoolmeals.usda.gov/8001>.
- The Dietary Guidelines for Americans are available on the Web at <http://www.health.gov/dietaryguidelines>.

LESSONS LEARNED FROM COMMUNITY NUTRITION EFFORTS

Community Investments in Child Health and Nutrition Make Sense

As early as the fourth century BC, the philosopher Plato stressed the importance of investing in children from an early age. Several millennia later, numerous studies confirm Plato's suppositions about the importance of investing in our children.[48] For example, supplementing the diets of pregnant women and infants and immunizing children against early childhood diseases save lives and improve health. It is to be hoped that, in the future, programs such as Head Start, EI, and WIC, with demonstrated success in strengthening the bodies and minds of children, will reach more of their target populations. Also, special attention must be paid to nutrition for children with special needs and other chronic health problems. Current programs do not cover them adequately.

Table 9.1-11 shows current federal spending for a number of key health and food programs involving children.

Community Health and Children's Health Care Must Be Equal Partners

Community health and nutrition efforts expand the traditional focus of direct health services. Both are necessary to ensure child and family health. Also, broader economic factors that affect food insecurity must be dealt with.[49] The distinctions between traditional public health and personal health services are slowly blurring in this country. In the future, community nutrition concerns will need to be incorporated into both systems. There is the danger that nutrition will "fall through the cracks" because there are other pressing needs. Thus, it behooves all of those who are interested in the health of children to pay attention to ensuring that federal, state, and local governments employ nutritionists to look after community needs in nutrition. These professionals must work with others in health, welfare, education, and food agencies in the public and private sectors to ensure that all children are well nourished. At the same time, dietary concerns must be increasingly incorporated into personal health services. Only when these steps are taken will community nutrition realize its potential to have a positive impact on children.

Child Nutrition and Physical Activity Are Inextricably Linked, Like Siamese Twins

Both physical activity and sound nutrition in the community help to keep children healthy and ready to learn and also prevent later chronic disease risk.[50] Long-term community efforts at the school, family, and individual levels are necessary to yield the benefits of lower health risks over the long term. Community leaders, experts in health and education, and parents themselves must be involved in school-based and other prevention-oriented programs.

School-Based Programs Offer Much Potential for Health Promotion and Primary Prevention of Diet- and Physical Activity–Related Risk Factors if Supplemented by Parent, Family, and Community-Wide Efforts

School-based programs are excellent sites for these efforts. However, changes in the curriculum alone are not sufficient to bring about alterations in risk factors for cardiovascular disease or obesity; changes in school meals and alterations in physical education programs are also needed. More attention to physical training components that increase strength may be important in preventing later osteoporosis risk. Thus, multiple risk factors need to be targeted. Also, community efforts to reinforce these efforts are needed.[51]

In addition to school-based efforts, family and community efforts are also required. Children do not spend all of their waking hours in school. The microenvironment of the family is an important milieu for enhancing and carrying forward school-based health promotion and physical education efforts. The macroenvironment of the community must also be conducive to healthy lifestyles.

Healthful Eating Patterns for the Whole Family Are Critical

Foods must be eaten to be nutritious, and overall diets are the most important. Children and their families eat foods, not individual nutrients. There is often a gap in teaching about the merits and demerits of individual foods, and broader guidance on healthful diets or eating patterns is needed. Existing scientific evidence shows that overall eating patterns and diets and not consumption of individual foods or nutrients are most closely linked to positive effects on health. Therefore, families need information about healthful, enjoyable eating patterns that provide a broad, food-based context for healthful eating and about healthful physical activity and exercise patterns. When needs cannot be met by food-based solutions alone, supplementation with vitamins and minerals may be considered.[52,53]

Information on Healthful Eating and Physical Activity Must Be Communicated More Effectively at the Community Level

Consumers and policy makers must view the Dietary Guidelines for Americans and other nutrition education guidance and programs as acceptable and actionable as well as authoritative if they are to be used. The Dietary Guidelines,[54] the USDA's Food Group Pyramid,[55] the Healthy Eating Pyramid for children (which is based on the Dietary Reference Intakes and the Dietary Guidelines), food labels, and health claims provide such guidance to the community.[56] Information about them needs to be communicated, coordinated, and harmonized to facilitate food purchases and consumption decisions, and diet-related efforts must be accompanied and reinforced by physical activity programs. This challenge is one that food producers, marketers, public policy makers, and educators face together. Intervention strategies from the social and behavioral sciences may be helpful in tailoring messages to our diverse population.[57,58]

CONCLUSION

Community efforts in this country are in line with those of the overarching goals of the World Health Organization's Health for All campaign in the twenty-first century to increase healthy life expectancy, ensure universal access to quality health care, and achieve greater equality in health status within and among countries.[59]

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CHAPTER 9.2

COMMUNITY NUTRITION AND ITS IMPACT ON DEVELOPING COUNTRIES (THE CHILEAN EXPERIENCE)

Gerardo Weisstaub, MD, MSc, Magdalena Araya, MD, PhD, Ricardo Uauy, MD, PhD

NUTRITION A KEY FACTOR FOR HUMAN AND SOCIAL DEVELOPMENT

The nutritional status of children is directly related to their health condition, and both, in turn, are key determinants of the human and social development of communities around the world. Improvement of nutrition and health increases the chances of child survival and is a precondition for economic development. UNICEF has proposed a conceptual model to understand the causation of malnutrition beyond the obvious immediate determinants (Figure 9.2-1). Undoubtedly, the basic determinants relate to the social, economic, cultural, and political structures of society. These define what resources are controlled by individual families, including access to information and education, household food security, care of women and children, and access to health and a healthy environment. It is within this context that children have inadequate access to food in terms of quantity and quality; in addition, infection will further compromise nutrition by augmenting nutrient losses and increasing nutrient needs.

Nutrition has been considered a basic human right and has been expressly recognized by international human rights covenants since 1924,[1] yet this right is commonly the subject of political demagogy rather than being actively upheld, respected, protected, and promoted. The relationship between poverty and malnutrition has been well established in both directions, that is, how poverty conditions nutritional status and vice versa. Moreover, the correlation is by no means linear. There are multiple examples that illustrate how nutrition can improve despite economic limitations. Economic development is by no means sufficient to improve nutrition, especially in countries where wealth is concentrated in a few hands. The United Nations' Human Development Index illustrates how nutrition and health can be dissociated with economic status.[2] For example, Indonesia has a higher per capita gross national product than China, but malnutrition is presently rare in the latter, whereas it is frequent in the former. Brazil has experienced significant economic growth over the past decade, but malnutrition in children under 6 years of age remains high. Recent analysis of trends reveals significant reductions in malnutrition assessed by underweight or stunted linear growth except in sub-Saharan Africa and Central America. These regions have experienced protracted civil wars, and, more recently, that African region has been stricken by human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and its consequences. On the contrary, Latin America and the Caribbean combined have reduced malnutrition to about a third of the 1970 figure, despite the unchanged proportion of families living in poverty (as shown in Figure 9.2-2).[3] This concept should be stressed because health professionals frequently work under the assumption that nothing can be done in terms of prevention and control of protein-energy malnutrition (PEM) unless social conditions change and poverty reduction is achieved. Undoubtedly, both should proceed in tandem because improved nutrition will contribute to socioeconomic improvement.

The World Health Organization (WHO), UNICEF, and other international organizations concerned with malnutrition have recognized for several decades the role of malnutrition in defining infant mortality. The immediate cause of death may be diarrhea or pneumonia, but the risk of dying from these conditions is increased manifold by severe and moderate malnutrition. The work of Puffer and Serrano in the Americas and more recently Pelletier and colleagues, using data from Africa and Asia,

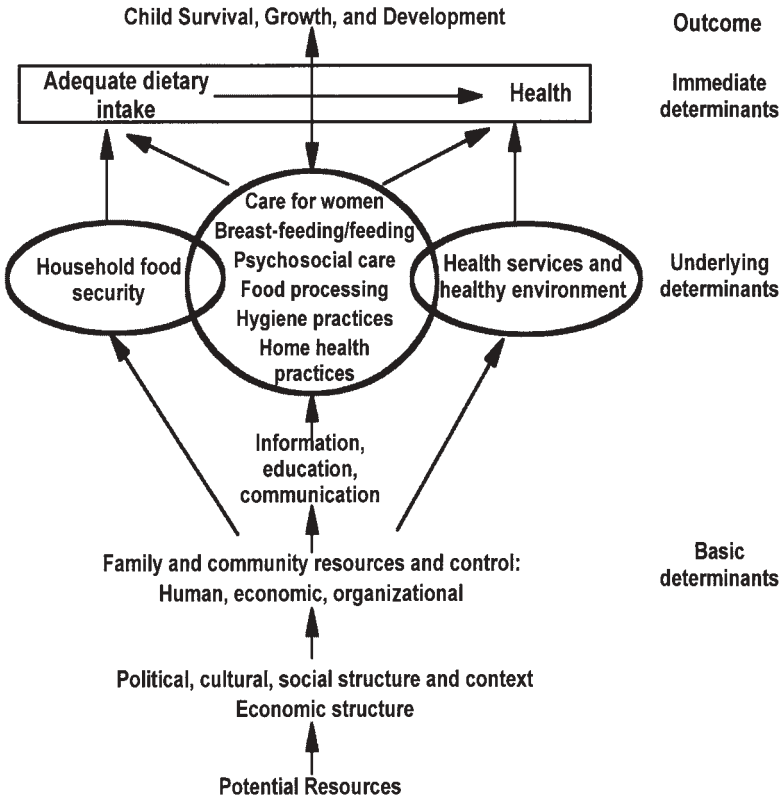

FIGURE 9.2-1 Conceptual model of child development useful in the analysis of prevention and control of malnutrition. Adapted from ACC/SCN Commission on the Nutrition Challenges of the XXI Century.[3]

has documented with precision the contribution of malnutrition to infant mortality.[4,5] The conclusion reached by both is that over half of all infant deaths are determined by malnutrition. UNICEF, in its annual report on the state of the world's children, stated that "malnutrition is directly related to over half of all infant deaths that occur worldwide."[1] Chapter 11, "International Nutrition," discusses nutrition and infection interactions as crucial factors contributing to infant death.

MALNUTRITION AS A GLOBAL PUBLIC HEALTH PROBLEM

Weight, height, and head circumference measurements have been widely used as indicators of nutritional adequacy. Malnutrition as a public health problem is assessed based on growth indices relative to those derived from a standard population. Yet most growth standards describe what may be considered normal growth based on values

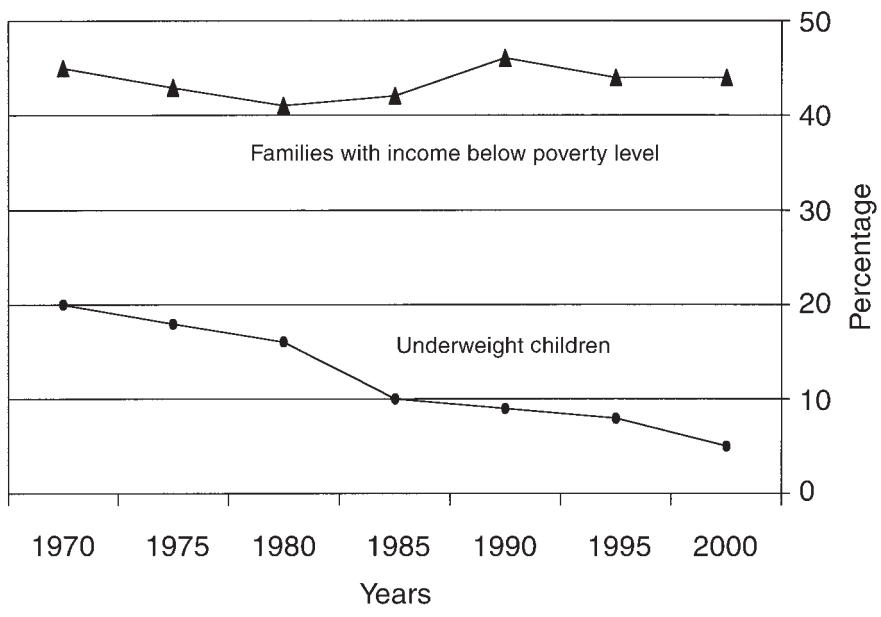

FIGURE 9.2-2 Child undernutrition in Latin America and the Caribbean: trends, reasons, and lessons. Over the past 30 years, population under the poverty line has remained stable, but malnutrition has declined significantly.

obtained in a given normative population. Normal is derived from statistical normalcy rather than based on specific health and/or quality of life outcomes related to a set of growth parameters. For example, the National Center for Health Statistics (NCHS) growth reference standard, used as the basis for the present WHO international standards for infants 0 to 36 months, is derived from children growing in a relatively affluent, predominantly artificially fed, rural community from Yellow Springs, Ohio, over 30 years ago.[6] New growth standards are being developed by WHO/United Nations University (UNU) based on the growth of infants from middle-income and well-educated families who are exclusively breast-fed for 4 to 6 months and given appropriate complementary foods after weaning. Preliminary findings indicate that infants fed according to present WHO recommendations and living in appropriate conditions grow less rapidly than the present NCHS median reference value, particularly after 4 to 6 months (unpublished). A significant discrepancy of approximately half a standard deviation in estimated height status arises around 2 years of life. The limitations in present growth standards led a WHO Expert Committee in 1995 to support the development of a new growth reference.[7] The WHO multicountry (Brazil, Norway, India, Ghana, United States, and Oman) growth reference study is presently in progress, more than 13,000 healthy infants and children are involved, and data collection is expected to be complete by the end of 2003. This new reference will provide a scientifically reliable descriptor of physiologic growth and a powerful tool for advocacy in support of good health and nutrition.[8] Another objective of the new reference is to support, based on actual evidence, the concept that human growth during the first years of life is very similar across groups of children of different ethnic backgrounds. This confirms that existing differences in growth across countries are predominantly environmentally derived and can be narrowed over time. Prevalence estimates of global malnutrition based on the new reference will clearly be affected to the extent that the new reference may differ from the current WHO norms in median values and/or distribution.

Patterns of change in prevalence of underweight (low weight for age), stunting (low length for age), and wasting (low weight for length) are being monitored systematically by WHO (241 countries) by de Onis and colleagues.[9] The evolution in prevalence of underweight and stunting reveals significant reductions for most countries over the past two decades, yet the rate of progress (0.5% per year) is insufficient to achieve the stated goal of the world summit for children. Although the prevalence of malnutrition in developing countries as a whole fell from 46.5 to 31% between 1970 and 1995, about 15 percentage points in all for this 25-year period, progress in reducing malnutrition has varied greatly from one region to another. Malnutrition has declined the fastest in South Asia (by 23 percentage points) and the slowest in sub-Saharan Africa (4 percentage points), but the rate of progress is decelerating. During 1970 to 1985, the prevalence of malnutrition fell by 0.8 percentage points per year; during 1985 to 1995, it fell by only 0.3 points. The situation is particularly troubling in sub-Saharan Africa, where the prevalence of underweight children actually increased from almost 29% in 1990 to 31% in 1995. In West and East African regions, the prevalence in underweight and stunting has actually increased over the past three decades. In Central America, there is no improvement, whereas in South America and South-Central and Southeast Asia, progress has been significant. Since 1970, the prevalence of underweight children has decreased in 35 developing countries, held steady in 15, and increased in 12, with most of the countries with increases in sub-Saharan Africa.[10]

The causes behind the insufficient progress are multiple and complex in their interactions. Political strife, government unresponsiveness to the needs of the community, stagnant economies, low status of women and unequal rights, poor education and inadequate access to health care, poor sanitation and unclean water, high prevalence of infections, and low birth weight interact in determining poor postnatal growth and high rates of malnutrition.[9]

Because most of these factors are interrelated, it becomes virtually impossible to isolate their effects from retrospective trend data or regression models. Decreases in the prevalence of malnutrition have been described in relation to improvements in household food security, supply of clean water and environmental sanitation, education of women, early treatment of diarrhea with oral rehydration solutions in the community, early treatment of respiratory infections, promotion of breast-feeding, appropriate complementary feeding, immunization, growth monitoring, and surveillance for early identification of malnutrition.

Smith and Haddad have attempted to explain the key factors responsible for the different rate of progress across regions of the world (Figure 9.2-3).[11] They examined the contribution of national food supply, women's status, and women's education and health environment based on proxy indicators from available country data. Improvements in women's education contributed by far the most, accounting for 43% of the reduction in child malnutrition between 1970 and 1995, whereas improvements in per capita food availability contributed about 26%. Comparisons between regions were quite revealing.

The overall reduction in the prevalence of child malnutrition in South Asia for the 25-year period was estimated to be 16.5 percentage points. The greatest contributions to this reduction came from increased education of women and improvements in health environments; each accounted for about 28%. Gains in the status of women accounted for about 25% of the reduction and improvements in food availability for about 20%. The total reduction for sub-Saharan Africa's malnutrition rate over the study period was only 4.2 percentage points. Most of this was explained by increases in women's education, followed by improvements in health environments. Increased education of women made strong contributions in all periods except for the late 1980s, when enrolments actually declined. Improvements in health environments have made their greatest contribution after 1985. Women's relative status, as evidenced by gender differences in life expectancy, has continually declined in the region since

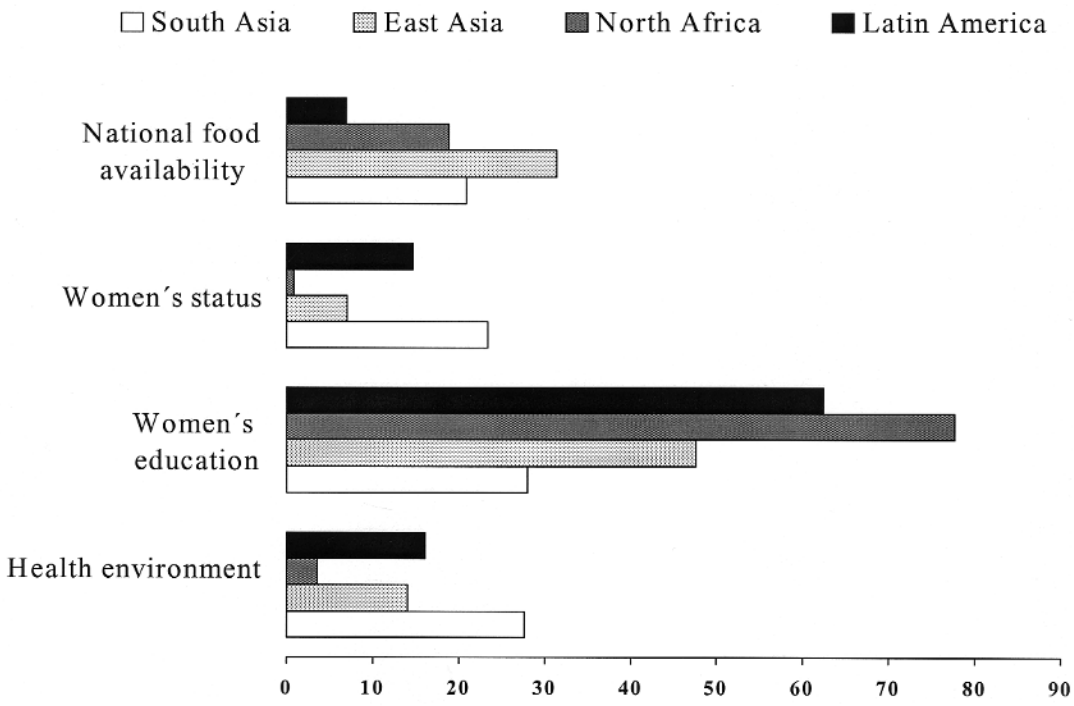

FIGURE 9.2-3 Estimated contributions of underlying determinant variables for malnutrition across regions of the world.

the 1970s, most precipitously after 1985. The consequence has been a recent worsening in prevalence of child malnutrition in the region. Changes in food availability have played a large role in both directions. Substantial improvements in the late 1980s and early 1990s were outweighed by deteriorations during the 1970 to 1985 period.

Latin America and the Caribbean experienced an estimated 11 percentage point reduction in child malnutrition over the study period, most of which took place during 1970 to 1980. Since then, reductions in child malnutrition have continued at a much slower pace. Like the other regions, the greatest contribution comes from women's education, which explained 62% of the improvement, whereas the contribution of environmental health to this improvement has steadily declined. Strong improvements in the status of women in the 1970s were followed by very small improvements in the 1980s. Food availability improved in the 1970s but declined slightly in the early 1980s.

Prevention and control of infections are clearly critical aspects of malnutrition reduction efforts. As documented in Chapter 11, infection has a definite adverse effect on nutritional status, whereas malnutrition compromises the host defenses and immune responses, increasing case fatality and disease susceptibility.[12] Relative risk (RR) of death from infection is directly correlated with severity of malnutrition: RR ± SD 8.4 ± 2.1 for severe PEM, 4.6 ± 0.9 for moderate PEM, and 2.5 ± 0.3 for mild PEM.[5] Yet because the severely malnourished represent a small proportion of the total population, mildly to moderately malnourished individuals are responsible for most of the malnutrition-related deaths. It has been estimated that close to 80% of all malnutrition infection–related deaths are attributable to moderate and mild malnutrition. Despite the obvious public health implications in terms of preventing death, given the high mortality of the severely malnourished, the cost-effectiveness of PEM treatment is greater than that of controlling moderate malnutrition.

The adequacy of breast-feeding and weaning foods also plays a key role in malnutrition prevalence, especially after 6 months of life. In most countries where malnutrition prevails, the time of onset is after 6 months; this is when breast milk is insufficient to meet infant needs and also a time when mothers have increased competition for their time/dedication to the infant. This is coupled with weaning foods that are inadequate and of low energy density and low nutrient density. Under these conditions, feeding frequency and added starch or oil to increase energy density become crucial to prevent malnutrition.[13] A study in Bangladesh examined the role of education during the weaning period, demonstrating that education on complementary feeding given to mothers was effective in enhancing weight gain despite the fact that no foods were actually provided. The authors suggest that the educational efforts on what constitutes adequate complementary feeding and on how to prevent microbial contamination of weaning foods are important as malnutrition prevention strategies.[14]

Although there are no easy answers or a magic "silver bullet" in combating malnutrition, several options can be suggested based on the success and accomplishments of some countries in malnutrition reduction. In most cases, poverty reduction efforts need to go hand in hand but should not be considered a precondition for success. Suggesting that poverty reduction is a precondition for success is simply not realistic because malnutrition is not only a determinant but also a consequence of poverty. Thus, the efforts should not be postponed until major political or

economic events improve the economic condition of the poor because reducing malnutrition contributes by itself to poverty reduction. The notion of human capital as a major determinant of economic growth has been recognized globally with the award of two Nobel Prizes in economics over the past decade.[15]

A strategy for action, based on what has worked in different settings around the world (Costa Rica, Thailand, Cuba, Chile, and Kerala-India, among others), is proposed in Figure 9.2-4. This serves to analyze the necessary interactions among the key social actors required for successful implementation of malnutrition control and prevention programs. The basic and critical component is social mobilization to establish the demands for action from the political actors; this process should lead to community actions as well as responses by government. A responsive government is one that responds to community demands; this requires some degree of participation by society in government, ideally but not necessarily a government by the people, from the people, and for the people. Communities that are so empowered and able to participate in the political process will be successful in demanding appropriate actions from governments. Malnutrition needs to become unacceptable to society to trigger the level of action required to address the issue frontally. What does it take to trigger this process? In most cases, proactive academics and/or nongovernmental organizations (NGOs) that have a strong voice, independent from government, have catalyzed the process and led the way. "Political will" does not come easily, nor is it generated from within; professionals, academics, NGOs, community leaders, and the press should act in concert to elicit action. The role of the press in generating public awareness and communicating public concern of malnutrition as a key restriction for national development is crucial. Recruiting and training select journalists will serve to generate widespread recognition of the problem and make people aware that the solutions are credible and feasible by illustrating what has worked elsewhere. Academics and professionals should propose the necessary actions that are required to implement effective programs to control and prevent malnutrition, ideally based on technical consensus rather than political considerations. They should promote a critical review of policy options based on what may work in a given setting; international organizations can assist in reaching a technical consensus by providing evidence and expert advice on successful examples of malnutrition reduction. The private industrial or business sector is usually a latecomer in this scene. Yet public private partnerships are a must for sustainable programs because industry is a key partner in the implementation of programs, for example, in nutrient supplementation, fortification, and other food-based strategies.[16] In the final analysis, unless we activate the political process and include industry, we get no action.

Governments must be committed to generate the actions necessary to solve malnutrition as a public health problem. Governments are usually restricted in meeting social demands by the available monetary resources and are not willing to commit funds unless they see a clear return on investment. Thus, it is crucial to clearly present the cost-benefit analysis of various programs for nutrition improvement. Moreover, if the community is truly aware and the issue has become a political priority, there may be a clear political benefit as well as an economic gain in terms of human capital formation. The involvement of the press in facilitating social communications is important in open societies. For example, the cost of providing half of all critical micronutrient needs per person per day for a year by fortifying a staple food has been estimated to be less than a dollar per year; this is less than a pack of cigarettes in most countries. The World Bank has estimated the benefit-to-cost ratio of micronutrient fortification to be at least 17:1. On a relative basis, not all programs are equal in terms of cost benefit or cost-effectiveness; thus, the tools of economic assessment should be used in defining policy options. As demonstrated by the International Food Policy Research Institute study, the mix of policies that will work differs in various settings (see Figure 9.2-4). The impact of maternal education has been shown to work across all regions, yet we must bear in mind that access to education by women is in itself an index of multiple social, economic, and cultural factors.

Nutrition and food policies should be integrated in the context of national development strategies. Nutritional problems are determined by economic and labor policies, health and education sector policies, and welfare policies. The integrated approach may be more difficult to implement in most settings because government structures are sectorial, yet harmonization of policies is a must to avoid duplication, wasteful use of resources, and overburdening personnel budgets.[17] Cost-effectiveness evaluation of programs should be included at the outset in the present climate of fiscal policies. Presently, program sustainability in a world of competing interests will progressively depend on the capacity to demonstrate cost-effectiveness over time. Technical considerations should prevail over political interest in defining what should be done; this is the best way to optimize chances of success. This is true at all lev-

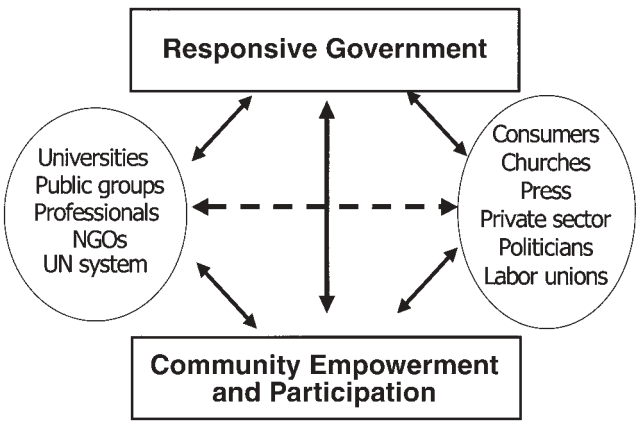

FIGURE 9.2-4 Scheme for strategic analysis of protein-energy malnutrition control and prevention. See text for details on dynamic interactions between stakeholders. NGO = nongovernmental organization.

els. National and international programs are not always guided by the best technical advice but, many times, respond to politically motivated actions.

The emerging orientation to guide nutrition and food policy by the ethical dimension and human rights concern can no longer be ignored. In a world of plenty, malnutrition can no longer be justified as a problem of the poor or a problem that affects others but not us. Globalization should be not only about business and trade but mostly about how we as humans face a common future. We cannot afford to have over a third of the people in the planet under conditions of poverty and malnutrition. Pediatricians should be concerned with the status of children worldwide. As we reflect on our own actions, our research should not ignore that we are progressively citizens of a common planet; our advocacy and our research in search for the truth should serve not only those around us but children around the world. Funding for applied research in the nutrition and health of children should be as important as the present emphasis on protection from bioterrorism and the war on terrorist activity worldwide. Providing for a better future for children across the world will do more for peace than the massive bombings that have recently taken place. Controlling and preventing malnutrition should top the list.

POTENTIAL STRATEGIES FOR THE TREATMENT AND CONTROL OF SEVERE AND MODERATE MALNUTRITION

First, we should clearly establish that prevention and treatment of malnutrition are complementary and do not contradict each other, as some would like to believe. The public health imperative of prevention is better than cure and cannot be used to negate or withhold treatment to those already affected by malnutrition. Both strategies must work in tandem to avoid malnutrition altogether and to recuperate those who are severely malnourished and at risk of death or severe disability as a consequence. The respective actions for prevention are quite different from those necessary for effective treatment but should be seen as part of the spectrum of efforts to combat malnutrition. What can we learn from experience, either success or failure, in the treatment of malnutrition?

The percentage of severely malnourished in a given population rarely exceeds 1 or 2% of children, yet their case fatality is high. Thus, they constitute an important proportion of preventable death and disease burden in most developing countries. Once they enter the hospital, up to 50% of malnourished children die depending on the quality of care they receive. A survey of the published literature reported by Schofield and Ashworth indicated that mortality from severe malnutrition ranges from 4 to 49% in 79 centers across the world.[18] The reason for this variance can be found in treatment practices. In fact, a controlled study demonstrated that even in a well-recognized high-quality center, mortality could be reduced from 20 to 5% if a standardized protocol was used.[19] Schofield and Ashworth concluded that inadequate treatment is the main reason for the high mortality and emphasized, as Chapter 10, "Protein-Energy Malnutrition: Pathophysiology, Clinical Consequences, and Treatment," does, the need to train and update health professionals responsible for the care of these children on the treatment of malnutrition. The most commonly used treatment for severe malnutrition has been care in hospitals and/or in closed nutrition recovery centers or ambulatory care in open recovery centers and/or primary health clinics. The respective actions are quite different and should be seen as part of the spectrum of efforts to combat malnutrition. We comment summarily on them in the next paragraphs:

1. *Hospital treatment.* In this case, the goal is to achieve nutritional recovery, preventing death and the sequelae related to severe malnutrition in the shortest possible time. The issue of duration of treatment is critical not only for cost-effectiveness but also to prevent risk from nosocomial infections and preserve the mother–child interaction necessary for normal growth and development.[20] For details on treatment and follow-up after discharge from hospitalization, see Chapter 10.
2. *Closed nutrition recovery centers (CNRCs).* These are institutions based in the community and established to treat moderate and severe malnutrition. Children enter the center after infections, electrolyte abnormalities, and other acute medical complications have been treated in the hospital. These centers are especially suited if there is a high prevalence of severe malnutrition in young infants and in settings where mothers have difficulties in caring for their infants. After nutritional recovery has been achieved, these children can be followed in the primary health care centers. Successful experience in using these centers has been achieved in Haiti, Costa Rica, Colombia, New Guinea, Uganda, Venezuela, Thailand, and Chile, yet in few countries has the effort been sustained sufficiently to effectively contribute to the reduction of malnutrition prevalence.

   Hospitalization is commonly considered most effective in attaining nutritional improvement over a short period of time, yet it is associated with a greater risk of hospital-acquired infections that prolong treatment and interfere with normal family life as the mother must continue taking care of the other siblings. Thanangkul and colleagues, based on their experience in Chiang Mai, Thailand, suggested that the duration of hospitalization should be as short as possible to prevent the adverse consequences of admission on mothers and children. Outpatient treatment was considered potentially equally effective and at much lower cost. The aforementioned survey suggests that hospitalized treatment under optimal conditions is very effective (up to 70% recovery) and is associated with a 5 to 7% mortality and a 1% recurrence rate.[21] However, the cost of treatment is high and sometimes unaffordable by families, thus limiting its widespread use.

   Ashworth and Khanum evaluated the cost of various treatment modalities in a controlled randomized

study in 437 Bangladeshi malnourished children aged 12 to 60 months. They were allocated to hospital admission, daycare nutrition recovery centers, and home care. The respective costs, to reach the target of 80% weight for height, in US dollar equivalents were 156, 59, and 29 per treated child, respectively. The costs of health personnel constituted the largest component for the treatments away from home. The days required to reach the target were lowest in the hospital at 18 days; 23 days in the daycare center and 35 days in the home treatment group were required. The cost per day of treatment per child was 8.6, 2.5, and 0.8 in US dollar equivalents, respectively.[22] Figure 9.2-5 summarizes these results. In the opinion of these authors, CNRCs may be more effective in nutritional recovery over time but often neglect other aspects, such as educating mothers and involving the family in the recuperation process. They propose that after initial stabilization has been achieved in the hospital over the course of a week, home treatment should be the preferred choice in terms of cost-effectiveness because it permits the treatment of more children with the same resources at an equivalent efficacy. In their study, mortality was equally low in the three groups (< 5%).[23] Moreover, when surveyed, parents indicated that they preferred either of the nonhospitalized treatment regimens, despite the higher cost to them, because they bore the cost of the complementary foods used in the nonhospitalized treatment.

3. *Daycare nutrition recovery centers and ambulatory care.* Daycare centers are also called open centers; these centers provide nutrition and related care for malnourished children during the day. They also provide education to mothers and psychomotor stimulation for the children. Mothers participate in the child's care and receive social support to enhance the chance of success of the recovery process. Various specific modalities of ambulatory care have been tested.

A community-based nutrition recovery effort was undertaken in a periurban slum area of Peru in 1988. The program included education and social support to mothers and family, growth monitoring and surveillance, management of common childhood illness, and use of low-cost complementary foods. Children under 3 years of age with moderate and severe malnutrition based on weight for age were included. Of the 54 children included, 1 died (2%) and 4 required hospitalization; after 3 months of the program, 19% remained moderately malnourished. The annual cost of the recovery program was $21 (US) per child. This program serves to illustrate the cost-effectiveness of a community-based nutrition recovery effort. The cost-effectiveness of community-based efforts in this case is over 20 times greater relative to hospitalized care.[24]

In Chile, a specific mode was foster care used in the case of malnourished children with difficult social situations that impeded home recovery efforts. If chil-

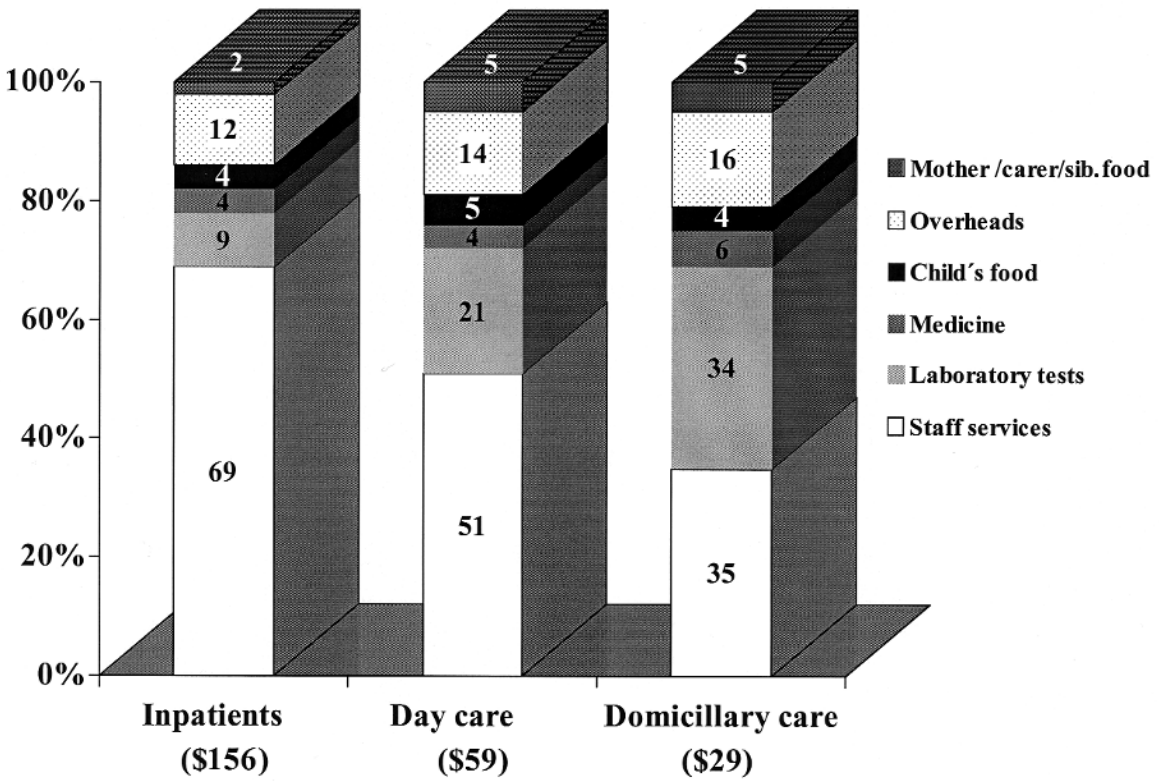

FIGURE 9.2-5 Cost-effectiveness of various treatments for severe malnutrition. Children were allocated to hospitalization (n = 173), daycare nutrition recovery center (n = 134), and ambulatory treatment (n = 130). All achieved a similar degree of recovery (weight for height 80% of World Health Organization standard). Cost is expressed in US dollars per treated child for treatment to reach the goal. The y axis represents the percentage of costs by various components detailed in the legend; the numbers in the bars correspond to the percentage of costs of each component for the three treatments.

dren could not be recovered within their home, they were placed in foster care until recovered. This program was implemented in 1983 by a multiprofessional team that included a physician, social worker, field nurse, and nutritionist. Specialized foster care was provided within the community by a specially trained caretaker; the biologic mother was able to visit the child as often as she wanted while she was receiving special training from the foster family. The evaluation of 291 children recovered under this mode of foster care revealed that the program was effective in normalizing weight for height and improved psychomotor development in 83% of the total.[25]

IMPLEMENTATION OF PROGRAMS TO PREVENT AND REDUCE MALNUTRITION AT THE NATIONAL LEVEL: THE EXPERIENCE OF CHILE

We need not only to examine the specific actions to treat severely and moderately malnourished children to understand how Chile succeeded in reducing malnutrition but also to assess the multiple programs that acted in synergy to achieve this goal. A key component was the primary health infrastructure with wide coverage and the human/material resources necessary for effective action. The capacity to identify and refer the severely malnourished to nutrition recovery centers when appropriate is vital for success. A nutrition recovery program focused on treatment of the severely malnourished working in isolation will have little or no impact unless it is coordinated with an effective primary and secondary prevention program working through the primary health system.[26]

Chile stands out among countries of Latin America and the Caribbean for the notable improvement of its health and nutrition situation, particularly in pregnant women and young children. This improvement has been achieved progressively and continuously through comprehensive health, nutrition, sanitation, education, and reproductive health strategies initiated in the 1940s. The results came 30 to 40 years later but much earlier than the considerable economic progress experienced by the country during recent decades. A key element in the success of the Chilean experience has been the uninterrupted application of programs defined based on technical consensus independent of major political, social, and economic changes. The programs remain in place and were expanded even in periods of social instability, radical political changes, and serious economic crisis. Only recently, poverty reduction has contributed to improved food security and to the improvement of the quality of life of low-income groups.

The achievements obtained in children's health can be appreciated in the declining rates of infant mortality and mortality owing to acute diarrhea and bronchopneumonia. Infant mortality dropped by approximately 90% and mortality owing to respiratory infections and acute diarrhea by over 95%. Between 1940 and 1960, total infant mortality was reduced in Chile from 193 to 120 per thousand live births. From 1960 to 1990, it fell to 17 per thousand, and over the past decade, it dropped to around 10 per thousand. See Table 9.2-1 for the degree of achievements of 2000 goals for nutrition of children and women; note the virtual eradication of malnutrition and the rise of obesity as the major diet- and nutrition-related public health problem.[27,28]

A key strategic factor in the development of nutrition programs in Chile has been the emphasis placed on the political dimension of nutritional problems. Nutrition of the population, especially its more vulnerable sectors, has been at the center of the political debate for the past 40 or 50 years. It has been transformed into a key indicator to assess social justice and equal opportunity for all. The 1970 presidential election campaign is a good example of this. All three main candidates for the presidency (one representing the conservative right, a second representing the center left [Christian Democratic], and the third representing the Socialist left) proposed the eradication of malnutrition as a key target of their respective future governments. Salvador Allende, the Socialist candidate, was elected on that occasion with the promise of providing half a liter of milk per day to every child up to 15 years of age in the country.

The community demanded access to health and food, not only to meet this basic need but also as a fundamental human right. The process initiated by academic researchers led to policy development and implementation of nutrition programs. The expansion of these programs became part of the social demands made by the population to the governments, and those politicians who satisfied these demands of providing more food to the economically vulnerable groups were elected and maintained in office. Community organizations, political parties, the Catholic Church, concerned academics, labor unions, and multiple social organizations played key roles in demanding action. Most of the nutrition programs were eventually built into the law specifying universal coverage and the respective yearly budget allocations. Any changes to the supplementary feeding programs have always been undertaken with extreme caution by governments because they are reluctant to take risks on a matter of such high political sensitivity.[27,28]

The National Supplementary Feeding Program (PNAC) is the main nutrition program for the prevention and control of malnutrition. It consists of the distribution of milk and other food products free of charge to children under 6 years of age, pregnant women, and breast-feeding mothers, with the sole condition of complying with the scheduled outpatient visits and preventive health actions determined by the Ministry of Health. In its present form, PNAC began operating in 1954 for the purpose of protecting and improving the nutritional state of pregnant women and children. Until 1974, it provided milk with variable fat content as the sole product. During the period from 1974 to 1981, studies were conducted with various milk-cereal blends for children after 2 years of age in an effort to reduce cost and to prevent the dilution of the product within the family. This alternative based on milk/wheat blends fortified with micronutrients has remained in place until now. All products are distributed in water-soluble dry powder form (except rice, which is given to families with greater need). PNAC's coverage was extended to all chil-

dren under 14 for a brief period (1971–1973), to return later to its original target population.[29]

Between 1975 and 1993, the protein-calorie malnutrition rate in the preschool population under control at the primary health care units of the National System of Health Services (SNSS) was calculated using the criterion weight for age below –1 SD of the median for age and gender (standard of reference based on the population described by Sempé and colleagues.[29a] These standard and diagnosis criteria were maintained over a period of almost 20 years. This makes it possible to appreciate the rapid reduction of malnutrition in the population under control in the public health system, which is equivalent to close to 75% of the total population of children under 6 in the country.

The National Nursery Schools Council (JUNJI), like the National Council for Students Assistance and Scholarships (JUNAEB), is an autonomous public corporation created by law in 1971 that is functionally dependent on the Ministry of Education. JUNJI plans, promotes, coordinates, provides incentives, and supervises the organization and functioning of daycare centers, which, as the name implies, provide day care for preschool children until they are old enough to start attending elementary education. JUNJI coordinates and supervises preschool education in the context of integral attention of preschool-aged children. Together with food and education in accordance with the child's age, this program also provides social assistance to the family when required.

The programs of food and social assistance to schoolchildren were initiated in 1929 with the Student Assistance and Scholarships Committees, which operated at the municipal level with local financing and some resources from the central government. In 1952, the Ministry of Education assumed, at the central level, the administration of these programs. This situation continued until 1964, when this and other responsibilities were handed over to an autonomous public corporation created by law for that purpose: the JUNAEB.

TABLE 9.2-1 Degree of Achievement of Nutritional Goals, Chile, 2000

Indicator	*Baseline 1987–1989 (%)*	*Goal 2000 (%)*	*2000* (%)*
Pregnant women with low W/H	25	15	15
Anemia in infants	30	10	5
Anemia in pregnant women	25	10	25
Newborn with low birth weight	6.9	6.0	5.0
Newborn with insufficient weight	21	15	12.5
Breast-feeding exclusively to 4 mo	44	80	60
Breast-feeding to 12 mo	20	35	34
Student grade 1 with height < – 1 SD	33	20	15.6
Under 6 yr old with W/A < – 2 SD	2.2	2.0	0.8
Food-insecure households	35	20	21
Indigent population	18	15	7
Obesity in preschool children	4.6	3	12
Obesity in children entering school	6.5	4.5	16
Obesity in pregnant women	12	8	32

Adapted from Plan Nacional de la Infancia, UNICEF, 1994.
W/A = weight/age; W/H = weight/height.
*Ministry of Health, Chile, 2001.

Conceived as a state assistance organization to support the work of the Ministry of Education, JUNAEB works on the basis of integral assistance for the purposes of providing maximum support to poor students, not only in terms of nutrition but also through programs of health, housing, educational recreation, scholarships, and so on.

JUNAEB provides orientation and plans and coordinates the execution of these social and economic assistance programs directed to students at the preschool, elementary, and high school level in order to make effective the equal opportunities in education. Program activities are aimed at providing incentives for incorporation and permanence in the educational system, preventing school desertion, and improving academic results of children in municipal and subsidized private schools. The School Feeding Program (PAE) takes up most of the institution's resources.

In 1951, fortification of wheat flour with B complex vitamins was established for the purpose of "improving the nutritional situation of the Chilean population." It included iron, calcium, thiamin, riboflavin, and niacin. Iron was added in low concentration and, owing to the presence of calcium and the type of compounds used (elemental iron), was probably of very low biovailability. In 1967, regulations on iron fortification were amended, making the process much more effective from a nutritional point of view. Bread made from wheat flour is the main source of calories in the Chilean diet. Total calorie consumption in the lowest income quintile is about 1,200 kcal/person/day, of which 40% comes from bread, whereas in the highest-income group (quintile V), with a total consumption of 2,085 kcal/person/day, only 20% is obtained from bread. Quality control is carried out by the Ministry of Health, which monitors the iron content in flour samples obtained in a regular and random manner from the mills. A study on iron content in bread obtained at commercial bakeries indicated that 87% of bakeries in the Metropolitan Region use flour without iron. Although it has been impossible to assess the efficacy of the fortification program, its impact has produced a change in the prevalence rates of iron deficiency anemia. Bread alone supplies 0.36 mg of iron per day in children 2 to 6 years of age and almost 1 mg/day in adolescents.[30] In fact, this problem has virtually disappeared in schoolchildren (7% in 1974 to less than 1% in 1994) and adolescents (5 to 1%). In contrast, the prevalence in infants remains high (approximately 23%). Iron-fortified cow's milk for infant feeding was introduced only in 1999.

Legislation establishing mandatory iodination of salt was enacted in 1959, and the Food Code of 1960 determined the obligation of salt fortification. This measure did not really become effective until 1982, when the Food Code was updated and the new version allowed the existence of both iodized and noniodized salt in the market. In 1989, the Ministry of Health established mandatory iodization, iodine added in the form of sodium or potassium iodates or iodides in a concentration of 100 ppm. A single producer supplies approximately 90% of the edible salt market and has maintained a good level of iodination. As a result, endemic goiter has been eradicated as a public

health problem. A study conducted in 1994 in four surveillance areas demonstrated that less than 10% of schoolchildren between 6 and 16 years of age showed goiter. When present, it was type Ia with high levels of urinary iodine. At present, a commission with the participation of the Pan American Health Organization (PAHO), UNICEF, the salt industry, and the Ministry of Health works to safeguard this achievement.[31,32]

In 1975, in Chile, severe malnutrition of the marasmic type was concentrated in children under 12 months of age. In fact, among the cases of severe malnutrition that were admitted to hospital, 76% were under 6 months of age. The population of these children, estimated at that time at around 15,000 at the national level, had an important effect on child mortality rates and overburdened pediatric hospital services, where their mortality, owing to intercurrent infections, was extremely high. Belonging, in general, to homes in extreme poverty, the severely malnourished infants who survived their hospital stay were discharged only partially recovered, or even with yet greater nutritional deterioration, to return to their homes where the existing poverty and marginality conditions determined their death or readmittance to hospital very shortly thereafter.

For the purpose of putting an end to this problem, in 1975 the Chilean Nutrition Foundation (CONIN) was created, a private nonprofit foundation that established throughout the country a system of 33 CNRCs with 1,400 beds provided for the integral treatment of children with severe malnutrition. This treatment includes, as basic elements, pediatric and nutritional attention; psychomotor, social, and emotional stimulation of the child; the incorporation of the mother to the child's recovery process; and integral child care training for the mother. At the same time, efforts are made to improve the socioeconomic situation of the family as well as the conditions existing in the home.

The CNRCs are directed by a pediatrician who has the collaboration of a professional team made up of a nurse, nutritionist, social worker, child care worker, nurse's aides, and a variable number of volunteer workers. CONIN provides support on technical aspects of the program through pediatricians with experience in public health and nutrition, psychologists and physical therapists who monitor the psychomotor stimulation program, and a social worker and a training unit that design strategies for education and social reinsertion of the mothers and family group of the children under treatment.

The CONIN program is to a great extent financed by funds provided by the Ministry of Health on the basis of the annual projected number of children to be treated. CONIN, through various mechanisms, generates supplementary resources. Volunteer workers play an important role in the institution, participating both in the care of the children and in the search for resources to assist the family group. In this task, CONIN centers generally count on the support of local governments.[26]

The program applied by CONIN has been successful. The reduction of malnutrition has led to the closing of many CNRCs, with only 18 remaining throughout the country. Of these, only some maintain their original objectives, although the children being treated today are, almost exclusively, suffering from moderate malnutrition owing to social deprivation and/or maternal neglect. Some other centers have destined their beds to reinforcement of the work of the Ministry of Justice with minors under socially deprived environment or maternal neglect. As primary malnutrition subsided, five of the existing centers are now concentrating their effort to the study and treatment of children with secondary malnutrition.

SELECTING THE BEST APPROACH TO TREAT SEVERELY MALNOURISHED CHILDREN

The selection of a treatment modality for malnourished children starts by defining the severity of the malnutrition. Gómez and colleagues, in the late 1940s, proposed the first classification of PEM based on weight expressed as a percentage of normal value for age. Despite the limitations of percent normal, it is still used by many because of its simplicity. First-degree or mild PEM is defined as between 75 and 90% of normal, second degree or moderate as 60 to 75%, and third degree or severe as < 60% of that expected for age.[33] Bengoa, with his functional classification in the mid-1950s, established treatment modalities based on the Gomez criteria, indicating that those with first degree should be treated in the primary health or outpatient health clinic by providing education and dietary advice and those with second degree should be treated in the daycare nutrition recovery center using complementary foods in addition to education. Finally, third-degree PEM should be treated in the hospital.[20] To a great extent, with the caveats described in the corresponding section, the Bengoa approach remains valid. Hospitalization should last strictly for the minimal time required to treat complications and stabilize the patient and then feed nutrient- and energy-dense foods as tolerated. CNRCs should be reserved to situations in which PEM is highly prevalent, particularly in young infants, and family conditions do not permit recovery at the home. The choice of treatment modality should also consider parental choice, cost-effectiveness of treatment under real-life situations, access to primary health care system, availability of health infrastructure, social support system available in the community, maternal education and overall condition, and psychosocial interactions within the family.[20]

The main barriers or impediments in control and treatment of malnutrition relate to the multiple conditioning factors presented earlier. Translating theoretic concepts into practices that lead to improved nutrition and health of children is also a challenge. Treatment norms and preventive strategies may be well known, but they are harder to establish as standards of practice. In addition, physicians commonly depart from rules to demonstrate their autonomy and status or challenge specific aspects of the norm based on anecdotal personal experience rather than on firm evidence. Health professionals often consider malnutrition as an unavoidable consequence of poverty and thus may accept it as a social problem outside the health realm. The common acceptance of malnutrition by communities and the political leadership as a chronic unsolvable prob-

lem inherent to social structure has traditionally led to passive acceptance and inaction. Physicians often define health expenditure priorities based on what is more attractive for medicine per se rather than on the impact on burden of death and disease. Some physicians are more interested in providing individual health care rather than addressing public health problems.

Physicians are weak in networking and partnership skills; they are not trained for teamwork and associate success with individual recognition. These traits prevent physicians from leading multiprofessional multidisciplinary teams such as those needed to address malnutrition effectively. The organizational environment becomes an important barrier; physician-led administration is usually centered on medical interest rather than on patients' need. Moreover, other health professionals are seen as subservient to the physician rather than team members with equal participation. Promoting new attitudes and skills, training for teamwork, active listening, and defining funding priorities based on the health needs of the community are key to establishing effective malnutrition prevention and treatment programs.

CONCLUSIONS

Presently, the world produces enough food to feed the 6 billion inhabitants of the planet. Food production increased by 25% over the last decade, reaching a daily availability of 2,750 calories and 76 g of protein per person.[9]

Yet undernutrition affects close to a billion people, and stunting and underweight affect close to 200 million children under 5 years of age, mostly found in South Asia and sub-Saharan Africa. The overall trend is toward a small decrease in the proportion of undernourished children with a minute decrease in the absolute number. Unfortunately, the goal established by the UN for the year 2000 two decades ago to reduce malnutrition by 50% was not met. The present level of progress of –0.72% per year is only half of the 1.5% decrease required to reach this goal in the next 20 years. Moreover, some regions, such as sub-Saharan Africa, show a rising prevalence of malnutrition. This situation is worse in countries affected by civil strife and drought, where famine conditions may cause the death of children at rates 20 to 40 times greater than those found in the general population. We can firmly state that malnutrition and growth failure of children remain issues that affect not only survival but also the quality of life of children in many parts of the world. Prevention is the best form of treatment. There is no doubt that sufficient knowledge exists to treat and prevent primary malnutrition in virtually all children. The condition should be considered a preventable disease, but its eradication requires full commitment by society to assign a high priority to the well-being of children. Changing the social, economic, and political forces that condition abnormal growth and development in PEM goes beyond the realm of specific medical action but requires concerted participation of physicians as advocates for children in the political process. Placing demands on political leaders is essential to ensure that children, from the time of conception throughout their various development stages, are provided with adequate nutrition to allow for the full expression of their genetic potential. Acceptance of this basic premise by the community is essential before appropriate prevention strategies can be successfully undertaken.[3]

Treatment of childhood malnutrition initiated as a response to a basic humanitarian duty to prevent death during the first half of the past century remains a problem in many regions of the developing world. Presently, the mandate is based on the right of adequate food and nutrition for all children as part of the global human and social development agenda. National and international nutrition and food programs developed over the past 50 years have been implemented as integral components of broader strategies of primary health care and education, oriented toward preventing deaths and improving the quality of life of low socioeconomic groups. Pediatricians worldwide also should be aware of malnutrition as a conditioning factor delaying recovery from illness and as a major determinant of the quality of life of children with chronic disease.[3]

The key for effective malnutrition prevention is integrating health care, household food security, and care as proposed by the UNICEF model (see Figure 9.2-1) presented at the outset. The following are some of the components of malnutrition primary prevention programs that have been developed and tested over past decades throughout the world in a variety of political and social settings:

1. Promote early contact between mother and infant to improve the chance for successful breast-feeding. Establish hospital and other health routines that support breast-feeding while in the maternity ward and later; successful early bonding and documented breast-feeding are vital. Support breast-feeding by the groups interacting with mothers (health team and others) and by legal frameworks that promote, protect, and sustain the right of working women to practice it.
2. Monitor growth and development with adequate standards (present standards are being revised based on present recommended feeding modes). Intervene only when appropriate to prevent malnutrition and specific micronutrient deficits. Mothers should be familiar with growth monitoring cards and be ready to take appropriate actions when growth faltering occurs. The degree of actions taken by the community will depend on the strength of the primary health care.
3. Introduce appropriate micronutrient-rich complementary foods and supplements at 6 months of age. If complementary foods are needed earlier, consider the risks associated with interference of breast-feeding. Ideally, these should be based on local foods that are accessible to the population. Micronutrients will be required in most cases; new developments include fortification at the household level either with tablets, sauces, or sprinkles. Food donations should be incorporated into existing programs and not depend on whether surplus exists in industrialized countries. Occasional food donations, no matter how well meaning, can have adverse consequences in the long term when they disappear.

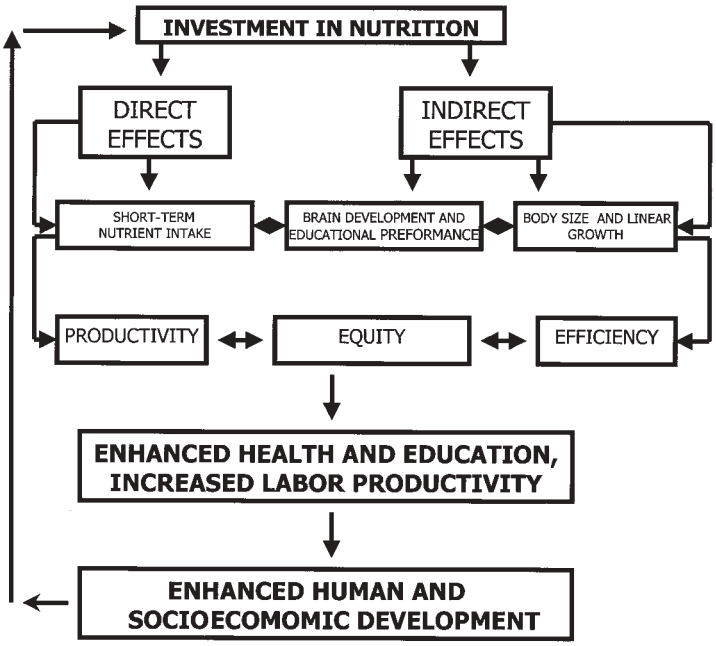

FIGURE 9.2-6 Model to explain how investment in nutrition contributes to economic growth and national development. Short-term improvement in food intake is coupled with better linear growth and enhanced mental development. These translate into better health, decreased infectious morbidity and mortality, enhanced educational performance, and increased capacity for physical work. These interactions in the appropriate social and political conditions lead to increased efficiency, productivity, and equity. The product of the investment is better health, education, and productivity, thus generating economic growth and greater human and social development. This virtuous cycle is closed as more investment in nutritional improvement takes place.

4. Identify infants at risk for malnutrition and growth failure based on biologic and social risk factors. Provide adequate social and medical support for families with children at risk. Early identification should be based on community surveillance not only of growth but also of caring practices and of critical food insecurity. Early interventions at this level are significantly more cost-effective. This area is presently receiving insufficient attention despite being at the core of the problem.
5. Educate parents and adolescent girls (who will be mothers) on how to promote growth and development through appropriate home environment, care, and stimulation. Verbal and cognitive stimulation for malnourished children results in higher growth rates than for children without such stimulation. Interactions with parents, caregivers, and other children are essential for the young child and can be improved by education of caregivers. Care initiatives should go beyond focusing on individual practices and behaviors to bring in dimensions of care for the family and the community.
6. Provide universal coverage of children for basic health care services, as well as full coverage for all children with immunizations to prevent infectious disease and avoid their adverse effects on nutritional status and provide early diagnosis and treatment of diarrheal disease at the community level using oral rehydration. Link this effort to the community-based surveillance for effective prevention and control of mild and moderate PEM. Depending on what is available in the country, the approach may not require expensive infrastructure but rather may be community based and sustained.

Treating hundreds or thousands of affected children will not solve the problem of malnutrition as a global public health problem. Unless society at large confronts this issue in its full dimension, the problem will continue. Access to adequate amounts and quality of food represents a basic human right and is a necessary precondition for health. In turn, good nutrition and health are prerequisites for human, social, and economic development (Figure 9.2–6). Physicians, especially pediatricians, should not be passive bystanders but rather activists in this process. Reducing malnutrition of infants and young children means a brighter future for humankind and will contribute to giving world peace a better chance.

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CHAPTER 10

PROTEIN-ENERGY MALNUTRITION: PATHOPHYSIOLOGY, CLINICAL CONSEQUENCES, AND TREATMENT

Mary E. Penny, MB, ChB

The number of children affected by and the long-term consequences of malnutrition place it among the greatest public health problems facing the world today. The World Health Organization (WHO) estimates that malnutrition contributes to 55% of child mortality worldwide.[1] Even mild degrees of malnutrition double the risk of mortality[2,3] for both respiratory and diarrheal disease mortality[4] and malaria,[5] but this risk is greatly increased in more severe degrees of malnutrition.[2,3] Severe malnutrition, also called protein-energy malnutrition (PEM), is eminently treatable, but, sadly, this is an area where the gap between existing knowledge of successful practice and the reality of the management of most malnourished children is abysmal. Recent reports illustrate how the adoption of improved management can drastically reduce mortality even in resource-restricted circumstances.[6] The global importance of malnutrition and the long-term consequences are dealt with in Chapter 11, "International Nutrition." The public health significance, as discussed in Chapter 9.2, "Community Nutrition and Its Impact on Developing Countries (The Chilean Experience)," emphasizes the necessity for the combination of policies designed to prevent malnutrition and the treatment of children with existing malnutrition. These authors describe the success in Chile of such an approach. Malnutrition is not only a problem of developing countries. Failure to recognize malnutrition may also contribute to increased morbidity and mortality in other conditions seen in developed countries such as congenital heart disease[7] and cystic fibrosis.[8] This chapter deals with the clinical management of severe malnutrition and attempts to show how an understanding of the pathophysiology provides a basis for the treatment of the severely malnourished child. The multiple factors that contribute to the development of malnutrition are detailed elsewhere; this chapter is principally concerned with severe PEM as a clinical entity because the failure to recognize the special needs of these children contributes to the high mortality.[9]

DEFINITIONS OF MALNUTRITION

Malnutrition has many causes. In any individual, inadequate food intake, infections, psychosocial deprivation, the environment, and perhaps genetic variability contribute. The clinical manifestations in the child depend on the duration and degree of shortfall in dietary intake, the quality of the diet, host factors such as age, and the interplay with infection.

The first step in the diagnosis of malnutrition is nutrition assessment. This is an essential part of any clinical pediatric evaluation and is discussed in detail in Chapter 2, "Nutritional Status Assessment for Clinical Care." Repeated nutritional assessments of all ill children are important to prevent the insidious onset of malnutrition, which may hinder recovery. Adequate growth is an indication of health and recovery. For the individual child, the most important information is gained from serial measurements indicating the child's growth, and this provides essential information for diagnosing cause and guiding treatment. The importance of using this often available but overlooked information cannot be overstated.

Although measurements of height and weight are the usual mainstays of diagnosis, additional information on body composition can be obtained from skinfold thickness and other more sophisticated methods. Biochemical and hematologic tests may also be useful, especially in monitoring progress. PEM is often associated with micronutrient deficiency, and examination should include a specific search for Bitot's spots or xerophthalmia, manifestations of vitamin A deficiency,[10] and signs of other micronutrient deficiencies.

Sole reliance on weight and length or height can lead to failure to recognize kwashiorkor and an underestimation of the severity of the malnutrition in these children. The scheme recommended by WHO (Table 10-1) has the merit of distinguishing these two entities and is useful in clinical practice.[11] Figure 10-1 illustrates a child with marasmus and shows the characteristic muscle wasting particularly evident in the buttocks, the pinched face, and anxious demeanor. Figure 10-2 shows the same child on recovery. Figure 10-3 illustrates a child with kwashiorkor. Symmetric edema is evident, especially in the lower limbs. The hair is sparse, and the flaky paint rash is seen on the buttocks, legs, and arms. Figure 10-4 shows the typical bilateral symmetric edema of the legs.

Marasmus is generally thought to be the result of a cumulative, usually slow, inadequate energy and protein intake. The child's metabolism has adapted, producing changes that prolong survival and protect essential visceral and brain function. This is the type of PEM traditionally seen in famine, food restriction, or anorexia. Kwashiorkor is also a severe form of malnutrition. The etiology is not well understood, but the long-held view that protein deficiency in the face of adequate energy intake causes kwashiorkor cannot explain all of the evidence. Observed findings are more in keeping with an interaction between nutritional deficits and the response to injury, infection, and oxidative stress. Marasmus and kwashiorkor commonly coexist, and although a simple unified approach to clinical management can be applied successfully to both conditions,[11] the two are clinically distinct entities.

FIGURE 10-1 Child with marasmus.

PATHOPHYSIOLOGY

Metabolic Responses to Inadequate Energy Intake

PEM is the result of a chronic and cumulative failure to meet physiologic energy and nutrient requirements.[12] The manifestations of this process depend on different factors: age, concomitant infection, prior nutritional state, and the nature of the dietary restriction, to name four. Both the early classic experimental studies of food energy deprivation and starvation in animals and humans and studies of severely malnourished children on admission and during recovery have contributed to our understanding, although the situation is complicated by the multifactorial causes of malnutrition in most children. A detailed description is

TABLE 10-1 Classification of Moderate and Severe Malnutrition

	Moderate Malnutrition	*Severe Malnutrition*	
Symmetric edema?	No	Yes	Edematous malnutrition or kwashiorkor
Weight for age			
SD score	–2 to –3	< –3	Severe wasting
% Median	70–79	< 70	or marasmus
Length for age			
SD score	–2 to –3	< –3	Severe stunting
% Median	85–89	< 85	

Adapted from World Health Organization.[11]

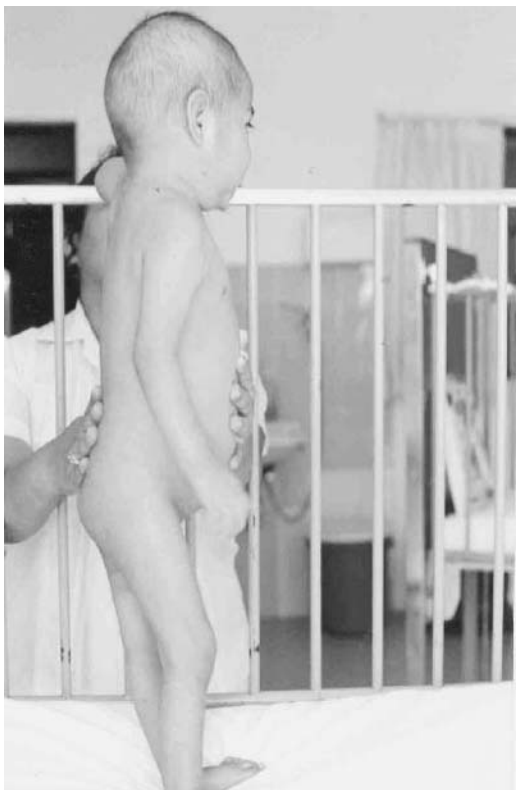

FIGURE 10-2 Same child as shown in Figure 10-1, on recovery.

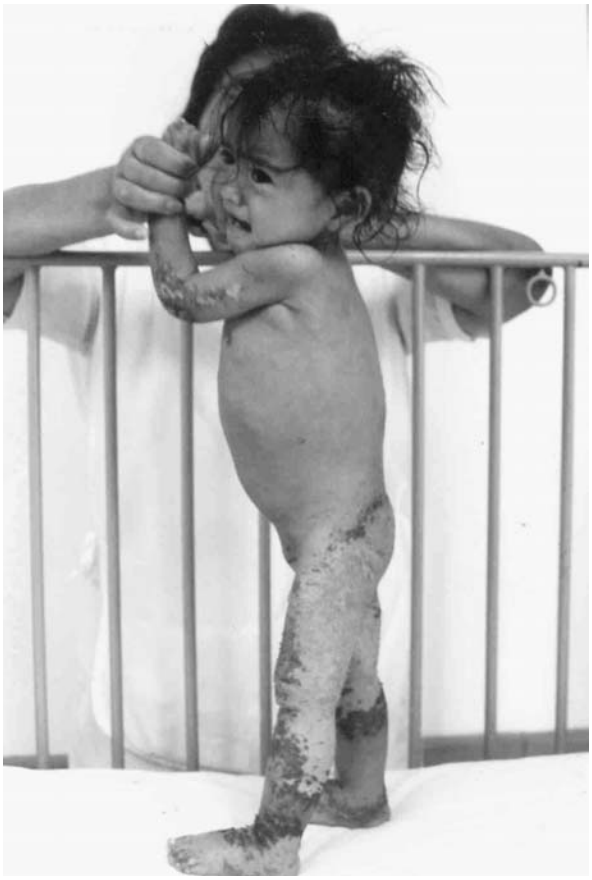

FIGURE 10-3 Child with kwashiokor.

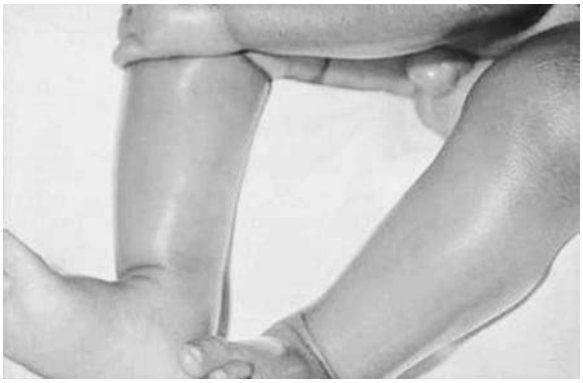

FIGURE 10-4 Lower limbs of a child with kwashiorkor.

beyond the scope of this chapter, but the interested reader is referred to excellent reviews.[13,14]

In the absence of infection, fasting results in an initial depletion of fat stores and then glycogen stores mediated by metabolic and endocrine changes that have the common goal of preserving vital functions, allowing the animal or human to survive until dietary energy can be restored. Early changes include a reduction in activity that conserves energy expenditure.[15] Growth is slowed, reducing the energy need to maintain this, and changes occur in body composition. Metabolic rate expressed in relation to height or lean body mass decreases.[14] Brain and viscera are relatively preserved (Figure 10-5),[16] resulting in the body composition typical of marasmic children.[17] There is an increase in total-body water, which is mainly extracellular but may also be intracellular.[12,13,18]

These metabolic adjustments to starvation are mediated, at least in part, by hormones. Cortisol concentration rises but remains responsive to stress.[17,19] Insulin secretion falls, and there is a reduction in plasma levels, a reduced response to glucose, and peripheral insulin resistance.[20,21] Growth hormone is generally high, and the normal suppression by glucose load is lost, although exceptions occur in marasmus.[22] There is low activity of insulin-like growth factor 1, the metabolic effector of the growth promoting the effect of growth hormone.[17] The net effects of these hormonal changes are mobilization of fat, degradation of

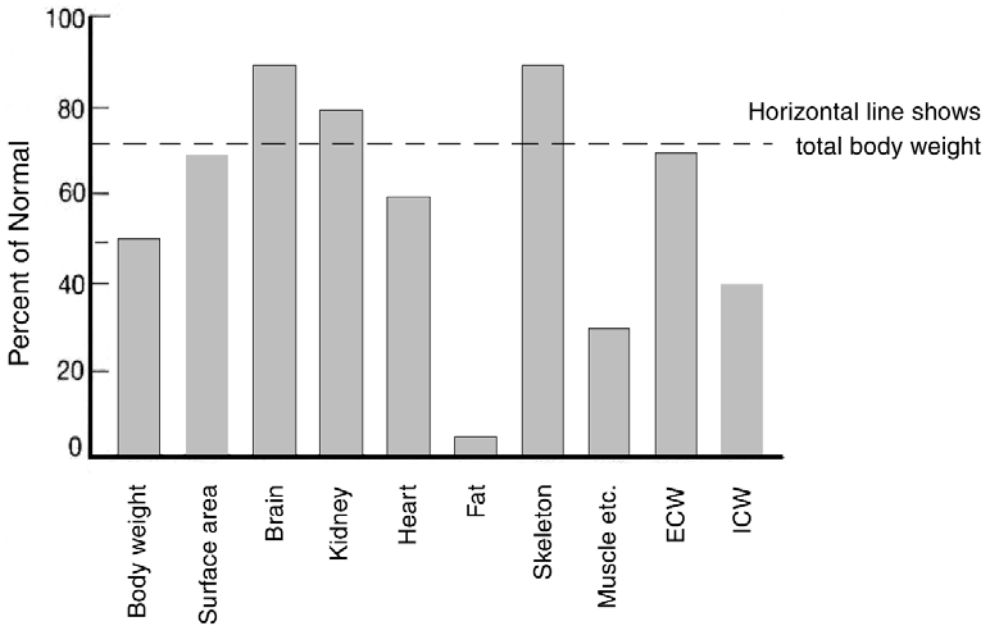

FIGURE 10-5 Weights of organs at death in atrophic children as percentages of normal age controls. ECW = extracellular water; ICW = intracellular water.

muscle protein, and reduction in basal metabolic rate. Increased aldosterone contributes to potassium loss already compromised by the effects of energy restriction and reduced adenosine triphosphate synthesis on the sodium pump.[23]

Adaptation to Reduced Protein Intake

During protein deprivation, skeletal muscle is lost as structural protein is recycled to conserve essential enzymes and provide energy for metabolic processes. There is both a fall in muscle protein synthesis and an increase in breakdown, which provides essential amino acids to the liver for protein synthesis and gluconeogenesis.[17] Within the liver, there is a shift in the rates of synthesis of different proteins; synthesis of albumin, transferrin, and apolipoprotein B are decreased, but the synthesis of other proteins is protected.[24]

Changes in Electrolytes

Changes in chemical composition of the body that occur during malnutrition have important consequences for treatment. Sodium, potassium, and phosphate merit special mention, but changes in other electrolytes, such as magnesium and calcium, are probably important but have been less studied.

The vast proportion of total-body potassium is intracellular, in contrast to sodium, which is actively removed from cells by the sodium pump. In both marasmus and kwashiorkor, sodium retention occurs, resulting in an increase in whole-body sodium, even though serum levels may be low, reflecting an increase in extracellular water. There is a decrease in total-body potassium,[25] although serum potassium may remain normal. Alleyne and colleagues described how potassium kinetics are altered during recovery.[26] There was an initial acute repletion of potassium when hypokalemia and whole-body deficiency improved, followed by a longer phase of cell membrane recovery and reestablishment of the normal Na/K gradients. A third phase occurred when rapid growth of skeletal muscle increased potassium requirements.[27,28] Nichols and colleagues calculated from balance studies that 7.0 mmol/kg of potassium was needed in the first week or acute phase of recovery, an amount similar to the level of supplement giving best results in a clinical trial in Malawi.[29,30]

The inconsistencies between serum and total-body potassium are explained by events at the cell membrane. In marasmus, there is a decrease in the activity of the ouabain-sensitive energy-dependent sodium pump, resulting in increased intracellular sodium and reduced potassium.[31] These cell membrane changes are associated with intracellular changes, with relatively low intracellular K and relatively high sodium. Different mechanisms operate in kwashiorkor, in which there is an increase in cell membrane leakiness. Sodium, responding to the electrolyte gradient, enters the cell, stimulating increased activity of the sodium pump but not enough to prevent Na increase and K loss.[31,32] Similar differences between marasmus and kwashiorkor were reported by Kaplay in India.[33] Forrester and colleagues found that these electrolyte changes could be reproduced in in vitro erythrocytes if glutathione was artificially reduced, resembling the situation in kwashiorkor.[34] Increased intracellular sodium is accompanied by increased cell water, which may be one of the explanations for edema in kwashiorkor.[35] Hypoinsulinemia is implicated in this process.[36] These electrolyte changes are the basis for the recommendations of dietary restriction of sodium, the use of low-sodium oral rehydration solutions (ORSs), and potassium supplementation in all severely malnourished children.

Hypophosphatemia has been shown to occur in malnourished children and is associated with high mortality. In a South African study, 10 of 60 patients died, all but one with very low serum phosphates.[37] The lowest levels of serum phosphate were associated with diarrhea and dehydration. A more recent study from Malawi supports the association of hypophosphatemia and increased mortality.[38] However, it is difficult to distinguish the effects of low phosphate from hypokalemia, which also causes hypotonia and sudden death. In Jamaica, serum phosphate levels were generally higher than those recorded in Africa and although correlated with edema were not associated with mortality. Repletion, even on a milk diet, took 2 to 3 weeks.[39] In India, severe hypophosphatemia was not seen.[40]

Interaction with Infection

Infection and nutrition are mutually interlocked in a vicious cycle that operates at many levels, from social cultural interrelations to intracellular metabolism. Environmental conditions that give rise to inadequate energy and protein intakes are also associated with conditions in which bacterial and other microbial contamination is often rife.[41] In addition, in famine or poverty, children's diets tend to consist largely of carbohydrate staples with little or no animal products or fat.[42] Animal products such as red meat, poultry, offal, fish, milk, and eggs are important bioavailable sources of minerals and other micronutrients that have an essential role in combating infections.[43] Fat, needed to provide essential fatty acid (EFA) and facilitate the absorption of fat-soluble vitamins such as E, D, and A, which also protect against infections, is also often low in these diets.

During infection, there are metabolic changes that concentrate body energy resources on production of acute-phase proteins in the liver and are often the opposite of those seen in starvation.[44] The production of acute-phase proteins and the metabolic consequences of infection are mediated by protein cytokines, lipid-derived factors that include prostaglandins, leukotrienes, and platelet activation factor. Endocrine changes also play a role; the concentration of catabolic hormones such as glucocorticoids, glucagons, and epinephrine increases. The cytokine interleukin (IL)-6 increases norepinephrine, cortisol, and glucagon and is the main stimulus for the mobilization of acute-phase proteins in the liver. Cytokines also enhance the effect of stress-related hormones on the production of acute-phase proteins.[45] Because of the interaction between food restriction and infection in the pathogenesis of malnutrition, any integrated approach to explaining the pathophysiology has to take both into account. The differences between kwashiorkor and marasmus may be partially explained by an increased shift toward the metabolic con-

sequences of infection in children with kwashiorkor. In addition, preceding nutritional status may modify the metabolic effects of infection. An example is the increased rate of breakdown and synthesis of protein in response to infection in children with marasmus but not those with kwashiorkor[46] and the slower recovery from infectious diarrhea.

Cytokines

Because of the fundamental role of cytokines in infection and the interaction with malnutrition, a brief summary of their action is necessary. For more detail, readers are referred to more detailed reviews.[45,47,48] Cytokines are small, nonstructural proteins that can be produced by nearly all nucleated cells in very small amounts, have local and systemic effects, and are involved in the primary response to infection. Synthesis of cytokines is rapidly induced in response to infection, trauma, ischemia, and other events. Cytokines are also involved in mediating the changes in protein metabolism and muscle function that accompany infections, fasting, and cancer cachexia. The family of tumor necrosis factors (TNFs), IL-1, and IL-6 are all proinflammatory cytokines. The proinflammatory cytokines mediate the local inflammatory response, which includes local heat, redness, pain, swelling, and systemic effects such as fever and anorexia. To avoid self-injury during the inflammatory response, the induction and synthesis of cytokines are controlled in a complex interactive process full of checks and balances. This tightly controlled system is disturbed in malnutrition. Children with severe malnutrition often have a reduced inflammatory reaction and blunted febrile response. In keeping with this, reduced levels of in vitro production of IL-1 and TNF by circulating monocytes have been reported in malnutrition.[49] In contrast, high concentrations of cytokine IL-6 and TNF have been reported in the serum of malnourished children without current infection.[50] Further studies are needed to sort out the role of these inflammatory mediators in malnutrition, but the consequence of a reduced inflammatory response to infections has important clinical management consequences as the usual manifestations of infection may be absent in PEM.

Acute-Phase Proteins

Cytokines modulate the production of acute-phase proteins. C-reactive protein, α_1-antitrypsin, and α-macroglobulin are examples of positive acute-phase proteins, so called because their synthesis by the liver increases in response to stresses, including infection.[44] Serum concentration of the so-called negative acute-phase proteins (albumin, prealbumin, fibronectin, retinol binding protein) is reduced in children with malnutrition[49,51] despite an overall net increase in hepatic protein synthesis. Low levels of fibronectin have been reported to be a useful early indicator of malnutrition.[52] Positive acute-phase proteins are an essential part of the defense against infections, but uncontrolled inflammation has been linked to adverse consequences, for instance, in inflammatory bowel disease, rheumatoid arthritis, and perhaps kwashiorkor. Studies are complicated by the coexistence of infection and malnutrition and the limitations of interpreting serum levels, which represent a balance between synthesis and catabolism. Studies in Ghana on children without sign of infection found raised concentrations of C-reactive protein in kwashiorkor and to a lesser extent in marasmus.[53] Alpha-1 acid glycoprotein levels were raised in kwashiorkor in Thai children.[51] On the other hand, Ekanem and colleagues,[54] studying children, 75% of whom had kwashiorkor, documented only slight increases in C-reactive protein in children without infection and large increases in infected children, indicating apparent preservation of the acute-phase response to infection in this population of children. This is in contrast to findings in Jamaica[55] of normal levels of C-reactive protein and serum amyloid A with a blunted response in the expected acute-phase response to diphtheria-pertussis-tetanus vaccination. Elegant recent studies in Jamaica using stable isotopes, in this case in mainly marasmatic children, with infections showed that the increase in plasma levels of acute-phase proteins was attributable to a reduction in catabolism rather than an increase in synthesis of the proteins, in contrast to the situation in normally nourished infected children.[56] Further studies such as these using labeled amino acids are needed to clarify the role of disturbances in the synthesis and catabolism of acute-phase proteins in the pathophysiology of severe malnutrition.

Kwashiorkor

Kwashiorkor has historically been attributed to a diet lacking in protein, and the edema was thought to be explained by low albumin. In consequence, children were treated with high-protein diets. However, several observations cast doubt on this hypothesis.[57] Kwashiorkor often follows infections such as measles and dysentery and has been reported in breast-fed babies, who presumably are ensured adequate protein intake, and children in the same community on very similar diets may develop kwashiorkor or marasmus. Edema has been shown to improve independently of albumin.[58] Golden demonstrated that recovery was possible with relatively low-protein diets and was dependent on energy intake and not protein.[59] It seems unlikely that simple protein deficiency is the cause of kwashiorkor.

Free Radicals

Excess free radical production has been suggested as the fundamental explanation of the clinical findings in kwashiorkor.[60] The acute inflammatory cells that form the first line of defense against infections respond with a respiratory burst during which free radicals are produced. This response to infection or cell injury relies on these free radicals for the destruction of bacteria. The free radicals are characterized by one or more unpaired electrons, which makes them highly reactive and unstable.[61] Reactive oxygen species include oxygen radicals such as singlet oxygen and nonradicals such as hydrogen peroxide; reactive nitrogen species include nitric oxide. The most potent free radicals include the hydroxyl radical and iron free radicals, which occur when unbound iron is present during free radical production. Free radicals are produced in normal metabolism, and a certain level of these radicals is required for normal functioning. However, this amount is kept to a

minimum by a number of scavenging mechanisms, which detoxify the radicals. Free radical production is increased by stresses, which include inflammation, infections, and environmental stresses.[62] Oxidative stress is a process in which the normal balance between pro-oxidants and antioxidants is shifted toward the oxidant side, resulting in an increase in free radicals that cause biologic damage.[63] Increased oxidative stress has been demonstrated in kwashiorkor.[64] The damage caused by free radicals includes disrupting enzymes and nucleic acids and the peroxidation of lipoproteins and EFAs in cell membranes by hydrogen peroxide. Dietary antioxidants protect from oxidant damage either directly by scavenging free radicals or because they are required for enzymes, which neutralize free radicals such as superoxide dismutase (copper, zinc dependent) or glutathione peroxidase (selenium dependent) and catalase. Many studies show low concentrations of antioxidants in the serum and red cells of children with malnutrition, especially kwashiorkor.[64–66] Blood cell concentrations of glutathione, vitamin E, and the vitamin E-to-cholesterol ratio are reduced,[50] resulting in diminished resistance to oxidative stress.

The hypothesis proposes that the balance between production and quenching of free radicals is perturbed in kwashiorkor, resulting in oxidative stress. This is attributable to low levels of dietary antioxidants, with possibly increased free radicals as a consequence of the disturbance in the acute-phase response to infections and other environmental stresses.

Lipid Metabolism, Polyunsaturated Fatty Acids, and Free Radicals

Recent research investigating the role of lipids in malnutrition lends support to the theory of oxidant stress as a cause of kwashiorkor. It has been known for a long time that there are changes in the lipid profile of red cell membranes and plasma in malnutrition.[67–69] Recent interest has focused on these EFAs and their metabolites as these have protean functions, which include maintaining the integrity of cell membranes and involvement in the synthesis of immunologically active elements such as prostaglandins and leukotrienes.[70] A low proportion of arachidonic acid, one of the EFAs, in the lipid profile of cell membranes and low concentrations in the plasma of children with severe malnutrition have been reported.[71] These changes in EFAs are not owing to dietary deficiency alone and are more likely a result of shifts in the metabolism of these EFAs. In particular, desaturation, which is subject to endocrine influence, is reduced, and low desaturase activity has been reported in PEM.[72] There may also be peroxidative degradation of EFAs in cell membranes. Levels of antioxidants are consistently reduced in PEM, and this increases the peroxidation of membrane long-chain polyunsaturated fatty acids (PUFAs).[73,74]

Leukotrienes are a family of mediators involved in the inflammatory response. The EFA arachidonic acid mentioned above is a precursor of the leukotrienes. Glutathione is also needed for the synthesis of leukotrienes from arachidonic acids, and several studies have documented low levels of whole-blood glutathione and low urinary excretion in kwashiorkor and marasmus patients,[66,75,76] suggesting that synthesis of the leukotrienes might be compromised in severe malnutrition. However, it seems that different leukotrienes are affected in different ways because concentrations of the cysteinyl leukotrienes LTE_4 and LTC_4, which mediate vascular damage and edema, have been found to be increased in the red cells of children with kwashiorkor but not marasmus, whereas LTB_4, which stimulates chemotaxis, was much reduced.[77] Cysteine supplementation improved the erythrocyte synthesis rate in children with kwashiorkor.[78]

The changes in sodium and potassium fluxes across cell membranes characteristic of kwashiorkor may also be explained in this model of reduced antioxidants. In an in vitro model, red cells depleted of glutathione showed increased leakiness to sodium and potassium, mimicking the findings seen in kwashiorkor.[66] The active transport of sodium out of the cell was increased but could not compensate for the increased permeability, resulting in the low K, high Na typical of malnutrition.

In summary, much remains to be learned about the pathophysiology of kwashiorkor. At present, it seems that the syndrome results from the interplay of nutrient deprivation and infectious or environmental stresses, which leads to a disturbed balance in the normal physiologic response to these insults. The syndrome may be predisposed by a specific pattern of nutrient deficiencies, which include protein, antioxidants, trace elements, sulfur amino acids, and probably others. In kwashiorkor, there is evidence of low antioxidants and increased oxidative stress, resulting in changes of free radical damage, increased sodium/K flux across membranes, triglyceride accumulation in the liver, low albumin, changes in n-6 PUFAs, and altered leukotriene production. The role, cause, or effect of changes in the acute-phase reaction, including the cytokine inflammatory response, remains to be elucidated.

Alternative theories to explain kwashiorkor have not been supported by more recent evidence. The postulated association with the hepatic toxin aflatoxin may be an example of one environmental trigger with a role in some geographic areas where fungal contamination of staple foods is common,[79] but this hypothesis has not been supported by absence of aflatoxins in liver samples from kwashiorkor, even in areas where aflatoxins are common.[57]

Changes in Organs and Systems in Malnutrition

In addition to the myriad cellular manifestations of PEM, widespread alterations in organ and system function occur, many of which are relevant to clinical management.

Endocrine System Endocrine changes mediate the metabolic adaptation to starvation and have been mentioned. These changes have important consequences on the clinical management of severely malnourished child. Pancreatic atrophy is a common finding in marasmus,[80] and the consistent findings in severe malnutrition of a reduction in serum insulin levels and impaired insulin response to a glucose load, glucagons, and arginine[12,20] explain the vulnerability of the child to delays in starting feeding and the need for fre-

quent small feeds. Hypokalemia contributes to this effect,[81] hence the importance of potassium supplements. There is also a reduction in insulin receptor affinity.[21] These hormonal effects rapidly reverse on refeeding, with weight gain.[82]

Studies in malnutrition have generally reported raised concentrations of growth hormone on admission,[22] but these concentrations reduce in those gaining weight on dietary treatment. Cortisol concentrations rise, especially in kwashiorkor, and the circadian rhythm is abolished, but the response to adrenocorticotropic hormone is preserved.[12,83] Cortisol levels also rise with infection; 80% of children with kwashiorkor showed a rise in cortisol in response to infection compared with only 50% of those with marasmus.[12] This reduced response in marasmus may explain why these children are so susceptible to hypoglycemia. High levels of adrenaline are reported early in hospitalization, especially in kwashiorkor.[12] Both the plasma concentration and the secretion rate of aldosterone are high.[23]

Thyroid gland function is altered in malnutrition.[84,85] During nutrition deprivation, at first thyroxine (T_4) increases, but as malnutrition becomes more severe, and especially if kwashiorkor develops, total T_4 decreases. There is also a decrease in thyroid binding proteins, but this does not account for all of the reduction in T_4 and suggests a primary effect on synthesis.[86] Increased thyroid-stimulating hormone secretion heralds recovery.[87] There is also a reduction in deiodination of T_4 to triiodothyronine (T_3), resulting in reduced T_3.

Immune System Children with severe malnutrition are very susceptible to infection, especially with gram-negative organisms, and deaths are often attributable to sepsis. The subject has been extensively reviewed by Chandra and others[88–92] and is dealt with in more detail in Chapter 20, "Malnutrition and Host Defenses." In summary, there are profound changes in cell-mediated immunity, the complement system, and function of polymorphonuclear cells and fewer reported effects on humoral immunity.

Cell-Mediated Immunity. Cell-mediated immunity is altered in severe malnutrition.[90] The thymus, necessary for normal differentiation of T cells, is consistently reduced in size,[93] and the production of thymic hormones is reduced.[91,92] Evidence of T-cell functional impairment also comes from the observation of reduced cutaneous tests to recalled antigens, for instance, the tuberculin test[94,95]; however, studies differ in reports of numbers of circulating T cells and the ratio and effect on T-cell subsets. In general, it appears that T4 cells are relatively reduced, and T8 cells are affected to a lesser degree. At the gastrointestinal level, atrophy of gut-associated lymphoid aggregates as a prominent feature of malnutrition has been reported.[96]

Humoral Immunity. Immune globulin production by B cells has been reported to be normal or raised,[90] and immunoglobulin (Ig)G seroconversion in response to several vaccines is preserved.[97] Increased IgA has been reported, but there was a reduced response of secretory IgA in nasopharyngeal secretions to measles vaccine,[98] and children with severe malnutrition in Brazil were found to have lower secretory IgA in urine, which increased on rehabilitation.[99]

The complement system shows consistent abnormalities with decreased C3 level.[100,101] This seems to be related to protein metabolism.[53] Some studies report particularly low concentrations of C3 in kwashiorkor. However, Ekanem and colleagues found that C3 levels, although low, rose significantly in the presence of infection.[54] C4 levels seem to be increased or unaffected by nutritional status.

Other potentially important disturbances in the immune system include impaired phagocytic activity by polymorphonuclear cells.[89]

The consequence of these various effects is a reduced capacity of the malnourished child to respond to and combat infections, leading to an increased risk of sepsis, one of the main reasons for mortality in malnourished children.

Liver In the liver, there is a shift from the production of carrier proteins and a relative increase in the production of acute inflammatory proteins, indices of response to injury or infection. This is particularly marked in kwashiorkor. The liver in kwashiorkor is often enlarged and shows a fatty infiltrate owing to accumulation of triglycerides.[102,103] These changes improve on clinical recovery, and there is no evidence that kwashiorkor per se results in long-term liver damage or cirrhosis.[104]

Cardiac System Cardiac output is reduced in children with acute PEM compared with cardiac output on recovery.[17] Cardiac muscle, however, shows only nonspecific changes, and muscle contractility is normal. Sinus bradycardia may be present, as well as mild hypotension. Concomitant deficiencies such as hypokalemia, anemia, and vitamin deficiencies may affect the heart. Pericardial effusion may be present in edematous malnutrition. During recovery, the heart size increases rapidly owing to chamber enlargement, and left ventricle musculature increases in proportion to increasing weight.[105] However, if dietary repletion is rapid, especially if there is also a high sodium load, heart failure may develop and sudden death occur. Prompt action to reduce hyperalimentation, restrict sodium intake, and administer diuretics can reverse the heart failure, but because this condition may not be recognized or is confused with sepsis, this complication is responsible for unnecessary deaths. This cardiac pathology is not considered primary to the heart but is more probably part of the refeeding syndrome described later.[17,105]

Respiratory System The reduction in muscle mass that occurs in severe malnutrition affects respiratory muscle, including the diaphragm; this leads to reduced muscular function, which influences vital capacity and maximal inspiration and inspiratory pressures.[106] This weakness may be exacerbated by electrolyte abnormalites such as low phosphate[107] and hypokalemia. The ventilatory response to hypoxia is blunted, but not the response to hypercapnia.[108] Despite these alterations, tachypnea and subcostal retraction remain useful signs in diagnosing pneumonia in malnutrition.[109]

Gastrointestinal Tract Diarrhea and malnutrition often occur together. Malnutrition increases the risk of more pro-

longed episodes of diarrhea,[110] and the combination of persistent diarrhea (more than 14 days of diarrhea) and malnutrition carries an especially high mortality.[111] Diarrhea and malnutrition so often coexist that it is difficult to determine the extent to which each contributes to pathology. Nevertheless, both animal and human studies suggest that severe malnutrition per se affects the intestinal tract with reduced gastric acid production, thinning of the small intestinal mucosa, and flattening or disappearance of the villi with relative sparing of the crypts.[17,112] There is increased cellularity of the lamina propia, especially in children with kwashiorkor.[112] These anatomic changes are reflected in impaired mucosal function, increased permeability as demonstrated by the double sugar technique,[113,114] and malabsorption as shown by nutrient absorption studies.[115] The mucosa seems to be particularly affected in kwashiorkor. In children with PEM in Malawi, kwashiorkor was associated with abnormal results, and persistent diarrhea was not an independent risk factor for altered permeability.[114] Loss of the villous architecture of the small intestine for any reason reduces disaccharide activity because the disaccharides, especially lactase, are found at the villous tips. Thus, lactose malabsorption is a common finding in both infectious diarrhea and in PEM.[116] Fat malabsorption is also seen in both persistent diarrhea[117] and PEM.[118] As well as the mucosal changes, bacterial overgrowth in the upper small intestine has been described in PEM and may lead to bile salt conjugation, further impairing fat absorption.[119] On the other hand, the human intestine has remarkable reserve capacity, and the clinical consequences of the demonstrated pathology need to be put into context. In the first place, the intestinal mucosa receives nutrients directly from the lumen, and enteral feeding is necessary for recuperation of intestinal health. We now know that even the damaged intestine benefits from food. Even in the face of malabsorption, diets can be designed to capitalize on remaining function. Carbohydrates are well absorbed in the small intestine until disaccharidase capacity is overwhelmed, at which point, the unabsorbed sugars cause osmolar diarrhea and the risk of dehydration. Presenting a mixture of different carbohydrates in small frequent feeds in presentations with relatively slow gastric emptying, such as milk, allows even lactose to be tolerated. Studies in children with persistent diarrhea, many of whom were malnourished, demonstrated that locally prepared diets with less than 3 g/kg body weight/day as lactose were well tolerated and led to prompt recovery.[120] In contrast to carbohydrate, fractional fat absorption remains constant over a wide range of intake,[121] so more fat in the diet results in more fat absorbed, and in practice, the increased fat loss is of little clinical consequence.[118] This is of considerable practical importance because the high energy density of fat means that more calories can be given in smaller volume, which is essential when feeding PEM children, who are usually anorexic. Although we lack randomized clinical controlled trials of early feeding in PEM, such as those that provided conclusive evidence for continued feeding in acute diarrhea,[122] cumulated experience demonstrates the success of this strategy. Early initiation of oral feeding was one of the major management changes associated with the introduction of a specific protocol for PEM in Bangladesh that halved mortality. Specifically, deaths from hypoglycemia were reduced.[6] Further aspects of gut function are discussed in Chapter 19, "Immunophysiology and Nutrition of the Gut."

Hematology: Anemia Anemia is common in severe malnutrition and may be attributable either to iron deficiency and/or reduced red cell production in adaptation to a smaller lean body mass.[123] Despite the fact that most children will have been consuming a diet deficient in bioavailable iron, in kwashiorkor, there is elevated hepatic iron, and bone marrow iron shows stainable iron in half of children. This is an unusual finding in marasmus.[124] Iron is tightly bound to proteins during storage and transport to prevent free iron forming the extremely damaging hydroxyl radical. In kwashiorkor, the reduced plasma levels of transferrin mean that iron binding capacity is reduced and the concentration of free iron may increase.[125] Low transferrins have been associated with increased risk of mortality in hospitalized children with PEM.[126] It has been suggested that this free iron causes or contributes to the etiology of kwashiorkor,[127,128] although not all children with kwashiorkor have raised indices of free iron. The homeostatic control of intestinal iron absorption is maintained in children with kwashiorkor.[129] Those with high serum ferritin and percent saturation of transferrin were found to absorb less oral iron than those with low serum ferritins.[129] The iron issue is important not only because of its possible role in the etiology of kwashiorkor but also because iron supplements might actually increase mortality in acute PEM. Smith and colleagues, in a small nonrandomized study in Nigeria, found higher mortality; 10 of 31 children given iron supplements at admission or day 3 died compared with 2 of 12 nonsupplemented children.[130] Whatever the role of iron supplements during the acute phase of malnutrition, during recovery, with its accompanying increase in lean body and red cell mass, iron is required, and stores are quickly exhausted so that classic iron deficiency features occur.[131] Iron supplements should be given during this stage.

Little is known about the relative role of other micronutrient deficiencies in contributing to the anemia of malnutrition. In studies in South Africa and Egypt, there was no evidence of vitamin B_{12} deficiency, but serum folic acid levels were low.[132,133] In Cairo, low serum folate levels correlated with megaloblastic findings on bone marrow and with improvement in these parameters following treatment with injected folic acid, but in South Africa, serum folate was unrelated to hemoglobin levels, which improved without folic acid supplements. Copper, riboflavin, and vitamin E deficiencies may contribute to the anemia of PEM.

Skin and Hair In marasmus, the dry wrinkled loose skin is a result of almost total loss of subcutaneous fat. This leads to a relative increase in surface area, reduced protection from ambient temperature, and therefore increased susceptibility to hypothermia. Hair is thin, grows slowly, and falls out readily, and on microscopy, there is a lack of hair root

bulbs and a shift to the resting state of hair growth.[134] In kwashiorkor, skin changes may be florid and show the characteristic signs described earlier, or they may be absent. Some changes are similar to those seen in acrodermatitis enteropathica, and improvement may occur with zinc ointments, suggesting that concomitant zinc deficiency may be implicated.[135] Other nutrient deficiencies, such as EFA deficiency, the B vitamins, and amino acid deficiencies, also cause skin changes and may contribute. Hair is also affected; depigmentation is a classic sign. Hair follicles show fewer and abnormal growing bulbs, showing atrophy and shaft constriction with depletion of pigment.[134]

Brain Function and Development Most child malnutrition occurs at a time of rapid development, so any insult at this time may have far-reaching consequences. In addition to primary effects on neuronal tissue, there may be secondary effects owing to anemia, micronutrient deficiencies, apathy, and reduced activity. The environment in which most malnourished children live often fails to provide the stimulation and support that the developing child needs to realize his/her potential. The clinically recovered child usually returns to this same environment, thus making it difficult to determine the impact of malnutrition per se on long-term development. Early studies comparing the outcome of children recovered from severe malnutrition who either returned home or were adopted into families with more resources suggested that environmental influences outweighed the sequelae of the malnutrition.[136] The randomized trials conducted by Grantham-McGregor in Jamaica and others have contributed greatly to our understanding of the importance of stimulation as well as dietary therapy in reversing developmental delay.[137,138] This important subject is further addressed in Chapter 21, "Brain Development."

Bones

Children with severe malnutrition often remain stunted after recovery. Branca and colleagues used pyridinoline and deoxypyridinoline, cross-linking amino acids of collagen that are excreted in the urine in proportion to skeletal turnover, to study bone turnover in severe malnutrition.[139] They found low rates of bone turnover during the acute phase of malnutrition and much higher levels during recovery. Age, severity of wasting on admission, and cross-link excretion accounted for 44% of the variability in height velocity during recovery.[139–141] Bone demineralization has also been reported and may be attributable to phosphate deficiency.[142] Concomitant nutrient deficiencies such as vitamin D deficiency causing rickets and osteomalacia, scurvy caused by vitamin C deficiency, and bone changes typical of copper deficiency may also be present.

CLINICAL MANAGEMENT

Treatment regimens for the clinical management of severe malnutrition have been developed by a limited number of specialist centers across the world. These regimens tend to be experience rather than evidence based, and there is a need for clinical trials to clarify many different management issues. Nevertheless, the WHO, in consultation with experts from many parts of the world, has recently formulated recommendations, and this clear, didactic protocol is now available for centers wherever malnourished children are treated.[11] The following discussion of management adheres in general to the WHO guidelines.

Clinical Assessment and Triage

When malnourished children first present, health personnel are usually faced with a question about whether hospitalization is advisable. This is often a tricky decision and deserves some discussion. Risk factors for mortality in a series of studies include severity of malnutrition, young age, pneumonia, severe diarrhea (more than six stools a day, dehydration), signs of sepsis, hypothermia, fever, and electrolyte abnormalities.[143–145] Children with these risk factors should be admitted urgently. Table 10-2 lists factors to be taken into consideration when deciding on admission.

Hospital versus Community Rehabilitation

Hospitalization is usually required for the severely ill child with PEM, but once the acute conditions have been treated, other alternatives include rehabilitation centers or community care. The relative merits of these different options are discussed in Chapter 9.2.

Phases of Treatment

The child admitted with PEM should be treated according to a locally developed protocol based on the WHO guidelines. The use of such protocols has been shown to reduce mortality.[6] The management of malnutrition is a team activity, and all staff who come into contact with the child or the child's caretaker in any way should be aware of the management plan.

Treatment can be divided into three phases:

1. The initial or acute phase (2 to 10 days) when the child is being treated for complications such as dehydration, hypoglycemia, and infections. Dietary therapy starts.
2. The second phase of recovery or rehabilitation (2 to 6 weeks) when the child will increase dietary intake and gain weight.
3. The follow-up phase (6 to 26 weeks), which may be after discharge.

Phase 1: Examination and Emergency Treatment A full clinical history should be obtained; symptoms suggestive of infection and diarrhea are particularly relevant. Birth history is important because low birth weight may explain the infant's low weight, and it is essential to review any growth data that may be available. A developmental history and past medical problems may reveal concomitant conditions that cause or contribute to the malnutrition. Most children will have been chronically ill, and information on medication and therapies, including traditional healers, may be relevant. It will be essential to have information on the child's diet history, including breast-feeding, family diet, food constraints, and access to food programs, as well as a full social and family history, but this information may be

TABLE 10-2 Factors to Consider When Admitting Children with Protein-Energy Malnutrition

Child Factors	
Severity of the malnutrition	The more severe the malnutrition, the greater the need for specialized refeeding, monitoring, and intervention to treat complications such as infection, electrolyte abnormalities, hypothermia, and hypoglycemia
Edema	Children with edematous malnutrition may not appear to be ill and do not induce the same shock horror response as a child with marasmus. Their edematous weight masks the severity of their condition.
Presence of infection	Malnourished children should be regarded as immunodeficient so that infections are more likely to need parenteral antibiotic treatment and close monitoring, which is difficult to do at home. Persistent diarrhea may present special problems and usually quickly improves with a clean diet and appropriate therapy in hospital.[120]
Presence of other conditions	Malnutrition is not always a consequence of primary energy and protein deprivation. The presence of other conditions such as congenital heart disease, cystic fibrosis, and tuberculosis may determine where these children will be best managed. Therapeutic malnutrition units may not be best able to cope with these pediatric emergencies.
Family Circumstances	
Social circumstances	The ability of carers to follow treatment schedules at home, who looks after the child, conflicting work and other family constraints on outpatient attendance, nearness to health facilities, availability of backup services and nutritional support in the community are all factors to be taken into consideration
Previous treatment	Previous attempts at treatment should be taken into account. A child who is worsening despite being in an outpatient or community care program should not have to wait to reach a specific degree of severity to be admitted once the alternatives have failed.
Home social circumstances	These include the nearness to health facilities able to deal with emergencies or monitor the child and the presence of community support with or without food supplements. Children treated in well-organized programs may avoid hospitalization, although there needs to be provision for those who deteriorate, and this may occur suddenly and catastrophically.
Economic considerations	Inevitably, economic considerations will influence decisions and sadly often are the deciding factor, although not in the interest of the child. However, it is very important that health professionals do not add to financial burden with unnecessary tests that do not change management or expensive versions of medicines or medicines of no proven efficacy that compete in the household budget for the food that the child needs or dissuade parents from seeking help for their children.
Hospital Facilities	
Infection risk	Children with severe malnutrition are vulnerable. If admission to hospital means being on a general ward with children with measles and diarrhea, then they may be safer at home, despite the severity of their condition. Obviously, the best option is to provide isolation facilities and hand washing, but this may not always be the case in practice.
Feeding arrangements	Children with malnutrition require frequent feeding. Emergency departments may not have provisions for feeding; even on the ward, provision of food may depend on parents, and this may present an additional complication for caretakers if their time is split between home and hospital. Families may have to buy or prepare the food for their child.

better obtained once the acute phase is completed and is part of building up a relationship with the family.

A detailed clinical examination is essential, but care should be taken not to stress the patient and to protect him/her from cold. Table 10-3 shows some signs and symptoms of particular importance and their management.

Management of Diarrhea and Dehydration. The principles of management, rehydration, and continued feeding are no different in the malnourished child. Signs of dehydration and their management are shown in Table 10-4. Particular attention has to be paid to the volume of fluid given and electrolyte management.

Most children with dehydration can be managed with oral rehydration therapy. In moderate dehydration (WHO plan B), 70 to 100 mL/kg of ORS should be given over 8 to 12 hours, starting frequently (5 mL/kg every 30 minutes). ReSoMal is the preferred option (Table 10-5). The child's clinical state should be monitored at least hourly. If vomiting occurs, then rehydration can be detained 30 to 60 minutes and then resumed. If the child refuses to drink or becomes very tired by the effort of drinking, a nasogastric tube should be used. If the child drinks avidly, then only small amounts should be offered by spoon, never by bottle, as taking a large amount at a time may provoke vomiting. If the child does not show signs of recovery (improved general condition, passing urine), consider sepsis. If diarrhea is ongoing, estimate diarrhea losses and increase the rehydration fluid volume accordingly. A diarrheal stool in a child less than 2 years can be estimated as 50 to 100 mL and 100 to 200 mL in an older child or in very severe diarrhea. Once the child has clinically recovered and signs of dehydration have improved, the child can be started on diet, even though the programmed amount of ORS has not yet been completed or diarrhea continues. Alternate ORS and diet.

Intravenous Therapy. Intravenous infusions should be avoided as far as possible. If unavoidable, for instance in shock, the volume of intravenous therapy should be kept to a minimum, and particular attention should be paid to protecting the site of intravenous access from infection. If antibiotics are to be given intravenously, a heparinized cannula, rather than a continuous infusion, is safer to avoid fluid overload. It may be difficult to establish venous access in malnourished children, especially those with edema, but prolonged attempts and "cut-downs" performed without anesthesia and with little attention to sterility place the malnourished child at risk of hypoglycemia, hypothermia, sepsis, and stress, which increase mortality. Sometimes an intravenous line is started because it is a "routine in all sick children" or "in case it is needed later." Such practices should be avoided in children with PEM. The only absolute indications are circulatory col-

TABLE 10-3 Identification and Management of Complications of Protein-Energy Malnutrition

Sign or Symptom	*Findings*	*Management*
Edema	Usually symmetric and positional; pretibial edema may be evident only on pressing on the shin with a finger and looking for the indentation. The presence of edema also means that gross weight underestimates the child's degree of malnutrition	Edema indicates kwashiorkor and is an indication of severity. Dietary guidelines for kwashiorkor should be applied.
Odd facies, palmar creases, heart murmurs, cyanosis, signs of congenital abnormalities	Chromosomal and congenital disorders may contribute to malnutrition	These children should receive the same treatment for their malnutrition, but concomitant conditions will affect outcome and long-term management
Developmental assessment	An adequate developmental assessment is not possible in a sick or malnourished child, but signs such as increased tone and contractures may point to cerebral palsy and degenerative neurologic disorders may be discernable	
Infection	Malnourished children may not mount a full-blown inflammatory response to infection, so signs may be attenuated and diagnostic tests misleading. The febrile response is reduced.[146]	WHO recommends starting all children with severe malnutrition on a broad-spectrum antibiotic such as cotrimoxazole (sulfamethoxazole 25 mg plus trimethoprim 5 mg) even in the absence of signs of infection
Sepsis	Difficult to distinguish from dehydration. Recent apathy, reduced level of consciousness, jaundice, abdominal distention (babies), fever or hypothermia, hypoglycemia, petechiae, and poor peripheral perfusion are all indicators of possible sepsis.	If there is any doubt, the child should be treated as septic and intravenous antibiotics used. These should be broad-spectrum and cover gram-negative bacteria. Combinations of aminoglycosides such as gentamicin (7.5 mg/kg IM daily) with ampicillin (50 mg/kg 6 hourly) or amoxicillin or third-generation cephalosporins such as ceftriaxone are recommended.
Focal infections	Pneumonia is very common,[147] but cough may be absent. Tachypnea and subcostal recession are preserved. In otitis media, the tympanum may not appear red, and infections may present with perforation and otic discharge. Urine should be examined for urinary tract infections, but false positives owing to dehydration mean that it is better to obtain nonurgent samples after rehydration. The skin should be carefully examined all over.	Infections should be treated as in well-nourished children, using appropriate antibiotics preferably based on local sensitivity patterns. Because of the depressed immunity, disturbed gut function, which might reduce absorption of oral preparations,[148,149] and limited muscle bulk for frequent intramuscular injection, intravenous antibiotics should be used for all serious infections.
HIV/AIDs	In many parts of the world, a large proportion of children presenting with severe malnutrition will have HIV/AIDS	The same management principles apply and the malnutrition should be treated actively. Improving the malnutrition will improve the child's quality of life.
Tuberculosis	Clinical manifestations may be absent. Radiographic changes may be seen only when the child starts to recover from malnutrition. Tuberculin skin tests are usually negative.[94] A positive family history should be sought.	Tuberculosis therapy should be started once tracheal aspirate or gastric cultures have been collected. A trial of therapy is sometimes needed in children in whom there is a suspicion of tuberculosis.
Diarrhea and dehydration	Diarrhea is common, and signs of dehydration should be sought (see Table 10-4)	Diarrhea is not a contraindication to starting diet. Dehydration should be managed as indicated below.
Electrolyte disorders	All malnourished children should be considered to have sodium retention and potassium depletion. Measurement of serum electrolytes is useful to guide management, but low serum sodium is not an indication for administering sodium. Children with kwashiorkor may urinate infrequently and in small volume; neither this nor normal serum potassium should deter the administration of potassium supplements. Hypotonia may be a manifestation of hypokalemia.	Severely malnourished children are best managed with relatively low sodium oral rehydration solutions. The old standard WHO oral rehydration solution (90 mmol sodium) is not recommended. A solution with 60 mmol sodium was found to be superior and to speed recovery.[150] WHO recommends ReSoMal (see Table 10-5), but if not available, the new standard 75 mmol oral rehydration solution could be used. Potassium at 40 mmol/L is recommended. Treatment schedules are given below.
Hypoglycemia	Blood sugar < 54 mg/dL or 3 mmol/L. Floppiness, unresponsiveness, hypothermia, convulsions, and coma are signs of hypoglycemia. If the child is convulsing, hypoglycemia should be assumed and treatment started empirically even before procedures such as lumbar puncture to exclude meningitis.	If the child is conscious, oral glucose (50 mL of 10% solution) may be given, by nasogastric tube if necessary. Follow with milk or diet as soon as possible. If in coma, an intravenous infusion of 10% glucose (5 mL/kg) should be given and followed by oral glucose or diet. Children with hypoglycemia should be considered septic and treated with antibiotics.
Hypothermia	Rectal temperature is more accurate, and, ideally, a low reading thermometer should be available. Rectal temperature < 35.5˚C is diagnostic. Axillary temperature < 35˚C is suggestive.	The child should be warmed gradually either by wrapping in blankets, warming the room, or using the skin to skin kangaroo technique. If the child is hypothermic, assume sepsis.
Anemia	Malnourished children are often anemic, but in nonmalarial areas, severe anemia, < 8 g/dL, should not be assumed owing to nutritional deficiency, and other reasons should be sought.	Intestinal parasites, especially hookworm, may be present and should be treated. Anemia is usually chronic and only needs immediate treatment if there are signs of cardiac failure or hemoglobin < 5 g/dL. In this case, transfusion should be given with great care as discussed with intravenous therapy.

TABLE 10-4 Signs of Dehydration and Interpretation in Severe Malnutrition

Sign	*Plan A*	*Mild or Absent* *Plan B*	*Moderate* *Plan C*	*Severe (with shock)* *Comment*
Conscious level	Normal/alert	Agitated/ irritable	Lethargic/comatose	Agitation is typical. Infection and hypoglycemia also give lethargy.
Eyes	Normal	Sunken	Very sunken	Ask mother about eyes
Tears	Present	Absent	Absent	Tears often absent
Buccal mucosa	Moist	Dry	Very dry	Mouth breathing may cause dryness
Skin pinch	Returns quickly	Returns slowly < 2 s	Returns very slowly > 2 s	More difficult in PEM
Thirst	Drinks normally	Drinks avidly	Unable to drink	If avid, useful

PEM = protein-energy malnutrition.

lapse caused by severe dehydration or septic shock. In this case, solutions with low sodium, such as half-strength Darrow's solution, Ringer's lactate, or half-normal 0.45% saline, all with 5% glucose, should be used. Potassium chloride should be added to provide 20 mmol/L, infused at 15 mL/kg per hour, preferably using a programmable pump. The child's hydration status, pulse, and respiratory rate should be reviewed at least hourly. If the child was dehydrated, improvement should be obvious; if not, septic shock is likely, and parenteral antibiotics should be started, if not already given, and blood transfusion considered. If blood is not available, plasma is an alternative. Transfusion should be given slowly (10 mg/kg over 3 hours) with close monitoring of jugular veins and respiration rate as malnourished children are at high risk of congestive heart failure. Diuretics such as furosemide 1 mg/kg may be given if there is any suggestion of heart failure.

Parasites and Gut Flora. Parasites should be treated if identified in the stools. If *Giardia lamblia* is present, metronidazole is recommended. A lower than usual dose, 12.9 mg/kg/day, has been suggested on the basis of pharmacokinetic studies.[149] Bacterial contamination of the small intestine has been described in children with PEM, but the functional significance of this is not clear.[151] Children admitted to the hospital from highly contaminated home environments were found to have bacterial contamination of duodenal fluid regardless of nutritional or diarrheal status.[152] The bacterial flora reduced within days of eating a clean diet and without antibiotic therapy.[117] The need to treat all children with PEM for bacterial overgrowth remains controversial, and randomized controlled trials are needed.

General Care of the Malnourished Child. Sadly, the mortality rate for children hospitalized for severe malnutrition is often high,[9,153–156] and some of these deaths are a consequence of hospital practices, such as long waits without food, indiscriminate use of intravenous fluids, and the dangers of admission to a high-risk environment. Adoption of recommended guidelines and the use of protocols that facilitate a team approach have resulted in spectacular reductions in mortality rates.[6] An important aspect of these improvements is the organization of services with a view to preventing complications. Early deaths, within the first day, are often attributable to hypoglycemia and/or failure to recognize and treat infections adequately. Later deaths may be owing to overwhelming infections, but sudden unexpected deaths after a few days may be caused by cardiac failure associated with the refeeding syndrome.

Prevention of Hypoglycemia. It is important to give thought to how to prevent hypoglycemia. Travel to the hospital and waits to be seen in the emergency or outpatient department can place the child at risk, and this may be exacerbated by hospital policies such as "nil by mouth" until the child is reviewed and reluctance to start any "treatment" until experts are consulted or test results are available. Mothers should be encouraged to breast-feed their babies while waiting, and a triage system that quickly identifies children with severe malnutrition and directs them into a protocol providing immediate feeding will reduce the risk of hypoglycemia and the attendant mortality. Frequent feeds every 2 to 4 hours are needed at first. Nighttime, when staffing levels are reduced, often provides a challenge, and health facilities should have a plan to cope with this. This might involve having prepared diets or

TABLE 10-5 Composition of Oral Rehydration Salts for Severely Malnourished Children (ReSoMal)

Component	*Concentration (mmol/L)*
Glucose	125
Sodium	45
Potassium	40
Chloride	70
Citrate	7
Magnesium	3
Zinc	0.3
Copper	0.045
Osmolarity	300

Adapted from World Health Organization.[11]

TABLE 10-6 Preparation of F75 and F100 Diets

	Energy	
Ingredients	*0.75 kcal/cc*	*1 kcal/cc*
Dried skimmed milk (g)	25	80
Sugar (g)	70	50
Cereal flour (g)	35	—
Vegetable oil (g)	27	60
Mineral mix (mL)	20	20
Vitamin mix (mg)	140	140
Water to total volume (cc)	1,000	1,000

Adapted from World Health Organization.[11]

ingredients always available in the emergency department or on the ward and using nasogastric tube feeds if staff or family are not available for the time-consuming process of encouraging the malnourished child to eat frequent feeds. Monitoring is very important. If the mother is accompanying the child, she should have access to refreshments; otherwise, she may be tempted to share the child's ration.

Prevention of Hypothermia. Children with PEM, especially those with marasmus, have less insulating fat and a relatively large surface area, so that body temperature tends to reflect ambient temperature, and they are very vulnerable to hypothermia.[157,158] Prevention requires planning to avoid having the child unclothed for long periods, for instance, while having radiographs or during medical examination, and providing an ambient temperature that is warm, 25°C to 30°C, and without draughts. Washing should be kept to a minimum, and the child should be dried and wrapped immediately. At night, temperatures often fall, so additional precautions may be necessary.

Dietary Management. Dietary therapy must be started rapidly, and this requires a protocol. The health care professional should specify dietary therapy when the child is first seen. The exact diet to be used will depend on local circumstances. In some cases, it may be easiest to have infant formula available when the diet kitchen or daytime nursing is not available, even though it is too expensive to continue. When families are expected to provide food for patients, a special diet will need to be prescribed and made available until family food can take over. This might be the WHO-recommended F75 and F100 (Table 10-6), which have been designed and tested in malnutrition treatment centers.[11] The F75 is designed for the initial phase and F100 for the rehabilitation phase, but many centers use F100 from the start, especially in marasmic children. Alternative local diets have been used successfully; an example used at the Instituto de Investigacion Nutricional, Lima, is given in Table 10-7. Whatever diet is chosen, this should have an energy density of 75 to 100 kcal/100 mL, the osmolarity should be lower than 350 to 400 mOsmol/L,[159] and 6 to 12% of the calories should come from protein[159,160] and at least some of this from an animal source (milk, chicken meat, or egg). Techniques such as fermentation and the combination of complementary vegetable proteins can improve the protein quality and may add valuable vitamins.[161] Although diets based on vegetable protein have been used successfully, nitrogen retention is usually less than that seen with milk diets (Table 10-8).[162,163] At least 50% or more of calories can come from fat; higher fat results in higher overall energy absorption.[164] Diets should be liquid if nasogastric tube feeding is to be used; they should not thicken on standing, a problem of higher proportions of carbohydrate, and they should be palatable. Sodium should not exceed 2 mmol/kg/day, and potassium should be added to give 5 to 7 mmol/kg/day. Additional vitamins and minerals should be added to provide one to two times the daily requirement. A local vitamin supplement can be used, but it is often harder to find a mineral source, and WHO provides a recipe for a mineral mix that can be made in a local pharmacy or biochemistry department.[11] An exciting new advance is the recent development of high-fat solid rehabilitation diets resistant to bacterial contamination and with excellent preservation of micronutrients.[165]

TABLE 10-7 Preparation of Rice Milk Diet

Ingredients	*Energy 1 kcal/cc*		*Household Measures for 100 cc*
Full-fat dried milk (g)	76	7.6	5 heaped spoonfuls
Rice (g)	74	7.4	5 heaped spoonfuls
Vegetable oil (cc)	33	3.3	1 ounce or measure with syringe
Sugar (g)	27	2.7	2 heaped spoonfuls
Kalium (cc)	9	0.9	Measure with syringe
Water to total volume (cc)	1,000	100	

Diet used at the Instituto de Investigacion Nutricional, Lima.

Children should receive 80 to 100 kcal/kg/day; < 80 kcal/kg is insufficient to maintain metabolic needs, and > 100 kcal may put the child at risk of the refeeding syndrome discussed below. Feeds should be given every 2 to 4 hours at first. The amount actually consumed should be monitored by direct observation. Continuing or developing diarrhea does not necessarily mean that the diet should be changed. Only if diarrhea becomes worse, for instance more than six voluminous liquid stools per day, or dehydration occurs is it necessary to change to a low-lactose diet with the same calorie content. Oral rehydration fluid should be given between meals to compensate for stool losses. An algorithm illustrating the dietary management in the acute phase is shown in Figure 10-6.

Breast-fed Children. The mothers of breast-fed children should be encouraged to nurse as breast milk continues to provide important nutritional support even through the second year of life.[42] Breast-feeding should be encouraged in the hospital whenever the child is strong enough to suck; if possible, breast milk may be extracted to add to the diet, and this may help the mother feel involved and important.

Younger exclusively breast-fed babies may occasionally present with PEM, and it is not reasonable to assume that a baby who has become severely malnourished on the breast will improve if no action is taken. These babies need additional food. Improving breast-feeding technique and

TABLE 10-8 Composition of Mineral Mix Solution

Substance	*Amount*
Potassium chloride	89.5 g
Tripotassium citrate	32.4 g
Magnesium chloride ($MgCl_2.6H_2O$)	30.5 g
Zinc acetate	3.3 g
Copper sulfate	0.56 g
Sodium selenate*	10 mg
Potassium iodide*	5 mg
Water to make	1,000 mL

If it is not possible to weigh very small amounts accurately, this substance may be omitted.
Adapted from World Health Organization.[11]

relactation may be tried to increase breast milk supply once the baby is improving but are not suitable for the initial phase of management. For babies under 4 months of age, a modified cow's milk formula is the recommended food; for infants older than 4 months, a cereal milk diet can be given. The youngest babies present a problem when infant formulas are beyond the resources of parents or the hospital, but priority should be given to obtaining milk formula for babies under 4 months. Complementing with another woman's breast milk is possible only if a safe sterile supply is available.

Mineral and Vitamin Supplements. Micronutrient deficiencies are common in malnutrition. Regardless of signs of vitamin A deficiency, this should be assumed and retinol palmitate given orally on admission, 50,000 IU for children < 6 months age, 100,000 IU for children age 6 to 12 months, and 200,000 IU for older children. A repeat dose should be given the next day and a third dose after 2 weeks or on discharge, whichever is sooner. A single oral dose of 5 mg folic acid on admission is recommended followed by 1 mg daily. Other vitamins and minerals are best given with the diet or as a daily supplement during recovery.

Zinc supplementation of malnourished children has been shown to improve weight gain[166,167] and improve immunologic outcomes, and 1 mL/kg/day of a 1.5% zinc acetate solution daily is recommended. Care should be taken not to provide too much zinc as mortality was increased in Bangladeshi children receiving 6 mg/kg/day.[168]

Copper deficiency has been reported in malnourished children,[169] and copper sulfate should be added to the diet if not included in the mineral mix.

Iron supplements are not recommended during the acute phase because of the risk of producing iron free radicals, as described earlier in the chapter.[125] However, iron supplements are essential once growth and rehabilitation start and muscle and blood are being synthesized.[170] Ferrous sulfate or fumarate syrup may be given 4 mg elemental iron/kg body weight.[171]

As mentioned earlier, electrolyte disturbance is part of the pathophysiology of malnutrition. A triad of interrelated electrolyte deficiencies, potassium, magnesium, and phosphate, occurs. Deficiency of these elements may become especially critical once treatment is instigated and recovery starts. Potassium should be added to the diet to ensure a total of at least 5 mmol/kg/day or more. Magnesium is needed for potassium to enter cells, and magnesium supplements should be added to the diet and, if possible, mineral ORS used(ReSoMal). If not given in the diet or ORS on the first day, an alternative is to give magnesium sulfate 50% solution, 0.3 mL/kg intramuscularly (maximum 2 mL) once, and then include it in the diet. Hypophosphatemia is associated with increased risk of dying and should be included in the diet. Milk provides an excellent source.

Refeeding Syndrome. The refeeding syndrome is a potentially lethal complication of an increase in calorie intake following starvation. Sudden onset of lethal cardiac failure occurring during refeeding was first reported in the classic studies of experimental starvation in adults in Minnesota and later in starved Japanese prisoners of war, the survivors of concentration camps, and following the wartime famine in the Netherlands, when, following starvation, there was sudden access to unlimited food.[172,173] This syndrome also occurs in severely malnourished children and may be responsible for considerable mortality, although the precise incidence is difficult to know as, clinically, the syndrome may

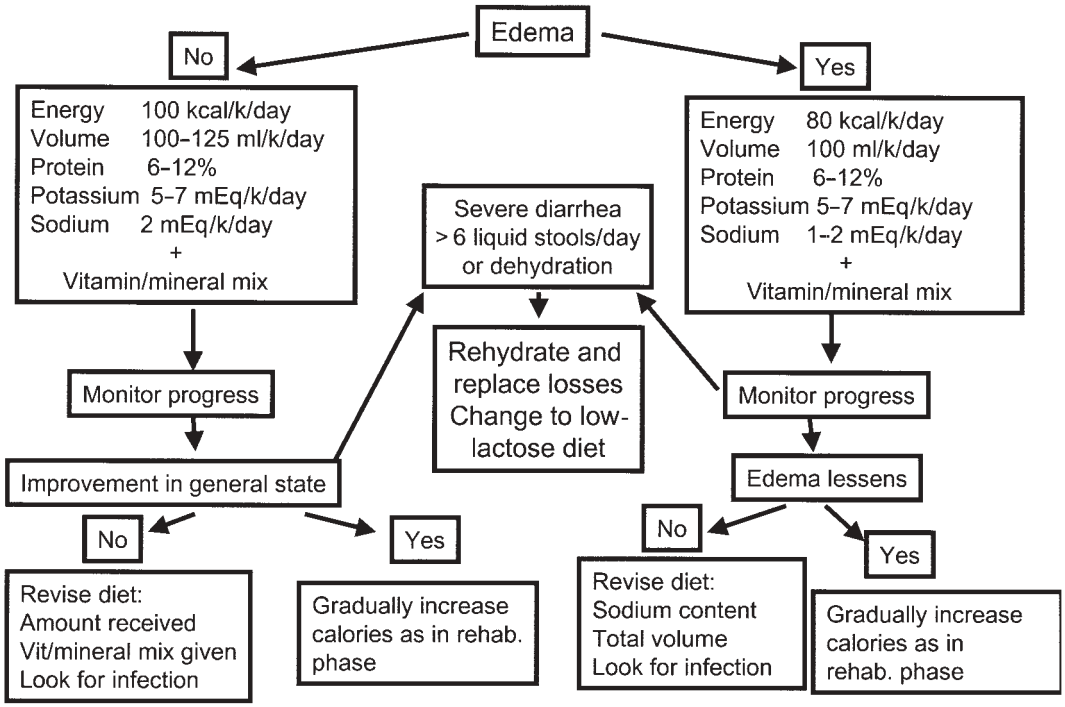

FIGURE 10-6 Phase 1: Nutritional Management.

be difficult to distinguish from pneumonia and sepsis deaths. Sudden death shortly after refeeding has started in a child who seemed to be doing well is suspicious. The syndrome also occurs with parenteral and enteral feeding.

When glucose becomes available during refeeding, gluconeogenesis is inhibited, and there is a rise in plasma glucose and insulin excretion. Rebound hyperglycemia may occur with polyuria and dehydration. There is a flux of glucose, potassium, magnesium, and phosphate into cells, which may result in rapid lowering of serum levels. The sudden reduction of serum levels of these three electrolytes is thought to explain most of the consequences of the refeeding syndrome. Phosphate depletion results in anorexia, adverse neuromuscular effects (eg, diaphragmatic weakness and respiratory insufficiency), and a reduction in myocardial contractility.[174] Cell membrane electrolyte fluxes are perturbed, and there is an intracellular accumulation of calcium, sodium chloride, and water, which may result in edema and is probably one of the mechanisms that explain recurring edema when children with kwashiorkor are refed too rapidly. There is also a derangement of phospholipids in cell membranes.[175] When refeeding with high-carbohydrate diets occurs, there is an increased need for phosphate for phosphorylation and protein synthesis and a shift of available phosphate into cells. Although hypophosphatemia was thought to be the main cause of the refeeding syndrome, the clinical effects of potassium and magnesium deficiency are similar, and it is likely that all three electrolyte disturbances contribute to a certain extent. Thiamin deficiency may also be important and has been reported in refeeding alcoholics and following starvation treatment of obesity. Its role in the refeeding of malnourished infants is not known. Thiamin is an essential cofactor for various enzymes, and carbohydrate refeeding causes increased thiamin use.

The key to prevention of the refeeding syndrome is the avoidance of rapid refeeding, especially with high-carbohydrate diets, whether intravenous or enteral, and the replenishment with potassium, magnesium, and phosphate and restricted sodium intake. The safest way to correct phosphate deficiency is with milk diets because oral phosphate salts are laxatives and may well exacerbate diarrhea. Milk is also useful as a good source of magnesium, as well as protein and energy, but needs to be mixed with a cereal such as rice or sugar to reduce the sodium and protein and lactose load. If intravenous treatment is unavoidable and oral feeding is delayed, phosphate can be given intravenously with care and should be included in parenteral feeding regimens. If children are dehydrated, magnesium and potassium can be added to oral rehydration therapy as in the ReSoMal recommended by WHO. Vitamins, including thiamin, should be added to the diet from the start. The reader is referred to several recent reviews of this subject.[173,176,177]

Skin and Eye Care. The skin lesions of kwashiorkor improve with dietary therapy but, in the initial phase, may become infected and are a potential source of pathogens causing sepsis. Care should be taken to avoid pressure on affected areas and the skin should be kept clean and dry; 1% potassium permanganate solution may be applied to the worst areas. If possible, the perineum and buttocks should be left uncovered and carefully cleaned and dried immediately after defecation.

Special care should be taken of the eyes of children with signs of vitamin A deficiency (xerophthalmia). Retinol supplements should be given immediately in the same doses noted above,[10,171] and the eyes should be protected with pads soaked in saline. Atropine and antibiotic eye drops should be applied at least four times daily until there is no sign of inflammation.[10,171]

Phase 2: Rehabilitation The initial phase of management lasts while metabolic and electrolyte abnormalities are corrected and infections treated. This phase may last from 1 to 7 days, sometimes longer, if infection is difficult to treat and edema slow to resolve. The recognition of recovery is subjective but usually obvious to staff. There is a general improvement in the child's condition. The return of appetite, reduction in apathy, and return of smiling are encouraging signs indicating improvement. Weight gain may not occur at this stage, and in kwashiorkor, there is usually a brisk weight loss as edema disappears. If the child does not seem to be recovering and edema continues without obvious cause, suspect occult infection, for instance, tuberculosis, inadequate potassium repletion, and phosphate deficiency. An algorithm for the dietary management of the child during this phase is shown in Figure 10-7.

If the child shows signs of improvement, the rehabilitation phase can start. In this phase, emphasis is on intensive feeding to restore lost weight and emotional and physical stimulation to optimize recovery. For long-term successful recovery and to prevent relapse, the clinical unit needs to work closely with the family during this phase. Ideally, this phase should be 2 to 6 weeks to give the child, especially his/her immune system, the best chance to recover before being challenged by the home environment. A reasonable goal is for the child to reach –1 SD (90%) of the median weight for length[178] before discharge. In some settings, it is very difficult to retain the child in the hospital for this time, and when children are exposed to other ill children, the hospital may not be the safest place.[179] An alternative is to seek out or establish rehabilitation care in the community, and several successful models have been reported. Too early discharge in the absence of follow-up rehabilitation leads to very high postdischarge mortality.[180]

Diet. During the rehabilitation phase, the dietary calorie intake should be increased. This should be gradual, for instance, an additional 25 kcal/kg/day every other day,[159] to avoid the refeeding syndrome and should be guided by the child's appetite and general condition. Diets are calculated based on body weight, so correction will need to be made for the child's changing weight. Most children will reach intakes of between 150 and 250 kcal/kg/day, and rapid weight gain at this stage is desirable as it is associated with the same body composition as lower weight gains.[181] The same diet started in the initial phase may be continued; if F75 was used, then F100 should be substituted. Readers are referred to a review of the criteria for rehabilitation diets

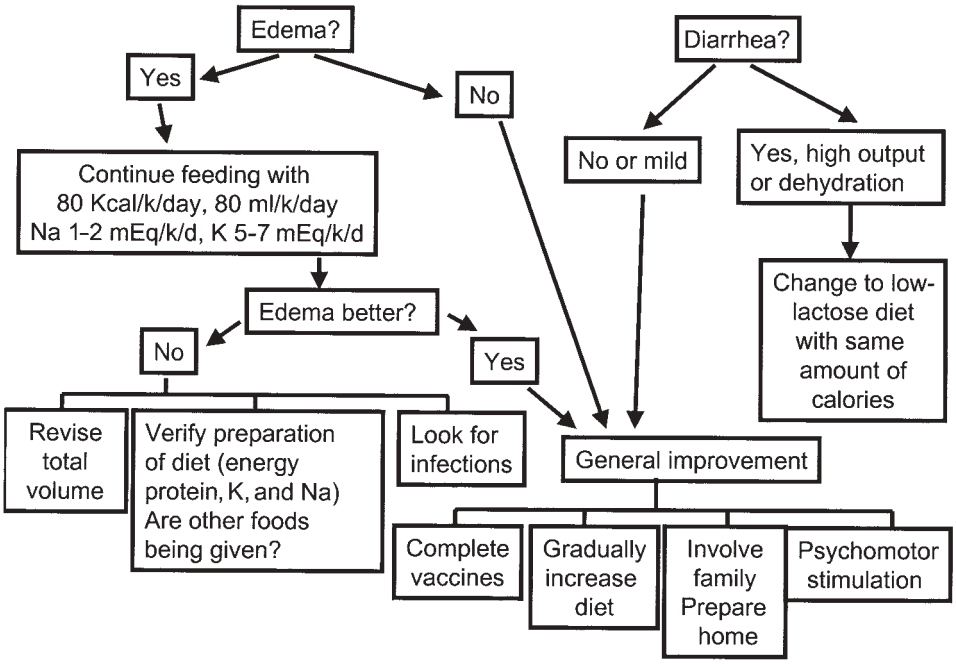

FIGURE 10-7 Rehabilitation phase.

and guidance on practical aspects.[159,182,183] At first, it is useful to continue a set diet as it is easier to calculate intakes, but as the child improves, the diet should be varied, and the child should be encouraged to eat a variety of locally available solid foods. Wherever possible, mothers not only should be taught about diets based on nutrient-dense local weaning foods but should prepare and feed these preparations in the hospital or rehabilitation unit.

During this phase, iron supplements should be started at 3 to 4 mg elemental iron/kg/day and other micronutrient supplements should be continued.

Physical and Emotional Stimulation. Early physical and emotional stimulation are very important. Even during the initial phase, mothers can be encouraged to talk to and hold their children. They can be taught to massage their children, which has been shown to increase growth recovery. Children should de provided with a visually interesting environment. As soon as possible, play therapy should be instigated. The WHO manual provides examples of easy-to-make toys.[11] Studies in Jamaica and India showed that an early stimulation program improved growth, complementing micronutrient supplements.[137,138]

Phase 3: Follow-up Before the child is discharged, arrangements should be made for follow-up in the community or in the outpatients department. Recently recovered malnourished children often relapse, and children have a high mortality rate after discharge.[180] Families should have easy and rapid access to medical care, ideally on the unit where the child is known. The choice of follow-up, like the length of hospital stay, will depend on the availability of services. The availability of a well-designed follow-up program can make all the difference to subsequent risk of dying.[184] Studies following children treated for severe malnutrition have shown variable recovery of nutritional status and intellectual development.[185,186] Sustained recovery of nutritional status is possible, although stunting usually remains.[187] Growth following rehabilitation depends on the favorable home circumstances.[136] When family circumstances remain unchanged, the outlook is poor.[188] A study in Lima comparing children returning home with those who had to be adopted and were integrated into families with few resource constraints showed both the importance of follow-up care but also the potential for recovery of these children.[136] Children should be followed up for at least 6 months to ensure successful rehabilitation.

CONCLUSIONS

The last few years have brought exciting advances in management of severe malnutrition. Lessons learned in the past are now being applied in hospitals and rehabilitation centers all over the world, although much more needs to be done to ensure that this information reaches and changes practice in all of the situations in which severe PEM is treated. Greater understanding of the pathophysiology of PEM has contributed to more rational therapy, and some clinical trials of therapies, new diet possibilities, and management strategies are being reported. Nevertheless, there is a great need for more research. The pathophysiology of kwashiorkor is still unclear, and the complicated interplay between infection and nutrition in PEM and its consequences are not resolved. Many of the recommendations for management have never been properly assessed.

The long-term goal, of course, is to prevent PEM. Some aspects could be relatively easily achieved. Medical practices, for instance, that deprive children of food while they are ill, especially with diarrhea, have been unequivocally

shown to be unnecessary and harmful, but the use of diluted diets or "resting the gut" continue. Attention is now being given to early enteral feeding of critically ill children, which reduces malnutrition and mortality.[189] Great strides have been made in understanding the importance of exclusive breast-feeding and the requirements for adequate complementary feeding practices, but much work is still needed to change complementary feeding practices in many countries and overcome the restraints on food security. Infections, which are very common among the most deprived populations, contribute to malnutrition. Whereas children with access to sufficient food of high nutritional value experience only transient effects, those on marginal diets are caught in a cycle of infection, exacerbating malnutrition and vice versa. Interventions that reduce the burden of disease will reduce malnutrition in these populations. Measles was once a common precursor to kwashiorkor and severe vitamin A deficiency but, with vaccination, has now disappeared in many countries. Other vaccines against diarrheal diseases could make important contributions. Severe PEM is an entirely preventable disease, but it will continue to kill and contribute to the deaths of millions of children while war and natural and man-made disasters continue to affect large parts of the world.

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CHAPTER 11

INTERNATIONAL NUTRITION

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The implications of global health issues for the medical practitioner have become increasingly apparent over the past decade. The acquired immune deficiency syndrome (AIDS) epidemic, the emergence of new communicable diseases, and the global epidemic of obesity are examples of major domestic public health issues closely linked to the global situation. In addition, the dramatic expansion in travel and communications and the globalization of the economy are weakening cultural and geographic barriers and exposing a variety of populations to similar dietary and lifestyle factors affecting the risk of disease.

The field of international nutrition attempts to identify and study the health consequences of these global changes. In this chapter, we focus on how the current situation impacts on survival, growth, and well-being of infants and children.

CHILD SURVIVAL AND GROWTH: GLOBAL TRENDS

Mortality

Estimates indicate that malnutrition is associated with as much as 60% of deaths during the first 5 years of life (Figure 11-1). Protein-energy malnutrition (PEM) and micronutrient deficiencies (such as vitamin A and zinc) are major contributors to the higher mortality rates from illnesses and diseases such as pneumonia, malaria, diarrhea, and measles in the developing world.

Over the past 40 years, global child mortality rates for children under 5 years of age have declined by half.[1] Figures for United Nations (UN) regions and worldwide rates are presented in Table 11-1. Rates exhibit a wide range, from 5 per 1,000 live births in Scandinavian countries to 334 in 1,000 live births in Niger.[1] Declining trends in mortality have been, as expected, more pronounced in countries with initially high rates, ranking the West Africa region as the most pronounced, followed by Latin America, North Africa/Near East, and Asia. Minor increases in mortality rates over the past decade occurred in East and Southern African regions.[2–4]

Mortality is the end result of a complex interaction of health, nutritional, and environmental factors. The relative contribution of each of these is still a matter of intense study and debate, but it seems clear that among these, current dietary intake and prior nutritional status are paramount.[2–4] Stunting and wasting are both significant contributors to mortality rates for a number of primary diseases, particularly infectious diseases. Of the dietary factors, breast-feeding duration and timing of introduction of complementary foods are prominent.[5,6] Other determinants include access to and use of prenatal care, immunizations, maternal education, and access to electricity.

The phenomenon of decline in mortality rates observed in developing countries over the past five decades has been somewhat independent of changes in socioeconomic status. Major factors are likely to be mass immunization, widespread use of oral rehydration therapy, and promotion of breast-feeding.[7] Integrated programs that combine promotion of breast-feeding with immunizations and micronutrient supplementation are also important contributors on the prevention side, as are programs aimed at improving case management, such as the World Health Organization's (WHO) Integrated Management of Childhood Illnesses program. Improvements in the availability of health services, particularly for pregnant women, were also important contributors.[8] However, trends toward reduction in mortality were partially offset in some cases by economic decline and social and political instability.[3,9] In any case, sustainability of many of these programs is frequently uncertain, depending in large part on political decisions at the level of countries or regions.

Growth

Stunting is the term used to define chronic malnutrition, in which a child's weight is proportional to his/her height, but height is below the reference standards for age (< 5th height-for-age percentile). This type of growth delay usually results from frequent acute episodes of growth deceleration, most commonly related to infectious episodes.[10–12] Current (1995–2000) data on the prevalence of the different forms of PEM are presented in Table 11-2.

Over the past two decades, a consistent decline in stunting has been documented. In 1980, 41% of children under 5 years of age had some degree of growth retardation for their age. At present rates, it is projected that that figure will fall to 32.5% by 2005, equivalent to a reduction of 40 million in the number of stunted children.[7] Encouraging as these data may be, it is sobering that this positive

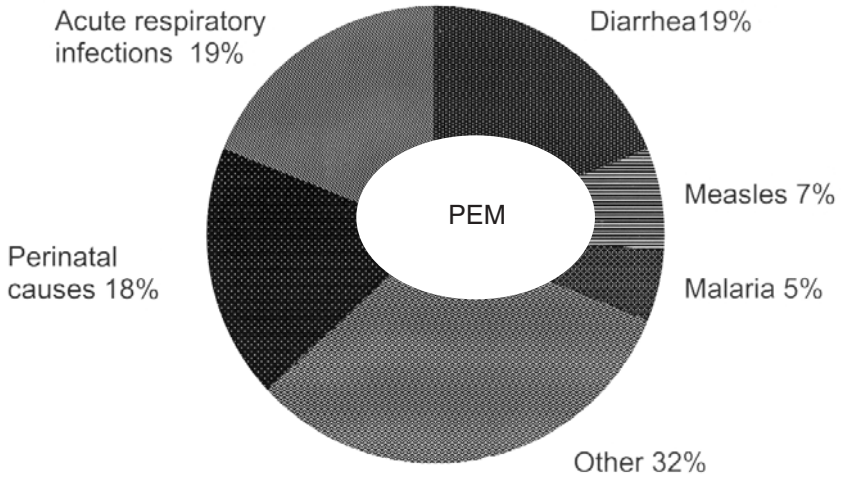

FIGURE 11-1 Major global causes of death among children under 5. Adapted from The Global Burden of Disease 2000 Project: aims, methods, and data sources. Global Programme on Evidence for Health (EIP) Policy Dicussion Paper #36. Geneva: World Health Organization; 2001.

trend would still leave about 192 million children with inadequate growth.

The geographic prevalence of stunting is far from uniform. Whereas one-third of children in the developing world are currently defined as stunted, 70% of these children live in Asia (61% of the total number reside in South Asia), 26% in Africa, and the remaining 4% in Latin America and the Caribbean. Similarly, whereas the overall trend is in decline, rates are actually increasing in sub-Saharan Africa, at a rate of 0.08%/year.[7] Figure 11-2 depicts trends in stunting in UN regions from 1980 through projections for 2005.[1,2,7]

Several studies have demonstrated an inverse correlation between stunting, cognitive and physical development in young children, and consequently lower intelligence levels in older children and functional impairment in adulthood, both in terms of intellectual and physical aspects, impairing work capacity. Stunting also increases obstetric risk in women and also has a transgenerational effect, leading to the perpetuation of suboptimal growth in the population as a whole.[13]

TABLE 11-1 Global Trends in Childhood Mortality Rates, 1960 and 2000

	Infant Mortality Rate			
	*Under 5**		*Under 1†*	
	1960	*2000*	*1960*	*2000*
World	198	83	126	57
Industrialized countries	37	6	31	6
Developing countries	223	91	141	63
Least-developed countries	279	161	170	102
Sub-Saharan Africa	254	175	153	108
Middle East and North Africa	250	64	157	49
South Asia	244	100	148	72
East Asia and Pacific	212	44	140	34
Latin America and Caribbean	153	37	102	30
CEE/CIS and Baltic States	103	37	78	30

Adapted from UNICEF.[2]
*Expressed as per 1,000 live births; †expressed as per 1,000 live births, at exactly 1 year of age.
CEE = Central and Eastern Europe; CIS = Commonwealth of Independent States.

Wasting, usually measured by weight for height, is an indicator of acute malnutrition. A low weight for height can occur in a previously healthy child, but more commonly it affects populations of children who are already suffering from chronic malnutrition (stunting). Acute weight loss may be linked to inadequate dietary intake owing to illness or simply to unavailability of food, such as in natural or man-made disasters that suddenly displace populations from their natural habitat. Values 2 standard deviations below the median value are considered moderate wasting, with < 3 standard deviations defining severe wasting. Wasting can also be estimated using the mid-upper arm circumference (MUAC), a more rapid assessment method frequently used in refugee camps to triage emergency assistance.[14,15] Severely wasted children would have lost most of their subcutaneous fat, as well as some of their muscle mass, resulting in a very low MUAC.

Recent analysis of available global data for the period 1995 to 2000 indicates that about 9% of children are moderately to severely wasted (see Table 11-2). Wasting has a low to moderate prevalence in Latin America and the Caribbean and a high prevalence in South Asia. In Africa, prevalence shows substantial variability across countries, with an increasing trend from West to East. Sub-Saharan Africa, which has the highest rate of stunting in the world, shows only low-to-moderate rates of wasting.[2]

Whereas stunting has long-term implications for adult health and productivity, wasting is closely linked to child mortality.[16,17] By increasing the frequency and severity of infectious diseases, acute malnutrition significantly increases mortality from communicable diseases.[18–20]

Fetal Growth and Birth Weight

Birth weight is a potent indicator of infant growth, response to environmental stimuli, and ultimately to infant survival. Low birth weight (LBW: < 2,500 g) carries a 10-fold higher risk of neonatal mortality compared with newborns weighing 3 to 3.5 kg.[21,22] Twenty-one of the 25 million LBW infants born every year are in the developing world. The distribution of LBW by region of the developing world is shown in Figure 11-3. Whereas prematurity

TABLE 11-2 Current Prevalence of Low Birth Weight and Malnutrition

	% of Infants with Low Birth Weight (1995–2000)	*% of Children Under 5 (1995–2000) Suffering from:*		
		Underweight, Moderate and Severe	*Wasting, Moderate and Severe*	*Stunting, Moderate and Severe*
World	14	27	8	32
Industrialized countries	7	—	—	—
Developing countries	14	28	9	32
Least-developed countries	18	37	10	43
Sub-Saharan Africa	12	30	10	41
Middle East and North Africa	11	15	7	23
South Asia	26	46	15	45
East Asia and Pacific	8	17	4	21
Latin America and Caribbean	9	8	2	16
CEE/CIS and Baltic States	9	7	4	16

Adapted from UNICEF.[2]
CEE = Central and Eastern Europe; CIS = Commonwealth of Independent States.

is the main contributor to LBW in the developed world, the vast majority of LBW infants born in the developing world are born at term but of small size for their gestational age, that is, with intrauterine growth retardation (IUGR). The prevalence of LBW in the developing world ranges from 26% of live births in South Asia to 12% in sub-Saharan Africa.[21]

IUGR has two distinct patterns: asymmetric versus symmetric. Asymmetric IUGR is usually associated with energy restriction during the second and third trimesters, as well as with prematurity, preeclampsia, and tobacco smoking. Asymmetric IUGR carries a higher risk of death during the neonatal period than symmetric IUGR.[23] The more common type of IUGR in the developing world is symmetric IUGR, reflecting a sustained energy restriction throughout pregnancy. Hypoglycemia, hyperviscosity, hypothermia, perinatal asphyxia, and aspiration are more frequent in the wasted neonate. These findings persist despite correction for both birth weight and gestational age.[24]

In the developing world, maternal prepregnancy weight is strongly correlated with birth weight. A maternal prepregnancy body mass index (BMI) of < 18.5 is associated with higher morbidity and mortality for both mother and fetus.[19] Thus, there is an intergenerational effect of stunting because stunted girls reaching their reproductive age will have an increased risk of producing LBW babies. Maternal behaviors and cultural factors determining level of physical activity and food intake also influence energy balance during pregnancy.[19]

In addition to dietary energy, micronutrient deficiencies can significantly affect fetal growth, as well as impact on obstetric mortality. Vitamin A deficiency appears to have a significant effect on maternal mortality, as suggested by studies in Nepal in which vitamin A supplementation reduced mortality by 30%.[25] Whereas maternal zinc supplementation has not yielded a demonstrable effect on birth weight, duration of gestation, or postnatal mental development,[26] significant positive effects on fetal neurobehavioral development have been reported.[27,28] Zinc supplementation may act by other mechanisms enhancing neonatal survival, such as by augmenting the acquisition of natural immunity.[27] Additional maternal factors increasing the risk of LBW are low maternal age (< 18 years), chronic infections such as malaria, gastrointestinal parasites, sexually transmitted diseases, and first-time births, the latter also seen in the industrialized world.[21]

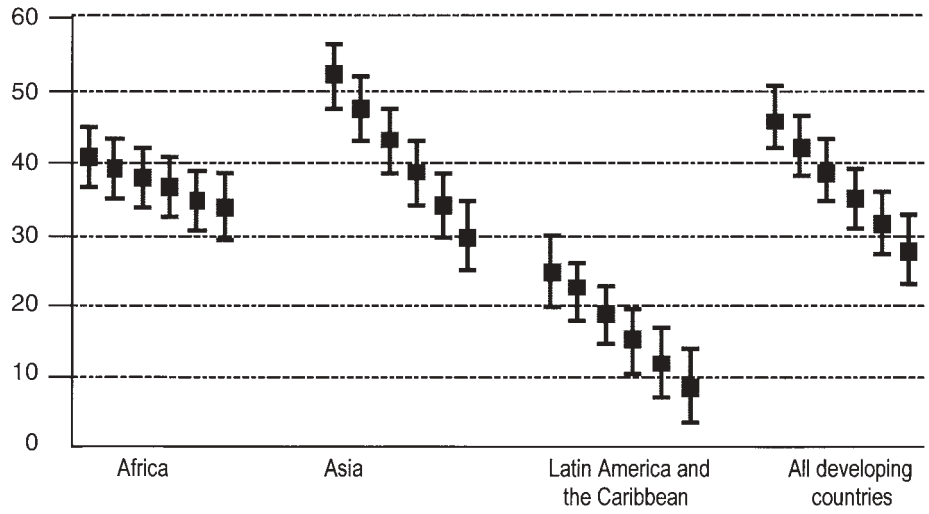

FIGURE 11-2 Trends in chronic childhood malnutrition (stunting) by region, from 1980 to 2005. Box-whisker plots are at 5-year intervals, depicting 95% confidence interval. Reproduced with permission from de Onis M et al.[7]

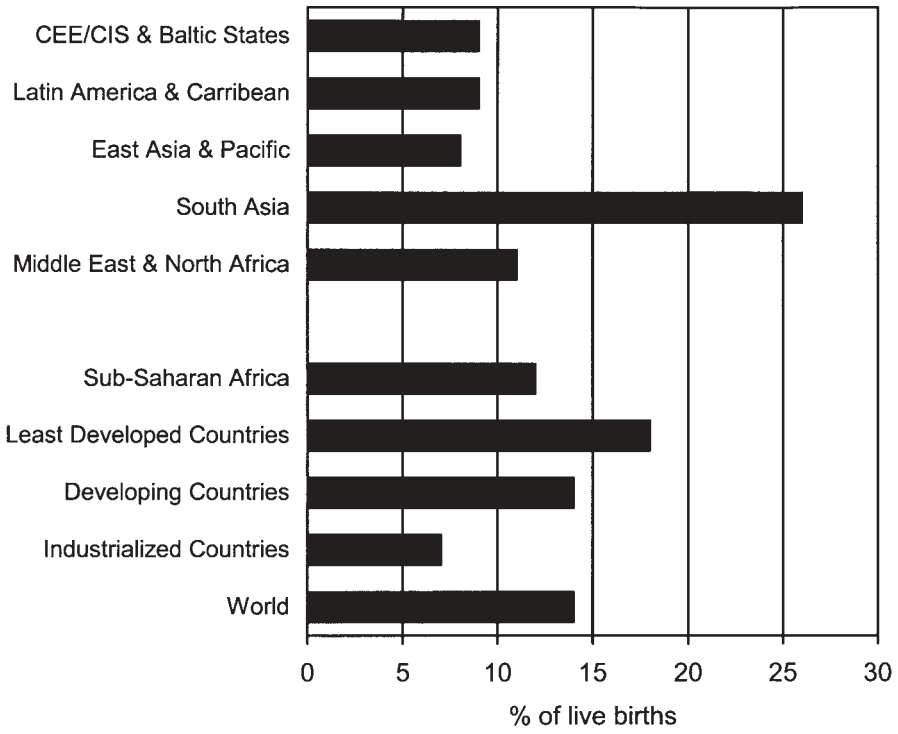

FIGURE 11-3 Rates of low birth weight (≤ 2,500 g), expressed as a percentage of live births, by region. CEE = Central and Eastern Europe; CIS = Commonwealth of Independent States. Adapted from UNICEF.[2]

The implications of IUGR extend beyond those of anthropometrics and growth. Studies in the developing world have reported lower Bayley scores and lower mental development index scores in LBW infants. These findings, however, are associated with environmental factors as well, such as standard of living, housing, and parental education. The trends in these studies would suggest that cognitive development and deficits change over time, and many of the conclusions drawn depend on the age at which they are actually followed up and may actually be transient.[29–31]

The Guatemala longitudinal study documented some degree of catch-up growth of infants with IUGR during the first 2 years of life, with subsequent stabilization at the centiles achieved by that age.[12] Body weight and height deficits in 17 to 19 year olds were evident, averaging 5 kg and 5 cm below non-IUGR children.[32,33]

Different approaches for the prevention of IUGR have been evaluated over the past decades.[34] These include macronutrient or micronutrient supplementation during pregnancy, interventions targeting nonpregnant women of reproductive age, management of obstetric disorders, increasing access to primary health care, and others.[34–36] Other important components of IUGR prevention include tetanus immunization, malaria prevention and treatment, reduction of tobacco exposure during pregnancy, and increasing prenatal care and peer counseling.

INTERACTION OF NUTRITION AND INFECTION

The vicious circle of PEM, impaired immune response, increased infections, and decreased food intake has been well recognized since the seminal work of Scrimshaw and colleagues.[37] Several of the essential host defenses against infection, including epithelial and mucosal integrity, mucociliary clearance, gastric acid production, immunoglobulin synthesis, and lymphocyte differentiation, are impaired to variable degrees in PEM.[20,38,39] In addition, specific micronutrient deficiencies, particularly hypovitaminosis A, have a significant effect on immune function. Zinc deficiency is also associated with thymic impairment and is commonly seen in the tropics and in response to diarrheal disease. Zinc deficiency states impair gastrointestinal mucosal integrity, alter taste perception, and promote anorexia, which in itself can contribute to decreased oral intake.[40–44]

Other effects of PEM on the immune system include impaired differentiation and functioning of CD4+ cells and natural killer cells, reduced complement activity, and intracellular killing of bacteria. In response to stimuli, immunoglobulin A responses may be impaired as well, in terms of both magnitude of response and antibody affinity.[45]

The cumulative effect of mild but repeated infectious episodes on child growth has been well documented in a variety of settings in the developing world.[10,46–49] Figure 11-4 depicts the growth pattern of a child in the village of Santa Maria Cauque, Guatemala. Decreased dietary intake owing to anorexia or withholding of food by caregivers, excess nutrient losses, and increased nutrient requirements are the usual mechanisms by which infection aggravates nutritional status. In addition, the immune response to infection induces a catabolic state that may persist beyond the clinical course of the infectious episode, as shown by the pioneering studies of Beisel.[38] A novel mechanism for the nutrition–infection interaction was recently described in mice, consisting of mutation of the viral genome by sele-

nium deficiency in the host, resulting in enhanced or newly acquired virulence.[50]

The vicious circle of infection-impaired nutrition infection results in a significantly higher morbidity and mortality when an infection affects a malnourished host. This increase in mortality is more or less proportional to the severity of the underlying PEM. It is estimated that an impaired nutritional status contributes to 56% of deaths owing to infectious diseases in children.[18]

EARLY GROWTH PATTERNS AND ADULT DISEASES

The long-term health effects of transient nutritional events that occur at critical periods of development are receiving much attention. This phenomenon was first documented by Widdowson, who showed that a short-term food restriction in rats had dramatically different effects depending on when it occurred in the life cycle of the animal.[51] An early restriction caused a permanent change in food intake and thus in growth rate, whereas a restriction after weaning was quickly compensated by transient overeating and catch-up growth. The notion that early metabolic events can affect risk of disease much later in life has been termed "metabolic programming" and "imprinting" and is also known as the "Barker hypothesis." This British investigator presented a series of descriptive epidemiologic evidence linking respiratory, cardiovascular, and metabolic diseases in the adult with birth weight, indicating that lower birth weights increased the risk of acquiring those diseases in adulthood (Figure 11-5).[52–54] In spite of the descriptive nature of these studies, they inspired further research, most of them confirmatory of an effect of early nutrition status on the risk of disease in adulthood.[55–59] Most of these data were obtained in developed countries. Although there are few comparable studies in developing countries, some recent results seem to confirm that these conclusions are also valid in developing countries.[60] Nevertheless, the potential implications are clear, given the high proportion of LBW that exists in most developing countries.

One central proposition of the "fetal origins" hypothesis is that fetal adaptation to a limited energy supply (commonly owing to maternal malnutrition or placental dysfunction) is achieved at the expense of selective differentiation of certain metabolic pathways and physiologic functions. This differentiation, although it may have short-term benefits for survival, may become detrimental to health later in life, when energy supply is plentiful.[61] An

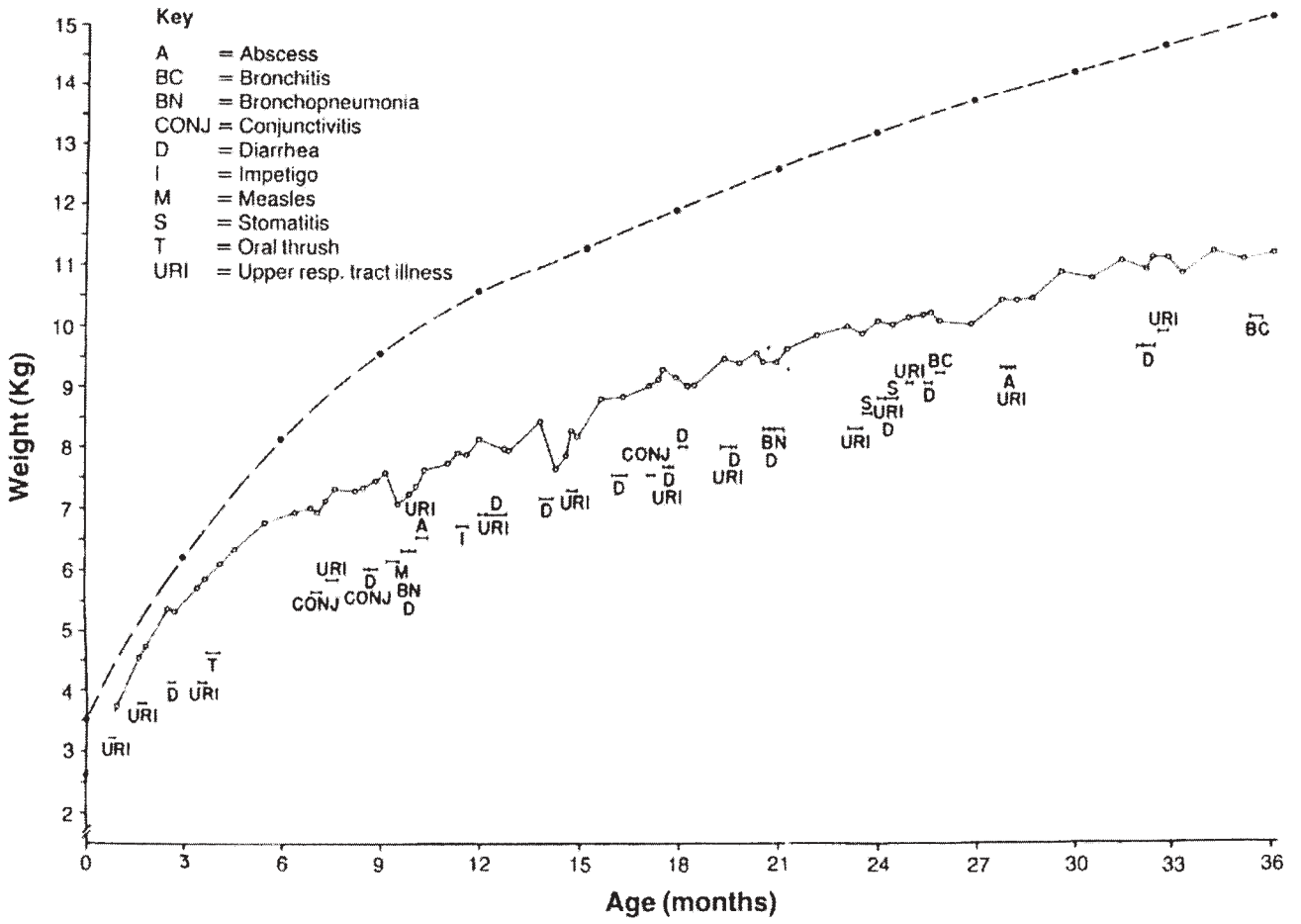

FIGURE 11-4 The impact of repeated infections on growth of a child in rural Guatemala. The *solid line* represents the weight of the child; the *broken line* is the 50th percentile of reference weight standards (Institute of Nutrition of Central America and Panama, 1956). *Horizontal lines* above disease codes indicate duration of each infectious episode. Reproduced with permission from Mata L.[10]

example would be the maximization of energy conservation pathways when there is a deficient maternal energy supply. This response, if irreversible, may result in an increased risk of obesity later in life, particularly in the face of unrestricted dietary energy availability.[59,62–65] Similar explanations have been put forth to explain hypertension risk based on restricted placental blood flow and diabetes risk based on impaired glucose supply,[66–71] as illustrated in Figure 11-5.[72]

Chronic maternal nutrient deprivation and fetal nutritional stress seen in children born in the developing world usually result in symmetric/proportional growth retardation. These may have a significantly different impact on the development of organ systems, lean tissue mass, subcutaneous fat deposition, and thus different health consequences.

There is evidence suggesting that the type and timing of feeding during the first 12 months of life may have an impact on the risk of adult disease. One study among Pima Indians, who exhibit widespread obesity as adults, showed that breast-feeding during 2 to 4 months significantly reduced the risk of obesity and of type 2 diabetes in adulthood.[73] Similarly, a cross-sectional study conducted in Germany by Von Kries and colleagues found a lower prevalence of obesity at age 5 years in children who had been breast-fed: 2.8% versus 4.5% in non–breast-fed infants.[74] Further analysis of the data suggested a dose-response relationship in breast-fed children, according to duration of breast-feeding.[74]

MICRONUTRIENT MALNUTRITION

Single- and multiple-nutrient deficiencies are widespread, affecting over 2 billion persons worldwide, mostly but not only in developing countries. Iron deficiency is considered the most prevalent single-nutrient deficiency, affecting more than 1 billion persons, followed by hypovitaminosis A and iodine. The global prevalence of deficiencies for vitamin A, iodine, and iron is presented in Table 11-3. Much less is known about the global prevalence of zinc, calcium, and folate deficiencies, but they are receiving increasing attention as potentially significant problems. Although multiple vitamin and mineral deficiencies are usually part of the malnutrition syndrome, the identification and treatment of individual micronutrient deficits are appealing because of their cost-effectiveness.[75]

Infectious diseases are an important contributor to micronutrient deficiencies. They increase gastrointestinal losses and may impair effective use of dietary sources as well. Conversely, micronutrient deficiencies may increase susceptibility to infection, as noted above.[76,77]

Vitamin A deficiency is one of the major single-nutrient deficiencies in the world. Every year there are about 10 million new cases of xerophthalmia in children. Indirect estimates indicate that vitamin A deficiency affects 130 million preschool-aged children worldwide, with 1 to 2 million dying each year.[78] Among the many factors contributing to this deficiency are low consumption of animal protein sources, reduced bioavailability and bioconversion of dietary provitamin A (betacarotene), and excess losses during episodes of acute infection.

Traditionally linked to blindness, the role of vitamin A deficiency on child mortality was demonstrated by the landmark studies of Sommer and colleagues in the early 1980s, showing that a single large dose of vitamin A resulted in a 30% reduction in child mortality.[79] Numerous subsequent trials in different countries have confirmed those findings, yielding, on average, a reduction of about 20% in mortality.[80–84] Supplementation is now national policy in several countries with endemic hypovitaminosis A. The effect of vitamin A on mortality is likely attributable to its positive effects on the integrity of epithelia, cell differentiation, and the immune system, thus reducing the severity of many infectious diseases, particularly gastrointestinal and respiratory.[82,85]

It has been postulated that micronutrient content of breast milk depends on maternal intake for some micronutrients but is independent of others. Vitamin A, B complex vitamins, and iodine are expressed in lower concentrations in the case of relative maternal deficiency but increase in response to maternal supplementation. Vitamin D, folate, zinc, iron, and calcium are maintained at relatively stable concentrations in breast milk, even in maternal deficiency states. The former category has been labeled as priority I, with the latter as priority II in the literature. The data to date on these findings are limited and are contradicted across different studies.

Multiple-nutrient deficiency is receiving increasing attention, particularly during reproductive age. The role of folic acid on pregnancy is well recognized in developed countries, but there is less information for developing countries, where populations are likely to present it combined with other micronutrient deficiencies. Several multiple micronutrient trials are currently under way, with fetal-neonatal growth and development and maternal mortality as major outcome variables.

As a corollary of the early clinical trials, in which micronutrient supplements (usually as capsules) were distributed in the study population, several countries have implemented distribution programs at the regional or national level. These can be mass distributions or can target at-risk groups. Although, in some cases, this has resulted in significant reductions in child mortality, supplement distribution is regarded as a temporary

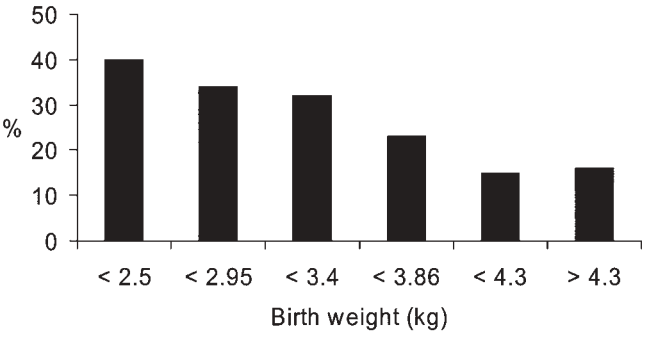

FIGURE 11-5 Association of birth weight with risk of impaired glucose tolerance and non–insulin-dependent diabetes in adulthood. Adapted from Phipps K.[72]

TABLE 11-3 Extent of the Major Micronutrient Deficiencies in Different World Regions (in millions of persons)

	Iodine		*Vitamin A*		
Region	*At Risk*	*Affected*	*At Risk*	*Affected*	*Iron**
World	1,005	225	190	13.8	2,150
Europe	82	14	—	—	27
Eastern Mediterranean	33	12	13	1.0	149
Americas	55	30	2	0.1	94
South and Southeast Asia	280	100	138	10.0	616
Africa	150	39	18	1.3	206
Western Pacific and China	405	30	19	1.4	1,058

Adapted from Second report on the world nutrition situation. Vol. 1: global and regional results. Geneva: World Health Organization; 1992.
*With and without anemia.

approach.[75,86] The ultimate goal would be to ensure the availability of foods of enough quality and quantity to supply the requirements for all micronutrients. Nevertheless, given the complexity of factors affecting food availability and intake in different populations, micronutrient supplementation will continue to be a cost-effective temporary strategy for the immediate future.

Food fortification is a powerful approach to combat micronutrient malnutrition. Although its implementation and sustainability are more complex than for supplement distribution, it can take advantage of the market forces and food distribution channels, requiring little direct involvement from the target population. A successful fortification program depends on a variety of conditions. First, the food item to be fortified should already be consumed by the majority of the population. Second, the fortification process should not change the properties of the original product to avoid rejection by consumers. Third, the fortified item should not be priced significantly higher than the original product. Finally, an inexpensive and effective monitoring and quality control mechanism should be available.[86] A number of countries have implemented fortification programs with varied degrees of success. Perhaps one of the generally successful programs is salt iodization. This intervention has reduced the incidence and prevalence of iodine deficiency–related diseases, including cognitive and mental impairment, growth failure, and cretinism on a global scale. Impediments to the use of iodinated salt may occur when in direct competition with local salt production, as in mountainous regions, and when smaller markets and more remote populations impair distribution. The choice of a preferred approach for the control of micronutrient deficiencies depends on several factors. These include the severity and extent of the problem, cultural factors, and linkage to existing health programs and resources.

On the government level, agricultural policies can provide incentive to rotate crops and to enhance the diversity and yield of foods grown and available. Agricultural technology, selective crop breeding, and transfer of technology may aid in increasing the micronutrient content of particular foods. Subsidization of certain seed types and of fertilizers may aid in encouraging the horticulture of certain crops as well. Development of appropriate preservation modalities and transportation infrastructure is also key to public policy.

The emergence of subsistence horticulture has also received much attention and allows for considerable food quantities for individual household consumption and its control, as well as providing a potential source for income supplementation through sales of surplus. Successful implementation of this approach in Taiwan is encouraging.[75]

Food-based strategies need to consider economic sustainability, which is linked to cost and effectiveness. Sustainability is also reliant on the education of the population and to eventual behavior change to accommodate changes in dietary intake into their lifestyle. Initial political commitment is required to effect mass public awareness and education campaigns, which in themselves need to be multifaceted in their approach to ensure success. Technical adaptability, both to short-term seasonal and climactic changes and to long-term predictable/eventual issues in water supply, waterlogging, and salinity, must be taken into account in the initial planning stages. Integration of these approaches and establishment of food security can aid in effecting behavior change in a population and render it somewhat resistant to political changes/instability from a health perspective.

NUTRITION TRANSITION

The dramatic advances in communications and transportation and the globalization of economic markets are promoting rapid changes in diet and lifestyle in developing countries. This phenomenon, often termed the nutrition transition, is a key factor in the changing disease patterns for developing countries. Projections from data for the past decade indicate that by the year 2020, chronic, noncommunicable diseases will account for 70% of the disease burden in these transitional countries.[87] This, in turn, will impose tremendous demands on the health care system of these countries, currently geared predominantly toward maternal and child care. A detailed analysis of the nutrition transition can be found in a recent book by Caballero and Popkin.[26]

Urbanization, which occurs at a faster pace in the developing world, is having a profound effect on dietary patterns and lifestyle. The UN predicts that almost 90% of the projected population growth for the next 20 years will

occur in urban areas of the developing world (Figure 11-6). This, the absolute number of persons whose diet and lifestyle will be modulated by the urban environment, will increase dramatically.

The urban environment has two major effects on disease risk. First, consumption of processed foods, usually having a higher fat content, increases substantially. Second, daily energy expenditure decreases significantly: intense physical labor of field work is replaced by sedentary, low-energy work of service jobs or automated manufacturing.[88] Television viewing is also a well-documented factor in increasing sedentary time in adults and adolescents. Thus, an increased energy intake and a reduced energy output are likely to result in weight gain and obesity. In addition, sedentary lifestyle per se carries an increased risk for cardiovascular diseases.[89] The impact of urban dwelling on obesity prevalence has been documented for several regions in the developing world. Figure 11-7 presents obesity data for several Latin American countries reported by Martorell and colleagues.[90]

In spite of the recognized diversity of the transition in different countries, some general trends can be suggested. In most cases, the diet tends to increase in its animal protein, saturated fat, and total fat content. Consumption of processed foods also increases.[91] Unlike developed countries, food price exhibits strong elasticity, thus linking dietary patterns to market forces and socioeconomic status.[89]

A few countries have begun to consider the long-term implications of their socioeconomic changes on the health of the population. Most notably, Brazil has pioneered the linking of federal subsidies to diet quality, particularly in schools. It has also launched a program to increase physical activity throughout the day, Agita Sao Paulo, which has become a model for a WHO initiative.[92,93] Other countries, such as China, are testing regional programs to promote healthful eating and lifestyle, particularly in the urban population. There are some comprehensive experiences in preventive interventions in developed countries that can provide insight into effective approaches. Among these, the North Karelia study is well recognized as a successful model of integration of public and private efforts to use market forces, the media, and consumer education to improve dietary patterns.[94]

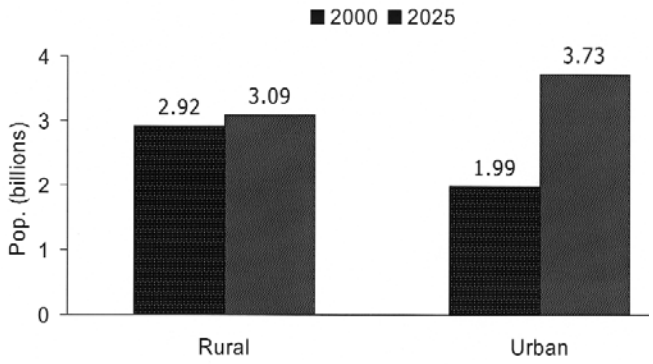

FIGURE 11-6 Actual and projected population growth, 2000 and 2025. Relative population increases in urban and rural areas. Adapted from World urbanization prospects: the 2001 revision data tables and highlights. New York: Population Division, Department of Economic and Social Affairs, United Nations Secretariat; 2002.

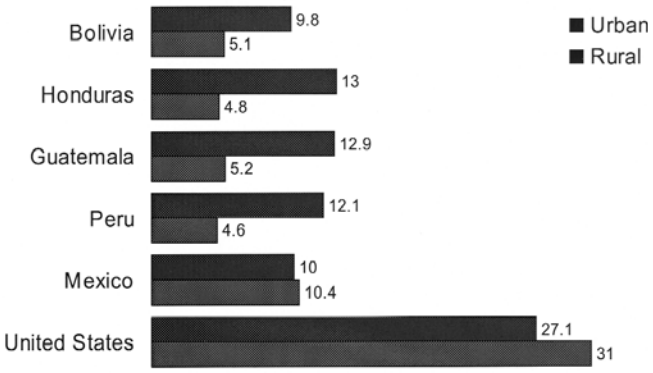

FIGURE 11-7 Comparison of obesity (body mass index ≥ 30) prevalence in urban and rural areas of selected countries in Latin America and in the United States. Adapted from Martorell R et al.[90]

CONCLUSIONS

This chapter has summarized current global trends in child survival and health, emphasizing their close links with nutritional status. Positive trends in child survival are certainly encouraging, but there is still much to be done to ensure that those children who survive past their first year of life have adequate access to food, are protected from infections, and have the opportunity to grow and develop into healthy adults. This task is certainly more challenging and complex than preventing early death: they require lifelong health care interventions and important improvements in social and economic equity. In spite of these challenges, the success of several programs aimed at reducing malnutrition, controlling micronutrient deficiencies, improving food security, and expanding immunization coverage is encouraging. Community involvement, empowerment of women, and recognition of unique local social, cultural, and economic conditions all seem to be key ingredients for success.

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CHAPTER 12

NUTRITIONAL EPIDEMIOLOGY

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Nutritional epidemiology is the study of relationships between diet and disease. Although the effects of nutritional deficiencies have been recognized for centuries, the chemical structures of compounds responsible for these deficiencies have been determined only this past century. Globally, the four most commonly recognized deficiencies in children include protein-calorie malnutrition and iron, iodine, and vitamin A deficiencies. The importance of folate deficiency has also become apparent in the past two decades. Interventions have evolved beyond the treatment of deficiencies to the reduction of disease risk (eg, food fortification with iodine, iron, and folate; zinc and vitamin A supplementation programs; and breastfeeding campaigns). More recently, the relationship between nutrition and disease has been expanded from that of deficiency to that of excess; the concept of *nutrition transition* has been developed. Countries undergoing modernization and westernization are faced with diseases associated with both under- and overnutrition. Globally, overnutrition and related complications have become the most important nutritional problem.

In contrast to those of most adults, children's needs vary with time as they grow and mature; therefore, assessment of pediatric diet, nutrition, and associated diseases is more challenging than that of adults. The dietary choices of children depend on their food preferences and on parental choice and control, food availability and cost, peer pressure, and advertising. Young children's ability to report their dietary intake is limited; thus, dietary assessment often requires a surrogate reporter. Despite these differences in approaches to assessment, current national surveys conducted in the United States have shown overall similar dietary trends in adults and children aged 2 to 18 years.

The development of techniques to assess diet and breastfeeding, the refinement of anthropometric methods, and the identification of biochemical indicators of diet (biomarkers) specific to population groups have greatly facilitated the field of nutritional epidemiology. Information from basic research has been used at the population level, and new questions in epidemiologic studies have been brought to the laboratory bench and the clinical setting. Methods used to investigate the relationships among diet, nutrition, and diseases include descriptive, analytic, and experimental studies. The development of hypotheses often comes from ecologic observations, and prevalence rates and diet–biochemical relationships are typically based on cross-sectional studies. The assessment of etiologic relationships is usually performed using case-control studies and prospective studies, which are typically expensive and of long duration. Each type of study has its own benefits and pitfalls. Although the best evidence for causation comes from experimental studies such as randomized, double-blind trials, in many situations it is not feasible to randomly assign subjects to diet for long periods of time.

In this overview of nutritional epidemiology, we briefly describe issues and approaches for assessing dietary intake and nutritional status, the application of different study designs, and considerations in the analysis and interpretation of data. Because of its vital importance to child health, we use the relationship between folate intake and incidence of neural tube defects to illustrate various approaches in nutritional epidemiology.

ASSESSMENT OF DIETARY INTAKE

Diet exposure can be measured either in terms of foods or as nutrient and nonnutrient components. The power to detect an association between diet and disease is usually greater when using nutrients (from all foods) rather than one food or food group to represent diet, and interpretation of associations is easier to explain biologically. However, food analyses are used frequently because people eat foods, not nutrients, and food can reflect the combined effects of multiple nutrients and differences in bioavailability of nutrients. Each dietary representation has its benefits and weaknesses, and the use of both methods provides the greatest insight.

An association between a food and disease can lead to the identification of a substance that is responsible for disease or its prevention. A classic example is that of scurvy. As recorded by Hippocrates, symptoms of scurvy were already recognized in ancient Egypt, Greece, and Rome. Later, a tree extract provided by North American Natives cured scurvy among members of an expedition led by Cartier in the sixteenth century. Lind, in his *Treatise of the Scurvy* (1753),[1] documented that lemons and oranges also cured subjects with scurvy. However, the relationship between scurvy and vitamin C deficiency was made much later. Celiac disease

provides another example.[2] Although descriptions of symptoms compatible with celiac disease were recorded in antiquity, Samuel Gee (1888) defined the classic symptoms of celiac disease in the mid-nineteenth century. These symptoms included chronic diarrhea, abdominal distention, and poor weight gain several months after the introduction of solid foods. The relationship between certain types of cereals and celiac disease was determined when the typical symptoms of pediatric celiac disease disappeared during the food shortages of World War II and relapsed after cereal supplies were restored.[3] Gluten, the major component of cereal proteins, was implicated.[4]

Intake of nutrients or foods is typically interrelated, which can result in difficulties in interpreting findings. For example, an inverse relationship exists between dietary fat and fiber intake among children.[5] Therefore, associations between food and disease could be attributable to foods either high in fiber or low in fat, or both. Sometimes multivariate analysis can be used to disentangle these associations. To minimize interrelations, investigators sometimes use food groups or account for the contributions of nutrient intake from various food groups. Also, "pattern analysis,"[6] based on factor or cluster analysis, groups together subjects with similar intakes of food. These patterns can then be evaluated in relation to disease risk.

Dietary Assessment Methods

Methods to measure dietary intake include 24-hour recall, food records, food frequency questionnaires (FFQs), diet histories, and observation (Table 12-1) The validity and the reliability of dietary intake methods among 2- to 18-year-old children and adolescents from industrialized countries have been reviewed elsewhere.[7–9] Most validation studies have used observation, diet records, or repeated 24-hour recalls as reference standards. Assuming energy balance, the doubly labeled water method is considered the best method for validation of energy intake using traditional dietary assessment methods.

The doubly labeled water method is the first truly noninvasive means to measure total daily energy expenditure accurately in free-living humans and is based on measurement of CO_2 using a nonradioactive isotope. The technique was introduced in the 1950s, but applications started being made among adults in the 1980s. The total energy expenditure obtained from the doubly labeled water method can be accurate,[10] but large interlaboratory variability has been found in a blinded evaluation of multiple laboratories.[11] Also, the reproducibility of this method at an interval of several months or more has not been evaluated in free-living populations. Overall, studies show that current dietary assessment methods provide better estimates for the composition of the diet—after adjusting for energy intake—rather than absolute intake of nutrients or energy and for a group rather than individuals.[12,13]

24-Hour Recall The 24-hour recall method is based on an interview, typically conducted by a trained dietary interviewer. It provides appropriate mean estimations for groups but not for individuals because of large day-to-day variation in individual intakes. Surrogate reporters are required for children who are young (preteen),[9,14] mentally retarded, or too sick to respond by themselves. Reporting problems can arise if parents spend less time with their children, for example, when they work outside of the household or have a large family.[13]

Twenty-four-hour recalls by children aged 2 to 18 years, or by surrogate reporters, have been compared to reference standards (observations, food records, and food chemical analysis) and summarized elsewhere.[8] In their review, McPherson and colleagues showed correlation coefficients (r values) of .2 to .9 for energy intake and .4 to .6 for most nutrients compared with the standard methods.[8] The correlation coefficients for nutrients improved after adjusting for energy intake. Compared with the standard method, recalls tended to either over- or underestimate energy intake.[8] The extent of underreporting was greater in adolescents than in all other age groups.[15,16] Food eaten varied from 68 to 84% when diet recall was compared with the validation standard.[8] The validity of the dietary recall improved when individual meals were compared rather than using 24-hour periods. Baxter and colleagues found that the accuracy of dietary recall did not vary with gender or ethnicity.[17]

The number of days for which dietary recording is necessary to accurately identify specific nutrient intakes in children has been calculated by determining the day-to-day intraindividual variation in dietary intake data for infants 4 to 6 months of age[18] and preschool children.[19] Quandt obtained dietary information using 24-hour recall among 28 mothers for their infants' diets on four random days over approximately 1 month.[18] In contrast to what is the case with adults, investigators found no effect of day of the week on nutrient variation in this age group. Interindi-

TABLE 12-1 Advantages and Disadvantages of Dietary Assessment Methods

Method	*Recording Time*	*Period*	*Interviewer Training*	*Subject Literacy*	*Affects Diet Intake*	*Memory Based*	*Subject Burden*	*Food Description*	*Automated Procedure*	*Budget*
Recall	Short	Defined	High	No	No	Yes	No	Yes	Yes	Expensive
Food record	Defined	Defined	High	Yes	Yes	No	Yes	Yes	Yes	Expensive
Food frequency	Short	Long	None	Yes	No	Yes	Yes	No (ranks)	Yes	Relatively inexpensive
Histories	Long	Imprecise	High	No	No	Yes	Yes	Yes	No	Expensive
Observation	Long	Defined	High	No	No	No	No	Yes	No	Expensive

vidual variation exceeded intraindividual variation for all nutrients except vitamin C.

Stein and colleagues measured intraindividual day-to-day variation and tracking of nutrient intakes in a longitudinal study of 181 preschool children (93% Hispanic) aged 45 to 60 months recruited through a hospital-based pediatrics practice in New York.[19] In that study, 24-hour dietary recalls were administered four times in the first year and three times in the third year to children's mothers. Although the reliability of estimates (intraclass correlation coefficients) of energy and nine nutrients obtained from a single administration of the dietary recall ranged from .15 to .38, the authors were able to show substantial tracking of underlying diets among preschool children over a 19-month period, despite day-to-day variation.

Fisher and colleagues showed that body weight also influenced the accuracy of dietary reports made by children and their parents in a sample of 146 children aged 4 to 11 years using the doubly labeled water method to validate the energy intake measured using 24-hour recalls.[20]

Food Record The food record method consists of a detailed diary of foods consumed over one or more days.[21] It provides appropriate mean values for groups but not for individuals, unless the number of days is substantial. The information is collected at the time of consumption so that memory is not a limitation. However, assessment is imprecise when dining out and can interfere with dietary intake. McPherson and colleagues pointed out that there were no specific validation studies of portion size collection and none of the studies reviewed presented results on validity in reporting food items.[8] Underreporting in children's adult-assisted food records increased with age (9 to 12 years old) when energy expenditure was measured with doubly labeled water.[22] In that study, the investigators found differences in reporting by race but not by gender. African American children were significantly more likely to underreport energy intake than were white children.

Black and colleagues studied the day-to-day variation in energy intake of 48 breast-fed infants using 4-day diet records at monthly intervals from age 1.5 to 7.5 months and of 37 fully weaned infants studied at 10, 12, 15, and 18 months of age.[23] Dietary variation was lowest in fully breast-fed infants, increased as solids were introduced, and approached values found for adults in the 18-month-old infants. Nelson and colleagues showed that with the exception of ascorbic acid, intakes were the lowest in the youngest age groups (less than 36 months of age) and rose through childhood to peak in adolescence and young adulthood.[23] In contrast to the homogeneity of the intragroup coefficient of variation (CV_w) of specific nutrients among children and adults, the intergroup coefficient of variation (CV_b) varied largely by age group and gender, resulting in variance ratios that were relatively low for toddlers, high for children aged 5 to 17 years, and intermediate for adults. These authors found that up to 4 years of age, 7 days were adequate to estimate all macronutrients except type of fat. For animal protein, the number of days required to achieve a level of accuracy of ranking at and above .9 was 18 days (Table 12-2).

As determined by the doubly labeled water method, underreporting of energy intakes on children's assisted food records increased with age.[8,24] Using that same reference method, other investigators have also shown that estimations by food record can be made at the group, but not individual, level. O'Connor compared measurements of energy intake from diet records and total energy expenditure using the doubly labeled water method in 47 children aged 6 to 9 years.[25] Although the mean energy intake and the total energy expenditure were not significantly different, the authors showed no significant correlation between energy intake and total energy expenditure. Findings of this study confirm the notion that energy intake assessed by diet records is not representative of total energy expenditure at the individual level but that 3-day food records could be used to estimate energy intake at the population level. Even longer periods of dietary records (eg, 7 days) compared to the doubly labeled water method can underestimate energy intake, especially in overweight adolescents.[26]

Food Frequency Questionnaire In contrast to food records and 24-hour recalls, food frequency questionnaires are relatively inexpensive and aim to represent long-term intake. The food frequency method relies on a food list, and participants are asked to report the frequency of consumption of each food item; the design of these questionnaires is described in detail elsewhere.[13,9] FFQs can be used to rank respondents by levels of intake. The period of time covered by the FFQ can be weeks, months, or years, and the questionnaires can be classified as quantitative (ie, food models shown for usual portion size), semiquantitative (ie, standard serving size used), or nonquantitative (only frequency assessed). Overestimation of intakes of energy and other nutrients was observed in studies using a validation standard (diet record or repeated 24-hour recall) when adults' rather than children's portion size were used in children studies.[8]

When multiple 24-hour recalls, rather than just one, were used as the validation standard, investigators observed similar estimates for energy intake obtained with the 24-hour recalls and the FFQ, referred to as the Youth-Adolescent Food Frequency Questionnaire.[9] In that study,

TABLE 12-2 Number of Days Dietary Records Are Required for a Correlation Coefficient of .9 between Observed and True Intakes

	Days for Children 1 to 4 Years Old	*Days for Boys 5 to 15 Years Old*	*Days for Girls 5 to 15 Years Old*
Protein	5	6	15
Animal protein	6	7	18
Fat	7	8	12
Saturated	8	6	12
Polyunsaturated	15	18	28
Monounsaturated	11	9	14
Cholesterol	27	18	21
Carbohydrate	6	10	9
Folate	6	9	22

Adapted from Nelson M et al.[23]

further adjustment for intraindividual variation in recalls improved the nutrient correlation coefficients. Inner-city sixth and seventh grade students demonstrated the ability to provide valid estimates of intake of calories and a variety of nutrients over 1 year. However, children in the fourth and fifth grades in inner-city schools experienced difficulties in completing the same FFQ.[27] This finding shows that surrogates are needed in older children from disadvantaged populations. Blum and colleagues recently also validated the use of a shortened version of the Youth-Adolescent FFQ in Caucasian and Native American children ages 1 to 5 years, with a parent or guardian filling out the questionnaire.[28] The average correlation was similar to that found in validation studies among adolescents and adults.

In contrast to the accuracy of repeated 24-hour recalls[29] and weighed diet records,[16] when the doubly labeled water method was used as a standard, energy intake was overestimated by 50% in infants when FFQs were used.[30] Using the same doubly labeled water method as a standard in a group of older children (9 to 16 years old), energy intake obtained from the Youth-Adolescent FFQ was underestimated. However, the authors showed that despite a wide range of variability in reporting accuracy across adiposity status and gender, this method estimated the mean energy intake of a group with appropriate accuracy.[31]

Diet History Diet history provides information on typical meals, food intakes, and preparation of food using a questionnaire, an interview, or both. This method is more qualitative than FFQs; the interview can take between 1 and 2 hours. Studies in children have shown overestimation of nutrients and energy intakes in the first interview compared with overestimations in subsequent interviews.[32] In addition, Livingstone and colleagues validated the energy intake assessed by 7-day weighted food records and diet histories with that obtained using the doubly labeled water method in 78 subjects aged 3 to 18 years.[16] Food records underestimated energy intake, whereas diet histories tended to overestimate energy intake in most age groups if it is assumed that the results from the doubly labeled water method were without error.[11]

Observation Trained personnel can observe patients in a variety of settings, especially schools. Food intake can be measured once or multiple times. The method is intrusive and is impractical in large studies. However, this method is often used as a validation standard for school-aged children and is reliable.[33]

Special Case for Dietary Assessment: Breast-Feeding

Studies relating breastfeeding to illness are difficult to evaluate because of the use of a variety of definitions for breastfeeding,[34,35] selection bias,[36,37] confounding,[38] and reverse causality.[37] As reviewed below, few studies have addressed the reproducibility and validity of breastfeeding assessment methods. Several techniques have been used to evaluate the intake of breast milk among breastfeeding children. The doubly labeled water method is considered the gold standard for evaluating energy intake in breast-fed children.[39,40] Other techniques include test weighing and the evaluation of the duration and frequency of breastfeeding using observation, recall, and record studies.

Doubly Labeled Water Technique The use of doubly labeled water has been validated against periodic open circuit respiratory gas exchange in infants.[41] Prentice and colleagues first showed that the energy requirements of infants were lower than recommended intakes, based on the combination of energy deposited during growth and total energy expenditure obtained by the doubly labeled water technique in 355 healthy infants aged up to 3 years.[42] Butte and colleagues conducted a validation study of conventional weighing techniques to estimate milk intake in breast-fed and formula-fed infants using the doubly labeled water method.[40] They found a mean difference between methods of 14% (106 g/day) in breast-fed infants and 8% (70 g/day) in formula-fed infants. Based on this method, these researchers also showed that energy requirements of infants and toddlers were 80% of current recommendations and were lower in breast-fed than in formula-fed infants.[39]

Test-Weighing Techniques Conventional test-weighing techniques include weighing either infants or mothers before and after a known or unknown amount of breast milk intake. Brown and colleagues conducted validation studies of different test-weighing techniques among 64 infants before and after the consumption of a known amount of milk.[43] The measured bottle weight corresponded to 94.9 ± 13.2% of the estimated change in weight of the infant. These techniques allowed good estimates of breast milk consumption to be made, noting that the average amount of breast milk received declined with time from 632 g/day for the 5 to 12 month olds to 368 g/day for the 24 to 30 month olds.[44] Because of the intrusive nature of test weighing, it generally will not be directly useful in epidemiologic studies, but it could serve as a standard in validation studies of other methods.

Observation, Recalls, and Questionnaires Piwoz and colleagues conducted a validation study of breastfeeding recall using observation as the reference standard.[45] He obtained 1,574 single-day dietary intakes (12-hour observations plus 12-hour recall) and mothers' monthly reports of usual feeding practices. They demonstrated that single-day studies produced a different view of feeding practices compared to the mothers' reports. Exclusive breastfeeding was observed 25% more frequently among infants younger than 4 months than was self-reported. In contrast, self-reported formula consumption was 30% more frequent compared to observation data. Differences between reported and observed practices were related to mothers' age and education, number of children younger than 5 years in the home, and infant age and disease on the observation day. The investigators concluded that consumption of breast milk or formula during the past 24 hours should not be used alone as the basis for classifying infant feeding practices in surveys.

Most epidemiologic studies have used recalled or observed data to provide information on breastfeeding. Investigators have used information on the duration, frequency, and minutes of breastfeeding rather than test-weighting or isotopic methods to evaluate the relationship between breastfeeding and outcome (ie, growth and disease), and some, but not all, studies have gathered information on additional sources of foods beside breastfeeding. For example, Zeitlin and Ahmed examined the relationship among breastfeeding, total energy intake, and growth of infants in Bangladesh using observation (minutes of breastfeeding) and 24-hour recall to estimate breast milk and other food intake in infants and children aged 5 to 23 months.[46] Beaudry and colleagues used a self-administered standardized questionnaire mailed to every mother 1 week before infants reached 6 months of age to evaluate past breastfeeding and weaning behaviors.[47] Some authors suggested that clarification of the intensity and duration of breastfeeding might help detect dose-response effects of breastfeeding.[35]

ASSESSMENT OF GROWTH AND BODY COMPOSITION

The focus of many studies in nutritional epidemiology is body weight, but recent techniques have evolved to better characterize changes in body weight in terms of body composition. Chapter 4, "Body Composition and Growth," describes the theory and practice of many of these techniques, as well as what is known about developmental changes in body composition.

Because nutritional epidemiologic studies in pediatrics often employ a variety of body composition techniques, the relationships among them are of interest. Densitometry is typically considered the gold standard for a two-compartment model of fat and nonfatty tissue in adults and depends on measurements of total body density. Despite the lack of data on fat and fat-free mass densities in children,[48] densitometry has been compared with anthropometric measurements involving weight, height, and skinfold thickness measurements (Table 12-3). Likewise, anthropometric data based on weight and height indices have been compared with skinfold thickness measurements (Table 12-4).

Data on weight and height were also compared more recently not only to measurement of skinfold thickness but also to dual-energy x-ray absorptiometry (DXA) among children aged 2 to 19 years.[49] Compared to weight for height and the Röhrer's index (Wt/Ht^3), the Quetelet index, or body mass index (BMI; Wt/Ht^2), was identified as the better predictor of overweight (but not underweight) when average skinfold thickness measurements were used as standard. BMI was also shown to perform better than the Röhrer index when the standard for percent body fat or total fat mass was estimated using DXA in children aged 3 to 19 years. No differences were found between BMI and weight for height in detecting overweight or underweight.

As reported in Table 12-5, anthropometric measurements and bioelectric impedance are most useful in large-scale studies. Although BMI does not directly measure body fat, it is typically used to evaluate adiposity in adults and has been recognized as a useful predictor of adiposity in children and adolescents, which, in turn, also predicts risks for present or future medical complications of obesity.[50] The weight indices are considered adequate when the correlation with percent body fat is high and the correlation with height is low. Although there is no perfect weight index of over- and underweight—irrespective of height and width—BMI turned out to be a reasonable index from childhood to adulthood.[51] Transformation of weight and height is also discussed in Gasser and colleagues' review.[51] Frontini and colleagues further demonstrated that the association of weight to height index was not superior to BMI as an indicator of adiposity compared to skinfold thickness measurements as reference standards and related cardiovascular risk factors during childhood in the Bogalusa Study.[52]

Self-reported weight and height among adults is frequently used in nutritional epidemiology. In contrast to the findings in adult studies, results from adolescents aged 12 to 17 years in the Third National Health and Nutrition Examination Survey (NHANES III) showed that self-reported weights were missing in 40% of 12 year olds and 25% of 13 year olds. Based on their findings, the investigators did not recommend the use of self-reported weight and height as proxy measures of weight and height among adolescents aged less than 14 years.[53] In contrast to these findings, Strauss considered that the *available* self-reported weights and heights among 12 to 16 year olds in NHANES III were reliable (n = 1,657 of 1,932).[54] In that study, correlations between self-reported weight and actual weight ranged between .87 and .94, depending on gender or race. Another recent study of first and fourth grade students in Japan showed that the child's weight and height obtained from parents was accurate.[55] The renewed interest in body composition, combined with the awareness of the growing obesity epidemic, has resulted in the need for improved reference data for body composition (see Chapter 55, "Obesity").

BIOMARKERS OF DIETARY INTAKE

Biochemical indicators (biomarkers) of dietary intake—blood, urine, stool, and tissue nutrients—can reflect nutrient intake. Biomarkers are important in epidemiology because they can be used as surrogates for dietary intake when the nutrient content in a food varies greatly. They can also be useful as determinants of disease, even if they reflect intake poorly; serum cholesterol provides a good example. Biomarkers can also be used to validate nutrient intake assessed by dietary assessment methods. When biomarkers need to represent the intake of a specific nutrient in an epidemiologic study, the most important requirements are its sensitivity to changes in dietary intake and its ability to reflect the cumulative average intake over an extended period of time.[13]

Sensitivity of a Biomarker

The sensitivity of a biomarker depends on how well the biomarker reflects true nutrient intake, which can vary with the chemical form of the nutrient. For example, the bioavailability is lower for dietary folate than for supplemental folate, so serum levels will differ with the form of folate. Serum sodium is an example of a biochemical measure biomarker that is not

TABLE 12-3 Correlations between Anthropometric Measurements and Total Body Densitometry

Author(s)	*Sample*	*Weight*	*Height*	*Weight/ Height*	*Weight/ Height²*	*Weight/ Height³*	*Triceps Skinfold*	*Subscapular Skinfold*
Parizkova*[99]	*N* = 62 white girls 12–16 yr	—	—	—	—	—	– .74	– .80
Seltzer et al†[100]	*N* = 32 obese white girls 12–18 yr	– .53	– .23	—	—	—	– .69	– .59
Young et al‡[101]	*N* = 102 white girls 9–16 yr	– .36	—	—	—	—	– .73	—
	N = 41 prepubertal	– .75	—	—	—	—	– .82	—
	N = 15 pubertal	– .69	—	—	—	—	– .78	—
	N = 46 postpubertal	– .42	—	—	—	—	– .70	—
Harsha et al[102]	White, 6–16 yr; *n* = 79 boys, *n* = 64 girls	– .17/– .52	.31/.03	—	—	—	– .76/–.75	– .75/–.80
	Black, 6–16 yr; *n* = 49 boys, *n* = 50 girls	– .36/– .59	.25/.14	—	—	—	– .82/–.82	– .75/–.87
	N = 242 boys and girls 6–16 yr	– .32	.18	—	—	—	– .81	– .76
Roche et al[103]	*N* = 68 boys, *n* = 49 girls 6–12 yr	.74/.74	—	.75/.62	.90/.84	.66/.55	.81/.74	.84/.80
	N = 63 boys, *n*= 81 girls 13–17 yr	.65/.88	—	.91/.87	.88/.89	.91/.82	.93/.86	.94/.87
Maynard et al[104]	*N* = 35 boys, *n*= 39 girls 8 yr	—	.27/.34	—	.93/.67	—	—	—
	N = 49 boys, *n* = 56 girls 9 yr	—	.27/.46	—	.86/.74	—	—	—
	N = 79 boys, *n* = 63 girls 10 yr	—	.46/.43	—	.90/.79	—	—	—
	N = 90 boys, *n* = 79 girls 11 yr	—	.51/.42	—	.94/.78	—	—	—
	N = 103 boys, *n* = 86 girls 12 yr	—	.44/.28	—	.90/.85	—	—	—
	N = 103 boys, *n* = 81 girls 13 yr	—	.39/.39	—	.89/.82	—	—	—
	N = 101 boys, *n* = 74 girls 14 yr	—	.30/.16	—	.86/.84	—	—	—
	N = 94 boys, *n* = 80 girls 15 yr	—	.13/.01	—	.83/.88	—	—	—
	N = 91 boys, *n* = 87 girls 16 yr	—	.22/.19	—	.83/.85	—	—	—
	N = 90 boys, *n* = 83 girls 17 yr	—	– .09/.07	—	.90/.90	—	—	—
	N = 100 boys, *n* = 85 girls 18 yr	—	.03/.11	—	.84/.85	—	—	—

*The relationship between body density and triceps skinfold for the nonobese adolescents was [body density = 1.128 – .78 log triceps skinfold].
†Arm circumference had the highest correlation with both weight (r = .90) and bone density (r = – .63). The authors showed body densities for their subjects similar to those shown by previous authors estimated from skinfold thickness measures [bone density = 1.1516 – .09256 log triceps skinfold] and comparable to real body density measurements.
‡Total skinfolds provided (at least 12 sites from the chin to the knee). Overall, correlation for triceps was – .79 and – .72 for subscapular.
Of note, the correlation coefficients between predictors of adiposity and total body densitometry tend to be positive when authors have transformed body density measurements using an equation to estimate fat (as in Maynard or Roche) but tend to be negative when using direct measurements of hydrodensitometry (as in Horsha). In the Bogalusa Study, the authors used W/H^p rather than W/H^3. They calculated the optimal "p" for each category of gender, race, and age because they wanted to obtain an index that was independent of H during growth and early life development [log(W) = a + p log(H) + e].

sensitive to intake because it is tightly regulated to remain within a specific range. The 24-hour urinary measurement of 3-methylhistidine is an example of a good biomarker for animal protein intake (r = .77).[56]

Period covered by a biomarker

Studies of chronic diseases require biomarkers that are less susceptible to short-term fluctuations. For example, serum folate is sensitive to changes in intake and modestly sensi-

TABLE 12-4 Correlations of Body Mass Indices with Skinfold Thickness Measures in Large Studies

Study	*Sample*	*Skinfold Thickness*	*W/H*	*W/H²*	*W/H³*
Forsyth County study[1]	*N* = 832 5–12yr boys	Triceps	.72	.81	.81
	N = 835 5–12yr girls		.73	.80	.64
	N = 66 boys/*n* = 80 girls 5yr		–	.24/.68	–
	N = 98 boys/*n* = 86 girls 6yr		–	.53/.71	–
	N = 107 boys/*n* = 121 girls 7yr		–	.67/.66	–
	N = 110 boys/*n* = 116 girls 8yr		–	.79/.75	–
	N = 137 boys/*n* = 144 girls 9yr		–	.78/.84	–
	N = 110 boys/*n* = 88 girls 10yr		–	.82/.81	–
	N = 89 boys/*n* = 83 girls 11yr		–	.89/.86	–
	N = 115 boys/*n* = 118 girls 12yr		–	.79/.81	–
Bogalusa Study[52]	*N* = 821 white boys 4–5yr	Triceps/subscapular	–	.53/.52	.53/.51
	N = 523 black boys 4–5ry		–	.50/.44	.51/.44
	N = 838 white girls 4–5yr		–	.61/.71	.60/.67
	N = 499 black girls 4–5yr		–	.63/.60	.63/.56
	N = 1570 white boys 12–13yr		–	.72/.86	.76/.81
	N = 925 black boys 12–13yr		–	.64/.81	.67/.71
	N = 1462 white girls 12–13yr		–	.81/.84	.77/.82
	N = 821 black girls 12–13yr		–	.83/.84	.81/.81
NHANES (3rd)[49]	Boys/girls 2–5yr	Average triceps and subscapular	.67/.73	.68/.71	.61/.66
	Boys/girls 6–11yr		.79/.82	.81/.85	.77/.82
	Boys/girls 12–19yr		.79/.83	.81/.85	.79/.84

TABLE 12-5 Selective Body Composition Measurements in Children

Characteristics	*Weight*	*BMI*	*Skinfold*	*Conduction**	*Densitometry*	*Isotopes*[†]	*Radiology*[‡]
Advantages							
Convenient	Excellent	Excellent	Very good	Good	No	No	No
Reproducible	Excellent	Excellent	Very good	Good	Very good	Very good	Very good
Fast	Excellent	Excellent	Very good	Relatively	No	No	No
Expensive	No	No	No	No	Yes	Yes	Yes
Correlates with morbidity	Excellent	Excellent	Excellent	Good	Good	Good	Excellent
Large studies	Good	Good	Good	Good	Not good	Not good	Not good
Standard	Excellent	Excellent	Excellent	Good	Very good	Very good	Very good (some lack)
Disadvantages							
Correlates with height	Highly	Not highly	Not highly	No	No	No	No
Assess fat distribution	Poorly	Poorly	Excellent	Poorly	Poor	Poor	Excellent
Equations	No	No	Many	Many	Many	Many	Many
Training	Some	Some	High	High	Very high	Very high	Very high
Radiation	No	No	No	No	No	No	Yes (CT)

Adapted from Ellis[2] and the American Academy of Pediatrics.[3]
*Conduction studies such as bioelectrical impedance, total-body electrical conductivity.
[†]Isotope studies such as ^{40}K, doubly labeled water.
[‡]Radiology studies such as computed tomography (CT) scan, magnetic resonance imaging, and ultrasonography.

tive to temporary changes in folate metabolism. Data from the Framingham Study demonstrated a strong inverse correlation between plasma homocysteine and folate intake over long periods, assessed using FFQs.[57] Another example is that of plasma amino acids. There is evidence that plasma amino acids are indicators of dietary amino acids if they are measured within 2 hours of a protein meal.[58] Plasma amino acid measurements in the postabsorptive state (at least 8 hours without food consumption) are an indicator of dietary intake of amino acids when similar protein meals have been consumed for at least 2 weeks.[59]

Source of Biomarker Measurements

Sources of biomarkers in humans include direct measurements of nutrients, enzyme activity, products of the metabolic pathway, and challenge (tolerance) tests. The biomarker can be measured directly in body fluids or tissues such as plasma, serum, erythrocytes, adipose tissue, muscle, urine, stool, hair, and nails. For example, mean population intakes of iodine and sodium can be estimated by casual urine samples.[60] Enzyme activity can be used to evaluate specific dietary nutrients (eg, alkaline phosphatase for zinc, glutathione peroxidase for selenium, and erythrocyte transketolase for thiamin).

Plasma homocysteine is a sensitive, but not a specific, marker of folate, and 1,25-dihydroxyvitamin D is a good marker for vitamin D deficiency. Although serum ferritin is a sensitive test of iron status and continues to be the leading single determination for individual iron status, it is not recommended in inflammatory states because it is an acute-phase reactant. Serum transferrin receptor is a promising alternative because it is more specific than ferritin. Another example of a nutrient that can be confounded by inflammation is serum betacarotene.[61] Finally, by-products of nutrients can be related to disease, such as protein carbonyl content, which is the most widely used marker of oxidative modification of proteins.[62]

Factors Influencing Biomarker Measurements

The relationship between dietary nutrients and biomarkers can be influenced by sample collection, storage techniques, seasonal timing, time of day, study design, contamination (eg, zinc collected in ethylenediaminetetraacetic acid tubes), stability, storage temperature, and freeze-thaw cycles, as well as level of quality control.[13]

Biomarkers to Validate Dietary Assessment Methods

Biomarkers can be useful for validating other methods of dietary assessment such as FFQs, diet records, or recalls. A major advantage is that the source of error in the biochemical measure and intake assessment should be independent. For example, good correlations between folate intake and serum or red cell folic acid provided important documentation about the assessment of dietary folate, despite concerns about bioavailability and stability in food processing.

TRACKING DIETARY INTAKE

For adults, year-to-year dietary intakes, assessed by FFQs, show correlations of .6 to .7,[13] with decreasing correlations over longer intervals,[63] but diet tracking varies according to age category among children. Although parents have a dramatic influence on their children's dietary intakes, young children's preferences are not necessarily similar to those of their parents; however, as children grow older, their preferences become more similar.[64] Energy-density manipulation studies show that children are able to adjust their daily energy intake when they focus on their own hunger and satiety cues rather than on their parents asking them to "clean their plates."[64]

There was substantial tracking of underlying diets in a study of preschool children (45 to 60 months old) over a 19-month period.[19] After correction for intraindividual variation, the correlations ranged between .2 and .6. The correlation between nutrient intake at age 2 and at age 4 was examined in the Bogalusa Study cohort of children aged 6 months to 4 years.[65] Total protein, animal protein, total sugar, sucrose, starch, total fat, saturated fatty acids, polyunsaturated fatty acids, and cholesterol showed correlations of .5 to .6 in children aged 2 years compared with children aged 4 years. At 2 years of age, 47 to 65% of children in the top tertile for total fat, saturated fat, and cholesterol intake remained in the top tertile by age 4.

Tracking of diets has also been studied in older children and adolescents. Tracking of fruit and vegetable intakes (food records) among children in third grade showed correlations of .4 to .5 over 2 years.[66] Calcium and dairy intake (diet histories) from adolescence into adulthood (13 to 27 years old) showed a correlation of .4.[67] Using three 24-hour recalls per survey, a longitudinal study of 984 children aged 6 to 13 years tracked nutrient intakes over a 6-year period in China.[68] The authors concluded that even under conditions of rapid socioeconomic change, children were likely to maintain their dietary intake patterns from childhood into adolescence. The correlations between dietary intakes measured at a 6-year interval ranged between .28 and .51 for macronutrients and major food groups (vegetable and fruit, meat, and edible oils).

TRACKING OF NUTRIENTS AND BIOMARKERS

Using 3-day dietary records, participants in the Penn State Young Women's Health Study showed weaker tracking of nutrients over a 6-year period among subjects who were 12 years of age at initiation of the study until they reached 18 years.[69] Although the year-to-year correlation coefficient for body weight over the 6-year period of that study was .9, rank and correlation analyses showed low tracking among nutrients examined (fat, sugar, iron, and vitamin C). Another longitudinal study of tracking between 13 and 33 years of age in Amsterdam showed that tracking of nutrient intakes showed relatively low but significant stability coefficients for all macro- and micronutrients (.28 to .52).[70] Overall, most nutrient tracking studies have shown that patterns of dietary intake are already present by 2 years of age. Although tracking varies with age, most studies show a low to modest correlation over time. Possible reasons for conflicting results of tracking could include study design, age groups under study, dietary instrument used to assess diet, socioeconomic background, and prevalence of overweight, among others.

Studies of tracking of diet and disease using biomarkers in pediatrics are few, except for those of cardiovascular disease. One example is that of diet and cardiovascular disease risk factors in the Bogalusa Study, carried out in Louisiana.[71] Dietary cholesterol changes correlated significantly with serum total cholesterol changes (r = .42) and low-density lipoprotein cholesterol (r = .50) from 6 months to 4 years of age. The correlation between dietary intake and subscapular skinfold thickness measurements was .3 to .4 for total protein, total fat, starch, and energy.[71,72] In another longitudinal study from birth to 5 years of age, tracking of serum cholesterol was similar to that in older children and adolescents once the weaning process was completed.[73] The composition of fatty acids in blood has been shown to reflect the quality of dietary fat. Therefore, the long-term stability (tracking) of the serum (and hence dietary) fatty acid composition of serum cholesteryl ester fatty acids were analyzed in a randomly selected population sample of 1,029 Finnish boys and girls aged 3, 6, 9, 12, 15, and 18 years and again 3 years later. The correlations were high for all fatty acids; both linoleate and arachidonate had correlations of .6.[74]

EVALUATION OF DIET–DISEASE RELATIONSHIPS

The ability to detect an association between a dietary variable and disease requires adequate interindividual variation in that dietary factor.[13,75] This implies that the likelihood of detecting a risk associated with a specific food or nutrient among homogeneous populations who are characterized by little variation in the food or nutrient studied will be low. Dietary intake can vary with cultural background (eg, among religious groups), type of foods consumed (eg, vegetarianism), type of soil (eg, soil with little selenium or iodine), food preparation (eg, manioc with cyanide), and disease state (eg, lactose intolerance, heart disease). The detection of an association between food and disease or nutrient and disease can also be limited by errors in measuring dietary intake. Variation in diet over time can be considered to be an error if long-term average intake for an individual is etiologically important. Specific data collection and statistical procedures can be applied to minimize the effects of error.

Adjustment for Energy Intake

The major components of energy intake have been reviewed elsewhere[13,76] and include body size, growth, physical activity and fidgeting, and metabolic efficiency. Most of the variation in energy intake among subjects is attributable to differences in body size and physical activity. Although metabolic efficiency and fidgeting also vary among subjects, they are not measured in nutritional epidemiology because of the lack of practical measures. In addition, a large proportion of the variation in nutrient intake is attributable to total energy intake. Adjusting for total energy intake can be viewed as a measure of nutrient composition rather than as a measure of absolute intake. Even though the association between nutrients and predictors of total energy intake is complex, failure to adjust for energy intake can result in misleading conclusions. Thus, and for the same reasons that animal studies of nutrient effects are conducted under isocaloric conditions, taking total energy intake into consideration when evaluating the relationships between diet and disease is usually important. An exception could be when the outcome being eval-

uated is growth or weight gain. Because adjusting for total energy is important in nutritional epidemiology, especially when energy intake is related to disease, models have been proposed and are reviewed elsewhere (Table 12-6).[13,77]

Residual Model Nutrient residuals are computed using a regression model with the absolute nutrient as the dependent variable and calories as the independent variable and then entered into a regression model with disease as the dependent variable. This model is comparable to isocaloric metabolic studies, in which total energy intake is constant, except for the modification in one nutrient. In the case of macronutrient calories, this model can also be viewed as the caloric substitution of one macronutrient for a similar number of calories from other sources.

To make the interpretation of actual nutrient intake easier, a constant (typically the mean nutrient intake of the study population) is added to the residual values, which have a mean of zero and include negative values. When total energy intake is an important predictor of disease, total energy intake is added to the model, which already includes the nutrient-adjusted variable, as summarized in the second equation in the first model in Table 12-6. However, the magnitude of the relationship between total energy intake and disease can vary among studies because the contribution of foods to total energy intake can be different.

Standard Multivariate Model In the standard multivariate model, both absolute nutrient intake and calories are considered independent variables in a regression model. Although the nutrient is adjusted for total energy intake in this model, the meaning has changed to calories independent of the nutrient. If we consider that total energy intake includes only protein, fat, and carbohydrate calories and the nutrient studied is protein, then energy intake corresponds to carbohydrate and fat calories. Although the meaning of total energy intake has changed, the coefficient of the nutrient studied is the same as that of the second residual model presented in Table 12-6. Some authors have concerns about this type of model, in which variables can be strongly correlated. McGee and colleagues have shown that results can vary widely when using highly correlated variables.[78] They suggest that variables with coefficient correlations of approximately .6 should not be included in the same model.

Energy Partition Model The energy partition model is very different from the two preceding models. This is not an isocaloric model. Using the same example of total energy intake being equivalent to calories from protein, carbohydrate, and fat, this model implies that we examine the relationship between disease and increasing amount of protein in the diet, while keeping term for other calories (including fat and carbohydrate) constant. Therefore, the relationship between nutrient and disease can still be confounded by total energy intake and could erroneously indicate an effect of protein on disease.

Multivariate Nutrient Density Model In the multivariate nutrient density model, the nutrient density is calculated as the nutrient divided by the total energy intake in a regression model, in which a term for calories is added as a second independent variable. This is an isocaloric model. This model can be interpreted as the relationship between the nutrient composition of the diet with disease when total energy intake is constant. Because nutrient densities are not highly correlated with total energy intake, the calories will retain their meaning of total energy intake.

Unlike in the residual model with calories and the standard multivariate model, in which the effect of the nutrient is considered similar in subjects consuming high- or low-energy diets, the nutrient density model can be useful when body size (and therefore total energy intake) varies widely among subjects. However, nutrient densities can result in an erroneous relationship. For example, when a nutrient has a weak correlation with total energy intake or a low variability and is subsequently divided by total energy intake, the nutrient can become highly correlated to total energy intake. Therefore, dividing by another variable does not necessarily mean that its effect is removed. As for absolute nutrient, nutrient densities can result in erroneous conclusions when total energy intake is associated with disease. Given the inclusion of the inverse of total energy intake in nutrient densities, nutrient densities tend to be associated with disease in the direction opposite that of total energy intake.

It is clear from this discussion that the interpretation of energy intake depends on the other variables added in the models. Therefore, the addition of predictors of energy intake to a model will also modify its interpretation. For example, if we assume energy balance, the interpretation of total energy intake in a model in which physical activity and body size were included would be that of metabolic efficiency. In another example, when residuals of weight on height (remove the effect of height on weight) and residuals of height on weight (remove the effect of weight on height) are included in a model with energy intake, height represents lean body mass, weight represents fat, and energy intake represents both physical activity and metabolic efficiency.[13]

The relationships between dietary intake and disease are complex. Although the interpretation of energy intake varies with the analytic method, the association between absolute nutrient intakes and disease should take into account total

TABLE 12-6 Possible Models That Account for Total Energy Intake in Epidemiologic Studies

1. *Residual model*
   Disease = nutrient residual
   Disease = nutrient residual + calories
2. *Standard multivariate model*
   Disease = calories + nutrient
3. *Energy partition model*
   Disease = $\text{calories}_{(\text{nutrient})^*}$ + $\text{calories}_{(\text{other})^\dagger}$
4. *Multivariate nutrient density model*
   Disease = (nutrient/calories) + calories

Adapted from Willett W. [13]
*$\text{Calories}_{(\text{Nutrient})}$ corresponds to caloric intake from a specific nutrient.
†$\text{Calories}_{(\text{other})}$ corresponds to calories from other nutrients than those under study.

energy intake because the observed association can simply reflect that of total energy intake and disease. The presentation of various analytic approaches could further strengthen the findings of an association between diet and disease.

Type of Studies

The case of the relationship between folate deficiency and neural tube defects (NTDs) will be used to illustrate the contribution of a variety of study designs to the determination of a causal relationship between nutrient intake and an important health outcome. In addition, this example shows how the knowledge of a relationship between a nutrient and an outcome might not be sufficient to develop prevention interventions. Finally, it also demonstrates the value of nutritional epidemiology in establishing and evaluating public health policies.

Descriptive Epidemiology The description of variation in rates of disease among different populations and locations, and over time, is generally called descriptive epidemiology. An environmental role in the development of NTDs was suspected from ecologic (differences in rates among geographic areas) and migration studies. The frequency of NTDs was higher in the northern United Kingdom and decreased when populations moved from high-prevalence areas in the United Kingdom to the United States. High prevalence of NTDs seemed to plague disadvantaged populations. For example, an epidemic of NTDs was observed during the Great Depression in Boston.[79] Another example comes from the decreasing rates of NTDs in Ireland over one decade concurrent with the use of fortified breakfast cereals.[80]

Clinical Observations and Intervention Studies Clinical observations often provide important leads for further study. The finding of a relationship between socioeconomic background and NTDs resulted in a study of mother's and children's folate status in the United Kingdom. Smithells and colleagues performed blood tests to study micronutrients and found that folate, among others, was low among mothers whose infants had NTDs.[81] It was also observed that drugs interfering with folate metabolism were associated with the risk of NTDs.[82]

Risk of recurrence was examined in a nonrandomized prevention trial of multivitamin and mineral supplementation in England and suggested a beneficial effect of supplementation.[83,84] Supplementation started at entry to prenatal care for all women. Women who received supplements before 6 weeks of gestation (which corresponds to the cutoff point for neural tube closure) were further compared with women who received supplements later. Other smaller intervention studies showed nonsignificant lower risk of NTDs among supplemented women. Overall, intervention studies showed a fourfold decrease in risk of NTDs among women taking a multivitamin, but the studies have been criticized because many of the data were from nonrandomized trials.

Case-Control and Cohort Studies of Vitamin Supplements In case-control studies, previous diet or use of supplements by cases (or, in this example, mother of the case) is compared with that of controls. In cohort studies, nutrient data are collected before the occurrence or recurrence of disease; thus, these studies tend to take longer and are more expensive. However, cohort studies are less subject to methodologic bias.

Only four studies examined folate intake from the diet; others used information on supplements containing folic acid. Mulinare and colleagues used a birth defects registry to identify children born with NTDs and retrospectively asked about periconceptional multivitamin use (a period of up to 14 years before the interview).[85] The risk of NTDs was approximately 60% lower for women who reported taking supplements. In contrast, Mills and colleagues did not find a significant relationship between folate and NTDs.[86] Shaw and colleagues found a similar reduction in NTD risk when folate supplementation was started after 3 months of gestation, raising concerns about the causality between folate and NTDs.[87] Milunsky and colleagues conducted a prospective cohort study of multivitamin use and NTDs by telephoning mothers at the end of the first trimester of pregnancy to inquire about the type of supplement taken.[88] Findings showed a strong inverse relationship between multivitamin intake during the first 6 weeks of pregnancy and protection against NTDs.

In summary, all case-control and cohort studies except one supported a protective effect of periconceptional multivitamin use. It was unlikely that results observed in most studies were attributable solely to chance because of the variety of design and the choice of controls. However, confounding factors could have led to these findings. For example, NTDs occurred more often in populations of lower socioeconomic background, so that, in principle, socioeconomic background could have been a confounding factor. Also, the association between folate and NTDs might have been attributable to other vitamins in the multivitamin preparation.

Case-Control and Cohort Studies of Serum Folate Daly and colleagues collected blood samples prospectively from more than 50,000 women attending their first antenatal clinic in Dublin maternity hospitals from 1986 to 1990.[89] They used a nested case-control design (sample from all cases and a matched sample of mothers who did not develop an NTD pregnancy) comparing early pregnancy blood folate concentrations in 81 women with pregnancies subsequently affected by NTDs and in a systematic sample of 247 control pregnancies. Folate levels were found to be lower for mothers who later had children who developed NTDs. The same authors found that a woman's risk of having a child with an NTD was associated with early pregnancy red cell folate concentrations in a continuous dose-response relationship.[89] However, in the absence of double-blind randomization, the social and reproductive differences between mothers who took the supplement and those who were considered part of the control group (mothers received supplements after the periconceptional period or refused to take the supplement) led to uncertainty as to the significance of the results.

Randomized Trials The evidence for the relationship between folate intake and NTDs from randomized trials

comes from two studies. One was on the *recurrence* of NTDs (history of previous pregnancy resulting in an NTD) conducted by the Medical Research Council (MRC) Vitamin Study Research Group. This was a randomized trial conducted in five European countries, Israel, and Canada.[90] The other trial was on the *occurrence* of NTDs (first pregnancy resulting in an NTD), conducted in Hungary.[91] In the MRC study of recurrence, women were randomized in a 2×2 factorial design to 4 mg of folate versus placebo or to other vitamins typically contained in multivitamins versus placebo. The trial was stopped early because of the findings of a 72% protection rate for folate. The Hungarian study used a multivitamin with trace elements and folate versus trace elements and vitamin C. This trial was also stopped because of a high occurrence of NTDs in the placebo group.

Implications The findings from these studies led to policy responses that were controversial and unclear. A variety of strategies could have been used to improve the folate status of the population: (1) increase intakes of foods rich in folate, (2) recommend routine use of supplements, or (3) suggest the fortification of foods.

Although increasing intakes of fruits and vegetables rich in folate would be beneficial in many respects, its effect on occurrence of disease would be minimal. Not only would large amounts of folate be necessary to increase plasma levels, but national programs to increase fruit and vegetable intake have not been particularly successful in the past. In addition, the bioavailability of folate in foods is not as good as that of supplemental folate.[92] Cuskelly and colleagues conducted a randomized trial of strategies to provide a daily intake of 0.4 mg of folate through either supplementation, food fortification, free provision of folate-rich foods or dietary advice regarding folate-rich foods compared with a control group over a 3-month period.[93] Concentration of folate in red cells increased significantly only in the groups receiving folate supplements or folate-fortified foods. This study reinforces the concern of the effectiveness of dietary interventions in view of social and economic barriers.

The strategy that consisted of recommending folate supplementation to women during their reproductive years was supported by most epidemiologic studies and was endorsed by the Centers for Disease Control and Prevention (CDC) in 1992. The CDC recommended the use of 0.4 mg of folate daily in women who planned a pregnancy and 4 mg for those who had a history of NTD pregnancies. Although multivitamin consumption was affordable for most, the timing of supplementation and compliance were of concern. Many institutions supported the notion of informing women about folate supplementation; failure to provide this information was considered negligent. Targeting supplementation to a population at risk was difficult because there were no clear affordable screening tools available to identify subjects at risk and the population as a whole seemed to be at risk, based on Daly and colleagues' study.[89]

Finally, the strategy of fortifying the food supply had been used long before with success in many countries (eg, with iron and iodine). Fortification of the food supply would have an impact on the entire population and would not require ongoing educational campaigns. Nevertheless, the level of fortification and the type of foods to be fortified were the center of intense debate. The main concern was the masking of vitamin B_{12} deficiency. However, given that about 25% of the population of the United States consumed multivitamins with 0.4 mg of folate, the rare report of neurologic complications associated with vitamin B_{12} was reassuring. Nevertheless, the US Food and Drug Administration (FDA) considered that levels of folate consumption from food and supplements above 1 mg of folate daily were concerning.

Although flour was a good candidate for fortification because it is consumed by most subjects in the population, the amount of consumption varies in the population. Therefore, simulations of food fortification of specific foods were performed by artificially increasing the folate content of products made of flour in existing food intake databases. Results from these simulations showed that folate intakes higher than 0.4 mg would have to be tolerated to increase folate intake of the entire population. Using this method, Oakley and colleagues showed that fortification with 0.35 mg of folate in 100 g of flour would increase the average intake by 0.25 mg, but 30% of women would still have a total folate intake below the recommended 0.4 mg and 15% of the women would have an intake above 1 mg per day (for most multivitamin users). Fortification with 0.14 mg of folate in 100 g of flour would result in an average increase of only 0.1 mg per day.[94] The FDA recommended the use of 0.14 mg of folate in 100 g of flour; this was implemented in 1998.

The demonstration that folic acid plays a major role in the prevention of *recurrence and occurrence* of NTDs stimulated further research on the possible mechanisms underlying the relationship and a possible nutrient–gene relationship. The association of a polymorphism in a folic acid metabolizing gene with the risk of NTD strongly supports the role of folate in the etiology of NTDs and could indicate a group with a higher folate requirement. A polymorphism in the 5,10-methylenetetrahydrofolate reductase gene is associated with a reduction of activity of that specific enzyme. An increase in the prevalence of this polymorphism was observed in infants born with NTDs and in their parents compared with controls.[95] The possible role of vitamin B_{12} in NTDs is still unclear, as reviewed elsewhere.[96]

Findings on folate and the risk of NTDs have given credibility to the search for other examples in which suboptimal intakes of nutrients could lead to high risk of chronic disease. The case of folate and NTDs was resolved in a relatively short time, in part because of the short interval (first 6 weeks of pregnancy) of exposure during which a nutritional imbalance could result in detrimental effects. In addition, the period between exposure and outcome was relatively short, the exposure could be evaluated by dietary assessment techniques and biomarkers, safe randomized trials could be conducted, and the strength of the relationship was large. Although a causal relationship is typically based on randomized clinical trials, the case of folate and NTDs suggests that a combination of study approaches can provide sufficient evidence when randomized studies cannot be easily performed.

SUMMARY

Nutritional epidemiology can potentially contribute substantially to our understanding of disease in children and to the relationship between diet during childhood and risk of chronic diseases and cancer. The latency period between dietary exposure and disease can be years rather than weeks. Support for the long-term effects of diet comes from studies of diabetes and cardiovascular disorders[97] that led to the Barker hypothesis of fetal origin of chronic disease, as well as from studies of cancer.[98] A variety of approaches will provide the best evidence on these relationships, particularly when used in conjunction with clinical, biochemical, and molecular data.

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CHAPTER 13

FOOD SAFETY

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Safe food and water supplies are prerequisites for good nutrition and the overall health of a population, especially for infants and children whose immune systems are immature and therefore more vulnerable to foodborne infections. Foodborne hazards encompass microbiologic, chemical, and physical agents that can cause injury and disease when ingested. Microbiologic agents include pathogens and parasites that are either present in food when purchased or introduced into food by cross-contamination during preparation or eating. Chemical hazards are substances that are naturally occurring toxicants or that are introduced into food intentionally (such as pesticide residues or food coloring or preserving additives) or through environmental contamination. Physical hazards include pebbles, glass, metal, wood, or plastic shards that can cause physical injury or choking when ingested.

Infants and young children are among the most vulnerable to foodborne infections because of their lower body weight and immature immune systems. A dose of foodborne pathogen that may cause no illness or only mild illness in an adult can cause severe illness in a young child. Therefore, extra care needs to be taken in preparing food for young children to minimize the chance of cross-contamination.

FOODBORNE DISEASE

The terms "foodborne disease or illness" and "food poisoning" are often used interchangeably to describe general symptoms associated with consuming a contaminated food. Specifically, food poisoning refers to all forms of serious injury from gastroenteritis, whereas foodborne disease can be more broadly interpreted as encompassing all injury or illness associated with eating foods contaminated with pathogenic chemical or physical agents. In addition, the term foodborne disease can include all chronic sequelae, such as arthritis, associated with foodborne pathogens.

Agents of foodborne illness can be classified into one of three categories: biologic, chemical, or physical. Biologic pathogens include bacteria, fungi, parasites, viruses, and prions. Pathogenic chemical agents linked to foodborne illness include pesticides, herbicides, naturally occurring toxins produced by bacteria or mushrooms, mycotoxins produced by fungi, radioisotopes, and toxic heavy metals, such as copper, arsenic, and zinc. Glass, dirt, rocks, and plastic are examples of physical agents that can be introduced into the food supply and, when ingested, cause injury. Some agents associated with foodborne illness, notably bacteria and fungi, are capable of rapidly multiplying and producing toxins in foods. Foods, on the other hand, merely serve as vehicles of infection for viruses and parasites.

This chapter focuses on some of the key agents associated with foodborne illness and provides background information on how to protect infants and children from foodborne illness. Only the most serious or common agents associated with foodborne illness in children are profiled, including a general description of the agent, high-risk foods, modes of transmission, and notable symptoms of illness, including incubation periods (time between consumption of agent and onset of illness) and, where relevant, infectious dose (the amount generally required to cause illness in a "healthy" individual) and recent outbreaks, to further illustrate the nature of the agent being discussed.

BACTERIAL FOODBORNE PATHOGENS

Bacteria are small, single-celled organisms that possess no distinct nucleus. They are probably the most adaptable organisms on earth and are known to exist in all environments—in the air, in soil, and on rocky surfaces. Bacteria can be found in extreme climates, from the Arctic cold to the scorching temperatures of geysers, and have evolved to survive and thrive at high acid and high salt concentrations. Many environmental bacteria form spores—resistant, dormant structures within the cell—that protect the organism from adverse conditions, such as when adequate nutrition or moisture is lacking. Such bacteria are capable of staying in a dormant state for a couple of months, until optimal conditions are restored. With such abilities to adapt to various stresses and the capability of thriving in practically all environments, it is no wonder that bacteria exist in a wide variety of foods.

Bacteria are classified on the bases of shape (spherical [cocci], rod [bacilli], or spiral), group orientation (some bacteria such as *Bacillus* sp are noted for lining up into "chains," for instance), oxygen tolerance (aerobe,

microaerobe, facultative anaerobe, and anaerobe), cell wall structure (gram positive or gram negative), the capability to form spores, motility (possession of a flagellum), ability to ferment different sugars, and the presence of certain surface antigens, to name just a few characteristics. Most of these organisms exist as free living, but a few have ecologic niches in the external, mucosal, and other surfaces of humans and other creatures. Bacteria, for the most part, are harmless and perform beneficial roles to the environment and their human or animal host. A tiny minority, however, possess certain characteristics, such as the ability to produce toxins, that give them the capacity to threaten their host. Over 200 different species are considered to be pathogenic toward humans, many of which are associated with foodborne illness. The Centers for Disease Control and Prevention (CDC) recently estimated the number of foodborne illnesses associated with various pathogens.[1] The top seven bacteria in the analysis, including estimated foodborne illness and hospitalizations, are listed in Table 13-1. A brief review of some of these bacterial pathogens, as well as additional agents that are responsible for foodborne illness in children, is explored in this section. Emphasis is placed on organisms with higher rates of hospitalization, not necessarily those associated with higher estimated rates of illness

TABLE 13-1 Estimated Number of Foodborne Illnesses and Foodborne Hospitalizations from 7 Bacterial Pathogens

Bacteria	*Estimated Foodborne Illnesses*	*Estimated Foodborne Hospitalizations*
Campylobacter spp	1,963,141	10,539
Salmonella, nontyphoidal	1,341,873	15,608
Clostridium perfringens	248,520	41
Staphylococcus food poisoning	185,060	1,753
Shigella spp	89,648	1,246
Yersinia enterocolitica	86,731	1,105
Escherichia coli O157:H7	62,458	1,843

Adapted from Mead PS et al.[1]

Campylobacter jejuni

Campylobacteriosis is the leading cause of diarrhea in the developed world, with the number of cases exceeding those of salmonellosis and shigellosis.[2] *C. jejuni*, the bacterial agent responsible for the illness, is a gram-negative, slender, curved rod. It grows under microaerophilic conditions (in an atmosphere of approximately 5% oxygen) and has the unusual property of having an optimal temperature for growth of 42°C instead of the more typical 37°C, which is associated with most human pathogens. *C. jejuni* is found in the normal gastrointestinal and genitourinary flora of many animals, including sheep, cattle, chickens, wild birds, and domestic dogs.

C. jejuni, when ingested, colonizes the intestinal mucosa, but the exact mechanism behind its pathogenesis has yet to be fully elucidated. It is postulated that gastrointestinal illness from *C. jejuni* infection results from toxin production and bacterial invasion and proliferation with the intestinal mucosa.[3] The infectious dose, as indicated by volunteer human feeding studies, appears to be very low—around 100 organisms.[4] Onset of illness typically occurs 2 to 5 days after consumption, with symptoms consisting of severe abdominal pain, fever, and bloody diarrhea with nausea; vomiting is not commonly associated with *C. jejuni* food poisoning. Symptoms are usually self-limiting, lasting for several days to more than 1 week. *C. jejuni,* in extreme cases, can result in acute and chronic sequelae such as bacteremia, urinary tract infection, meningitis, endocarditis, peritonitis, and reactive arthritis. *C. jejuni* has also been linked to being the potential cause of Guillain-Barré syndrome (GBS), an autoimmune disorder of the peripheral nervous system, which is characterized by limb paralysis. *C. jejuni* is the most common microorganism identified in patients with GBS.[5] Nevertheless, fatalities from *C. jejuni* are very rare.

Because a number of animals serve as reservoirs for *C. jejuni*, many foods can be associated with *C. jejuni* contamination. Undercooked meat and chicken are typical sources of *C. jejuni* infection. Unpasteurized milk and nonchlorinated water can also harbor the organism. *C. jejuni* is very susceptible to heat and low pH, so typical cooking temperatures and acid washes, when applied properly, can kill the organism. But, owing to its low infectious dose, it is still a very difficult organism to control. Cross-contamination during food processing in the factory or food preparation in the kitchen can be a real problem with any organism with such a potent pathogenicity.

C. jejuni accounts for a large number of sporadic cases of illness throughout the summer months; large outbreaks are rare. Most outbreaks are attributed to the consumption of contaminated milk. One such outbreak occurred in 1986, when 172 students at an elementary school were infected from improperly pasteurized milk. The dairy supplying milk to the school did not vat pasteurize the milk at a high enough temperature or for the required length of time.[4]

Salmonella spp

Salmonella spp are gram-negative, facultative anaerobic, non–spore-forming bacilli that are widely distributed in nature. They reside in the intestinal tracts of animals and humans. The bacteria are excreted in the feces, where they can contaminate virtually any object that comes into contact with the feces. Over 2,000 distinct antigenic variants of *Salmonella* have been identified based on analysis of cell wall, capsular, and flagellar antigens. Human infection is linked to only a few of these serotypes, however.

The symptom of illness greatly depends on the type of *Salmonella* involved. *S. typhi* is the most serious of the *Salmonella* spp, being the agent responsible for enteric (typhoid) fever. *S. typhi* can penetrate the intestine and enter the bloodstream. There the organism has the ability to evade the initial immune response by entering macrophages and multiplying. Illness occurs 7 to 28 days after exposure, with symptoms that include high fever, headache, vomiting, and diarrhea.

Symptoms of nontyphoid salmonellosis are similar to those associated with enteric fever, only milder. The bacte-

ria, following ingestion, pass through the stomach and adhere to the epithelial cells lining the small intestine, causing inflammation. Ingestion of 10,000 or more bacilli is required to cause illness in healthy individuals; in children and immunocompromised individuals, the required dose is much smaller.[4] Clinical manifestations of salmonellosis, following a broad incubation period of 6 to 72 hours, include nausea and vomiting followed by nonbloody diarrhea and abdominal cramps. Diarrhea persists as the major symptom for 3 to 4 days. The illness is usually self-limiting after about 7 days. Occasionally, the microorganisms can enter the blood and cause sepsis. Once in the bloodstream, the bacteria can cause a number of problems by invading tissue. Arthritis, aneurisms, and meningitis are just a few of the chronic sequelae that can result from salmonellosis.

Raw meats, fish, poultry, eggs, and milk and dairy products are the typical risk foods for *Salmonella* spp contamination. Outbreaks associated with orange juice, tomatoes, cantaloupe, cilantro, and alfalfa sprouts have also been reported.[6–10] Thorough cooking of foods can control the organism because they are susceptible to heat (71.7°C for 15 seconds has been shown to be effective in destroying the bacteria). *Salmonella* spp are also susceptible to acidic conditions (pH 4.0) but are resistant to both freezing and drying.[11]

Salmonella spp account for a large number of reported outbreaks. A large salmonellosis outbreak in US history, involving 16,284 confirmed cases, occurred in 1985. The cause of the outbreak was believed to be pasteurized milk, which had been cross-contaminated with raw milk.[12] The largest US outbreak of salmonellosis occurred in 1994 when 224,000 people, nationwide, became ill from ice cream contaminated with *S. enteritidis*.[13] Surprisingly, the cause was not linked to an egg product in the ice cream but resulted from an unsanitized truck in which some of the product had been transported. The truck had previously hauled nonpasteurized liquid eggs containing the pathogen.

Escherichia coli

Of all of the members of the family Enterobacteriaceae, *E. coli* is the largest colonizer of the intestine of humans and animals. *E. coli* probably holds the honor of being the most feared bacterial pathogen among the general public owing to recent dramatic reports of outbreaks associated with *E. coli* O157:H7. Most strains of *E. coli* perform a beneficial role for the host, aiding in the digestion of foods, the destruction of other pathogenic bacteria, and the production of vitamins. However, a few strains are capable of producing harmful toxins that can cause a variety of conditions, ranging from mild diarrhea to death.

E. coli is a gram-negative, rod-shaped organism. It is classified as a facultative anaerobe and is a typical coliform—an enteric bacterium that ferments lactose to acid end products. Transmission of the bacteria occurs through fecal contamination. In nature, the organism can survive readily with minimum nutrients. *E. coli* can also colonize the skin as well as the female genital tract.

Pathogenic *E. coli* that causes gastroenteritis is classified in accordance with its virulence properties. The four types of diarrhea causing *E. coli* are enterohemorrhagic (EHEC), enteroinvasive (EIEC), enteropathogenic (EPEC), and enterotoxigenic (ETEC). EIEC, as the name implies, invades and proliferates within epithelial cells of the intestine, causing a mild form of bacillary dysentery. ETEC adheres to the mucous layer of the small intestine and produces toxins that result in watery diarrhea. EIEC and ETEC are uncommon agents of foodborne illness in developed nations; therefore, they will not be discussed in any more detail in this section.

EPEC is a very common cause of infant diarrhea. EPEC cells form small clumps by binding tightly to the enterocytes of the small intestine, causing the lining cells to disrupt. Resulting symptoms can include bloody or watery diarrhea. The infectious dose for infants is believed to be very low, although no exact figures are reported. In healthy adults, a dose of 10^6 cells is probably required for associated illness to occur.[4]

EHEC includes *E. coli* O157:H7, a recent emerging pathogen that was identified in 1982 as the cause of two major outbreaks of hemolytic colitis in Oregon and Michigan attributed to hamburgers.[14] *E. coli* O157:H7 produces a very powerful toxin similar to the one associated with *Shigella dysenteriae*, a bacterium that causes a severe form of bacteria dysentery. The incubation period is somewhere in the range of 3 to 9 days. Characteristic symptoms of infection include intense abdominal pain and nonbloody diarrhea, which progresses within 1 to 2 days to bloody diarrhea that can become quite severe. Vomiting and low-grade fever can occur as well. Illness usually persists for about 8 days and then subsides. *E. coli* O157:H7 is also a major cause of renal failure (hemolytic uremic syndrome [HUS]) in humans and the leading cause in children.[15] About 10% of cases progress into HUS.[16] The infective dose of *E. coli* O157:H7 is unknown but is believed to be very low—less than 10 organisms.[4]

The majority of reported *E. coli* O157:H7 outbreaks are linked to undercooked ground beef, but associations with raw milk, vegetables (including sprouts), cheese, water, juice, and fruit have been reported. Many foods can account for EPEC illness. As with *E. coli* O157:H7, raw beef and chicken are the primary risk foods. More importantly, contaminated water is probably the number one vehicle for EPEC transmission.

E. coli O157:H7 is sensitive to heat (grows poorly at 45°C) but has an unusual resistance to acid. Studies have demonstrated that the organism can survive in apple cider with a pH of 3.6.[17, 18]

There are numerous reports in recent years of outbreaks associated with *E. coli* O157:H7. The largest outbreak in the United States occurred in 1993 throughout the Pacific Northwest (Washington, Idaho, California, and Nevada).[19] In all, over 700 cases were confirmed; 178 people were hospitalized and 4 children died. Contaminated hamburgers from a fast-food chain were determined to be the cause of the outbreak. The largest outbreak in world history occurred in 1996 in Japan.[20] Radish sprouts contaminated with the organism were responsible for over 10,000 illnesses, a vast number of them being school-aged children. Unpasteurized, commercially sold apple juice

was the source of an unusual 1996 outbreak in the United States. The reported median age of the 45 victims was 5 years, with 12 persons being diagnosed with HUS.[21]

Fecal to oral transmission is also a common cause of outbreaks with *E. coli* O157:H7. This is especially true for daycare centers. An example of this was reported in Minnesota, where 68 cases of *E. coli* O157:H7 infection were identified over an 18-month period, involving nine daycare facilities.[22] In addition, younger children have been reported to shed the organisms for longer periods after resolution of symptoms compared with adults, which makes the risk factor of daycare centers even greater than once suspected.[23] *E. coli* O157:H7 transmission via the fecal-oral route also can occur by swimming in contaminated waters, as was demonstrated in an outbreak involving 12 individuals, ages 2 to 12 years, in 1995.[24]

Listeria monocytogenes

To avoid the possible misconception that only gram-negative bacteria are responsible for foodborne illness, *L. monocytogenes* is a small, gram-positive bacillus that is also a very important foodborne pathogen. It is found everywhere in nature—in the soil and water, for example. The bacterium also colonizes the intestine of humans and animals, primarily ruminants (ie, cattle, sheep, goats, deer, and elk). It is one of the few environmental gram-positive bacilli that do not form spores. Owing to its omnipresence, foods can easily become contaminated with *L. monocytogenes* through fecal or environmental transmission.

Listeriosis rarely occurs in healthy adults; however, it is a grave threat to the immunocompromised populations (human immunodeficiency virus [HIV]-positive individuals, patients subjected to chemotherapy, etc), the elderly, infants, and pregnant women. The symptoms of listeriosis are highly variable, depending on the host and particular strain of infection. In healthy individuals, symptoms are typically very mild and go unnoticed. As an opportunistic infection, symptoms may include nausea, vomiting, and abdominal pain, followed by fever. Pregnant women may also suffer flu-like symptoms. The onset of illness, like the symptoms, varies greatly, spanning from as short as 1 day to as long as 3 weeks after consumption. The very serious clinical features of listeriosis include meningitis, septicemia, and encephalitis. Listeriosis in pregnant women can lead to spontaneous abortion or stillbirth. Additionally, mothers can contaminate the skin and respiratory tract of their newborns by transmitting the organism from their gastrointestinal tract and perianal region if they are carriers.

The infectious dose of *L. monocytogenes* is unknown, but in susceptible people, fewer than 1,000 organisms can probably cause disease.[4] *L. monocytogenes* produces a hemolysin that, in conjunction with other factors, allows the organism to evade macrophages. In this respect, the organism is able to spread, avoiding much of the immune response. This is the reason that the strength of the immune system is extremely crucial in the ability of the body to adequately defend against the organism.

Beef, pork, ready-to-eat foods, soft cheeses, foods purchased at delicatessen counters, milk, poultry, fruits, and vegetables are all examples of reported sources of contamination.[25,26] *L. monocytogenes* is extremely hardy for an organism that does not form spores. The organism has the ability to grow at refrigeration temperatures (3°C) and is resistant to acid pH and salt treatments that are often used to ensure food safety. However, cooking or pasteurizing foods can effectively eliminate the risk of foodborne listeriosis in foods that can be cooked.[27]

Listeriosis occurs sporadically, but, from time to time, outbreaks of *L. monocytogenes* do occur, associated most typically with contaminated cheese or milk. Southern California was the scene of a mass outbreak in 1995, in which 142 people became ill from consuming Mexican-style soft cheese contaminated with *L. monocytogenes*.[28] There were 48 deaths, of which 10 were neonatal and 20 fetal. Hot dogs and delicatessen meats contaminated with a rare strain of *L. monocytogenes* were the culprits in a large multistate outbreak in late 1998 and early 1999 that resulted in 20 deaths.[29]

Chocolate milk, contaminated from a tank drain at the dairy, was the vehicle of *Listeria* transmission at a picnic in Illinois, which resulted in 45 cases.[30]

Clostridium perfringens

C. perfringens is a large, anaerobic, spore-forming, gram-positive rod that is widely distributed in nature, residing in the soil. The organism can be harbored in the intestine of humans and many animals, where it is passed in the feces. *C. perfringens* is the agent responsible for a common form of food poisoning as well as gas gangrene, anaerobic puerperal sepsis, and anaerobic cellulites.

Food poisoning resulting from *C. perfringens* is typically a mild illness. The illness has an incubation period of 8 to 24 hours, followed by nausea, abdominal pain, and diarrhea. Fever is not associated with illness; vomiting is rare. The illness usually self-resolves within 24 hours. In fact, the illness is often mistaken for a case of the "24-hour stomach flu." The infectious dose required for onset of associated symptoms is quite large—10^8 vegetative cells.[4] After ingestion, the bacteria release an endotoxin into the upper gastrointestinal tract, which is responsible for the clinical manifestations of infection.

The spores of *C. perfringens* are very resistant to heat, being able to withstand temperatures of 100°C for more than 1 hour. Foods associated with *C. perfringens* illness include meats, meat products, and gravy.

Outbreaks associated with *C. perfringens* are very common, even though many cases go undetected or unreported, owing to the mild symptoms associated with the illness. Two outbreaks of *C. perfringens* following St. Patrick's Day meals occurred in 1993.[31] Over 200 people became ill in two states after consuming contaminated corned beef. In one state, the delicatessen that had served the meat initially boiled it for 3 hours and allowed it to cool to room temperature before refrigeration. The corned beef was then heated to 120°F (48.8°C), sliced, and served to the public. Some of the product, which was made for catering, was allowed to stand at room temperature for several hours before serving. It was recommended by the state health department, after the outbreak, that the meat, not served directly after cooking, be

divided into small pieces, placed in shallow pans, and chilled rapidly on ice before refrigeration. Before reserving, it was further recommended that the meat be rapidly heated so that the internal temperature of the meat would reach at least 165°F (74°C).

An unusual outbreak occurred in 1990 at a conference for cake decorators.[32] Thirty-two of the 42 attendees became ill after consuming contaminated minestrone soup. The soup, which consisted of chicken, fresh vegetables, canned tomatoes, chicken base, navy beans, and peas, was heated under boiling (a temperature too low to destroy vegetative cells). Also, it was determined that the chicken stock used in the soup was not chilled before preparation and the leftover soup was held at room temperature for too long before reheating.

Clostridium botulinum

C. botulinum is a gram-positive, anaerobic, endospore-forming bacillus that is widely found in the soil. *C. botulinum* produces seven different types of a very potent toxin, referred to as types A, B, C, D, E, F, and G. Humans are susceptible to types A, B, and E and animals to types C and D. Because of its potency, botulinum toxin is an agent associated with biologic warfare because only a few nanograms of it can cause death.

The toxins produced by *C. botulinum* are responsible for causing three types of botulism: foodborne, infant, and wound. Wound botulism is quite rare and occurs when the organism is introduced into the body through a wound. Foodborne botulism results from the ingestion of the toxin through a food source. Symptoms for foodborne botulism begin to develop between 12 and 36 hours after the toxin is introduced into the body. The botulism toxin works by binding to the neuromuscular junction of nerves, preventing the release of acetylcholine, which results in muscle paralysis. Dizziness, weakness of limbs, blurred vision, general fatigue, and difficulty in swallowing are all early characteristics of infection. Vomiting, nausea, and diarrhea may occur also but usually are not accompanied by fever. Antitoxin serums and respiratory support systems are often required treatment in more severe cases. Death is usually caused by paralysis of the diaphragm, leading to asphyxiation.

Infant botulism occurs when the ingested spores of *C. botulinum* germinate and colonize the child's gastrointestinal tract. The defining symptom of infant botulism is a severe loss of head control. Other symptoms include constipation, weakness, and poor feeding. Most cases require mechanical ventilation. A 12-year case study at one tertiary care hospital revealed that 68% of its infant patients were mechanically ventilated during the course of their illness.[33]

Any food that has a low acidity and salt concentration and supports an anaerobic environment for the organism is a high-risk food. Foods that are sources of foodborne botulism include canned and bottled foods (especially home-canned foods) and foods that are submerged in oil or fat. Honey is the primary food of concern for infant botulism. It is reported that 25% of honey products have been found to contain spores.[34]

Although *C. botulinum* spores are very resistant to heat, the toxin itself is very susceptible to heat. Certain processing conditions have to be met to ensure safety from botulism, especially in the canning industry. Food processors exploit the fact that the organism is very sensitive to acidic conditions to achieve this. *C. botulinum* is not capable of producing the toxin in such conditions.

Because of dramatic changes in food safety practices in the canning industry, outbreaks of foodborne botulism are not as common as they once were. When they do occur, it is usually the result of an isolated flaw in production, such as a leak in a can. Occasionally, ethnic foods cause an outbreak of foodborne botulism. Eight individuals in the United States and Israel became ill after eating a salted fish known as *ribyetz*, a Russian food, contaminated with type E botulism.[35]

Infant botulism occurs sporadically. A typical case resulting from the consumption of honey contaminated with spores is described in a recent report in which an 11-week-old child was admitted to a hospital with infant botulism:

> "The child was initially admitted with the sole symptom of vomiting. Soon she progressively became weak and noticeably floppy in appearance. She had poor head control, decreased limb tone, and a "frog-like" leg posture. The baby required intubation and artificial ventilation for 18 days. She was treated with cefotaxime and ampicillin for 48 hours and was discharged after 33 days. She was readmitted after 4 days owing to respiratory difficulty. After another stay of 12 days, this time not requiring respiratory assistance, she was discharged. A history examination revealed that the mother had dipped the infant's pacifier in commercial honey.[36]

OTHER BACTERIAL FOODBORNE PATHOGENS

There are numerous bacterial agents that are capable of contaminating our food system and causing some form of illness. The focus of this chapter does not allow for full coverage of all of the important agents; a clinical microbiology text could easily do more justice to the subject. Instead, the brief profiles are included as a quick reference point for a more detailed study. Some of the other microorganisms that are frequently associated with foodborne illness include *Shigella* sp, a group of bacteria that consists of some strains that produce toxins similar to *E. coli* O157:H7, and *Yersinia enterocolitica*, an organism whose infection can produce intense abdominal pain, similar to appendicitis. *Bacillus cereus* and *Staphylococcus aureus* are both gram-positive, toxin-producing bacteria that can contaminate food. The toxin associated with *B. cereus,* a common soil bacterium, produces symptoms almost identical to that of *C. perfringens* infection. *S. aureus* is a bacteria that is harbored in the nose and throat and on the hair and skin of humans, which links the organism to a number of foods. Its toxin is fairly potent and results in a quick onset of illness, with symptoms that include abdominal cramping, nausea, and vomiting.

VIRAL FOODBORNE PATHOGENS

Foodborne viruses infect through ingestion and are passed through the feces. With very few known exceptions, trans-

mission of viruses occurs via the fecal-oral route or through contaminated water or food. Viruses are thought to be the major causes of unexplained foodborne outbreaks because, unlike bacteria, very few specific foodborne viruses have been identified. Children are a high-risk group for foodborne viral infections because many such illnesses are associated with schools and daycare centers.

Rotavirus

Rotavirus is the most common diarrheal pathogen in the world and infects an estimated 2.7 million children in the United States each year.[37] The *Rotavirus* virus particle is a spherical, "wheel-shaped" structure (65 to 75 nm in diameter) that contains a genome consisting of 11 segments of double-stranded ribonucleic acid (RNA), surrounded by a double-shelled outer capsid. Different serogroups of the virus exist, based on the variety of antigens present on the outer capsid. Transmission of the virus occurs via the fecal-oral route.

The majority of infections are asymptomatic in neonates and adults.[38] Onset of symptomatic illness occurs 1 to 3 days after ingestion of the virus particles, with the initial symptom of vomiting followed, within hours, by watery diarrhea that is characterized by brown, copious stools. Low-grade fever may also be present. In severe cases, the diarrhea becomes clear. The illness is usually self-limiting, with vomiting lasting for 1 to 3 days and diarrhea for 5 to 8 days. Death rarely occurs, but when it does, it is typically in the elderly and infant populations. The virus is especially contagious because so few particles are required for infection (10 to 100), yet so many are excreted in the feces (up to 1,000 particles/mL feces).[4]

Foods that are eaten raw such as salads and fruits can serve as good vehicles for the virus. The virus is fairly resistant to low pH and low temperature (it can survive at a pH of 2.8 and a temperature of 4°C for 3 days) but is susceptible to heat; a temperature of 60°C for 10 minutes will destroy it.[39] Thorough cooking and reheating of potentially contaminated foods should be effective in eliminating the virus. The peak time of year for infections is in the winter months, probably because this is when people are in close proximity to each other, allowing for the easy transmission of the organism. Group A *Rotavirus*, although it is the most important serotype of *Rotavirus*, is rarely associated with foodborne or waterborne outbreaks. Group B *Rotavirus* has been found only in China, and group C *Rotavirus* is rarely detected owing to a lack of adequate diagnostic methods.[40]

Hepatitis A

The hepatitis A virus is an unenveloped, small molecule (27 nm diameter) that consists of a single strand of RNA surrounded by a protein capsid. There are at least five different hepatitis viruses, of which hepatitis A and E are associated with foodborne illness. Hepatitis A and E are transmitted through the fecal-oral route. Hepatitis E infection is usually acquired from contaminated water, whereas A is commonly transmitted through food and water.

The hepatitis A virus replicates in the gut mucosa and spreads to the liver. Necrosis of the liver parenchymal cells is the determining factor in the severity of the disease. Infection is associated with a very long incubation period (14 to 40 days). Symptoms at the onset include fever, nausea, abdominal pain, and anorexia, followed in several days by jaundice. The infectious dose is believed to be in the range of 10 to 100 particles.[4] Age and previous exposure are important factors on the infection-to-disease ratio. This is one of the rare pathogens in which adults are at greater risk of suffering clinical disease from the infection than children. Once infected, most people develop a lifelong immunity to the virus. Currently, no treatment exists for hepatitis A infection, but, owing to the mild nature of the illness, adequate nutrition and rest are sufficient.

A number of foods can be contaminated by the virus—lettuce, delicatessen meats, fruits, juices, milk, vegetables, raw seafood, and iced tea—because the virus is stable at cold temperatures (–20°C) and low pH.

Outbreaks are usually associated with conditions of crowding such as hospitals, restaurants, and schools. In 1997, frozen strawberries, imported from Mexico, were responsible for an outbreak in three different school districts in Calhoun County, Michigan.[41]

Norwalk Virus

The Norwalk virus is the leading reported cause of viral gastroenteritis in adults and older children in the United States and the most commonly identified cause of illness, along with *Salmonella*, in school-related outbreaks.[42,43] A member of the Calicivirus family of viruses, Norwalk virus particles are 27 to 38 nm in diameter and consist of a single positive strain of RNA. The organism is transmitted from person to person through the fecal-oral route.

Infection has an incubation period of 10 to 51 hours. Symptoms are very similar to *Rotavirus*, consisting of vomiting, nausea, abdominal pain, and diarrhea. The nature of the illness is mild and self-resolves in about 1 to 2 days. The inoculation dose is unknown but believed to be very small.

Norwalk virus is very hardy and can remain active after exposure to acid (pH 2.7) and heat (60 minutes at 60°C).[44] Foods that have been reported in outbreaks include salads, fruits, eggs, coleslaw, and raw shellfish. Outbreaks are usually associated with public food facilities, such as cafeterias and restaurants. An example of this occurred recently at a Texas university, where 23 students were treated for acute gastroenteritis at a local hospital. Reverse transcriptase polymerase chain reaction methods were employed to determine that the vehicle was delicatessen-served foods, at the university cafeteria, that were contaminated with the Norwalk-like virus.[45] A food handler denied having the illness but quit her job instead of submitting a stool specimen for confirmation.

PARASITES

In developed nations, foodborne parasitic infection is not a common problem. Globally, however, the burden of such infection is tremendous. The two parasites discussed in detail in this section, *Cryptosporidium parvum* and *Toxoplasma gondii*, are protozoa. Other protozoa that are sig-

nificant foodborne pathogens include *Entamoeba histolytica,* which causes amebic dysentery, and *Giardia lamblia*. Both of these organisms are transmitted in a very similar manner, through fecally contaminated water or food, and cause illness when an individual consumes cysts that contain the organism larvae. There are several helminths that are associated with foodborne disease because they use an animal as a host during some stage of their life cycle. Tapeworms, flukes, and roundworms are different groups of helminths that are of concern to human health and are notable for being associated with eating raw or undercooked meats and fish.

Cryptosporidium parvum

C. parvum is a protozoan that accounts for a significant number of diarrheal illnesses in children. The life cycle of the organism consists of an egg (cysts), which is ingested by a human or an animal. Sporozoites are released from the cysts in the small intestine. Several stages of the life cycle occur in the cell membrane of the small intestine, where the organism reproduces, before new cysts are shed in the feces. Transmission of the cysts to humans can occur through contaminated food, water, animals, or other humans.

In individuals with healthy immune systems, symptoms include severe, watery diarrhea that can last 2 to 14 days and can result in dehydration. The infection dose is very low, about 10 organisms.[4] Onset of illness occurs 1 to 2 weeks after exposure. *C. parvum* is also a very important opportunistic pathogen. Illness from *C. parvum* infection in the immunocompromised host can result in severe, prolonged diarrhea that can lead to death.

Because the cysts are transmitted through fecal contamination, virtually all foods can be potential sources of contamination. Oocysts are susceptible to freezing and high temperatures. For this reason, foods that are considered low risk include frozen, pasteurized, or processed canned foods.

Large outbreaks are usually associated with contaminated water. The largest outbreak of cryptosporidiosis in US history occurred in Milwaukee, Wisconsin, in 1993 in which 403,000 people contracted the illness from a contaminated public water supply.[46]

Daycare centers are very common settings for cryptosporidiosis outbreaks, where diaper changing close to food preparation areas can contaminate food or formula. An outbreak at a daycare center was reported in Georgia in 1989, and stool samples from 39 children and 3 staff members were found to contain the organism.[47] Diarrhea in some children resolved only to reappear again later on, indicating the potential for reinfection under conditions of poor hygiene.

Toxoplasma gondii

Toxoplasma gondii is an opportunistic pathogen and a concern for pregnant women. It is a two-host parasite that uses the domestic cat as the definitive host and warm-blooded mammals as intermediate hosts. Humans can become infected with the organism either by ingesting sporulated oocyst in contaminated meat or water or by consuming cysts in undercooked, contaminated meats. Domestic cats pass unsporulated oocysts in their feces, which can be easily introduced into a food or water source through fecal contamination. The rate of placental transmission is reported to be between 17 and 25%, although infection of the fetus occurs only if the woman has no prior exposure to the organism.[48] When this occurs, abortion and stillbirth can result. An estimated 1 child per 1,000 to 10,000 is born with toxoplasmosis each year in the United States.[49]

In healthy adults, *T. gondii* infections are often asymptomatic. Antibody data suggest that 30 to 60% of the US adult population has been infected with the organism at one point or another.[48] In liveborn children with toxoplasmosis, symptoms may not appear for months or years later and may result in such chronic sequelae as epilepsy, palsies, slight deafness, and retardation.[50] Ocular toxoplasmosis occurs when cysts rupture in the retina of the eye, resulting in vision impairment.

A number of meats can be associated with *T. gondii* contamination, including pork, lamb, and beef. The biggest risk factor, however, is the presence of cats in the household. Pregnant women should avoid contact with cat feces and soil and wash their hands before eating and after handling raw meat.[48] Cooking meat at a temperature of 61°C or higher for at least 3.6 minutes has been demonstrated to be sufficient in inactivating cysts.[51]

To date, no outbreaks of toxoplasmosis have been reported in the United States. Occasional small outbreaks occur worldwide. Two separate outbreaks of human toxoplasmosis occurred in Korea in late 1994 and early 1995.[52] All three infected individuals in the first incident suffered vision loss and all five in the second one had lymphadenopathy. In both cases, eating undercooked pork was linked to infection.

FUNGI

Fungi are a broad class of microorganisms that require organic compounds for energy and carbon. They share the characteristic of being eukaryotes that possess an outer cell wall. Fungi exist everywhere in nature, and some are parasites on humans and animals. For the most part, they perform a beneficial role by contributing to the decomposition of matter and recycling of nutrients. A small number cause illness in humans, however. Of the over 100,000 species of fungi that exist, only about 100 have been identified as being pathogenic toward humans.[53]

The fungi kingdom consists of molds and yeasts. Yeasts are nonfilamentous, unicellular organisms, whereas molds are multicellular and have hyphae (long filaments of cells joined together). Several species of yeast, such as *Candida albicans* and *Cryptococcus neoformans,* are pathogenic in humans and account for a considerable number of illnesses among the immunocompromised. Although yeast can cause spoilage in foods, only molds produce toxins that result in foodborne illness. These mycotoxins, as a general rule, are extremely resistant to high temperatures; they cannot be destroyed by merely cooking food, in other words. However, measures can be taken to avoid fungal

contamination of foods. Certain foods, such as grains and plant products, are high risk for mold contamination because of frequent environmental exposure. Aflatoxin, one of the most familiar myotoxins associated with foods, is discussed in brief as an example of the risk associated with mold contaminations and preventive measures that can be taken.

Aflatoxin

Aflatoxins are secondary metabolites produced by certain strains of *Aspergillus* (*A. flavus* and *A. parasiticus*). *Aspergillus* spp are fast-growing molds that can be found everywhere. The major aflatoxins of concern to humans are aflatoxins B1, B2, G1, and G2. The B and G letters refer to the colors produced (blue or green) under ultraviolet light and the numbers 1 and 2 refer to their separation patterns on thin-layer liquid chromatography plates.[54]

Acute toxicity from aflatoxin exposure is quite rare. Of more concern are the potential long-term effects of low-level consumption: necrosis, cirrhosis, and carcinoma of the liver in animals and humans.[54] Reports have also indicated that exposure may play some role in mental retardation development.[55]

A. flavus is one of the most common mold contaminants in peanuts, oilseeds, and corn. Cereals and spices are also associated foods, but aflatoxin production in these is rare and the result of poor drying, handling, or storage.[54] Aflatoxin can also be found in milk as the result of cows eating moldy corn. Relative humidities of 88 to 94% and storage at temperatures between 25°C and 30°C provide optimal conditions for *A. flavus* growth.[56] Although the toxin is resistant to heat, reduction of oxygen through packaging can inhibit aflatoxin production. Also, caffeine has been shown to be effective in inhibiting the growth and mycotoxin production from *Aspergillus* spp.[56]

Outbreaks of aflatoxin poisoning are very rare in developed countries but do occasionally occur worldwide. A tragic incident was recently reported in Malaysia, where 13 children died from acute hepatic encephalopathy as the result of consuming noodles that contained high levels of aflatoxin.[57] In all, 17 were infected. Initial symptoms reported included vomiting, hematemesis, seizures, diarrhea, fever, and abdominal pain. All of the victims were reported to have liver dysfunction.

CHEMICAL CONTAMINANTS

Children today are exposed to nearly 15,000 synthetic chemicals, with the potential toxicity of more than half of these being untested.[58] Many of these chemicals are dispersed widely in the environment and contaminate much of our food supply. In addition to these synthetic chemicals, children can be exposed through food ingestion to the toxic effects of a vast number of natural elements, including heavy metals and toxins produced by fish.

Nearly all of the synthetic chemicals that were produced within the last 50 years pose food safety risks and include pesticides, industrial chemicals and by-products, and food additives. Synthetic and naturally occurring toxic chemicals can account for a variety of disorders and diseases. Excessive exposure to some of these agents has been linked to neurotoxicity, growth retardation, sexual and endocrine disorders, and cancer, to name a few.[58] Children are especially vulnerable to the potential threat posed by environmental contaminants because, pound for pound, they consume more food and drink more water than adults do and their metabolic pathways are immature.[59]

Pesticides

Pesticides have proven to be of value to society by increasing crop yields, improving the quality of fruits, and controlling insects and rodents in the household. Persistent organic pollutants (fat-soluble chemicals that degrade slowly) accumulate in the environment and pose a threat to health, especially children.

There are several different types of pesticides, including insecticides, herbicides, fungicides, wood preservatives, rodenticides, and insect repellents. Many different categories of chemical structures exist for each of these different types of pesticides. Organophosphates and carbamates are discussed in more detail here because they are the compounds that most commonly cause systemic illness.[60]

Organophosphates and carbamates are toxic compounds and include many insecticides used today.[61] Both of these compounds inhibit the breakdown of the enzyme neurotransmitter acetylcholinesterase. This inhibition results in overstimulation of certain parts of the nervous system that contain acetylcholine.[62] Acute symptoms may appear within 4 hours of exposure and can include headache, dizziness, nausea, and abdominal pain initially. Blurred vision, anxiety, confusion, vertigo, convulsions, and possibly coma may result from the nerve stimulatory effects of the compounds.[63] Poisoning from both compounds exhibits similar symptoms, but carbamate insecticide poisoning is more reversible; therefore, it is considered less severe than poisoning from organophosphates.[60] Symptoms from carbamate poisoning may last for only 6 to 8 hours.

Aldicarb is a specific example of a pesticide that is an important threat to children because it can be found in various vegetables and fruits, such as bananas. Some bananas have aldicarb levels that are reported to be 10 times greater than the legal limit established by the Environmental Protection Agency (EPA).[64] Aldicarb is a carbamate insecticide that is used on a variety of crops, including citrus fruits, nuts, potatoes, and ornamental plants. It is applied to the soil and is absorbed by the root system of the plant; therefore, residues can contaminate the edible portion of food crops.[64] Like other carbamate pesticides, toxicity is associated with acetylcholinesterase inhibition. When ingested, aldicarb is absorbed through the gut and is distributed throughout the body. Symptoms from aldicarb poisoning vary depending on the dosage and age of the individual and can include skeletal muscle weakness, diarrhea, excessive sweating, nausea, vomiting, nonreactive contracted pupils, blurred vision, dyspnea, and muscle convulsions.[65]

The EPA has placed aldicarb in its highest acute toxicity category.[66] Various outbreaks and incidents of aldicarb poisoning have been reported. Documented ingestion of

the pesticide has been linked to suicide attempts and from consuming cucumbers.[67,68] The largest foodborne outbreak associated with a pesticide was the result of aldicarb-contaminated watermelons.[69] In 1985, 1,373 people throughout the states of Oregon, Washington, and California reportedly became ill from consuming the contaminated watermelons.

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are a family of compounds that are nonvolatile, hydrophobic oils that were extensively used by industry from the 1930s through the 1970s as hydraulic fluids, plasticizers, adhesives, fire retardants, wax extenders, lubricants, and inks, among many other things.[70] Even though PCBs are no longer used today—production was banned by the Toxic Substances Act of 1977—much of what was produced remains in the environment.[63] PCBs are a common food contaminant, especially in fish. These compounds are a special concern because they cannot be metabolized or excreted from the body (except through breast milk); therefore, even a little exposure can accumulate to significant amounts over time.

The pathology behind the toxic effects of PCBs is not understood. Symptoms from acute exposure of the compounds can include diarrhea and chloracne, a specific skin reaction associated with cyclic halogenated compounds that is characteristically similar to acne vulgaris except that cysts tend to be more severe and inflammation less prominent.[70] Prenatal exposure, through the cord blood, can occur.[63] Long-term effects from such exposure are debatable, but compelling evidence suggests that it can be quite damaging. An extensive study conducted on Michigan children whose mothers consumed fish from Lake Michigan revealed that elevated cord serum PCB levels correlated with lower birth weights and a reduction in head circumference and gestational age. These same children at the age of 4 had lower body weights and poorer short-term memory compared with other children.[71] A follow-up study on Japanese children who suffered during a massive epidemic from cooking oil contaminated with PCBs in 1968 found that the children 9 years later showed apathy, lethargy, soft neurologic signs, and growth deficiency.[72] A similar study, following a 1979 outbreak in Taiwan, reported that the children several years later showed an average reduction of 5 to 8 points on standard IQ scales, short stature, and hyperactive behavior.[72] During the 1968 epidemic in Japan, one of the children was stillborn, which suggests that high levels of prenatal exposure can prove fatal as well.

Breast milk can be a significant source of infant exposure to PCBs. However, studies suggest that the chemical levels of breast milk do not pose a significant threat to the health of infants.[73] The American Academy of Pediatrics (AAP), after considering this topic, still recommends breast-feeding.[63]

PCBs are unavoidable contaminants found in fatty foods, such as meat, fish, milk, and milk products. The US Food and Drug Administration (FDA) established tolerances for PCB levels in these foods. Milk, eggs, other dairy products, poultry, fish, shellfish, and infant foods are required to contain less than 0.2 to 3 parts of PCBs per million parts of food.[74]

Mercury

Inorganic and organic mercury are toxic to humans, but organic mercury (in the form of methylmercury) is associated with ingestion more than inorganic mercury. Inorganic mercury salts are poorly absorbed after ingestion; dermal exposure is more toxic. In contrast, nearly 100% of methylmercury is absorbed after ingestion.[63] Inorganic mercury in lakes and streams can be converted into organic mercury by bacteria and enter the food supply.[75]

Methylmercury is consumed primarily through eating fish because all fish are contaminated to some extent with the compound.[76] About 95% of methylmercury that is ingested is absorbed in the gastrointestinal tract and is rapidly distributed to all tissues.[77] It can pass easily into the nervous system, where it irreversibly damages the cells of the granular layer in the cerebellum, the cerebral cortex, and the calcarine cortex. Methylmercury crosses the placental barrier and accumulates in the fetal brain and blood.[78]

The latent period for mercury poisoning can be very long—several weeks to months to years. Clinical manifestations that result from long-term methylmercury poisoning can include paresthesia of the mouth, lips, tongue, hands, feet, fingers, and toes; constriction of visual fields; hearing difficulty; speech disorders; weakness and fatigue; memory loss; emotional instability; ataxia; coma; and, in the most extreme cases, death.[78]

To limit consumption of methylmercury, avoid eating large, long-lived fish that feed on other fish because they accumulate higher mercury levels than other fish. Examples of such fish would include shark, swordfish, king mackerel, and tilefish. Pregnant women are advised to limit consumption to 12 ounces per week of cooked fish.[79]

PHYSICAL CONTAMINANTS

Objects from the environment (pebbles, twigs, etc) and production equipment (shards of metal, plastic, glass, etc) occasionally contaminate food products. Every year, numerous recalls occur as the result of such findings in commercial food products.[80–84]Occasionally, ingestion of objects in food can cause lacerations of the mouth and digestive tract and occasionally broken teeth. Most are passed harmlessly in the feces. With children, it is probably best to closely examine foods for any evidence of foreign objects and avoid foods with damaged packaging.

FOOD SAFETY PRACTICES IN THE HOME ENVIRONMENT

So what can parents or child care providers do to prevent foodborne illness in infants and children? A wealth of information devoted to educating the general public on food safety issues can be located throughout the Internet and on bookshelves. Reliable sources of publications include government agencies (such as the Department of Agriculture Food Safety Inspection Service, the FDA, or

the CDC), international organizations devoted to health issues such as the World Health Organization (WHO), or professional and scientific societies such as the AAP and the American Society for Microbiology.

Unfortunately, the general public remains unaware of some fundamental knowledge and simple steps to be taken to prevent foodborne illnesses. For instance, a national survey in 1993 revealed that consumers falsely believe that foodborne illness is a minor sickness and that such illnesses usually result from eating a contaminated food at a restaurant.[85] Table 13-2 summarizes the recommendations of several reliable organizations.[86–90] Although some of this advice seems obvious and merely common sense, it is warranted to briefly discuss it in more detail because the general public is not fully aware of these basic concepts.

Cook Foods Properly

Probably the best defense mechanism against foodborne illness is heat. All foods should be thoroughly defrosted before cooking. It is important to cook foods until steaming hot throughout, making sure that the internal portions of meat are not left merely warm; a minimum internal temperature of 160°F should be reached for beef, 180°F for poultry, 160°F for pork, and 145°F for seafood. Thermometers should be used to determine that hamburgers have reached an internal temperature of 160°F to ensure that *E. coli* O157:H7 is killed. Microwave ovens need to be used with extreme caution because they do not uniformly heat foods. In addition, high salt concentrations in foods suppress microwave heating.[91] When heating foods in microwave ovens, make sure to use appropriate containers recommended by the manufacturer of the unit. To ensure that foods are heated uniformly in microwave ovens, avoid salting foods before they go into the microwave and occasionally mix the foods when heating.

Properly Store Cooked Foods

It is important to properly store foods before and after they are cooked. When serving infants, serve cooked foods immediately after preparation and avoid, if at all possible, storing leftovers altogether. If foods are stored, keep the foods at either cold temperatures (below 45°F) or at high temperatures (above 140°F). Remember, some organisms, most notably *L. monocytogenes,* can survive in the cold environment of the refrigerator; therefore, always reheat foods before serving to a temperature of at least 74°C (165°F). Always refrigerate leftover foods immediately and re-serve within 3 days unless the foods are frozen completely. Make a habit of checking the temperature on your refrigerator and freezer. Refrigerators should operate at a temperature range of 40°F to 42°F and freezers should be kept at a temperature of 0°F.

Be Cautious of Raw Foods

Raw foods provide very attractive vehicles for a number of microorganisms and should be handled with care. Avoid cross-contaminating raw foods with cooked foods. For instance, avoid having cooked foods or foods that will be served raw coming into any contact with utensils, dishes, or cutting boards that were previously in contact with raw meats or seafood. It is important to separate raw food items from other foods in the grocery cart and bag as well. Avoid serving raw meats, raw unpasteurized milk, or cheese made from raw milk. Also, avoid items that contain raw eggs, such as homemade ice cream or mayonnaise; *Salmonella* can be harbored in uncooked whole eggs.

Clean Hands are Essential

Proper hand washing technique is paramount to ensuring food safety in the home. Most people are under the mistaken impression that splashing the hands with running faucet water and patting them dry with a towel is the required approach to achieving sanitized hands. When washing your hands, always use warm, running water and soap. Rub the hands together until a soapy lather develops and continue for at least 20 seconds. Rinse your hands and dry with a clean towel. Always wash your hands before preparing food, after handling raw meat and poultry, and after any interruption, such as going to the restroom, coming into contact with pets, or changing diapers.

Use Clean Equipment

A clean kitchen with clean appliances is also an essential requirement for food safety. A seemingly clean kitchen may not actually be so. A study of 14 households revealed that the sites in the households that were contaminated with the most fecal bacteria were the sponge/dishcloths in the kitchen and the kitchen sink drain area; the areas that had the lowest contamination were the bathroom countertops and the toilet seats.[92] The point is that if dirty dishcloths are used to clean dishes and surface areas in the kitchen, the work is done in vain. Change hand and dish towels frequently and use hot soapy water or a disinfectant solution when cleaning kitchen surface areas. Also, do not soak dishes in water without detergent. Use only hard wood or nonporous cutting boards because these surfaces can be disinfected.

Other important advice includes always washing fruits and vegetables before serving. With infants, peel the fruit or vegetable if possible. Avoid serving honey to children under the age of 1 year owing to the risk of infant botulism. In group settings with children, such as daycare centers or schools, make sure that children do not share foods and that diaper-changing areas are located away from food preparation areas. Avoid serving apple cider or unpasteurized fruit juices to children; *E. coli* O157:H7 can grow at a pH less than 4.0, meaning that it can survive in apple cider and unpasteurized juices.[93] If you cannot determine if a juice product has been pasteurized, avoid it. Make sure that you store all food items away from garbage, pesticides, disinfecting agents, or other chemicals. Finally, clean water is an essential prerequisite for food safety. Ice made from unsafe water is unsafe itself.

Traveling

Food safety is very important to consider when traveling with children. When traveling on the road with food for longer than 30 minutes, always place items in a cooler with ice or freezer packs. Meat and poultry should be packed

TABLE 13-2 Guidelines for Food Safety

Agency/ Organization	*Cook Foods Properly*	*Properly Store Cooked Foods*	*Be Cautious of Raw Foods*	*Clean Hands Are Essential for Food Safety*	*Food Safety Also Means Using Clean, Proper Equipment*	*Other Advice*
World Health Organization[86]	All foods must be cooked at minimum temperature of 70°C.	Keep cool (below 10°C. When served again, heat to at least 70°C.	Do not cross-contaminate cooked foods with raw foods. Hands and utensils should be washed after coming into contact with raw foods.	Wash hands thoroughly before preparing food and after every interruption (ie, changing baby, using toilet, coming into contact with animals, etc).	Avoid feeding infants with a bottle. It is usually difficult to get bottles and teats completely clean. Cups, spoons, dishes, and utensils should be washed thoroughly.	Water used in preparing food should be bottled unless the food is adequately cooked.
American Academy of Pediatrics[87]	Cook all foods thoroughly. Use a meat thermomenter for large items like roasts or turkeys and cut into pieces to see if it is done.	Do not let prepared foods stay at room temperature for more than 2 hours. Freeze immediately if stored. When reheating, cover and reheat thoroughly.	Wash hands and all surfaces that have come into contact with raw meat with hot, sudsy water. Do not serve raw meat. Do not use raw milk or cheese made from raw milk.	Always wash hands before preparing meals and after going to the bathroom or changing your baby's diaper.	Carefully examine any canned food for signs of bacterial contamination. Look for cracked jars, loose lids, and swollen cans or lids.	Do not give honey to a baby under 1 year of age. Buy all meats and seafoods from a reputable supplier.
Centers for Disease Control and Prevention[88]	Make sure that all meats, especially poultry and hamburger, are cooked completely.	Foods should be kept at 40°F or colder or at 140°F or warmer. Leftovers should be refrigerated immediately.	No foods containing raw eggs should be served, including homemade ice cream with raw eggs.	Use proper hand washing techniques. Don't handle food if you change diapers. In this case, proper hand washing is essential.	Use only approved food equipment (check local child care licensing regulations). Only use cutting boards that can be disinfected (made of nonporous materials such as glass, Formica, or plastic).	Don't prepare or serve food if you have diarrhea. Supervise meal and snack times to make sure that children do not share plates, utensils, or food.
Food Safety Inspection Service[89]	Cook ground meats to 100°F, ground poultry to 165°F, and all fresh pork to 160°F. Whole poultry should reach 180°F.	Discard any food left out at room temperature for more than 2 hours (1 hour if above 90°F). Place food into shallow container and immediately freeze. Use cooked leftovers within 4 days.	Separate raw meat from other foods in grocery cart and refrigerator. Always wash hands and utensils with hot, soapy water after they have come into contact with raw foods. Never serve food on a plate that previously held raw foods.	Wash your hands with hot, soapy water before and after handling food.	Keep sponges and dishcloths clean. These items can harbor bacteria.	When packing a lunch, keep hot foods hot and cold foods cold. A thermos or an ice pack will help. Keep lunch in coolest place possible; never leave in direct sun.
Food and Drug Administration[90]	Cook beef at 71°C (160°F), poultry at 82°C (180°F), and seafood at 63°C (145°F) for 15 seconds.	Cooked foods should not be left out more than 2 hours. Refrigerate leftovers as quickly as possible. Use within 3 days. Reheat foods to at least 74°C (165°F).	Always wash boards after exposure to raw meat. Keep raw foods from other foods.	Wash hands with warm water and soap for at least 20 seconds. Hot water that is comfortable for hands is not hot enough to kill bacteria. Always use soap.	Use only hard wood or nonporous cutting boards. Always use clean utensils. Wash the lids of canned foods before opening. Clean blade of can opener before use.	Don't serve juice or cider if you cannot determine if it has been pasteurized.

while frozen and kept separate from other items. When hiking or camping, do not drink from streams or rivers; instead, pack bottled drinks, especially water. Do not eat anything that sits at ambient temperatures for too long.

When traveling in developing nations, pack or order bottled drinks, such as water or carbonated sodas. If such items are not available, boil water and let it cool before consumption. This applies to unpasteurized milk also. In areas of poor sanitation, bottled or boiled water should be used to brush teeth.

Peel fruits and vegetables before eating them. If this is not possible, cook the foods first. Raw foods should be avoided because they pose a heavy risk of contamination. Foods that have been cooked and are still hot can be considered safe. Seafood in certain tropical areas of the world can be unsafe, even when cooked, owing to the presence of toxins. This especially applies to fish that are caught on tropical reefs.

Traveler's diarrhea can be a real problem when traveling in developing regions. The illness is not associated with any particular pathogen and usually is self-limiting after a few days. Sometimes the illness can be severe, however, if dehydration occurs. Pack oral rehydration solution (ORS) when traveling with infants or young children. These items can usually be located at most pharmacies. If diarrhea occurs, drink more fluids, such as bottled water, fruit juice, or soup; avoid dairy products. In the case of mild dehydration, the ORS should be used. The solution should be prepared as instructed on the package. Parents should be counseled to seek medical assistance about treatment of diarrhea in children and infants. It is recommended that children or persons with serious infection should not be administered antidiarrheal medications, such as Lomotil™, for instance. If bloody diarrhea, dehydration, fever in excess of 102°F, or persistent vomiting occurs, seek medical help immediately.

Food Safety Applied to Each Stage of Childhood

Until this point, food safety issues have been discussed in general terms, without any real consideration of the different stages of child development, but some concerns are different for each stage of childhood feeding. Steps for ensuring food safety for children ages 3 years and up are very similar to those of adults. Food safety for the infant is addressed in further detail owing to a few unique considerations for each stage.

Breast-feeding is widely recommended over formula feeding, despite the presence of chemical residues, such as DDT (dichlorodiphenyltrichloroethane) and PCBs.[94] This is because human milk provides hormones, enzymes, and immunoglobulins that simply cannot be replicated in infant formula.[95] The advantages of breast milk far exceed the minimum hazards that it poses. Local health departments provide advice specific to pediatricians when local food habits may put breast-fed infants at risk.

When formula is administered to a child, special care needs to be taken to follow label instructions. Most liquid formula should be fed directly and not diluted. Formula prepared from powder should be prepared using ingredient water (commercially sterilized). If distilled, deionized, or bottled waters that are not commercially sterile are used, water must be brought to a boil for at least 1 minute and cooled before use in infant formula preparation.[96] Reports of powdered milk–based infant formulas contaminated with the enteric bacterium *Enterobacter sakazakii* led the FDA to recommend that boiling water should be used to reconstruct powdered infant formula instead of letting the water cool.[97] In addition to using sterile water, sterile equipment (bottles, nipples, utensils used in the preparation procedure, etc) is extremely important. Honey, syrups, raw eggs, or unpasteurized milk should never be added to formula. Formula should be refrigerated properly and not stand at room temperature too long. Refrigerated formula should be used within 24 hours after preparation or discarded. Care should also be taken when electing to heat formula using a microwave oven owing to issues of uneven heating. Protocols for microwave heating of refrigerated infant formula have been established.[98] Finally, homemade infant formulas should be avoided.[99]

Introducing solid foods to the young child's diet requires some additional care. Prepare fresh fruits by scrubbing and peeling them. All bones, skin, gristle, and fat should be removed from meats. Make sure that all foods are cooked thoroughly and prepared using clean equipment and utensils. As mentioned before, avoid cross-contaminating raw foods with cooked foods and never serve unpasteurized juices or ciders. Store-bought baby foods can be considered to be safe because federal standards are stricter for processed foods. In such foods, residue levels of pesticides are generally lower. Some manufacturers of baby foods voluntarily make their products free of all pesticides.[63] Do not let baby foods sit out at room temperature for more than 2 hours and refrigerate as soon as possible. Always seal foods in clean containers tightly when storing them. Cooked vegetables or fruits should be served within 3 days and raw fruits and meats within 24 hours.

Other Factors That Influence Food Safety

Geography influences the safety of some foods. The Great Lake basin, for example, is contaminated with a wide array of chemical contaminants, including PCBs, DTT, and hexachlorethane, to name a few.[100] Consuming fish from these waters poses an increased risk, and advisory messages are periodically issued warning pregnant women and other vulnerable groups about these risks. Likewise, the Hudson River is known to be contaminated with PCBs owing to old industrial facilities along the river that still leak up to 3 ounces of PCBs each day.[101] The EPA has measured PCB levels as high as 41 ppm in fish caught in the Upper Hudson River.[101] Even though commercial fishing has been banned in the area, people still consume fish that is caught in the contaminated waters. Also, people residing in countries bordering the Gulf of Mexico are at a higher risk of consuming food or drinking water contaminated with *Vibrio* bacteria, one species of which, *Vibrio cholerae,* is the agent that causes cholera.[102]

Certain ethnic food practices, lifestyles, and feeding habits can result in increased risk of foodborne illness. As

part of the traditional Eskimo diet, for example, salmon heads, salmon eggs, whale muktuk, and seal flippers are placed in a shallow wood or animal skin and covered with moss underground, which ferments the food. This tradition has resulted in outbreaks of botulism.[103]

FOOD SAFETY TECHNOLOGY

The US food supply is one of the safest in the world, largely attributable to the work of the government and the food industry. Food processors have a wide array of techniques to use to help reduce the threat of microbial contamination of their products. A variety of physical methods of food preservation are currently used in the industry, including freeze drying, ohmic heating (electrical heating), pasteurization (a mild form of heating that minimizes damage to food but helps destroy 99 to 99.9% of bacterial cells), high hydrostatic pressure preservation, and electric and magnetic field effects, to name only a few examples. Chemical preservatives and antimicrobial compounds are added to foods to help retard microbial growth or kill microorganisms.

One of the most promising recent techniques in food technology is the use of irradiation to reduce the risk of foodborne illness. Food irradiation (sometimes called cold pasteurization) employs ionizing radiation at doses sufficient to damage the DNA of bacterial cells, destroying them in the process. Irradiation of foods is a safe process and does not induce additional radioactivity into foods.[104] Irradiation can be performed after foods are packaged, preventing additional handling. Currently, it is used on spices and certain imported fruits and vegetables and is approved for use in raw poultry and meats.

Finally, a mention must be made of the importance of the Hazard Analysis Critical Control Point System (HACCP), which has revolutionized food safety during the past 20 years. HACCP provides a systematic, structured approach to food safety. The principles behind the system can be adopted and followed by any sector of the food industry to help design programs to assist in the production of safer products. The basic idea behind the system is examining all steps of a production process, identifying places in which problems are likely to occur, and developing measures to address these potential hazards. HACCP systems are required for all meat, poultry, and seafood processors. Currently, the FDA is phasing in requirements for HACCP systems to be in place for fruit juice processors as well.

Even though the food industry does a great deal to improve the quality and safety of its food products, the threat of foodborne illness is still very present. It is essential that the general public become more educated about food safety.

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CHAPTER 14

DRUG THERAPY AND THE ROLE OF NUTRITION

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The nutritional status of patients and the components of their diet can significantly impact a drug's pharmacokinetic and pharmacodynamic properties.[1,2] These can affect the absorption, distribution, metabolism, transport, and excretion of drugs. Body weight and/or surface area are also important determinants of proper dosages, and abnormal body composition may impact proper drug dosing. Various nutritional components can impact gastrointestinal motility, blood flow rates, gastric secretions, and enzymatic activity, ultimately affecting drug metabolism and disposition. These interactions, however, are highly variable, complex, and often difficult to predict. When developing a therapeutic plan for the pediatric patient, it is important that practitioners consider the interactions that occur between nutritional status, age, disease state, and drug action. This chapter discusses the developmental changes that occur in the pharmacokinetics and pharmacodynamics of drugs and presents a discussion on the impact of nutrition on these factors. By definition, pharmacokinetics is the action of drugs in the body over a period of time, including the processes of absorption, distribution in tissues, metabolism, and elimination. This contrasts with pharmacodynamics, which is the study of the biochemical and physiologic effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure, as well as the effects on the actions of another drug or nutrient.

DEVELOPMENTAL CHANGES IN BODY COMPOSITION

Unlike the adult, the pediatric patient is undergoing tremendous growth and development. Children should not be thought of as "little adults" because there are a number of developmental aspects that must be considered when approaching pediatric therapeutics. Drug–receptor interactions, ontogenetic changes in receptor number, receptor affinity, receptor-effector coupling, and receptor modulation and regulation change as the child grows.[3] Moreover, during infancy and childhood, the proportions of body weight contributed by fat, protein, intracellular water, and extracellular water change dramatically. In the full-term neonate, total body water comprises approximately 70 to 80% of body weight.[4] By age 5 months, this decreases to 60%. From infancy to young adulthood, extracellular water decreases, although the percentage of total body water does not change significantly. In addition, neonates have reduced muscle mass, lower concentrations of albumin, and less intracellular fluid than adults.[5,6] The change in body water content may significantly affect the volume of distribution of drugs, especially those that are highly hydrophilic. Changes in serum protein (eg, albumin) may alter the free concentration of certain drugs and thus change the patient's pharmacodynamic response. During the second year of life, fat mass is reduced with a corresponding increase in protein mass. For additional information, refer to Chapter 4, which discusses the differences in body composition in premature infants, neonates, and adults.

As the child grows, there is a corresponding change in liver and kidney size, with each organ reaching maximum relative size for weight in the 1- to 2-year-old child, when the capacity for drug metabolism and elimination is high.[3] In the infant and young child, body surface area is greatest relative to body mass in comparison with the older child or young adult. Furthermore, the absorptive surface of small intestine is proportionately greater, whereas gastrointestinal transit time is shorter.

During adolescence, there is an approximately 25% increase in height, whereas weight nearly doubles.[3] In prepubertal males and females, lean body mass, skeletal mass, and body fat per unit body weight are similar, but, by maturity, women have twice as much fat relative to total body weight in comparison with adult men.

Factors That Impact Drug Kinetics

The aforementioned differences in body composition in the pediatric population are an important consideration when

determining the pharmacokinetics of a given medication. Nutrients and drugs delivered via the gastrointestinal tract need to go through an absorption phase prior to reaching the systemic circulation and the sites of action. Absorption from the gastrointestinal lumen into the hepatic portal vein and subsequently to the systemic circulation is a series of complex processes including the dissolution of the solid dosage form, passing of the chyme along the gastrointestinal tract (ie, gastric emptying and intestinal transit), passive diffusion, active transport, and presystemic metabolism of the compounds. Each of these processes alone may affect the pharmacokinetics of the drug.

Gastric Emptying and Intestinal Transit

With the exception of a few acidic drugs (eg, aspirin), maximal absorption of most drugs and nutrients takes place in the small bowel. Therefore, gastric emptying and intestinal transit time have a significant impact on the rate and magnitude of the oral absorption of the drugs and certain nutrients. Gastric emptying time changes in early postnatal life and is likely one of the many explanations for erratic drug absorption rate and oral bioavailability in infants and young children.[6] In addition, gastric acid secretion is low in infants and does not reach the normal adult gastric pH until 3 to 7 years of age.[7] The lack of developed physiologic regulation of gastrointestinal motility and gastric acidity during infancy and early childhood implies that the oral route may not be a reliable route for optimal drug delivery. For instance, delayed absorption and/or decreased bioavailability have been observed for acetaminophen, phenytoin, and phenobarbital in young children.[8]

As the child continues to grow, gastrointestinal motility increases by both neuronal and hormonal input.[9,10] Vagal stimulation increases upper gastric contraction and decreases pyloric sphincter and duodenal contractions. As a result, gastric emptying is promoted and the time it takes for the drug or nutrient to reach the small intestine is shortened. For drugs that are absorbed in the small intestine, this action can result in shortening the time of reaching peak plasma concentration and may promote faster onset of drug action. In addition, because of the decrease in intestinal motility, more complete absorption of the drug may be achieved. Anticholinergic drugs (eg, sedative antihistamines, phenothiazines, tricyclic antidepressants) can reverse these trends by counteracting the effect of the vagus nerve.

Presystemic Clearance

Presystemic clearance, also known as first-pass metabolism, refers to the metabolism of orally ingested compounds prior to reaching the systemic circulation. Presystemic metabolism occurs primarily in the intestine and the liver, whereas the stomach has only a minor role.[11,12] Type III alcohol dehydrogenase, for example, is present in the gastric mucosa and is responsible for the activation of some biogenic amines and steroids.

A significantly higher content of drug-metabolizing enzymes is present in the intestinal epithelial tissues. For example, cytochrome P-450 (CYP)3A4 isoenzyme is present in the small bowel and plays a role in the regulation of oral bioavailability of a large number of medications. Induction or inhibition of the enzyme in the gut by nutrients may lead to a significant change in oral bioavailability of drugs or vice versa. Certain nutrients are known to affect the enzymatic activity of intestinal CYP3A4 and change the pharmacokinetics of the object drugs. Grapefruit juice is a classic example of an intestinal CYP3A4 inhibitor.[12] Its action is discussed in further detail below. Water-soluble vitamin E (α-tocopheryl polyethylene glycol succinate) has also been found to increase oral absorption of cyclosporine.[13,14] It is unclear whether it affects intestinal enzyme or transporters. Further research is currently under way to determine the mechanism of interaction that leads to increased oral drug absorption.

HEPATIC METABOLISM

The metabolism of a drug involves different steps once it has been absorbed from the gastrointestinal tract. As drugs are metabolized, they first undergo biotransformation (ie, phase I metabolism), which results in the formation of a more polar compound by oxidation, reduction, hydroxylation, etc. This results in either an activation of the drug or a deactivation. The second phase (ie, phase II reaction) is a synthetic process, involving conjugation of the polar compound with endogenous molecules such as glucuronic acid, sulfate, glutathione, glycine, and acetate, resulting in a more hydrophilic compound that is more suitable for excretion into bile or urine.[15] It is important to point out that some drugs do not have to go through phase I metabolism prior to undergoing phase II metabolism. Lorazepam, for example, undergoes phase II metabolism (glucuronidation) by UDP-glucuronosyltransfersae (UGT) 2B7 without any phase I reaction involved. The resultant conjugated metabolite is then excreted renally. An enzyme system responsible for the metabolism of most nutrients and drugs is the CYP enzyme superfamily, principally located in the endoplasmic reticulum of the hepatocytes and enterocytes, which is somewhat unique in its ability to use a wide range of substrates.

The maturation of phase I and phase II enzymes varies among individuals. Limited studies suggest that fetal and neonatal CYP, the most important phase I enzyme in metabolizing drugs and biogenic amines and steroids, has about 50 to 70% of the adults' activity and continues to mature throughout childhood. Whereas some children may have fully matured CYP enzyme activities as early as 6 months of age, it may take up to 12 months for others.[7,16] For example, the serum half-life of theophylline, a bronchodilator primarily metabolized by CYP1A2 and CYP3A4, is significantly longer in neonates and younger infants than in adults. Similarly, *N*-demethylation of diazepam, a CYP2C19-mediated pathway, is also significantly slower in infants.[17] There is no well-documented dietary factor known to promote the maturation of these enzymes during the prenatal period and infancy.

RECTAL ADMINISTRATION

Rectal route of drug administration is an alternative way of drug delivery when the enteral route is not preferable.

Unlike the rest of the gastrointestinal capillary mesenteric circulation, the rectal capillary blood supply collects blood directly into the inferior vena cava instead of the hepatic portal vein. Although certain phase II enzymes are present in the colon (eg, UGT1A9), there is no strong evidence to suggest the presence of drug-metabolizing enzyme in the rectum.[18] Hence, presystemic metabolism of the administered drug is prevented. Therefore, compared with oral administration, the relative bioavailability of the drug is usually higher with rectal administration.[19] Drugs that are more commonly delivered rectally in children include anticonvulsants (eg, diazepam), antiemetics (eg, trimethylbenzamide), and sedative agents (eg, chloral hydrate).

DRUG AND NUTRIENT TRANSPORT SYSTEM

Intestinal transport molecules facilitate the absorption of drugs or nutrients.[20,21] In addition, some transporters efflux molecules already absorbed in the cytoplasm of the enterocyte back into the intestinal lumen, thus decreasing the bioavailability of certain compounds. This is believed to be an intrinsic protective mechanism by the host to minimize xenobiotic exposure. P-glycoprotein (Pgp) is a representative of this type of efflux system.[22–24] Pgp belongs to the family of adenosine triphosphate–binding cassette transporters and is an efflux widely distributed in normal tissues, including the intestinal epithelium, renal tubule, liver, and blood-brain barrier. Although no formal studies have been published, nutrients may interact with drugs by either inhibiting or inducing Pgp.

Research in the last decade has proved that CYP3A4 and Pgp are the two most important limiting factors in regulating the oral bioavailability of drugs and their first-pass metabolism.[25,26] For instance, cyclosporine is a known substrate for both CYP3A4 and Pgp. After oral administration, absorption of cyclosporine across the epithelium in the small intestine is limited by Pgp efflux and prehepatic CYP3A4 metabolism. The Pgp-mediated efflux of cyclosporine from the intestinal cell back into the lumen enables the CYP3A4 enzymes another opportunity to metabolize the drug when it again enters the enterocyte. These mechanisms explain why the oral bioavailability remains poor despite improvement of its formulation to microemulsion.[27] When cyclosporine is coadministered with a CYP3A4 and Pgp inhibitor, such as ketoconazole, erythromycin, or diltiazem, significantly increased maximum blood cyclosporine concentration is observed, indicating an increase in absolute oral bioavailability. Oral bioavailablity can be increased by over 40% with concomitant administration of water-soluble vitamin E.[13] The mechanism is believed to be mediated through intestinal Pgp inhibition by the vitamin. It is uncertain, however, whether the inhibition is caused by the inactive component in the formulation of the vitamin or vitamin E itself. Current research is being directed toward a more complete understanding of the cooperative nature between CYP3A and Pgp and what types of nutrients and drugs are substrates of these two systems.

Binding Interactions between Feedings and Drugs Revisited

Feeding and food intake are common causes of drug–nutrient interactions. Enteral feeding is the preferred method of providing nutrition support and also allows easy access for administering drugs to patients who are unable to swallow. However, enteral feeding formulas have been implicated in a number of drug–nutrient interactions.[28] For example, the oral absorption of warfarin, tetracycline, fluoroquinolone antibiotics, and phenytoin is decreased with concomitant enteral feeding.[29–31] Possible explanations include a decrease in the anticoagulant effect of warfarin caused by increased vitamin K absorption from the enteral formulas or binding of warfarin by a protein component of the enteral formula.[30] Drug–nutrient interaction through chelation of divalent and trivalent cations has also been proposed (eg, enteral feeding formulas or dairy products interact with fluoroquinolones).[27]

Effects of Malnutrition on Drug Kinetics

It has become increasingly recognized that nutritional status is capable of modifying the pharmacologic effect of a medication. Both malnutrition and obesity can substantially alter drug pharmacokinetics and pharmacologic responses by causing functional and structural alterations in organs that directly affect drug disposition.[2,32,33] These changes can affect the absorption, distribution, metabolism, and elimination of a medication that can ultimately affect the therapeutic or toxic response of the drug. Moreover, interindividual and intraindividual variations in the pharmacokinetic responses to a medication can further complicate interpreting the actual impact of altered nutritional status on drug disposition. The variation can be 3- to over 20-fold, depending on genetic (eg, genetic polymorphism) and environmental factors, patient variables, and underlying disease.[2,34] Pediatric patients, of course, have a higher incidence of undernutrition (see Chapters 52 and 53).

The pathologic changes seen in malnutrition can impact the pharmacokinetics of drugs in all phases of disposition within the body, suggesting that the degree of malnutrition can determine the body's response to a particular drug.[35] Physiologic changes of protein-energy malnutrition (PEM) may result in alterations in the absorptive capacity of the gastrointestinal tract, body fluid status, cardiac output, glomerular filtration rate (GFR), and plasma protein concentrations, as well as hormonal and metabolic changes. Therapeutic drug levels may be altered as a result of malnutrition-associated tissue receptor alterations.[36] It is conceivable that the risk of toxicities owing to a drug or its metabolites is greater in malnourished patients, with a subsequent risk of morbidity or mortality. This suggests that close drug therapy monitoring and modification of dosage in malnourished patients are imperative. Drugs with narrow therapeutic indices or narrow dose-response curves (ie, phenytoin, theophylline) are particularly susceptible as even small changes in absorption can become significant.

Relatively little is known about the handling of drugs in malnourished children despite the fact that the combination of malnutrition and accompanying disease (typically

infection) in need of treatment is a common pediatric problem in many parts of the word. It is possible that the high morbidity of mortality so characteristic of malnutrition may be enhanced by adverse drug reactions.[37]

Absorption

Little research has been done on the effect of malnutrition on drug absorption. O'Doherty and colleagues observed that phenytoin absorption was slow and erratic in PEM, although the peak concentration and time to reach peak concentration did not differ significantly from controls.[38] Mehta and colleagues reported similar findings with acetaminophen disposition in children suffering from PEM.[39] Like O'Doherty and colleagues, they observed that the absorption rate constant was not altered in malnutrition. This contrasts with work by Raghuram and colleagues indicating that tetracycline absorption was significantly reduced in subjects with malnutrition and pellagra but not in patients with vitamin B complex deficiency or in patients with severe anemia.[40]

Distribution

Only free, unbound drug molecules are pharmacologically active. Because the amount of serum protein changes over the first few years of life, the pharmacokinetics and pharmacodynamics of a drug may change. The important serum proteins that bind to drug molecules and biogenic amines and lipids include albumin, α_1-acid glycoprotein, sex hormone–binding proteins, and lipoproteins. Serum albumin concentrations in children and adults seem to be very similar. However, the serum concentration of α_1-acid glycoprotein is lower in children.[41] On the other hand, the concentrations of certain fetal serum proteins are higher in infants and may lead to relatively unique pharmacokinetic changes in this population.

Drugs can distribute into various body compartments such as the intracellular fluids, extravascular space, lean body tissue, and adipose tissue.[42] Alterations in body composition, particularly the presence of edema, can influence the plasma clearance of drug by changing the medication's volume of distribution.[43] Many medications, once in the systemic circulation, become bound to plasma protein, such as albumin, globulins, and lipoproteins. These binding proteins play an important role in the intravascular transport of the drugs to the target organs. In the bloodstream, drugs that are not bound to plasma proteins are free and are able to exert their pharmacologic response. Malnutrition can alter the rate of tissue protein synthesis as well as the concentration of plasma proteins. The extent of drug-protein binding depends on the concentration of plasma bind proteins as well as the physicochemical properties of the medication. In malnutrition, albumin and lipoprotein synthesis are reduced, whereas globulin and α_1-acid glycoprotein synthesis are increased.[27] Drugs extensively bound to α_1-acid glycoprotein, such as propranolol, have a decreased percentage of drug unbound in malnutrition, resulting in a lesser amount of active drug available to exert a therapeutic response. Other drugs, such as metronidazole, have no significant change in volume of distribution between malnourished and well-fed children.[44]

Metabolism

In chronic starvation, the body is able to adapt and various processes are altered to protect or maintain enzyme activities.[45] In fact, in chronic starvation, enzyme activity may even increase.[46] Endocrine tissue is typically affected in semistarvation as many hormones serve as substrates for drug-metabolizing enzymes.[47] For example, elevations in free cortisol are often seen in malnutrition that may enhance the metabolism of contraceptive steroids in malnourished women, thus increasing the risk of contraceptive failure in that population.[48]

Clearance

Hepatic clearance of drugs may be affected by several major physiologic changes that occur during malnutrition. Protein deprivation or malnutrition may result in a reduction in heart size with a subsequent decreased perfusion of the liver and kidneys.[49] Typically, hepatic drug clearance is determined by three independent factors: hepatic blood flow, the amount of free fraction of the drug in blood, and hepatic clearance of the unbound drug. Diminished hepatic blood flow can reduce the clearance of drugs with high extraction ratios (ie, those in which hepatic clearance of the unbound drug depends on hepatic blood flow but not on changes in protein binding). Presystemic metabolism can become altered. Increases in the unbound fraction of a drug owing to hypoalbuminemia provide more available drug for metabolism, resulting in lower serum concentrations.[49]

The kidney is extensively involved in drug elimination.[50] Renal elimination includes the processes of glomerular filtration, active tubular secretion, and passive tubular excretion. Drugs or their metabolites that are primarily filtered and excreted renally may be affected by nutritional status. Dietary protein increases renal blood flow, GFR, and renal tubular function.[51] Severe PEM is associated with decreased GFR and renal blood flow.[52] When renal perfusion is reduced, less drug is available to be filtered by the tubules. However, because plasma protein binding is also reduced, more free drug becomes available for renal excretion, thus further reducing plasma drug concentrations.[32] Medications that have decreased renal elimination in severely malnourished patients include penicillins, tetracyclines, cefoxitin, aminoglycosides, and methotrexate.[2,49]

Refeeding an undernourished patient can often increase the systemic clearance of a medication, necessitating a dosage adjustment to maintain efficacy.[53] For example, with theophylline, the volume of distribution decreases and the rate of elimination gradually increases in malnourished patients given a dextrose-based parenteral nutrition solution for at least 2 days.[54] The protein component of enteral or parenteral nutrition, however, appears to be the major macronutrient enhancing systemic clearance of affected drugs in patients transitioned from the "unfed" to the "fed" state. Lares-Asseff and associates confirmed these findings in their study investigating the pharmacokinetics of metronidazole in severely malnourished children.[44,55] Based on the clearance data, they recommended that the

daily maintenance doses for pediatric patients with severe malnutrition should be 60% less of the usual pediatric dose to achieve and maintain a therapeutic plasma concentration of metronidazole.

Drugs in Kwashiorkor

Kwashiorkor is associated with edema resulting from increases in total body water, extracellular fluid volume, and plasma volume along with a decrease in intracellular water.[56] Although the majority of kinetics studies investigating the impact of nutritional status and drug response have occurred in India and other third world countries, there have been several studies investigating the influence of nutritional status and drug response in children of more developed societies.[57,58] Lares-Asseff and colleagues studied the effects of nutritional status of children with autoimmune disease on the disposition of acetylsalicylic acid (ASA) and its metabolites.[57] They concluded that a decrease in the hydrolysis and oxidative reaction of the metabolic pathway of ASA and its metabolites occurs in children with PEM with juvenile rheumatoid arthritis. This suggests that the hepatic elimination of salicylates may be altered by disorders of nutritional state.

Based on these and other studies, it is thought that low protein intake results in a negative nitrogen balance that decreases drug metabolism, whereas drug metabolism in patients receiving adequate total calories but with less than optimal protein intake is not significantly impacted.[55,59]

Drugs in Marasmus

Unlike kwashiorkor, marasmus can be considered as an adaptation to an insufficient energy intake. There is decreased total body water, reduced intracellular water, increased extracellular fluid, and increased plasma volume.[2,32] Gentamicin, which distributes predominantly to extracellular fluids, has an increased volume of distribution in malnourished patients compared with well-nourished patients.[60,61] Antipyrine, a drug model commonly used as an index of hepatic drug-metabolizing capacity, distributes primarily in total body water and has been shown to have no variation in the apparent volume of distribution in malnourished children.[62] Likewise, in patients treated with metronidazole, a medication that also has a large volume of distribution, no difference in volume of distribution was observed between malnourished and nutritionally rehabilitated children.[44] A pharmacokinetic study by Treluyer and colleagues focused on the impact of human global PEM on quinine metabolism.[63] In that study, they reported that the metabolism of quinine is increased in children with global malnutrition, suggesting that the dosing interval in these children be reduced to obtain the same therapeutic quinine levels as seen in well-nourished children.

In summary, normal or increased drug metabolism occurs in mild to moderate cases of malnutrition, whereas decreased metabolism is seen in severe cases of malnutrition.[64] Given the unique needs of the malnourished ill child, special guidelines have been created for the use of antimicrobial agents.[65]

Obesity

Obesity (ie, ≥ 95th percentile for age and sex) results in altered body composition in which there is both an increased proportion and absolute amount of adipose tissue as well as an increase in lean body mass, blood volume, cardiac output, and organ size.[66] Drug distribution depends on body composition and may be altered in obese patients. Absorption of drugs evaluated to date appears to be unchanged owing to obesity.[67] The lipophilicity of a drug determines the extent to which obesity influences the volume of distribution and ultimately whether dosing should be based on actual or adjusted body weight. Highly lipophilic drugs, such as lidocaine, thiopental, phenytoin, verapamil, and most benzodiazepines, have an increased volume of distribution.[66] Modest increases in volume of distribution have also been reported for aminoglycosides, heparin, ibuprofen, methylxanthines, prednisolone, and vancomycin, suggesting that an adjusted body weight rather than actual body weight be used to avoid toxicity.[67]

Although the protein binding of acidic drugs is unchanged, the free fraction of basic drugs may be decreased.[67] Similarly, changes in hepatic drug clearance are variable. Phase 1 reactions and phase I acetylation appear to be unaffected by obesity, but the phase II glucuronidation and sulfonation pathways are enhanced. Obesity may also affect systemic clearance of highly extracted drugs such as aminoglycosides and unmetabolized procainamide.[67] Both glomerular filtration and tubular secretion also appear to be increased.[40] Renal clearance of other drugs, such as digoxin and cimetidine, are relatively unchanged in obesity.[67]

Aminoglycosides are distributed within the extracellular fluid compartment. Early dosing recommendations suggested that initial dosing be based on ideal body weight as it was thought that the drug distributed only into lean body mass. Schwartz and colleagues, however, have since determined that when the volume of distribution is corrected for total body weight, it is significantly smaller when compared with normal-weight subjects.[68] The distribution of aminoglycosides into excess body weight is estimated to be about 40% of that distributed into ideal body tissue. The authors concluded that initial dosing of aminoglycosides in obese patients be determined by adding 40% of the excess weight to the patient's ideal body weight, with subsequent dosage adjustments based on serum drug levels and clinical status.

Example: For a 7-year-old, 41 kg, 135 cm, gentamicin, 2.5 mg/kg/dose intravenously every 8 hours, is ordered:

1. Determine ideal body weight (IBW)[69]:

$$IBW = \frac{ht^2 \times 1.65}{1{,}000} \quad \text{IBW is in kg, height is in cm}$$

$$IBW = \frac{135^2 \times 1.65}{1{,}000} \quad IBW = 30 \text{ kg}$$

2. Determine dosing weight (DW):

   DW = IBW + (ABW – IBW) × 0.4

   DW is in kg, ABW is actual body weight in kg

   DW = 30 kg + (41 – 30) × 0.4

   DW = 34.4 kg

3. Calculate gentamicin dose using dosing weight:

   mg/kg/dose × DW = dose in mg

   2.5 mg/kg/dose × 34.4 kg = 86 mg intravenously every 8 hours

A similar controversy exists for optimizing theophylline dosing in obese patients and whether actual or ideal body weight should be used to calculate the initial theophylline-loading dose. This is attributable to conflicting data suggesting that variations in distribution volume may be the result of differences in the degrees of obesity within study populations.[70] Visram and colleagues suggested that the differences in theophylline volume of distribution based on ideal body weight and actual body weight increases as the degree of obesity increases.[70] They recommended that theophylline dosing in patients with mild to moderate obesity be based on actual body weight but that ideal body weight be used when initiating therapy in severely or morbidly obese patients.

Hepatic drug metabolism may also be altered in patients with nonalcoholic steatohepatitis,[44] including enhanced glucuronidation and sulfonation, causing a faster drug excretion compared with normal-weight subjects.[67] Patients with fatty liver may also be more susceptible to the toxic effects of drugs owing to impaired metabolism.[71]

Effect of Dietary Manipulation on Drug Kinetics

Several dietary factors can alter the rate of drug metabolism. Model drugs, such as antipyrine, theophylline, and acetaminophen, have often been used in these studies. Both food and fluids can alter the rate and extent of drug absorption. These alternations in response may occur as a result of influences on gastric pH, gastric emptying time, intestinal motility, and mesenteric and hepatic portal blood flow or biliary flow.[72] Direct physicochemical interactions with dietary components can also alter the absorption of susceptible agents.[73,74] Interactions such as the binding of the medication with metal ions, solubilization of the drug in dietary fat, or adsorption of the drug to insoluble dietary components may occur.[75]

Dietary changes can alter the expression and activity of hepatic drug-metabolizing enzymes.[76] This can lead to alteration in the systemic elimination kinetics of medications metabolized by these enzymes, although the impact of this change is typically minimal.[76–78] The rate of drug metabolism can be accelerated by drugs themselves or by a variety of dietary factors, such as protein supplementation or inclusion of cruciferous vegetables or charcoal-broiled meats in the diet.[79] It has also been reported that charcoal-broiled beef induces the metabolism of antipyrine and theophylline, reducing the half-lives of these drugs by 20%.[80] It has been postulated that these effects were related to the fact that charcoal-broiled beef contains large quantities of polycyclic aromatic hydrocarbons (PAHs).[81] PAHs are potent inducers of CYP1A2, the primary metabolizing enzyme for theophylline and antipyrine. Conversely, low-protein, high-carbohydrate diets and various vitamin and mineral deficiencies can reduce levels of drug-metabolizing enzymes and consequently the rate of drug metabolism so that the serum drug concentrations decline much more slowly, resulting in increased drug potency.[79]

In general, when orally administered medications are taken with meals, the rate rather than the extent of gastrointestinal absorption is delayed. Food affects drug absorption by enhancing gastric blood flow in conjunction with delayed gastric emptying. Food can increase, decrease, or have no effect on the absolute systemic availability of a medication.[82] Concomitant food ingestion reduces the absorption of drugs such as ampicillin, penicillin, and isoniazid.[2] Conversely, food may actually enhance the absorption of other medications, including diazepam, lithium, carbamazepine, and griseofulvin. Table 14-1 lists medications whose absorption is altered by food.

The composition of the meal will alter splanchnic blood flow. Blood flow can be doubled by a high-protein liquid meal and slightly reduced by a liquid glucose meal.[83] The significance of this effect on splanchnic flow is important for those medications with high hepatic extraction.[75] Food will also slow the rate of gastric emptying, which results in a delay in drug absorption from the gastrointestinal tract. Changes in gastric emptying are related not only to the physicochemical properties of the drug but also to the type of meal itself. Hot meals, highly viscous solutions, or those rich in fat can delay emptying.[75]

Melander and colleagues reviewed the impact of food on the presystemic clearance of drugs.[84] They observed that meals commonly enhanced presystemic clearance of lipophilic basic drugs (eg, propranolol, amiptriptyline) but rarely altered the clearance of drugs that were lipophilic acids (eg, salicylic acid, penicillin). Alternatively, food may reduce presystemic clearance of some lipophilic basic drugs via transient, complex effects on splanchnic-hepatic blood flow. Furthermore, repeated intake of specific nutrients (eg, protein) and food contaminants (eg, benzopyrene) can enhance presystemic drug clearance by enzyme induction.

In some instances, dietary manipulation can act as a therapeutic strategy. Nutt and colleagues reported evidence that large neutral amino acids and the medication levodopa compete for transport from the plasma to the brain and may be partly responsible for the "on-off" phenomenon often seen in patients treated with levodopa for Parkinson's disease.[85] By reducing protein intake, patients who failed to respond to a dosage adjustment in their levodopa may see clinical improvement.

IMPACT OF SPECIFIC NUTRIENTS ON DRUG KINETICS

Until recently, most practitioners dismissed the possibility that dietary substances could significantly alter medication

TABLE 14-1 Medications Whose Absorption Is Affected by Food

Drug Absorption Reduced/ Delayed by Food	*Drug Absorption Enhanced by Food*
Ampicillin	Atovaquone
Aspirin	Carbamazepine
Atenolol	Chlorothiazide
Azithromycin	Cefuroxime
Captopril	Clofazimine
Cefaclor	Diazepam
Cefixime	Erythromycin estolate
Cephalexin	Erythromycin ethyl succinate
Ciprofloxacin	Ganciclovir
Didanosine	Griseofulvin
Doxycycline	Hydralazine
Dirithromycin	Hydrochlorothiazide
Erythromycin stearate	Itraconazole
Famciclovir	Ketoconazole
Indinavir	Lithium
Isoniazid	Lovastatin
Loratidine	Methylphenidate
Naficillin	Metoprolol
Penicillin G or V	Nelfinavir
Phenobarbital	Nitrofurantoin
Phenytoin	Propanolol
Rifampin	Propoxyphene
Sucralfate	Ritonavir
Tetracycline	Saquinavir
Thioridazine	Spironolactone
Zafirlukast	

Adapted from Gura KM. Drug-nutrient interactions. In: Hendricks KM, Duggan C, Walker WA, editors. Manual of pediatric nutrition. Hamilton (ON): BC Decker; 2000.

response by affecting intestinal transporter and metabolizing enzymes. This is based on the commonly believed misconception that the absorption of most drugs is a passive process and that the role of the intestine in drug elimination is minimal.[76] Since the report of the interaction between grapefruit juice and several medications was described, this premise has changed, and the role of the diet on drug performance is being re-evaluated.[86]

Carbohydrates

The impact of carbohydrates on drug metabolism is conflicting. Some suggest that carbohydrates have little impact on drug metabolism.[87] Others, such as Kappas and colleagues, noted that antipyrine and theophylline metabolism decreased in carbohydrate-supplemented diets but increased in the protein-enriched diet, suggesting that carbohydrates and protein have opposite effects on oxidative drug metabolism.[88] Although many medications are often given to children in a sugar syrup, little research has been done on its effect on disposition and action. Animal studies by Sonawane and colleagues suggested that dietary carbohydrates and fat may significantly influence the hepatic drug-metabolizing enzymes.[89] It has been hypothesized that these changes may occur owing to alteration in the phospholipid composition of endoplasmic reticulum or by limiting the supply of cofactor(s) necessary for optimal functioning of CYP and UGT.

Protein

Several investigators have reported that medications that undergo extensive first-pass effect, such as propranolol, metoprolol, and lidocaine, can have enhanced bioavailability after a high-protein meal owing to enhanced hepatic blood flow. High-extraction drugs can then rapidly pass through the liver, allowing higher drug concentrations in the systemic circulation.[76,84,90] A decrease in dietary protein depresses creatinine clearance and renal plasma flow.[91] Dietary protein also affects the renal tubular transport of certain compounds, although the mechanism by which this occurs is still not understood.

Dietary Fat

Lipids are an essential part of cell membrane structure and are involved in many of the normal enzymatic activities located within the cell membrane.[87] Diets that are deficient in fat or essential fatty acids decrease the activity of the enzyme systems responsible for the metabolism of nutrients.[92] Plasma free fatty acid levels become elevated after consumption of a high-fat meal, increasing the potential to become bound to plasma albumin, and subsequently displace albumin bound drugs, increasing the risk of drug toxicity.[87]

The effect of food on the absorption of cyclosporine is controversial. There are conflicting reports stating that food impairs, enhances, or does not affect cyclosporine compared with the fasting state.[93,94]

The antiviral agent zidovudine is also impacted by dietary fat. When orally administered, its absorption is reduced when the drug is taken with a high-fat meal in comparison with when taken in the fasted state.[95] It is recommended that zidovudine be taken on an empty stomach to achieve peak serum concentrations.

Vegetables

Cruciferous vegetables, including brussels sprouts, cabbage, turnips, broccoli, cauliflower, and spinach, contain indols that induce aryl-hydrocarbon hydroxylase enzyme activity as well as the conjugation of phenacetin and acetaminophen.[96,97] In one study, patients fed a diet of brussels sprouts and cabbage had a 50% lower serum phenacetin level in comparison with the same subjects fed a control diet that contained none of the enzyme-inducing vegetables.[97] A later study investigated the effects of cruciferous vegetables on acetaminophen conjugation.[96] The researchers found that the test diet of cruciferous vegetables enhanced acetaminophen glucuronide conjugation as evidenced by a 16% decrease in the area under the curve (AUC), a 17% increase in metabolic clearance, and an increased plasma acetaminophen glucuronide-to-acetaminophen ratio.

Grapefruit Juice and Drug Interactions

Bailey and his colleagues discovered that grapefruit juice, which was used as a taste-masking agent for alcohol, caused a two- to threefold increase in oral absorption of the calcium channel blocker felodipine.[98] This finding has subsequently led to the intensive investigation of grapefruit juice and drug interactions. This interaction is the classic example of drug–nutrient interaction exclusively caused by inhibition of intestinal CYP3A4. Oral absorption pharmacokinetic studies of CYP3A4 substrates, such as

cyclosporine or felodipine, consistently showed that grapefruit juice increased the oral bioavailability of these agents. Interestingly, the plasma half-lives of most of the drugs studied were not affected, suggesting that the clearance or hepatic metabolism of these drugs was unchanged by grapefruit juice. It was later determined that this interaction occurs in the enterocytes but not in the liver. Furthermore, Lown and his colleagues showed that repeated consumption of grapefruit juice inhibits not only the intestinal CYP3A4 activity but also the expression of this gene in the enterocytes.[12] As grapefruit juice inhibits intestinal CYP3A4 expression and thus decreases the presystemic metabolism of certain drugs, the bioavailability of the affected agents will remain increased until the expression of the *CYP3A4* gene returns to baseline. This suggests that mere separation of the administration time between grapefruit juice and the potential interacting drugs cannot prevent this interaction. Rather than dose-reduce the affected drugs to avoid toxicity, patients should be advised to avoid grapefruit juice. In some centers, grapefruit juice has been removed from the institutional formulary to minimize the risk of this interaction.

High-Fiber Diets

Dietary fiber and other bulk-forming compounds may interfere with the gastrointestinal absorption of a medication.[99] The bioavailability of digoxin is reduced significantly when given with a fiber-rich meal, with almost half of the dose sequestered in or bound to the fiber.[100] Similar effects have been reported with lithium salts and lovastatin.[101] Stewart reported that several patients with recurrent major depression who had been successfully treated with tricyclic antidepressants became refractory to treatment after beginning a high-fiber diet.[102] Nutrient absorption can also be negatively impacted in the presence of a high-fiber diet. Zinc absorption in the intestine is reduced by the binding of zinc to a number of materials, including phytate, which is found in high fiber diets.[103]

Vegetarianism

Drug metabolism among vegetarians will vary dramatically depending on the protein intake. Most research has focused on Asian vegetarians in which the half-lives of drugs that underwent significant hepatic metabolism (antipyrine, acetaminophen, phenacetin) were significantly longer than in nonvegetarians.[104,105] When similar studies were conducted in white vegetarians, they found no significant difference in half-life between the vegetarians and nonvegetarians.[106] Moreover, the authors found that protein intake between the white vegetarians and the nonvegetarians was similar, which might account for these findings.

Parenteral Nutrition

Lack of oral nutrient intake during parenteral nutrition leads to mucosal atrophy of the bowel along with a reduction in gastric biliary, pancreatic, and intestinal secretions.[50] Bacterial overgrowth can result in a progressive decline in intestinal function owing to impaired motility and depressed enzyme activity. This may alter the rate and extent of absorption of specific nutrients as well as various drugs. Decreases in nutrient absorption include fat, iron, peptides, and vitamins A and B_{12} as well as drugs such as chloramphenicol, chloroquine, tetracycline, and rifampin.[49]

Studies using antipyrine as a marker have shown that parenteral nutrition regimens containing amino acids have higher antipyrine clearance than regimens consisting mainly of dextrose.[107] Burgess and colleagues investigated the response of total parenteral nutrition (TPN) regimens on antipyrine clearance.[108] Patients receiving a postoperative 2,000 kcal TPN regimen providing all nonprotein calories as dextrose showed a 34% reduction of mean antipyrine clearance after 7 days of TPN compared with controls. In patients receiving a 2,000 kcal TPN regimen in which 500 kcal were provided as lipid, mean antipyrine clearance was not significantly different from that of the control group. This study suggested that hepatic CYP1A activity may be affected by different TPN regimens.

Effects of Drugs on Nutrient Status

Drugs can alter the use of many nutrients by a variety of mechanisms, both specific and nonspecific.[53] Malabsorption syndromes may occur from direct toxic effects of the medication to the intestinal mucosa, inhibition of enzymes, binding of bile and fatty acids, alteration of dietary ions, or alteration of gastrointestinal pH. Indirect, nonspecific effects of a drug may manifest themselves as a decrease in appetite, ultimately leading to a decrease in food intake.

Although the concept of drug–nutrient interactions is not a new one, only recently has it reached the forefront in the medical world. Malnutrition, as well as the composition of the diet, can affect the disposition of a medication's half-life.[109] In addition to traditional dietary components, nonnutrient ingredients, such as food additives, preservatives, antioxidants, sweeteners, flavoring, and coloring agents, can interact with a medication. Natural products, such as plant food groups, contain alkaloids, flavonoids, and other compounds; can behave in the body in the same manner that a drug would; and, consequently, can be involved in a variety of interactions and are potentially toxic if they are consumed or accumulate in the body.[110] Drug–nutrient interactions are typically defined as situations that result from chemical, physical, physiologic, or pathophysiologic relationships between nutrients and drugs.[111]

Infants and adolescents, like the elderly, are at particular risk for drug–nutrient interactions. Several factors may influence the possible interactions: first, their nutrient needs are typically higher; second, the systems for detoxification of nutrients may be incomplete; and third, adolescents (especially females) tend to restrict their diets and thus are unable to meet the actual recommended intakes for a variety of micronutrients.[112] Furthermore, the minimum dietary requirement may be insufficient when a patient is under psychological and pathologic stresses, as in the case of pregnancy or athletic training. In pathologic states, the requirement for some micronutrients may be increased.

Drugs may potentially cause vitamin deficiency ranging from subclinical deficiency to clinical manifestation. The

intensity of the interaction may in many cases depend on the nutritional status of the patient. Patients with borderline intake of vitamins or those in poor nutritional health appear to be at greater risk of developing symptomatic vitamin deficiency states. Other factors include the type of drug treatment, dose, and duration of therapy, as well as the age of the patient.[112] For example, individuals on a normal diet rarely become vitamin K deficient, although malnourished patients, regardless of cause, often have moderate or significant deficiency, often with prolonged bleeding times.[113] Cohen and colleagues reported that hospitalized patients may become vitamin K deficient within 7 to 10 days after admission, with those at greatest risk being those who were previously malnourished and had received antibiotics for 7 or more days.[114]

Absorption of Nutrients

There are also many secondary mechanisms that can interfere with nutrient absorption. Medications may alter gastric or intestinal secretion, pancreatic exocrine function, or hepatic bile secretion. For example, H_2 antagonists and proton pump inhibitors inhibit gastric acid production. Chronic use of these medications can significantly decrease the absorption of vitamin B_{12}.[115]

The direct systemic effect of a drug on one nutrient may have secondary effects on another nutrient. Isoniazid and cimetidine inhibit the hydroxylation of vitamin D in the liver and kidney, and phenytoin and phenobarbital promote the breakdown of vitamin D metabolites, each resulting in a functional deficiency of vitamin D and secondary impairment of calcium absorption.[116] Neomycin, colchicine, and para-aminosalicylic acid may damage intestinal mucosa and destroy intestinal villi and microvilli, resulting in an inhibition of brush border enzymes and intestinal transport systems.[117] Nonsteroidal anti-inflammatory agents can cause multiple small hemorrhages of the intestinal mucosa leading to iron deficiency anemia and decreased absorption of vitamin C.[118] Folic acid deficiency and macrocytic anemia can occur in patients on chronic aspirin therapy, especially if their diet is low in dietary sources of folate.[119]

Laxative abuse has also been implicated with malabsorption of vitamin D and calcium. Use of irritant laxatives, such as phenolphthalein and bisacodyl, may damage intestinal epithelial cells and impair colonic reabsorption, resulting in steatorrhea, protein-losing enteropathy, and decreased absorption of glucose, potassium, calcium, and vitamin D.[120] Other stool regimen medications, such as docusate, alter electrolyte transport and can cause hypomagnesemia owing to gastrointestinal losses and failure of colonic reabsorption.[121] Orally ingested mineral oil can coat ingested food particles along with the surface of the intestines. This forms a mechanical barrier to the digestion and absorption of nutrients. Mineral oil also increases gastric motility, which reduces the time required to adequately absorb ingested nutrients.[122] Furthermore, studies have shown that mineral oil, especially when taken at mealtime or during the postprandial absorptive period of optimal nutrient absorption, can reduce the absorption of vitamin D.[122]

Alterations in vitamin and mineral absorption can also occur owing to chelation or precipitation with a medication. Cholestyramine, a basic anion-exchange resin, binds bile salts and impairs the absorption of fat-soluble vitamins, vitamin B_{12}, folic acid, and the minerals calcium, iron, and zinc.[123] Aluminum- and magnesium hydroxide–containing antacids may form nonabsorbable phosphate in the gut lumen, resulting in hypophosphatemia along with anorexia and secondary syndromes of hypomagnesemia and osteomalacia.[116]

Alteration in gastrointestinal pH may also cause drug-induced malabsorption. Drugs that increase gastric pH (eg, H_2 antagonists) can also decrease the breakdown of fat necessary to complex with calcium, thus reducing gut absorption.[124,125] Antacids can also reduce the bioavailability of riboflavin and folic acid as well as copper and iron, all of which depend on a low pH.[126]

Metabolism of Nutrients

Drugs may affect nutrient metabolism by several methods. They may inhibit the essential intermediary metabolism of a nutrient, usually a vitamin, or promote the catabolism of the nutrient. Medications with these properties may be used therapeutically, as in the case of coumarin anticoagulants or methotrexate.[127] In other cases, this may be an unwanted side effect, as in the case of pyridoxine antagonism seen in isoniazid and hydralazine use. Isoniazid and hydralazine can result in pyridoxine deficiency by the inhibition of pyridoxal kinase. Both compounds deplete pyridoxine stores and consequently the neurotransmitter γ-aminobutyric acid, resulting in seizures. Administration of pyridoxine in cases of isoniazid overdose eliminates seizures and metabolic acidosis, which often occur.[128]

Many medications induce drug metabolism enzymes. This results in greater activity of these enzymes, increasing the demand for their vitamin cofactor, and, with chronic drug therapy and marginal nutrient intakes, can precipitate signs of deficiency of several vitamins, especially folic acid. Triamterene can inhibit dihydrofolate reductase, resulting in megaloblastosis.[129] The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor class of antihyperlipidemic agents (ie, statins) can lower plasma concentration of endogenous ubiquinone (coenzyme Q), a cellular antioxidant.[130]

Patients receiving chronic anticonvulsant therapy are at particular risk of developing metabolic bone disease as a result of these types of reactions.[131] Several mechanisms have been suggested. One suggests that drugs such as phenytoin, a microsomal enzyme inducer, stimulate the catabolism of vitamin D to produce an inactive metabolite.[132] Another theory suggests that phenytoin, alone or in combination with phenobarbital, interferes with vitamin K metabolism, with a corresponding elevation in serum osteocalcin levels without α-carboxyglutamate (Gla) residues, resulting in metabolic bone disease because osteocalcin-containing Gla residue is necessary for normal bone mineralization.[133]

Patients treated with cephalosporin antibiotics may develop hemorrhagic states owing to drug-induced vitamin

K deficiency.[134,135] It is thought that these antibiotics block the vitamin K reductase, which is necessary for vitamin K activation.[136] They may also block carboxylation of vitamin K–dependent peptides to yield Gla residues that are required for calcium binding in the conversion of vitamin K–dependent proenzymes to their active state, which are needed in the coagulation cascade.[136]

Some drugs have been linked with subnormal serum folate levels, probably owing to weakly bound folate to serum proteins that can be easily displaced by drugs.[137] The mechanism for this interaction has yet to be described, but it appears that there is a decrease in serum binding of methyltetrahydrofolate caused by the drug itself or one of its metabolites.[138]

Folate deficiency secondary to long-term phenytoin therapy is a common occurrence; approximately 75% of patients taking anticonvulsants have low serum folic acid levels.[139] Progression to megaloblastic anemia is relatively rare, however.[140] Supplementation of folic acid with as little as 1 mg per day may lead to a significant decrease in serum phenytoin concentrations in 15 to 50% of the patients.[122] Although the exact mechanism is unknown, pharmacokinetic analysis of phenytoin suggests that folic acid may increase the affinity of the metabolic enzyme(s) involved in the elimination of the phenytoin without causing overall enzymatic induction.[141,142] To avoid potential folate deficiency and subsequent fluctuations in serum phenytoin levels, practitioners should routinely supplement all patients with folate when phenytoin therapy is initiated.[141]

Like phenytoin, sulfasalazine, an anti-inflammatory agent used to treat Crohn's disease and juvenile rheumatoid arthritis, is one of the leading causes of drug-induced folic acid deficiency in children.[142,143] Megaloblastic anemia, caused by folate deficiency, has been reported in patients receiving high doses of sulfasalazine for prolonged periods.[144]

Aspirin has also been linked with folate deficiency. Serum folate levels are known to be low in many patients with rheumatoid arthritis.[112] It is thought that aspirin alters the transport of folate by competing for binding sites on serum proteins.

Methotrexate, a chemotherapeutic agent that is also used to treat psoriasis, rheumatoid arthritis, and Crohn's disease, limits the availability of methyl groups derived from one-carbon metabolism by inhibiting competitively a key enzyme in the intracellular folate metabolism.[112] Methotrexate functions as an antimetabolite, reversibly inhibiting dihydrofolate reductase.[145]

Valproic acid (VPA), an antiepileptic agent, has been associated with folate deficiency. Like other agents, the mechanism is not fully understood, although it is thought that VPA causes an alteration in the methionine cycle.[146] This results in an elevation of tetrahydrofolate levels and a reduction of both formulated forms of folate. This could also explain VPA's role as a teratogen.[147] In addition, it has been established that VPA may induce L-carnitine deficiency. Patients who develop VPA-induced carnitine deficiency typically experience hyperammonemia syndrome with no other abnormality in the liver function tests. If diagnosed early, the clinical presentation, which includes altered mental status or encephalopathy, can be reversed by L-carnitine supplementation.[148]

Drug Effects on Nutrient Transport

There are several mechanisms by which a drug can impact nutrient transport and then lead to nutritional deficiency. A nutrient can become displaced from plasma protein binding sites by a medication, leading to an increase in the renal excretion of the nutrient, or a drug may compete with a nutrient such that intracellular use of the nutrient is impaired.[149] This may occur when folate stores become depleted in patients receiving therapeutic doses of aspirin.[149]

Excretion

Thiamin deficiency can occur in patients treated with chronic loop diuretic therapy. Seligmann and colleagues reported that patients with congestive heart failure treated with long-term furosemide therapy had increased urinary excretion of thiamin, leading to frank deficiency over time that may have contributed to poor cardiac performance.[150] Similar findings were reported by Brady and colleagues, who observed laboratory evidence of thiamin deficiency in congestive heart failure patients being treated with loop diuretics on a chronic basis.[151]

Drug-Induced Fluid and Electrolyte Imbalance

Several widely used medications can affect electrolyte balance, as summarized in Table 14-2. Sodium balance is altered by thiazide diuretics and the neuroleptic carbamazepine.[152,153] Patients treated long term with carbamazepine have been reported to develop the syndrome of inappropriate antidiuretic hormone (SIADH), resulting in hyponatremia and water retention.[153] In those patients, hyponatremia develops owing to the enhanced renal conservation of water. Similarly, patients receiving excessive diuretic therapy with fluid loss replaced with excessive water are prone to developing SIADH.[53] Conversely, certain medications can cause hypernatremia as a result of water loss and subsequent dehydration. Hypernatremia, secondary to excessive lactulose therapy for hepatic encephalopathy or constipation, is a common drug-induced cause of this disorder.[154]

Renal wasting of potassium, resulting in hypokalemia, has been associated with thiazide and loop diuretics, corticosteroids, amphotericin B, and antipseudomonal penicillins.[53] Insulin and inhaled β_2-agonists (eg, albuterol) can cause a shift of potassium from the extracellular to the intracellular spaces.

Potassium-sparing diuretics (eg, spironolactone), angiotensin-converting enzyme inhibitors (eg, enalapril), heparin, and trimethoprim can cause hyperkalemia.[155] A variety of mechanisms are involved. Trimethoprim has weak diuretic properties with potassium-sparing activity.[156] Heparin can suppress aldosterone, leading to sodium wasting and potassium retention. Patients with renal insufficiency or diabetes mellitus appear to be more susceptible to heparin-induced hyperkalemia.[157]

The impact of medications on phosphorus balance is important in patients receiving nutritional support as the

TABLE 14-2 Examples of Drug–Nutrient Interactions

Medication/Drug Class	*Nutrient*	*Interaction*
Albuterol	Glucose	Hyperglycemia (in diabetics)
Aminocaproic acid	Potassium	May cause hyperkalemia
Amitriptyline	Sodium	May cause hyponatremia
Amphotericin	Magnesium, potassium, sodium	Electrolyte wasting
Aspirin	Folic acid	Decreased serum folate levels
Calcium carbonate	Iron	Decreased iron absorption
Captopril	Potassium, sodium	May cause hyperkalemia, hyponatremia
Carbamazepine	Sodium	May cause hyponatremia
Chloramphenicol	Protein, riboflavin, vitamin B_6, vitamin B_{12}	Decreased protein synthesis
Cholestyramine	Fat-soluble vitamins	Decreased absorption of fat soluble vitamins
Cimetidine	Vitamin B_{12}	Depletion of B_{12} stores
Cisplatin	Magnesium	Magnesium depletion
Corticosteroids	Glucose	Hyperglycemia
Cyclophosphamide	Sodium	May cause hyponatremia
Digoxin	Bran fiber, calcium, magnesium, potassium	Decreased drug absorption, arrhythmias, hypomagnesemia or hypokalemia may enhance toxic effects of digoxin; arrhythmias
Fluorouracil	Thiamin	Inhibits conversion of thiamin to thiamin pyrophosphatase; increased thiamin requirements
Furosemide	Calcium, magnesium, potassium, sodium	Electrolyte depletion
Gentamicin	Magnesium	May cause hypomagnesemia
Insulin	Dextrose	Increased insulin requirements
Isoniazid	Potassium, pyridoxine, tyrosine-rich foods, histamine-rich foods, tyramine-rich foods	Hyperkalemia; vitamin B_6 antagonism; blocks conversion of tyrosine to niacin; may cause headaches, itching, redness, chills, hypotension; isoniazid has some monoamine oxidase inhibitor activity; tyramine-rich foods may cause hypertensive crisis
Lithium	Sodium, magnesium	Increased sodium intake, decreased lithium effectiveness, decreased sodium intake may increase lithium toxicity, may cause hypermagnesemia
Methotrexate	Folic acid	Methotrexate may cause folate deficiency, folate supplementation may decrease methotrexate effects
Mineral oil	Fat-soluble vitamins	Decreased absorption of fat-soluble vitamins with chronic use
Neomycin	Fat-soluble vitamins, medium chain triglycerides, vitamin B_{12}, sodium, glucose, lactose, sucrose, xylose	Impaired absorption
Nonsteroidal anti-inflammatory agents	Potassium	Hyperkalemia in patients with renal disease or receiving potassium supplements or potassium-sparing diuretics
Orlistat	Vitamin E	Reduced vitamin E absorption
Oral contraceptives	Ascorbic acid, folic acid, pyridoxine	Ascorbic acid, folic acid, and vitamin B_6 requirements increased
Para-aminosalicylic acid	Vitamin B_{12}, folate, calcium, iron, magnesium	Decreased absorption of B_{12}, folate, calcium, iron, magnesium
Penicillamine	Acidic foods/beverages	Decreased penicillamine absorption/inactivation
Penicillin	Acidic foods/beverages	Penicillin inactivation
Phenobarbital	Ascorbic acid, vitamin D	Decreases ascorbic acid absorption; interferes with vitamin D metabolism
Phenytoin	Folic acid, pyridoxine, vitamin D	High-dose folic acid may antagonize phenytoin effects; phenytoin may cause folate deficiency, resulting in megaloblastic anemia; may antagonize phenytoin; interferes with vitamin D metabolism
Primidone	Folic acid	May cause folic acid deficiency, leading to megaloblastic anemia
Pyrimethamine	Folic acid	Decreased serum folate levels
Spironolactone	Sodium, potassium	May cause hyponatremia, may cause hyperkalemia
Succinylcholine	Potassium	May cause hyperkalemia
Sulfasalazine	Folic acid	Inhibits the absorption of folic acid
Terbutaline	Glucose	Hyperglycemia (in diabetics)
Theophylline	Caffeine, carbohydrates, charcoal-broiled meat, protein	Increases theophylline side effects; decreased carbohydrate intake may decrease plasma half-life of theophylline; charcoal-broiled meat may decrease theophylline half-life; increased protein intake may decrease plasma half-life of theophylline
Thiazide diuretics	Magnesium, potassium, sodium	Increased wasting
Triamterene	Folic acid	May cause folic acid depletion
Trimethoprim	Folic acid	May cause folic acid depletion
Valproic acid	Carnitine	May cause carnitine deficiency with hyperammonemia
Warfarin	Vitamin K, onions, garlic, vitamin E	May inhibit warfarin response; increased dose needed; excessive amounts may increase the fibrinolytic activity of warfarin; may enhance anticoagulant effect of warfarin
Zidovudine	Carnitine, folic acid	May cause carnitine deficiency; may cause megaloblastic anemia

Adapted from Gura KM. Drug-nutrient interactions. In: Hendricks KM, Duggan C, Walker WA, editors. Manual of pediatric nutrition. Hamilton (ON): BC Decker; 2000. p. 544–67.

synthesis of new cells increases the need for phosphorus. Patients already at risk for refeeding syndrome are particularly susceptible to the effects of drugs known to decrease available phosphorus stores.[158] Drugs such as antacids and sulcralfate can alter the absorption of phosphorus from the gastrointestinal tract by binding to dietary phosphate, thus preventing its absorption. Conversely, patients with renal dysfunction are at risk for development of hyperphosphatemia owing to the inherent phosphate content present in the phospholipid emulsifiers in intravenous fat emulsion or clindamycin phosphate injection.[159]

As previously discussed, medications such as isoniazid and cimetidine can inhibit the hepatic and/or renal hydroxylation of vitamin D, leading to impaired calcium absorption.[160,161] Odes and colleagues concluded that even short-term therapy with cimetidine altered vitamin D metabolism in humans.[161] The researchers came to this conclusion after studying 25-hydroxyvitamin D_3 levels for 30 days in patients treated with cimetidine.

Chronic corticosteroid use can cause a net negative calcium balance and increased bone resorption owing to suppressed intestinal absorption of calcium in conjunction with increased renal calcium and phosphate excretion and a subsequent decrease in renal tubular calcium resorption, resulting in bone osteopenia.[116,162,163] Even frequent use of inhaled steroids has been associated with this response.[164]

Hypomagnesemia as a result of renal wasting can occur in patients treated with loop diuretics, thiazide diuretics, amphotericin B, aminoglycosides, cisplatin, or cyclosporine. Cisplatin-induced hypomagnesemia is dose and duration dependent.[165,166] Cisplatin induces hypomagnesemia by reducing magnesium reabsorption in the ascending loop of Henle and the distal tubule.[167] Forastiere and colleagues reported that the total exposure of free platinum contributes to direct injury and renal toxicity.[168] Carboplatin, an antineoplastic with a chemical structure similar to cisplatin, has been reported to have a lower incidence of hypomagnesemia.[169,170]

Renal wasting of magnesium is also common in patients on prolonged courses of high doses of aminoglycosides.[116,171] Aminoglycosides can inhibit the proximal tubular transport of magnesium in the kidney, predisposing patients with already low intakes of magnesium to hypomagnesemia.[171]

If left untreated, hypomagnesemia will ultimately lead to hypocalcemia. Magnesium deficiency can induce a transient hypoparathyroidism by reducing the secretion of parathyroid hormone (PTH) and a blunted PTH response. This results in an inhibition of the hypocalcemic feedback loop.[165] Other agents, such as aluminum salts, also suppress PTH secretion, resulting in hypocalcemia. Treatment for hypocalcemia induced by hypomagnesemia involves correcting the hypomagnesemia first and then managing the magnesium losses. In some cases, calcium supplementation may be unnecessary.[165]

Trace Elements

Zinc is essential for the function of hundreds of enzymes such as dehydrogenases, aldolases, and peptidases and is involved in a variety of metabolic processes.[172] The formation and activation of zinc-dependent enzymes are regulated by zinc tissue levels.[173] Zinc metalloenzymes are responsible for structural integrity at the cellular level and for the regulation of various aspects of ribonucleic acid (RNA) and DNA metabolism.[173] Zinc deficiency limits the activity of these enzymes, resulting in decreased cell replication and tissue growth and repair.

Zinc does interact with other nutrients. At supplemental doses, zinc may impair copper absorption.[174] Zinc deficiency can also negatively impact vitamin A metabolism by impairing the mobilization of retinol from the liver and altering retinal visual pigment metabolism, which may contribute to the night blindness seen in zinc deficiency.[175] It is thought that zinc deficiency may result in abnormal dark adaptation and/or age-related macular degeneration.[176]

Patients receiving parenteral nutrition are at risk for developing zinc deficiency. Zinc balance during parenteral nutrition depends on the infusion of zinc in amounts sufficient to offset urinary and gastrointestinal losses that occur independent of zinc intake.[172] Premature infants receiving parenteral nutrition will experience a progressive decline in plasma zinc levels despite 14 days of continuous treatment, reflecting their high metabolic demands.[177]

Glucose

Patients with diabetes mellitus or others with insulin resistance (eg, severe infections, catabolic stress) are susceptible to the effects of medications known to impact glucose metabolism. Thiazide diuretics, corticosteroids, and cyclosporine have all been associated with inducing hyperglycemia in susceptible patients.[178] Hyperglycemia occurs in approximately 20% of patients treated with pentamidine.[179] Moreover, protease inhibitors have been recognized as a cause of hyperglycemia.[180]

The long-acting somatostatin analog octreotide has been shown to inhibit insulin secretion and may result in a transient deterioration in glucose tolerance on initiation of therapy.[181] In most cases, alteration of carbohydrate metabolism does not appear to be a problem.

Hypoglycemia is the most common metabolic abnormality associated with pentamidine therapy.[182] The mechanism responsible for this adverse effect may involve a direct cytolytic effect on pancreatic beta cells, resulting in insulin release and hypoglycemia and a subsequent insulin deficiency owing to loss of beta cell function.[183] Eventually, however, pentamidine-induced pancreatic beta cell damage may lead to insulin deficiency and result in hyperglycemia, although this is considerably less frequent than hypoglycemia.[183]

Drugs or foods that have the ability to induce a rapid release of insulin can increase the risk of hypoglycemia, especially if taken with alcohol.[184] β-Blockers such as propranolol can inhibit glycogenolysis and, during periods of vigorous exercise, induce hypoglycemia.[184]

Fat

With increased awareness of lipid abnormalities and coronary artery disease, drug-induced liprotein abnormalities

must be considered, especially in patients in whom no other causes of dyslipidemia exist. Some of the most common causes of secondary dyslipidemia are medications. When a drug is used for a short period only, practitioners need to be aware of the effects on the patient's lipoprotein profile versus the chance that an underlying dyslipidemia has been exacerbated. Drugs used chronically may be more problematic as they may predispose the patient to atherosclerosis.[185] Table 14-3 lists medications associated with dyslipidemia.

Protease inhibitors interfere with some proteins involved in fat metabolism (ie, cytoplasmic retinoic acid–binding protein type 1).[186] Protease-inhibitor binding to low-density lipoprotein (LDL) receptor–related proteins (LRPs) impair hepatic chylomicron uptake and triglyceride clearance by the endothelial LRP-lipoprotein lipase complex. The resulting hyperlipidemia contributes to central fat deposition and insulin resistance.[186] It is also thought that protease inhibitors may also disrupt steroid hormone production, leading to lipodystrophy.[187] See Chapter 38 for a full discussion of human immunodeficiency virus (HIV) lipodystrophy.

L-Asparaginase has been reported to cause abnormalities in lipid metabolism, ranging from hypocholesterolemia and hypotriglyceridemia to hypercholesterolemia and hypertriglyceridemia. Parsons and colleagues suggested that this alteration in lipid metabolism is caused by structural changes in the high-density lipoprotein (HDL) particles from high density to lower density that is reflected in an altered ratio of lipid to protein.[188] The authors suggested that prior to the initiation of L-asparaginase therapy, HDL-cholesterol particles are protein rich but gradually become lipid rich because of an asparaginase-associated reduction in protein synthesis. They also concluded that modifications in asparaginase therapy are not necessary, although close monitoring is recommended for patients whose triglyceride levels exceed 2,000 mg/dL when the risk of pancreatitis is increased.

In addition to asparaginase-associated lipid abnormalities, patients being treated for acute lymphoblastic leukemia often receive corticosteroids that may alter lipid and lipoprotein metabolism by increasing hepatic cholesterol synthesis.[188] Corticosteroids increase the frequency of hypercholesterolemia and hypertriglyceridemia with elevations in LDL and HDL levels, often in a dose-related manner.[185] Females appear to be more susceptible than males to these changes. Switching to alternate-day therapy may reduce lipoprotein levels in some patients.[185]

TABLE 14-3 Medications Associated with Dyslipidemia

Medication	*Total Lipids*	*Total Cholesterol*	*Triglycerides*	*Low-Density Lipoprotein*	*High-Density Lipoprotein*	*Very Low-Density Lipoprotein*
Abacavir			↑			
Amiodarone		↑	↑			
Amprenavir		↑	↑			
Anabolic steroids				↑	↓	
β-Blockers			↑			
Calcitriol		↑				
Cholestyramine			↑			
Cyclosporine	↑	↑	↑	↑		
Dexrazoxane			↑			
Didanosine			↑			
Disopyramide		↑	↑			
Efavirenz		↑	↑		↑	
Enoxaparin	↑					
Ergocalciferol		↑				
Estrogen			↑			
Fluconazole		↑	↑			
Glucocorticoids	↑	↑	↑	↑	↓	↑
Interferons			↑			↑
Isotretinoin		↑	↑		↑	
Itraconazole			↑			
L-Asparaginase			↑			
Miconazole (IV)	↑	↑				
Mycophenolate		↑				
Nelfinavir	↑					
Paclitaxel			↑			
Phenothiazines		↑			↓	
Progestins			↓	↑	↓	↓
Propofol	↑					
Retinoids (vitamin A)			↑	↑	↓	↑
Risperidone			↑			
Ritonavir		↑	↑			
Testosterone	↑	↑		↑	↓	
Thiazide diuretics	↑	↑	↑	↑		↑
Vitamin E		↑	↑			

Adapted from Henkin J et al.[186]

Orally administered estrogens decrease serum LDL and increase serum HDL levels in a dose-related manner.[185] Moreover, these agents are known to increase serum triglyceride levels by 30 to 87%.[185] It has been suggested that low-dose estrogens be used to minimize elevations in triglyceride levels without compromising their favorable impact on LDL and HDL levels.[185] Interestingly, other routes of estrogen administration (topical, intradermal, intramuscular) tend not to have as pronounced an effect on lipoproteins, perhaps because these routes bypass first-pass metabolism through the liver, thus having a smaller impact on hepatic protein synthesis.[185,189] Progestins, often used in combination with estrogens in various oral contraceptive products, can also affect lipoprotein levels. Generally, progestins elevate LDL levels and decrease triglyceride, HDL, and very low-density lipoprotein levels, correlating with the androgenic activity associated with specific progestins.[185] Newer low-dose triphasic oral contraceptives (eg, ethinyl estradiol-levonorgestrel, ethinyl estradiol-norethindrone) do not have any appreciable alterations in lipid profiles or at best mild increases in serum cholesterol, LDL, and triglycerides.[190,191]

Like estrogens, anabolic steroids can also cause profound, dose-related effects on lipoprotein metabolism. Reductions in HDL levels in conjunction with an elevation in LDL levels are often seen in patients using these agents.[185] The exact mechanism has not yet been defined, but caution is advised in using these agents in patients prone to dyslipidemia or atherosclerosis.

Drugs and Appetite

Impairment of nutritional status owing to drug use often results in drug-induced nutritional deficiencies in those cases in which the medication results in appetite suppression and decreased food intake. Often these signs and symptoms of nutrient deficiencies are nonspecific and may mimic those of other diseases and conditions.

Drugs can reduce food intake through a variety of mechanisms. Drugs that affect appetite (Table 14-4) may do so by either a central or peripheral effect, including loss of appetite, inducing sedation, or evoking adverse response when food is ingested.[191] The primary effect typically centers around appetite suppression, a centrally acting mechanism that includes the catecholaminergic (eg, dextroamphetamine), dopaminergic (eg, levodopa), serotoninergic (eg, fenfluramine), and endorphin (eg, naloxone) modulators, which may all act to suppress appetite.[191] Peripherally acting mechanisms that can indirectly suppress appetite include those agents that inhibit gastric emptying (eg, levodopa) or bulking agents (eg, methylcellulose).

A secondary response may also occur when an adverse response to food caused by the drug results in a loss of appetite. The emetic center, located within the brainstem, is easily stimulated by the action of many drugs. These include drugs that cause nausea and vomiting (eg, digoxin-toxic dose), drugs causing a loss of taste (eg, penicillamine), drugs causing stomatitis (eg, fluorouracil), and hepatoxic agents (eg, alcohol).[191,192]

Another way in which medications can cause anorexia is through depletion of various nutrients. High doses of aluminum- or magnesium-containing antacids can result in phosphate depletion, leading to muscle weakness and anorexia.[193] Similarly, loop diuretics can lead to depletion of sodium, potassium, and magnesium, which can result in anorexia.[194] Drugs known to deplete folate, such as phenytoin, sulfasalazine, and trimethoprim, can result in weight loss and anorexia.[195] Penicillamine, which induces zinc depletion, can lead to diminished taste acuity and possibly decreased food intake.[196]

Ironically, even a nutrient can induce anorexia. Belle and Halpern reported that patients taking relatively large doses of niacin for hyperlipidemia experienced gastrointestinal symptoms that resulted in poor appetite and moderate weight loss.[197]

Zinc supplements have been used to treat drug-induced hypogeusia with mixed results. Although zinc supplementation has been used successfully to manage hypogeusia in patients undergoing dialysis, Dahl and colleagues did not see similar findings when patients with acetazolamide-induced taste disturbances were given zinc supplements.[198,199]

Appetite Enhancers

Appetite enhancers are useful in reversing the anorexia of disease, in particular cancer cachexia and HIV wasting. Several medications are frequently used, although none have yet become a standard of therapy.

The appetite-boosting properties of corticosteroids have been well established.[200] Their impact on weight gain seems to be short term, however. Moertel and colleagues suggested that patients treated with dexamethasone saw appetite improvement after 2 weeks of treatment, but the effect disappeared by week 4.[201] Some attribute the improved appetite to the mood-enhancing properties of steroids rather than a specific effect on appetite.[202]

TABLE 14-4 Drugs That Affect Appetite

Drugs That Suppress/ Decrease Appetite	*Drugs That Stimulate Appetite*
Alcohol	Anabolic steroids
Aluminum hydroxide	Benzodiazepines
Amphetamines	Clemastine
Cisplatin	Cyproheptadine HCl
Dactinomycin	Dronabinol
Digoxin	Glucocorticoids
Furosemide	Insulin
Griseofulvin	Megestrol acetate
Hydralazine	Oral contraceptives
Hydroxyurea	Phenothiazines
Methotrexate	Tricyclic antidepressants
Methylcellulose	
Mineral oil	
Penicillamine	
Spironolactone	
Sulfasalazine	
Thiazide diuretics	
Topiramate	

Adapted from Gura KM. Drug-nutrient interactions. In: Hendricks KM, Duggan C, Walker WA, editors. Manual of pediatric nutrition. Hamilton (ON): BC Decker; 2000.

The antihistamine cyproheptadine has become one of the most commonly used appetite stimulants in pediatric patients, particularly those with anorexia nervosa. It is a potent serotonin antagonist. By decreasing brain serotonin levels, appetite is enhanced and food intake is increased, resulting in weight gain.[203]

Megestrol acetate is a drug with antiestrogen properties whose original indication was in the treatment of breast cancer. It was one of the first drugs used to treat HIV wasting. It is a powerful appetite stimulant, and weight gain seen with its use is substantial, although it tends to be mostly fat, with minimal increases in lean body mass.[204] Megestrol also lowers testosterone levels in males, which may explain its minimal increases in lean body mass. Adrenal suppression has also been reported with long-term megestrol use; thus, abrupt discontinuation should be avoided.[205] Megestrol acetate also has been used to stimulate appetite and promote weight gain in a limited number of patients with cachexia associated with neoplastic disease. Although the exact mechanism of action has not been determined, it has been suggested that megestrol and/or its metabolites may, either directly or indirectly, stimulate appetite, resulting in weight gain, or may alter metabolic pathways by interfering with the production or response of mediators such as cachectin, a hormone that inhibits adipocyte lipogenic enzymes.[206]

Dronabinol is a derivative of marijuana that is primarily used in pediatric patients as an antiemetic but has some use in treating anorexia, primarily in HIV wasting.[207] Like megestrol, it can stimulate appetite as well as interest in food. Its effects on mental status, however, limit its usefulness.[208]

Because cytokine effects on appetite can contribute to the anorexia of disease, anticytokine monoclonal antibodies and receptor antagonists may have a role in inhibiting cytokine action.[209] Some agents, such as the corticosteroids, inhibit the transcription of interleukin (IL)-1, tumor necrosis factor (TNF), and other cytokinases. Other agents appear to act by binding a mitogen-activating protein kinase necessary for the translation of messenger RNAs.[209] Fish oil supplements that are rich in omega-3 fatty acids decrease the anorectic effect of IL-1 and TNF.[210,211] Unfortunately, the fishy taste associated with these supplements makes them a less than desirable option.

Appetite Suppressants

Although, for long-term success, weight loss takes a great deal of self-control to resist the many internal and external cues to eat, appetite suppressants can augment weight loss by reducing the hunger drive, thereby assisting the patient to adhere to a restricted caloric diet.[212] The major class of drugs currently in use for the adjunctive treatment is the centrally acting appetite suppressants. This class is further subdivided into those that act on the noradrenergic nervous system and those that act on the serotoninergic nervous system.

Given their high potential for abuse and numerous side effects, the noradrenergic agents (eg, dextroamphetamine) are no longer routinely used in weight loss management unless other therapies have been proven ineffective. These agents block the reuptake of dopamine and norepinephrine from the synapse, thus increasing the amount available in the cerebral cortex and reticular activating system.[212]

The neurotransmitter serotonin is responsible for appetite suppression and satiation. Serotonin, as part of a complex negative feedback loop, accumulates in certain areas of the brain in response to feeding.[212] Fenfluramine, dexfenfluramine, and fluoxetine inhibit serotonin reuptake at presynaptic spaces. They have few central stimulatory effects.

Other agents that have the potential to cause anorexia and may have a potential role in weight loss management are the thermogenic drugs.[213] These include endogenous hormones (ie, insulin, thyroid hormone) and sympathomimetic agents with α- or β-adrenergic properties.[213] Currently, exogenous thyroid has no role in obesity management owing to its adverse effects on protein breakdown, cardiovascular complications, and bone mineralization.[214]

Vitamin Supplementation/Hypervitaminosis

Megavitamin therapy has been advocated in the treatment of various disease states, including schizophrenia, cancer, and the common cold.[215] A megadose is generally considered to be 10 or more times the Recommended Dietary Allowance.[216] Although excess water-soluble vitamins are excreted and usually cause few problems, side effects have been reported in cases of excessively high doses.[217] Dietary supplementation can also impact response to medications. If used carelessly, vitamin and mineral supplementation alone or as part of a fad diet can potentiate or exacerbate nutrient–nutrient interactions, as summarized in Table 14-5. In some cases, this can be beneficial, as noted in Table 14-6.

Drug-metabolizing enzyme systems have been shown to be highly dependent on vitamin C status. Houston and colleagues showed that normal individuals receiving supplemental ascorbic acid had a substantial increase in antipyrine clearance, whereas Beatie and Sherlock reported that vitamin C deficiency was partly responsible for impaired drug clearance in patients with liver disease.[218,219] When ascorbic acid is taken in excessive amounts, enzyme saturation occurs, and the vitamin acts as a chemical and enters into nonenzymatic reactions.[220] Ascorbic acid is a strong reducing agent and is able to impact other dietary components as well as alter drug disposition.[220] Ironically, scurvy, the main deficiency state associated with inadequate dietary intake of ascorbic acid, a relatively rare condition today, can occur in infants born to mothers taking large doses of vitamin C.[220] Both the mother and fetus increase their metabolic destruction of ascorbic acid after maternal ingestion of large doses of ascorbic acid. At birth, any dietary ascorbic acid ingested by the infant is degraded rapidly, leading to a deficiency state. Reports of acute scurvy have been reported in infants breast-fed by mothers who had ingested more than 400 mg vitamin C daily during pregnancy.[221] A similar situation can occur in adults dependent on large doses of vitamin C. Therefore, it is recommended that patients receiving megadoses of vitamin C not be abruptly stopped but rather tapered by 10 to 20% until

TABLE 14-5 Examples of Nutrient–Nutrient Interactions

Nutrient	*Interaction*
Calcium	High calcium intake interferes with phosphorus and iron absorption
Cysteine	May chelate with copper in parenteral nutrition solutions
Magnesium	High magnesium intake may impair calcium absorption, decreases phosphorus absorption
Phosphorus	High intake decreases magnesium absorption
Zinc	High zinc intake may impair copper absorption
Vitamin A	Megadoses may interfere with iron, iodine, copper, calcium absorption; can also interfere with absorption of ascorbic acid, vitamin K, vitamin E, and vitamin D
Vitamin C	Increases iron absorption, impairs copper absorption, interferes with cyanocobalamin absorption
Vitamin D	Reduced intake impairs calcium and phosphorus absorption and utilization
Vitamin E	Inhibits the reticulocyte and hemoglobin response to iron

Adapted from Gura KM. Drug-nutrient interactions. In: Hendricks KM, Duggan C, Walker WA, editors. Manual of pediatric nutrition. Hamilton (ON): BC Decker; 2000.

discontinued or on maintenance doses. Other complications associated with megadoses of ascorbic acid include vitamin B_{12} deficiency. Herbert and Jacob reported that even ascorbic doses as little as 250 mg may destroy up to 81% of cyanocobalamin in a moderate vitamin B_{12}–containing meal and up to 25% in a vitamin B_{12}–rich meal.[222] To blunt the intensity of this interaction, the authors suggested that ascorbic acid be taken 2 or more hours after meals.

Oxalate stones may occur in susceptible patients receiving doses of greater than 4 g/day of ascorbic acid. Auer and colleagues reported that a hematuria and calcium oxalate dihydrate crystal formation in a 25-year-old male 8 days after ingesting 4 g of ascorbic acid daily resolved 5 days after discontinuing ascorbic acid supplementation.[223]

The daily consumption of vitamin B_6 (pyridoxine) in doses of 50 to 500 mg is not unusual given the currently available strengths of over-the-counter products. High doses, however, may have a toxic action on the nervous system.[224] Sensory neuropathies have been reported in adults who received daily doses of 2 g of pyridoxine over a 4-month period or as soon as 2 months when daily doses of 5 g were ingested.

Hypervitaminosis A and D has been described in children, but the occurrence is rare.[225,226] Both are life threatening on an acute basis; vitamin A may cause increased intracranial pressure, whereas vitamin D may cause fatal hypercalcemia. Infants and young children are especially susceptible to excessive doses of vitamin A. Acute toxicity has been reported in infants receiving doses of 50,000 to 100,000 μg (166,666 to 333,333 IU) retinol as palmitate. Individual variation is significant, however. Field studies have used periodic massive doses of vitamin A, with thousands of 1- to 6-year-old children receiving 200,000 IU of retinyl palmitate (60,000 μg retinol), with approximately 1% exhibiting signs of intolerance that disappeared within hours of administration.[227] Chronic toxicity seen in infants and young children usually results from daily doses of 10,000 to 50,000 μg (33,333 to 166,666 IU) for several months.[228] Symptoms gradually disappear on discontinuation. The American Academy of Pediatrics recommends that daily vitamin A supplementation of more than

TABLE 14-6 Examples of Vitamin–Drug Interactions

Nutrient	*Medication*	*Interaction*
Ascorbic acid (vitamin C)	Coumarin anticoagulants, gentamicin, iron salts, oral contraceptives, tricyclic antidepressants	Shortens prothrombin time, may antagonize warfarin response; acidifies urine, decreases efficacy of gentamicin; increased iron absorption; intermittent use may cause contraceptive failure; megadoses (> 2 g/day) may reduce therapeutic response of tricyclic antidepressants
Folic acid	Phenytoin, pyrimethamine	Reduces phenytoin bioavailability, may antagonize anticonvulsant action of phenytoin; reduces pyrimethamine efficacy
Niacin	Adrenergic blockers, aspirin, HMG-CoA reductase inhibitors ("statins"), isoniazid	Enhances vasodilation, may cause orthostatic hypotension; aspirin decreases flushing seen with niacin use; increased risk of statin-associated myopathy/rhabdomyolysis with concurrent use; increased niacin requirement seen with isoniazid use
Pyridoxine (vitamin B_6)	Barbiturates, levodopa, phenytoin	Reduced barbiturate response, reduces levodopa response; megadoses may impair phenytoin effect, cause decrease in phenytoin levels
Vitamin A	Aluminum hydroxide, coumarin anticoagulants, isotretinoin, oral contraceptives	Reduced vitamin A absorption; megadoses of vitamin A can enhance anticoagulant response, increase risk of bleeding; isotretinoin competes with vitamin A; increases serum vitamin A levels
Vitamin D	Digoxin	Vitamin D may cause hypercalcemia, leading to arrhythmias
Vitamin E	Coumarin anticoagulants, vitamin A, iron salts	Potentiates anticoagulant response; increases serum vitamin A levels; inhibits the reticulocyte and hemoglobin response to iron therapy
Vitamin K	Coumarin anticoagulants	Antagonizes anticoagulant response

Adapted from Gura KM. Drug-nutrient interactions. In: Hendricks KM, Duggan C, Walker WA, editors. Manual of pediatric nutrition. Hamilton (ON): BC Decker; 2000.
HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

3,000 μg (10,000 IU) for young children be used under medical supervision.[229]

In typical doses, vitamin D is used to prevent and treat rickets.[230] Serious poisoning can occur with excessive doses. Sustained daily intake of as little as 1,800 IU in children has been reported as toxic.[231] Excessive vitamin D leads to increased absorption of calcium from the gastrointestinal tract and enhanced bone resorption, with a subsequent loss of renal concentrating ability. Children typically will present with anorexia, vomiting, polyuria, or irritability associated with the increased serum calcium concentrations.[232] It should be noted, however, that very high doses of vitamin D have been effective in some patients with hereditary vitamin D–resistant rickets (HVDRR).[233] HVDRR accompanied by alopecia reflects a more severe form of vitamin D receptor resistance and is rarely responsive to vitamin D. Initial ergocalciferol therapy for children with vitamin D–resistant rickets is 1,000 to 2,000 μg/day (40,000 to 80,000 U) with phosphate supplement. The daily dose is increased at 3- to 4-month intervals in 250 to 500 μg (10,000 to 20,000 U) increments.[234]

In 1992, an outbreak of hypercalcemia owing to vitamin D intoxication was noted. In the case series, eight patients suffered vitamin D toxicity that was traced to excessive amounts of the vitamin in milk produced by a single dairy.[235] These were the first reported cases of hypervitaminosis D from commercial food products in the United States since fortification became commonplace in the 1930s. A second study summarized the findings of an analysis of 42 containers of milk and 10 cans of infant formulas from supermarkets in five states.[236] Nearly two-thirds of the milk container samples had less than 80% of the stated amount, whereas 4 of the 42 samples had over 120% of the labeled vitamin D content. The 10 infant formulas tested had vitamin D levels ranging from 111 IU for every 100 kilocalories to 250 IU per 100 kilocalories, exceeding the maximum permitted by the US Food and Drug Administration (FDA) regulation of 100 IU per 100 kilocalories. FDA-compliant studies on both dairy products and infant formulas compiled over a 10-year period also showed some variance in vitamin D levels but not to the extent that would constitute a health risk.[237]

Vitamin K–rich foods (ie, green leafy vegetables, cabbage, broccoli), when intake is irregular, can alter response to anticoagulants such as warfarin. When ingested in high amounts, these foods can be associated with anticoagulant failure, resulting in the need for higher doses. Similarly, when patients who have been stable on warfarin suddenly decrease their intake of these vitamin K–rich foods, they can put themselves at risk for bleeding because they are suddenly receiving too large a warfarin dose. Warfarin creates a partial deficiency of the active form of vitamin K involved in the post-translational modification factors (II, VII, IX, X, and proteins C and S). [238] Other sources of vitamin K, such as intravenous fat emulsions that are prepared from soybean or safflower and soybean oils, contain phytosterols that contain vitamin K.[239] Warfarin resistance has been reported in patients taking warfarin who also received intravenous fat emulsions.[239] This interaction presumably occurs because of the vitamin K content of the intravenous fat emulsion. Frequent monitoring of the international normalized ratio (INR) and warfarin dosage adjustments are imperative in these patients.

CONCLUSION

The human diet is highly heterogeneous in its composition, method of preparation, quantity, and time of consumption. Consequently, drug kinetics as a result of diet varies widely in subjects based on age, gender, culture, and economic status. Even within the same individual, seasonal variations will occur that impact dietary habits and ultimately drug-related effects. Although each factor may play a small role by itself, a much larger synergistic effect could occur when combined with other dietary factors, as well as genetic and environmental factors.

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CHAPTER 15

GENE EXPRESSION

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Altering the expression of genes has become a rapidly developing area of research in medicine. The realization that gene expression is important in a wide range of diseases, and not just in inherited disease, has resulted in recognition of the whole field of gene expression as one that may bring new therapeutic options. Although most recent attention has focused on the benefits of altering gene expression by inserting new genetic material into cells by a variety of vectors, the expression of genes can also be altered by other means, most notably by changing the molecular environment that cells inhabit. Using the natural responses of a cell to changes in its surroundings offers a new and amenable way to alter the expression of its genes. Many ways of altering these surroundings can be proposed, but no single act alters the environment of the cells of the body more than the ingestion of food. Thus, the future of nutrition as a therapeutic tool may lie in its potential for influencing gene regulation. This chapter examines this emerging field and outlines some concepts that may prove useful in establishing the scientific basis from which future treatments may develop.

The survival of a child to reproductive age and beyond requires an ability to respond to external demands. Every organ in the body is attuned to this need. Many organ systems have two levels of response to external changes. There is a rapid response, often occurring within seconds of a new stimulus; the contraction of muscle fibers following a neuronal impulse and the breakdown of glycogen by the liver during hypoglycemia are examples of how cells can quickly change. Such responses do not involve changes in gene expression. The cells maintain themselves in a state of readiness by synthesizing proteins whose activity can quickly alter in response to external stimuli. Behind this immediate response, there are other slower, but more lasting, responses that require genetic control. For example, when exercise increases on a regular basis, muscle mass increases, as does the activity of the attendant enzymes that serve the increased metabolic needs. Similarly, regular exposure of the liver to drugs induces the expression of enzymes that catalyze their breakdown.

There are few external stimuli on a child more important than his or her nutritional environment. The metabolic processes underlying the rapid response of cells to nutritional variations have long been documented in humans and other mammals.[1] However, the mechanisms whereby gene expression changes in response to nutritional stimuli is still poorly understood in humans or, indeed, in any multiorgan animal. This is, at first, surprising because in bacteria, the study of nutritional changes led to our understanding of some of the most fundamental mechanisms of gene expression. The elucidation of the induction of proteins that transport and hydrolyze lactose (the lac operon) after adding lactose to bacterial culture media was the first examination of any form of gene regulation.[2] These observations spawned an explosion of research in other regulatory genes in bacteria and in unicellular, eukaryotic organisms such as yeast. The up-regulation of the bacterial genes that handle tryptophan when this amino acid is scarce (the Trp operon) has become another well-understood example of nutrient–gene interaction.[3]

Progress in the study of nutrient–gene interaction in eukaryotic cells has been slower for two main reasons. First, the molecular mechanisms controlling gene expression are more complex than in bacteria, and, second, it is more difficult to identify the metabolites of nutrients that may be responsible for inducing such changes. This review therefore covers some of the recent advances in the study of nutrition and gene expression in the human and, where necessary, in other mammals. Nutritional changes ultimately impinge on most cells in the body; however, it is the epithelium of the gastrointestinal tract that first encounters any variation in nutrient intake. Much of this chapter

therefore concentrates on how nutritional factors can alter the expression of genes in intestinal epithelial cells. The relevance of nutrient–gene interactions to human physiology will also be stressed. Finally, because manipulating nutritional intake may be a way of treating disease in children, the review will discuss nutritional therapy in childhood in the light of its effects on gene expression.

PHYSIOLOGIC IMPORTANCE OF NUTRITIONAL REGULATION IN GENE EXPRESSION

The effect of nutrients on gene expression may have different implications in different individual situations (Table 15-1). First, genes may be up-regulated to better use the supply of a particular nutrient when it is scarce. Transporters of nutrients and the enzymes that metabolize them are examples of proteins that may be induced by nutrients. Second, the expression of genes required for the storage of a particular nutrient may be altered according to that nutrient's abundance. Third, nutrients regulate the secretion of hormones that control the homeostasis of metabolic processes. For example, insulin synthesis increases after increased carbohydrate intake to maintain glucose homeostasis. Finally, food is part of our external environment and, as such, represents a challenge to the cells that come into intimate contact with it. This challenge is met, in the main, by the epithelial cells lining the gastrointestinal tract.[4] The ability of these cells to alter the expression of their genes with changes in food intake is one of the ways by which the intestinal epithelium can dominate the intestinal environment.

Certain fundamental characteristics are found in the mechanisms that underlie each of these different aspects of nutrient–gene interactions. They include a specific interaction between the cell and a particular nutrient (sensing) and a pathway by which such an interaction may translate into alterations in gene expression (signal transduction) (Figure 15-1). We have little understanding of these mechanisms at present. However, some aspects of the molecular biology of these two functions will be examined later in this review.

TABLE 15-1 Physiologic Importance of Nutritional Regulation of Gene Expression

To satisfy the nutritional needs of an organ
Managing storage fuels required by other organs
Production of hormones essential to whole body metabolism
Direct interaction with the body's external environment along the gastrointestinal tract

GENES CONTROLLING THE NUTRITIONAL REQUIREMENTS OF INDIVIDUAL ORGAN SYSTEMS

Survival of cells depends on their ability to extract nutrients and other essential molecules from their surroundings, and they synthesize proteins specifically for this purpose. Broadly speaking, two categories of genes are involved: those genes that express proteins that transport nutrients across cell membranes and those genes that express enzymes that metabolize nutrients. In both cases, genes are regulated purely to satisfy the requirements of an organ system. This form of gene regulation is similar in concept to the regulatory genes of bacteria like the Trp operon.[3] The cells are changing their phenotype to their own advantage rather than to suit the needs of the body as a whole.

A good model of how cells may respond to their nutritional environment for their own needs is the use of glutamine by skeletal muscle.[5] Glutamine availability modulates muscle turnover, and glutamine is an important source of aminonitrogen for muscle cells.[6] Glutamine and glutamate are transported into cells by sodium-coupled transporters. For experimental purposes, rat skeletal muscle can be grown as primary cell cultures. These cells exhibit an up-regulation of the inward transport of both glutamine and glutamate when they are deprived of an exogenous glutamine supply.[7–9] In addition, the activity of glutamine synthetase (GS) simultaneously increases. This enzyme catalyzes the addition of an amino group to the carboxyl moiety of the glutamate molecule to form glutamine. Two different nutrients, glutamine and glutamate, can therefore ultimately satisfy the glutamine requirements of the muscle cell through separate pathways, each of which is under genetic control. This system exemplifies how different nutrients can cross-stimulate the expression of a related set of proteins: removal of glutamine or glutamate from the cell medium results in an enhancement of the transport of both amino acids. Not only does lack of glutamine and glutamate enhance the expression of their own transport proteins, but deprivation of either substrate will also up-regulate the transporter of the other.[8] A study of the

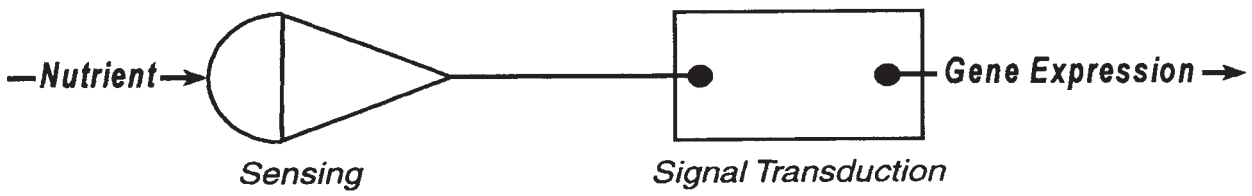

FIGURE 15-1 The regulation of gene expression by nutrients requires two generic mechanisms. First, molecules (either receptors or enzymes) within the cell must recognize the nutrient. Second, this interaction must initiate a sequence of events that ultimately alters the transcription or translation of genes. These functions of sensing and signal transduction have been depicted in this cartoon using electronic symbols.

kinetics of transport demonstrated that withdrawal of glutamine (or glutamate) enhanced the maximum rate at which the amino acid is transported into the cell (the V_{max}) and did not alter the affinity of the transporter for its amino acid.[9] This suggests that deprivation resulted in an increase in the production of the number of transporters available. The time required to double the V_{max} was 4 hours. This fact, taken together with the observation that the induction of both glutamate and glutamine transporters was lost when glutamine was withdrawn in the presence of actinomycin D (inhibitor of ribonucleic [RNA] synthesis), indicates that their regulation is mediated through the initiation of transcription.

In recent years, there has been an explosion in our understanding of the physiology of glutamine transporter systems.[10] At least four distinct families have been identified to date: the Na+-dependent glutamine transporter, system N (SN1), system A (ATA1, ATA2), system ASC/B, and system y (+)L, the latter encoding for Na+-independent glutamine transporter genes.[11,12] Molecular characterization of these systems suggests specific roles in glutamine efflux and uptake[12]; however, the exact mechanism(s) by which transport regulates gene expression remain unclear.

In vivo, glutamine homeostasis is to a large extent determined by the activities of GS and glutaminase.[13] Both enzymes exhibit regulation of gene expression at both transcriptional and post-transcriptional levels. During stress and sepsis, the production of glutamine is increased, primarily owing to greater GS activity in the skeletal muscle.[14]

Glutamate and glutamine regulation, although important, constitute only a minor part of nutrient homeostasis in vivo. Glucose, on the other hand, is central to human metabolism. Glucose, galactose, and fructose are the major dietary saccharides, and the derangement of glucose handling in diabetes mellitus constitutes the most common condition requiring nutritional advice. Intensive research in the last two decades has revealed the great complexity involved in glucose transport. Glucose is transported into enterocytes primarily by the sodium-glucose cotransporter (SGLT 1). Two Na+ ions must first bind to the transporter, and then one molecule of glucose or galactose may be actively transported into the cell. To date, six members of the SGLT 1 family have been identified on the basis of sequence homology within the human genome.[15] In addition to SGLT proteins, facilitative diffusion glucose transporter (GLUT) proteins catalyze glucose transport into cells. Until recently, five mammalian GLUT proteins had been identified, each a separate gene product with unique properties, for example, GLUT 5 being specifically activated by dietary fructose.[16] Interestingly, in the last 2 years, several novel genes with signature homology to GLUTs have been identified and characterized.[17,18] The GLUT family can be divided into three groups: class I (the previously known GLUTs 1–4), class II (GLUTs 5, 7, 9, and 11), and class III (GLUTs 6, 8, 10, and 12 and the myo-inositol transporter HM1T1). The new members exhibit both tissue and subcellular specificity, which most likely represents another level of regulation. Analysis of GLUT protein levels in patients with non–insulin-dependent diabetes mellitus revealed a four- to fivefold induction in SGLT 1, GLUT 2, and GLUT 5 protein levels, highlighting dysregulation in monosaccharide transport.[19] Identity of mechanism(s) by which these essential dietary carbohydrates directly affect their own uptake (via availability of GLUT and SGLT proteins) is most urgent if we are to understand the marked increase in the incidence of childhood obesity and diabetes facing the developed world.

Genes Regulating the Storage of Nutrients

The storage of nutrients is essential to provide energy in times of fasting, and the mechanisms that control this function must be regulated by nutrient intake to be effective. The two most important organs involved in nutrient storage are the liver and adipose tissue. Both cell types transport glucose and other nutrients and convert them into fat; in the case of the liver, glucose is also converted to glycogen. Insulin is the major hormone that promotes glucose use and induces storage. Its sensitive response to dietary intake complicates the study of the direct effects of nutrients on genes that regulate storage. The direct effects of glucose, in particular, on the expression of transporters and metabolic enzymes have to be dissected from the effects of insulin on these same genes. (The actions of hormones such as insulin on target organs are beyond the scope of this review, but it is well covered by a number of excellent articles within the field of endocrinology.[20,21]) Experiments performed in vivo make the distinction between the direct effects of nutrients and those mediated through hormonal changes difficult to achieve.

Until recently, the molecular mechanism(s) by which glucose directly modulates the transcriptional regulation of lipogenic enzymes was poorly understood. Kawaguchi and colleagues have identified a hepatic transcription factor, carbohydrate responsive element-binding protein (ChREBP), which is regulated at two different levels: nuclear entry and deoxyribonucleic acid (DNA) binding via phosphorylation events mediated by glucose and cyclic adenosine monophosphate (cAMP).[22,23] The transcription factor localizes to the cytosolic compartment of hepatocytes at low glucose levels but translocates to the nucleus in the presence of high glucose levels. Further phosphorylation of ChREBP by pyruvate kinase (PK) A led to an inhibition in its DNA-binding ability consistent with a negative feedback role for the glucagon/cAMP pathway.[24]

Earlier studies investigating the direct contribution of glucose toward increased nutrient storage in the liver have focused on the three main control points of glucose metabolism before it enters the mitochondrion as pyruvate. These are the enzymes glucokinase, 6-phosphofructokinase, and L-type PK. Fructose is also metabolized to pyruvate, bypassing the first two enzymes. PK is therefore a regulatory enzyme in the metabolism of both monosaccharides. The transcription factor ChREBP (described above) was purified by its ability to bind to the glucose-carbohydrate response elements present in the PK promoter sequence.[22]

Feeding a high-carbohydrate/low-fat diet to fasting rats resulted in the induction of genes involved in glucose uptake and lipogenesis.[25] Both insulin-mediated and

increased glucose metabolism were required for maximum induction of gene expression. Both in vitro and in vivo studies have identified a critical role for the transcription factor sterol regulatory element binding protein (SREBP) in insulin-mediated transcriptional control of genes involved in glucose, fatty acid, and triglyceride metabolism.[26,27] The involvement of at least two transcription factors (ChREBP and SREBP) for optimum lipogenesis may reflect the degree of molecular complexity required for coordinated integration of hormonal and nutritional signals in regulating energy requirements of a cell. Identification of signaling events regulating lipogenesis is crucial to further our understanding of disease states such as diabetes and obesity.[24,28]

Insulin has a major effect on the activity of the three glycolytic enzymes via transcriptional and/or post-translational modifications. Glucokinase messenger ribonucleic acid (mRNA) expression was induced by insulin via an insulin receptor substrate (IRS)-1-phosphatidylinositol-3 (PI3)-kinase–dependent pathway.[29] PI3-kinase and p44/p42 mitogen-activated protein kinase (MAPK) activities play a role in the transient activation of PK by insulin.[30] However, glucose independently alters the expression of PK by increasing the transcription of PK mRNA.[31,32] Glucose similarly enhances the expression of fatty acid synthase, a key enzyme in lipogenesis. Glucokinase regulates the flow of substrate to PK. Because glucokinase requires insulin for its activity, it has been difficult to study the independent effects of glucose and its metabolites on PK expression. Nevertheless, two separate approaches directly demonstrate the effects of glucose on PK expression. The first approach was to demonstrate that the effects of insulin on transcription of PK mRNA were glucose dependent, thus identifying glucose as a separate variable.[32] The second approach examined a particular hepatoma cell clone (mhAT3F), whose glucokinase (which is insulin dependent) had been replaced, through spontaneous mutation, by hexokinase (which is not insulin dependent). This allowed the effects of PK to be examined in the absence of insulin.[33] Several signaling pathways that may play a key role in glucose-dependent *L-PK* gene transcription have now been identified (for a review, see Hardie and colleagues[34]). The involvement of the cAMP-dependent and the adenosine monophosphate (AMP)-activated protein kinase pathways is well documented.[35] The glucose-response elements in the promoter region of the *L-PK* gene are known to interact directly or indirectly with various families of transcription factors, including the Sp1 family and the upstream stimulatory factors (USFs).[36,37] The complex interactions between the various factors (UFSs, chicken ovalbumin upstream promoter transcription factor II [COUP-TF II], ChREBP) are likely to act as a glucose-sensing mechanism, allowing the cell to respond appropriately to continuous variation in its nutritional status.

Nutrient Stimulation of Hormone Secretion

Insulin In children, hormones are secreted into the circulation in response to nutritional stimulation for two main reasons: to effectively store nutrients in appropriate storage molecules and to signal to tissues that substrate for growth is available to coordinate the cellular manifestations of growth (cell proliferation, differentiation, and controlled cell death) with the influx of nutrients. These two actions are mutually compatible, and a number of hormones and growth factors serve both functions to varying degrees. Insulin, for example, is mainly a storage hormone, but it is also able to stimulate growth; the increased weight of babies born to diabetic mothers is attributable to increased fetal insulin acting as a growth hormone. Similarly, factors primarily responsible for growth, such as insulin-like growth factor I (IGF-I), which mediates many of the actions of growth hormone (GH), are able to vary the rate of glucose uptake into cells.

The secretion of insulin by the pancreatic islets is tightly controlled by glucose concentrations in the blood. Alterations in gene expression play no part in these rapid responses to glucose. Regulatory proteins within islet cells are ready to respond to increases in glucose. Release of insulin from storage granules occurs following calcium influx, which, in turn, is probably induced by minor increases in adenosine triphosphate from the metabolism of glucose and other nutrients. Circulating hormones also affect insulin release. The quick-acting mechanisms that do not involve control lie beyond the scope of this review. Again, the reader is referred to several excellent reviews on the subject.[20,38,39]

In addition to these rapid responses, glucose also exerts a more lasting effect on insulin production through increased translation and transcription of the insulin gene. This allows a child to adapt to longer periods of starvation or carbohydrate repletion. Glucose enhances the rate of translation of proinsulin mRNA to protein by three methods.[40] It increases the transfer of initiated insulin mRNA from free to membrane-bound ribosomes. It also decreases the rate of pausing of the proinsulin mRNA as it passes along the ribosome. Lastly, glucose directly stimulates the cellular machinery involved in the elongation of proteins in pancreatic islet cells.[41,42] Long-term changes in insulin production are also mediated by transcription. Rats fasted over 4 days have low insulin mRNA concentrations, which return to normal on refeeding.[43,44] These changes control the ability of the pancreas to secrete insulin during dietary manipulations and enable the islet cell to adapt to long-term dietary changes.

In addition to whole-animal studies, pancreatic islet cell preparations have also been used to study how glucose alters insulin expression. Interesting information regarding signal transduction from nutrients to the initiation of transcription has been gleaned from this system (to be discussed). The studies on insulin expression complement those on the role of glucose in PK and fatty acid synthase expression.

IGF-I and IGF Binding Proteins Although we do not fully understand the mechanisms whereby children whose nutritional intake is reduced beyond a certain point stop growing, it is certainly true that nutrient intake has a significant effect on final adult height. This is common knowledge in developed countries with large immigrant populations from the developing world. The children in

the immigrant communities grow up to be taller on average than their parents, whose childhoods may have been spent in lands where food was less abundant. Poor linear growth also occurs in childhood diseases such as cystic fibrosis. In inflammatory diseases, such as Crohn's disease or juvenile rheumatoid arthritis, the characteristic rate of growth may, in part, be related to poor nutritional intake as well as to the direct effects of intestinal inflammation.[45,46]

IGF-I and -II are a family of polypeptide growth factors whose functions include mediation of GH action and stimulation of insulin activity and are autocrine regulators of cellular proliferation.[47,48] IGF-1 has been shown to be a key player in regulating organ and body growth during postnatal development both in rodents and humans.[49] There is now compelling evidence that IGF-1 secretion may be the point at which regulation of growth is controlled both in health and disease.[50–53] Although IGF is an important modulator of GH action, GH itself does not correlate with depressed linear growth under nutritional restriction or in children with active inflammation.[50,54,55] Alterations in tissue responses to growth hormone may therefore mediate the effects of nutrition on growth. This has resulted in two separate lines of investigation: the effect of nutritional alterations on expression of the GH receptor[56] and the study of nutritional factors on IGF-I and IGF-II secretion in association with secretion of IGF-binding proteins.

Nutritional status is a major determinant of IGF-I mRNA expression in liver and nonhepatic tissues. Fasting, caloric restriction, and animal model studies all show a decrease in circulatory IGF-I levels,[57] although circulating levels of GH remain elevated.[50] Although fasting reduces the binding of GH to its receptor,[58] down-regulation of the GH receptor does not occur with dietary restriction,[59] and it is believed that neither of the above are principal causes of reduced IGF-I. Further, administration of IGF-I, but not GH, stimulates mucosal hyperplasia in surgically stressed rats with intestinal atrophy induced by hypocaloric total parenteral nutrition.[60] Low protein intake studies in a liver-specific IGF-I-deficient mouse model led to a decrease in nonhepatic IGF-I secretion into the circulation, with an increase in GH levels. Lack of dietary protein led to induction of GH and IGF-I receptor expression in spleen. Increased IGF binding protein 3 (IGFBP) mRNA was also observed, which supports the hypothesis that the binding protein may contribute to greater sequestration of locally synthesized IGF-I.[61] These studies support the view that the splenic GH/IGF-I axis responds to nutritional stress to maintain tissue homeostasis.

Regulation of IGF mRNA expression is complex. The rat IGF-I gene contains six exons spanning 100 kb of DNA. Exons 1 and 2 encode alternative amino terminal sequences of the IGF-I protein. The gene has two distinct promoter regions upstream of exons 1 and 2, which can be separately activated. After transcription, alternative splicing results in further heterogeneity of the IGF-I mRNA. Furthermore, there are two different terminal poly A addition sequences in exon 6, adding to the general complexity. However, these myriad possibilities result in only three different-sized mRNA transcripts: a 3.8 kb, a 4.2 kb, and an 8 kb transcript. The importance of these different mRNAs to IGF-I production and to growth awaits further investigation, but they are of interest because several studies have demonstrated that different forms of malnutrition affect the transcripts differently.[47,52,62] Total energy restriction induces a coordinate decrease in all three forms of mRNA.[51] In contrast, protein restriction results in a profound decrease in the 8 kb fragment, with less effect on the two smaller fragments.[47,62] The observations open up two questions of further interest: How do different nutrients differentially affect gene expression in a particular family of genes? and How do these differences in gene expression translate into differences in a child's final phenotype? We return to similar questions when we consider the small intestinal epithelium, where nutritional variations are greater than those seen in the circulation. Corresponding changes in IGF-I have been seen in childhood illness. IGF-I concentration correlates with increased intake and subsequent growth of children with Crohn's disease, whereas growth has no correlation to GH production.[45,55,63] Children with cystic fibrosis frequently manifest hormonal abnormalities that may contribute to malnutrition. Interestingly, in a recent study, Bucuvalas and colleagues found no effect of exogenous IGF-I on linear growth in prepubertal children with cystic fibrosis, although an increase in glucose-to-insulin ratio was observed.[64]

In extracellular fluids, IGF-I is bound to IGFBPs, of which six have been cloned and characterized.[49] IGFBP-3 is the main carrier of circulating IGF-I, and in the presence of an acid-labile subunit, a bioinactive ternary complex is maintained during circulation. The complex allows greater control on IGF-I bioavailability.[65] IGFBP-3 may also modulate IGF-I-stimulated DNA synthesis.[66] The biologic function of each binding protein is under intense investigation. Protection from the hypoglycemic effects of IGF-I has also been suggested as a function. Nutritional factors alter the circulating levels of IGFBPs. There is an inverse correlation of the expression of binding proteins to that of IGF-I. Protein restriction results in an increase of IGFBP-1, which falls on refeeding. However, IGFBP-1 is sensitive to insulin, and it is not clear how nutrients in the liver alter their expression directly. Interestingly, IGFBPs are predominantly secreted by Kupffer's cells,[67] unlike IGF-I, which is synthesized by hepatocytes. The differences between these two cell types in terms of their location and their expression of surface receptors could allow for subtle regulation of IGF action in the face of nutrients and other factors in the circulation, such as cytokines.

Effect of Intestinal Contents on Genes in the Epithelium

The gastrointestinal tract is the only part of the body that normally comes into contact with nutrients before they are absorbed. The gastrointestinal tract is therefore exposed to a wider variety of nutrient molecules than any other organ of the body. The picture is further complicated because the lumen of the intestine is not a direct reflection of the food ingested. It also contains bacteria and their by-products and factors secreted into lumen in response to the inges-

tion of food (Figure 15-2). The study of nutrient effects on the enterocyte therefore should consider how changes in diet may affect the area around the apical aspect of a particular epithelial cell. The dissociation between nutrients ingested and the changes observed in the bowel lumen becomes greater the further one proceeds down the gastrointestinal tract. The contents of the distal colon are completely different from food, although even here they are affected to some extent by dietary intake. This relationship between ingested nutrients and the local environment of the lumen is a separate issue from the interaction of that local environment with genes in the enterocyte.

It has traditionally been assumed that the expression of genes in the small intestinal epithelium is preprogrammed and that their expression is not influenced by events in the lumen of the intestine. However, this view may be incomplete. An alteration in epithelial cell phenotype secondary to nutritional factors would have three possible advantages (Table 15-2). First, the intestine could adapt to absorb nutrients more effectively if specific digestive enzymes and transporters of the epithelium were up-regulated by the repeated intake of a particular nutrient. Second, as all mammals are fed from mother's milk, the opportunity exists for breast milk to influence the development of the epithelium through actions of its own constituents. Third, if the genes affected in the epithelium were immunologically important, the intestinal epithelium could influence mucosal immune responses by signaling information to the mucosal immune system and beyond through changes in the expression of epithelial cell genes. Each of these areas is likely to represent important physiologic mechanisms that have implications for child health.

TABLE 15-2 Relevance of Dietary Regulation of Enterocyte Gene Expression

Intestinal adaptation
Influence of maternal breast milk
Signaling from lumen to mucosal immune system

Polarity of Epithelia

The cell types discussed earlier in this chapter do not depend on a separation of functions to different cellular poles. For example, the pancreatic islet receives signals from the entry of glucose at any point on the plasma membrane, and, as far as we can judge, the insulin response is not affected by the site of glucose entry. Insulin can also be released in any direction, eventually diffusing into the circulation. Cells that form epithelia are different in that they exhibit polarity. This separation between the apical side (bordering the lumen in the case of the intestinal epithelium) and the basolateral side is central to epithelial activity. This property is well recognized in the field of intestinal transport. Ions, small molecules, and macromolecules are all transported differently across the apical membrane than across the basolateral membrane (Figure 15-3).[68–70] It is the polarity of the epithelium that gives direction to the movement of these substances across the epithelium into or out of the body. But this property must also be considered when one is examining all aspects of intestinal epithelial cell function. Polarity is also of fundamental relevance in the study of nutrient–gene interactions in the intestinal epithelium. The polarity of the epithelial cells distinguishes the two major mechanisms by which nutrients (and other luminal factors) affect genes: a direct effect on enterocytes and an indirect effect mediated through hormones, growth factor, and cytokines (see Figure 15-3). As with the effects of insulin on target tissues, the mechanisms of action of cytokines and growth factors on the epithelium are beyond the scope of this chapter. The reader is again referred to excellent reviews on how epithelial cell expression can be regulated by these agents.[71,72]

The apical membrane mediates the direct effects of luminal factors on the epithelium. The functions of nutrient recognition (sensing) and signal transduction (see Figure 15-1) will therefore lie between the apical membrane and the apparatus of gene expression. The exact molecular mechanisms involved require further investigation. For the purposes of investigation, they can be considered as a series of black boxes connecting the lumen and gene

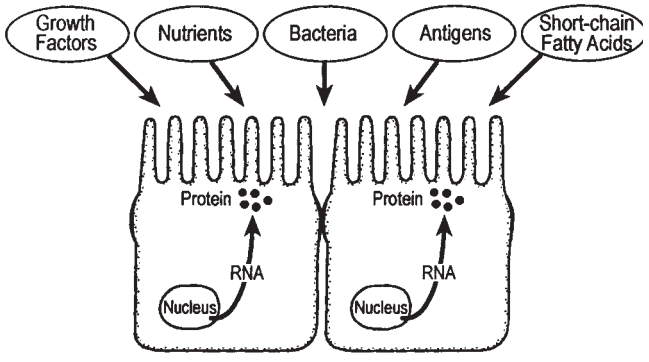

FIGURE 15-2 The luminal factors that influence gene expression in the enterocyte. Factors can affect individual genes or they may influence enterocyte differentiation and new cell lineages.

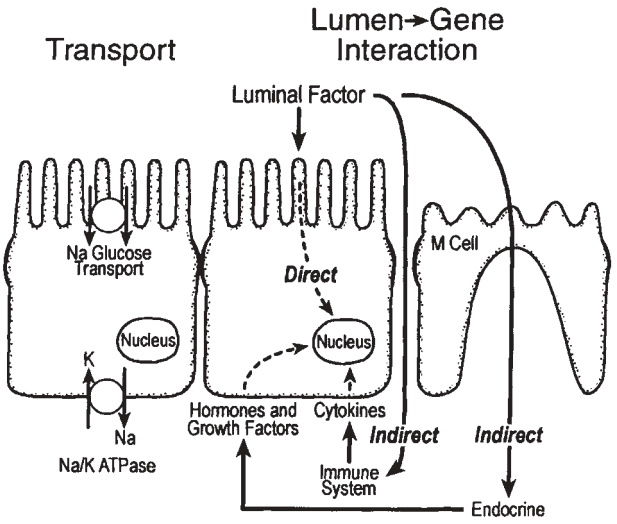

FIGURE 15-3 Dietary changes may affect gene expression directly (being mediated through the apical membrane) or indirectly (through the basolateral membrane).

expression (Figure 15-4). These black boxes contain the mechanisms that regulate gene expression and constitute the way by which molecules in the lumen "cross-talk" with the nucleus of the enterocyte. Figure 15-4 depicts the pathway linking single factors in the lumen to the expression of a single cell in a single gene. This is, of course, a gross oversimplification. As we have mentioned, an alteration in diet may alter different factors at the cell surface, and any one of these factors may have an effect on several different genes through different pathways (Figure 15-5). In addition, the methods by which a particular protein may be expressed is not necessarily always owing to the induction of a single gene in cells along the crypt-villus axis. It can also be caused by changes in the state of differentiation of the cells in the epithelium, the expression of a particular gene being just one component of that change. Lastly, alterations in luminal contents may not necessarily affect epithelial cells that are already formed along the epithelium but instead result in the generation of new lineages of cells that express the gene arising from the crypt. In this case, the mechanisms linking the lumen to gene expression would lie in the stem cell at the base of the crypt rather than in the individual enterocyte itself.

Adaptation of Enterocytes to the Nutritional Environment

The efficient use of food requires digestion, followed by absorption of digestion products and their release into the circulation. Adaptation is, by definition, the up-regulation of one or all of these functions in the presence of a relevant nutrient. Adaptive mechanisms are more likely to be associated with foods whose intake varies between different individuals. The similarity here with prokaryotic cells is clear. Bacterial gene regulation was discovered in the study of enzymes that metabolized nutrients whose abundance varied widely in the environment, like lactose or tryptophan. For children, of course, there are many foods whose abundance can vary, but to illustrate this section, we have chosen two: dietary fat and sucrose. These two examples demonstrate different aspects of adaptation. Fat digestion is primarily controlled by enzymes secreted from the pancreas and gastric glands, whereas digestion and absorption of sucrose are controlled entirely by the enterocyte itself.

Sucrose Intake The intake of sucrose can vary greatly between individual human beings. This is especially true when one compares individuals from different times in history. Until the industrial revolution, sucrose was present in the diet only when brought from the East as part of the spice trade, and its availability was limited. The introduction of plantations in the Caribbean in the eighteenth century, coupled with the industrial process of refining, resulted in an explosion of sucrose intake. In England in 1700, the estimated per capita daily consumption in adults was 4.5 g, rising to 37 g in 1800. By 1968, it had reached 140 g daily,[73] which is around 15% of the total energy derived from food. Sucrose is digested by the epithelial cell brush border, where it is hydrolyzed to fructose and glucose by sucrase isomaltase (SI). Fructose is absorbed by the carrier GLUT 5 and GLUT 16 and glucose by the specific sodium-dependent glucose transporter.[16,17] Both sugars exit the cell through the basolateral membrane by facilitated diffusion, probably via GLUT 2. The up-regulation of any of these proteins by their substrate would constitute a nutrient–gene interaction.

The four brush border disaccharidases represent the final step in the digestion of carbohydrates. Their activity can affect the glycemic response to oral carbohydrate.[74] More importantly, low levels of hydrolase activity in the face of carbohydrate in the intestine will result in osmotic diarrhea.[75] A mechanism whereby expression of these enzymes could be linked to sugar intake would therefore have clear benefits. SI is one of three β-glucosidases (together with maltase and trehalase). The remaining disaccharidase, lactase, is a β-galactosidase. Sucrase is anchored to the microvillus membrane of the enterocyte by the isomaltase subunit of the SI protein.[76,77] Both subunits are synthesized as a single protein that is later cleaved.

The regulation of the induction of sucrase is not simple. The timing of its appearance during ontogeny in rodents was elegantly shown to be independent of luminal contents.[78] When the investigators transplanted isografts into animals 5 days younger than the donors, sucrase appeared earlier in the transplanted intestine than in the host. Therefore, luminal factors in this case did not induce sucrase, nor did circulating factors in the host (whose intestine would have been susceptible to them). This evidence suggests that sucrase is controlled by an internal biologic clock within the intestine itself. However, luminal contents can have a marked effect on the activity of sucrase, which is separate from this internal mechanism: (1) early feeding with sucrose will induce precocious sucrase induction in rodents[79]; (2) reduction of carbohy-

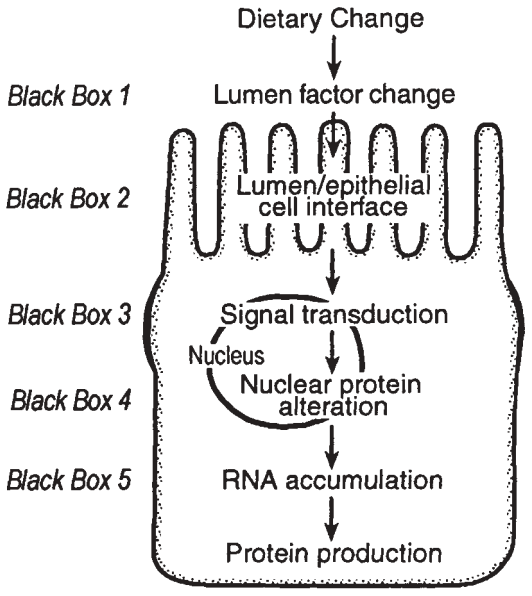

FIGURE 15-4 The pathway connecting dietary alterations to changes in gene expression is not well understood. It is likely that the pathway is mediated by a series of steps that, at present, we can regard only as black boxes. Different luminal events will influence gene expression through different series of black boxes.

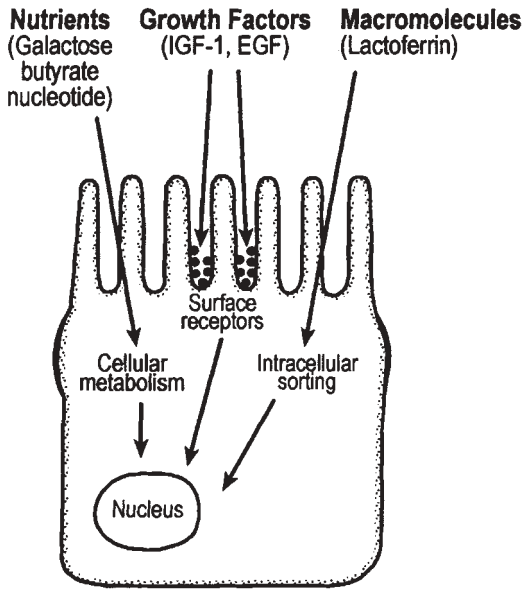

FIGURE 15-5 Cross-talk through the apical membrane will depend on the particular signal involved. EGF = epidermal growth factor; IGF = insulin-like growth factor.

drate intake results in a reduction of sucrase activity even when caloric intake is unchanged[80]; (3) feeding with glucose instead of sucrose reduces brush border hydrolase activity[81]; and (4) refeeding sucrose after a period of abstinence leads to rapid recrudescence of the hydrolase activity.[82] Increasing the intake of sucrose of mice from 2 to 55% of total energy intake had differing effects on the enterocyte, depending on the position of the cell in the small intestine.[83] Sucrase activity increased in the duodenum and upper jejunum but not in more distal segments of the intestine. The cells showing greatest alterations were those from the midvillus of the proximal intestine, with lesser increases in the villus tip and crypt-villus junction.

The control of sucrase activity is then a complex one and depends on events within the enterocyte in addition to external influences.[84] More recently, the molecular biology of sucrase expression has been examined. Sucrase activity depends mainly on events in the sucrase promoter because expression of GH mirrors that of sucrase in transgenic animals containing a sucrase promotor–GH construct.[85] The expression of sucrase may therefore reflect nuclear protein–promoter interactions.[86] In recent years, several SI promoter elements required for intestinal epithelial cell expression have been identified.[86] Evolutionarily conserved *cis*-acting elements in the promoter region have been found to interact specifically with transcription factors such as GATA-4 and caudal-related homeodomain (Cdx) proteins.[87,88] Further combinatorial interactions among hepatocyte nuclear factor (HNF)-1α protein, GATA-4, and Cdx-2 may play a critical role in the temporal and spatial regulation of the SI gene expression during postnatal development.[89] Post-transcriptional events may also be likely to influence enzymatic activity; for example, reduction in lactase activity following weaning does not necessarily correlate with lactase mRNA but may be regulated during translation.[90]

Glucose Transporter Expression Glucose enters the epithelial cell by active transport via a sodium-coupled glucose transporter, SGLT 1.[91] SGLTs represent part of a family of proteins that carry nutrients into the cell, across concentration gradients.[15] SGLT 1 is located in the brush border or apical surface of the enterocyte and, along with Na+, transports glucose and galactose into the cytosol. GLUT 2 is basolateral and transports glucose, galactose, and fructose (transported in from the lumen via GLUT 5) from the cytosol into circulation.

Direct transport studies undertaken before the identification of sodium-dependent transporters showed that glucose uptake increased with glucose feeding.[92] This increase was not attributable to changes in the affinity of glucose to the enterocyte (K_m) but to an increase in the maximum uptake (V_{max}), indicating an increase in the production of proteins that transport glucose. It is now well established that dietary sugars regulate the activity and the expression of intestinal SGLT 1. Structurally, an intact mucosa is necessary for rapid up-regulation of GLUTs by luminal glucose.[93] Modulation of SGLT 1 expression by dietary carbohydrates has also been observed in the human intestine.[94] Mechanisms involved in the regulation of glucose transport are complex and have been difficult to characterize as two distinct timescales of dietary carbohydrate exposure are now known to play a role (recently reviewed in Ferraris[95]). GLUTs can respond within an hour to glucose and also exhibit distinct changes in gene expression over a period of 1 to 3 days to a high-carbohydrate diet.[93,96,97] Intestinal glucose transport is also subject to diurnal changes, adding further complexity to the system. The increase in GLUTs in response to dietary changes is analogous to the acquisition in bacteria of enzymes and transporters that are induced by lactose (the lac operon). There are, however, notable differences between induction of enzymes and transporters in bacteria and those seen in the mammalian intestine. First, the activity of transporters in bacteria increases by 100- to 1,000-fold, whereas the nutrient transporters in mammals show smaller variation with diet. For example, feeding mice with diets containing high levels of either D-glucose or nonmetabolizable analogues of D-glucose led to only a two- to threefold increase in SGLT 1 activity.[98,99] Second, in bacteria, the cell that receives the stimulus is the same cell that exhibits alterations in gene expression. In the mammalian intestine, this appears not to be the case with the GLUT.[100,101] Sequential elution of different fractions of epithelial cells was used to distinguish different cells along the crypt-villus axis of mice.[102,103] Increase in carbohydrate intake resulted in enhanced expression of the GLUT (as measured by phlorhizin binding). Importantly, changes were observed in the crypts before they were seen in the villi. Similarly, when carbohydrate was stopped, it was in the crypts that the reduction in transporter was first observed. Thus, crypt cells respond to changes in diet before villus cells, indicating that the changes in the expression of the GLUT were effected by new cell lineages from stem cells. It is the stem cell producing the new cell lineage that therefore must contain the machinery for detection of carbohydrate. The resulting cell

population that ascends along the crypt-villus axis expresses this change. This separates carbohydrate detection temporally and spatially from GLUT expression. It is not known whether other genes in the intestine follow a similar pattern. Identification of molecular mechanisms underlying carbohydrate detection and signal transduction are currently under active investigation in several laboratories (see Figure 15-1).

Sucrose induces an increase in the enzyme that hydrolyzes it (SI) and in SGLT 1 that allows a greater influx into the enterocyte across a concentration gradient. This absorptive system is central to the efficacy of oral rehydration solution in the treatment of gastroenteritis and cholera.[104] The greater the number of transporters, the more sodium and fluid that can be transported into a child during dehydration. Up-regulation of SGLT 1 therefore has a potential therapeutic role in alleviating the loss of sodium and fluid with glucose solutions. An understanding of the mechanisms regulating this process would define to what extent and over what time period sodium and fluid transport could be maximized in children with gastroenteritis.

Intake of Dietary Fat The intake of fat as a component of total energy varies considerably between different children. Fat consumption has been increasing in children from developed countries and has accelerated over the last 100 years. Contemporary comparison of fat intake between nations now shows large variations. For example, Perissé and colleagues reviewed 105 countries for the Food and Agriculture Organization (FAO) of the United Nations and showed that between wealthy and nonwealthy countries, fat intake varies from about 12% of total energy intake to over 40%.[105] It is not only healthy children who have seen a change in fat intake; children with cystic fibrosis have been given much larger amounts of fats. This is because increased calorie intake, particularly that of fat, has resulted in improvements in respiratory function.[106–109] Much of this fat is digested in children with cystic fibrosis by the use of ingested enzyme preparations given with meals. However, lipases secreted in the gastrointestinal tract proximal to the duodenum (gastric lipase) may also play a prominent role. It is important, therefore, to document whether secretion of this enzyme varies with fat. A knowledge of mechanisms underlying this possible adaptive effect may lead to therapeutic optimization of enzyme production and better use of fat in children who are continually under threat of malnutrition.

Gastric Lipase

Gastric lipase accelerates the digestion of triglycerides in human milk by releasing free fatty acids, which enhance pancreatic lipase and colipase activities.[110] The actions of gastric lipase are magnified in children with little pancreatic lipase activity, as in cystic fibrosis. Newborn babies also have relatively low pancreatic lipase activity, and the relative importance of gastric lipase is exaggerated in the premature neonate.[111–114] There are significant biochemical differences between pancreatic and gastric lipase, most significant of which is the difference in pH required for maximal activity. In addition, gastric lipase activity requires no bile salt or colipase. In the human, the gastric mucosa secretes all of the preduodenal lipase.[115,116] In the rodent, the tongue is the most significant source, and here the equivalent enzyme is termed lingual lipase. There may also be some lingual production in the preterm human infant because lipase activity has been detected in esophageal pouches of infants with esophageal atresia with no communication to the stomach.[114] The rabbit predominantly secretes its preduodenal lipase from the gastric mucosa, making the rabbit a more appropriate model than the rodent in which to study the effect of dietary influence on this enzyme.

Gastric lipase activity is more susceptible than pancreatic lipase to dietary changes. Increasing the dietary fat intake in rabbits from 2.7 to 6% of diet for 2 weeks was sufficient to induce a 100% increase in gastric lipase activity.[117] This increase had no effect on pancreatic lipase production. Indeed, pancreatic lipase activity was enhanced only when the fat intake was increased to 12% of diet, and then the increase was only modest, a 10% increase in pancreatic lipase activity. Studies in adult human volunteers have shown similar data with a doubling (5.7 to 9.95 U/mL) of gastric lipase after changing from a low-fat to a high-fat diet.[118] The mechanisms that detect the amount of fat intake (see Figure 15-1) need further examination, but triglyceride composition had no effect on the adaptive response in the rabbit.[117] This implicates a metabolite of fatty acid breakdown, which is not specific for either saturated or unsaturated fatty acids as the cellular agent that initiates changes in gene expression. The signal may not have to come directly from the lumen of the gastrointestinal tract because there is preliminary evidence, in neonates at least, indicating that increasing lipid intake parenterally results in enhanced gastric lipase activity. This suggests that signals from the serosal side of the epithelial cell may be possible in this case.

Gastric lipase is therefore under the control of dietary signals. Although we do not at present understand the mechanisms that underlie this phenomenon, their elucidation may eventually allow us to manipulate gastric lipase expression when it is clinically important, as in the nutrition of cystic fibrosis and in the oral intake of the newborn.

Fatty Acid Uptake Fatty acid uptake in the gastrointestinal tract is facilitated by the presence of two transporter proteins, the cytosolic and plasma membrane form of the fatty acid binding protein (FABPc and FABPpm, respectively). Epidemiologic analyses of polymorphisms at codon 54(A/T) in the *FABP2* gene have revealed no clear correlation with postprandial lipemia.[118] In contrast studies in an ex vivo model of fetal jejunum explants implicated *FABP2* polymorphism may specifically influence small intestinal lipid absorption without modifying glucose uptake or metabolism.[119] Further studies are required to clarify the potential role of these transporters in health and disease. A third fatty acid transporter (CD36) associated with long-chain fatty acid as its ligand has recently been implicated to play a role in the pathogenesis of insulin resistance.[120] CD36 –/– mice exhibited enhanced insulin responsiveness

on a high-starch, low-fat diet. Based on this study, one may speculate that humans with a deficiency in this molecule are likely to exhibit enhanced/impaired insulin resistance depending on dietary influences.

Breast Milk and Gene Expression

The nutrition and protection of the infant are the primary roles of breast-feeding, and the nutritional and immunologic properties of breast milk are reviewed in Chapters 31 and 32 of this book. Nevertheless, the cells of the gastrointestinal tract are the first cells of the child to encounter breast milk, and it is not fanciful to suppose that breast milk may influence the development of these cells. A number of factors in milk can affect the expression of genes in the intestinal epithelium, particularly those genes that are associated with enterocyte differentiation. Growth factors such as epidermal growth factor (EGF) and vascular endothelial growth factor are found in breast milk and enhance brush border enzyme activity.[121–123] Although the exact effect of epidermal growth factor in breast milk on the development of the intestinal epithelium depends on the age of the subject, its effect on enterocyte growth and development is not surprising. Less expected, perhaps, is the demonstration that other breast milk components such as nucleotides also affect these same genes.[124,125] A list of how each constituent in breast milk may affect expression of genes in the intestinal epithelium would not present an illuminating picture of how breast milk affected enterocyte expression. Instead, it is more valuable to describe one factor, lactoferrin, as an example. We examine what is known about its interactions with the intestinal epithelium and how this knowledge may be increased in the future.

Lactoferrin Lactoferrin, an 80 kD iron-binding glycoprotein of the transferrin family, is a major component of mammalian colostrum and milk.[126] It is also found in mucosal secretions and neutrophil granules.[127,128] Lactoferrin has bactericidal properties and is a source of iron in breast-fed infants. The protein has been found to have diverse biologic functions, including facilitating iron absorption, host defense, regulation of cell proliferation and differentiation, modulating the immune system, and embryonic development.[129–131] Although neutrophil granules contain lactoferrin, its concentration in plasma, in contrast to transferrin, is relatively low.[127,132]

Specific binding sites for lactoferrin have been observed in activated human blood lymphocytes, liver cells, and cells lining the gastrointestinal tract.[133–135] The lactoferrin receptor has been detected in intestinal brush border membrane vesicles prepared from the human fetus, rhesus monkey, rabbit, and mouse.[136–139] Lactoferrin is relatively resistant to proteolytic degradation.[140,141] Intact protein with iron-binding capacity has been detected in the feces of mice and human infants.[142,143] The stability of the intact protein through transit in the gut suggests that it has the potential to interact directly with the intestinal epithelium. The lactoferrin protein consists of a bactericidal domain (lactoferricin), which can be generated in vitro by pepsin digestion.[144] An understanding of the actions of lactoferrin at the molecular level is particularly relevant as some artificial milk formulas now contain added bovine lactoferrin. Its major role is thought to be delivery of iron to the intestinal epithelium.[145] The number of lactoferrin binding sites increases in cultured epithelial cells when depleted of iron,[146] resulting in a specific increase of iron transport into enterocytes. The actions of lactoferrin are therefore interconnected with the actions of iron. Iron has well-characterized effects on the translation of ferritin and transferrin mRNA,[147] but its effect on gene expression in the enterocyte is less well understood.

Although lactoferrin increases the bioavailability of iron in the neonatal intestine, recent studies suggest that lactoferrin may also act as a proliferative factor in a variety of cell types, including human lymphocytes, mouse embryo fibroblasts, and rat myoblasts.[148–151] Lactoferrin also affects the proliferation of HT-29 human colon adenocarcinoma cells and adult rat crypt cells.[152,153] The effect of lactoferrin on the expression of brush border enzymes has also been examined. In tissue culture experiments, the effect of lactoferrin on sucrase- and alkaline phosphatase–specific activities depended on whether the protein was saturated with iron.[154]

There is a school of thought that proposes that the main function of lactoferrin in vivo is not to transport iron into the epithelium but to scavenge iron (and possibly other substances) in the intestinal lumen. This unbound iron might otherwise cause free radical–mediated damage to sensitive tissues.[155] Accordingly, lactoferrin would have no direct effect on the intestinal epithelium and only indirectly interact with it through the sequestration of other substances in the lumen. These luminal factors, if left free in solution, may have an impact on enterocyte gene expression. An example of this is lactoferrin's binding to lipopolysaccharide, a major component of bacterial cell walls, thereby modulating the effect of this moiety on the epithelium.[156] However, a purely luminal role for lactoferrin is difficult to reconcile with the identification of specific receptors for lactoferrin on the surface of the small intestinal brush border membrane.[138] Initially, the binding of lactoferrin to brush borders was explained on the assumption that lactoferrin was binding to transferrin receptors.[157] But the use of rhesus monkeys has made possible an examination of the specificity of lactoferrin binding to its receptor: binding was time dependent and saturable, competitive experiments with excess unlabelled lactoferrin showed that the binding was specific, and monkey and human lactoferrin effectively inhibited the binding of rhesus lactoferrin at 50-fold excess. A similar excess of bovine lactoferrin or human transferrin had no effect on binding.[137] Taken together, these results are good evidence for a specific lactoferrin receptor. The lactoferrin receptor has now been isolated from human fetal and infant small intestine.[136] Any direct effect of lactoferrin on gene expression should be transmitted through this receptor, and its analysis may therefore give clues as to how lactoferrin might do this. However, it has been difficult to isolate sufficient lactoferrin for structural analysis,[157] but the size and

number of peptide chains have been determined for both human and mouse lactoferrin receptors.[158–160] It is hoped that manipulation of lactoferrin DNA in transfected cell lines will give insights as to whether the receptor signals information to the molecular machinery of the enterocyte.

Because lactoferrin is secreted by neutrophils, its effect on the expression of genes in cells of the immune system has been closely studied. These observations have resulted in some intriguing studies on the actions of lactoferrin on gene expression, which may be relevant to the actions of lactoferrin in breast milk on epithelia. Lactoferrin interacts avidly with nucleic acids in a test tube.[161–163] Furthermore, lactoferrin is taken up by certain human myelogenous leukemia cells and appears in the nuclei bound to DNA.[164] Lactoferrin can therefore be added to culture media to study its effect on the expression of genes transfected into the leukemia cells. He and Furmanski have determined which nucleotide sequences of DNA specifically bind to lactoferrin.[165] They quantified the affinity of the binding of lactoferrin to DNA and have shown it to be greater with iron-saturated lactoferrin than with iron-unsaturated lactoferrin. Once the sequences for lactoferrin had been determined, these sequences were added to an artificial gene promoter attached to a reporter gene, which was transfected into the leukemia cells. The expression of the reporter gene was enhanced by the addition of lactoferrin to the culture medium. More importantly, gene up-regulation was much greater with iron-saturated lactoferrin than with the unsaturated form. Thus, in this system, lactoferrin specifically up-regulated an artificial gene inserted into myelogenous leukemia cells. Lactoferrin has also been found to alter the activity of promoters of natural genes in granulocytes.[166]

The exciting possibility exists, therefore, that lactoferrin from mother's milk may cross into the epithelium of the infant intestine by way of lactoferrin receptors and enter the epithelial cell nucleus, programming epithelial cells in some way. How this is achieved and what benefits this would have for the developing infant are questions that future research may well answer. Recent work in our laboratory has shown that lactoferrin affects the proliferation and differentiation of intestinal epithelial cells and that this effect depends on the degree of saturation by iron.[154] It is possible that these changes in enterocyte gene expression are mediated by mechanisms similar to those outlined by He and Furmanski in white cells. It would be particularly interesting if the entry of lactoferrin into enterocytes was a reflection of its interaction with molecules in the lumen of the intestine, in terms of the amounts of lactoferrin entering as well as of the particular ions that are attached to the lactoferrin once it has entered. It is not difficult to imagine how this molecule could then act as a modulator of enterocyte genes in the face of changes in the intestine.

Signaling from the Intestinal Lumen to the Mucosal Immune System

The function of the small intestinal epithelium is to absorb nutrients from the environment while providing a barrier to the external world.[4] The barrier is not complete as the intestine allows macromolecules to be sampled and to actively absorb nutrients. The success of the intestine in achieving the balance between these competing aims was the critical step in the evolution of multiorgan animals. The ability of the intestine to monitor the environment is a key element in this process in which the mucosal immune system plays an important part. Curiously, however, the possibility that the epithelium may respond to luminal factors (and signal their presence to the mucosal immune system) has been substantially ignored. The epithelium has mainly been regarded as a passive barrier with points of selective filtration (Figure 15-6, A), surveillance of the luminal contents occurring after this filtration has taken place.

Earlier in this chapter, we examined genes whose activity is restricted to the confines of the epithelial cell monolayer of the intestine (Figure 15-6, B). Nutrient transporters and disaccharidases all contribute to the actions of the epithelium. When genes within the enterocyte express proteins whose actions occur away from the epithelium, such as cytokines and growth factors, the relevance of luminal factors on enterocyte gene expression becomes different. In this new situation (Figure 15-6, C), the epithelium acts as a mediator between the luminal contents of the intestine and target cells beyond the epithelial barrier. Such cells include immunocytes from the mucosa, with the potential for additional cells being recruited from the circulation. The small intestinal epithelium is now recognized to be part of the mucosal immune system.[4,167] For example, it has receptors for bacterial products such as the toll-like receptor 2,[168] as well as expressing a range of molecules on its surface that contain immunoglobulin domains. The epithelial cell also expresses proteins that may interact with immunocytes within the intestine. These include surface molecules such as class II major histocompatibility complex (MHC) and secretory chemokines and cytokines that may directly alter immune responses. The epithelium also expresses families of growth factors and their binding proteins, which may affect the proliferation of immune cells. It also may itself directly present antigen to T cells. The molecular mechanisms governing the expression of these genes have features in common with other enterocyte genes that respond to nutrients and factors in the lumen. For example, the epithelial cell must recognize (or "sense") the nutrient or other luminal factor, and a mechanism must then "transduce" this recognition into molecular changes that can directly alter gene expression (see Figures 15-1 and 15-4). The main difference in molecular terms from the adaptive response described earlier (see Figure 15-6, B) is that the resultant proteins escape from the compass of the epithelium and interact with receptors on target cells (see Figure 15-6, C).

Signaling, by transducing molecular interactions with the epithelium into secretion of messenger proteins, allows luminal factors to influence immune responses while maintaining full epithelial barrier integrity (see Figure 15-6, C). Although the absorption of luminal factors (see Figure 15-6, A) is an important method by which the mucosal immune system surveys the intestinal lumen,[4] it requires the entry of molecules through the epithelial barrier. This provides a potential source for invasion by

pathogens. The poliovirus, for example, enters by this means, exploiting the normal uptake of macromolecules. The ability of the epithelium to signal information to the mucosal immune system without the need for a physical pathway from the lumen to the serosal surface offers obvious advantages in terms of epithelial protection.

The notion of epithelial signaling (see Figure 15-6, *C*) implies that the epithelium can modulate the level of immune activity in the mucosal immune system according to the environment of the intestinal lumen. Mucosal immune responses play a large part in gastrointestinal diseases, particularly Crohn's disease, ulcerative colitis, and celiac disease. The milieu of the intestinal lumen could therefore be manipulated for therapeutic purposes by alterations in diet.

Genes of Immunologic Importance in the Intestinal Epithelium. An increasing list of immunologically active proteins are now known to be synthesized by the intestinal epithelium (Table 15-3), and these were originally thought to be produced only by other cell types. Human diseases are associated with the increased production of some of these proteins in the circulation and gastrointestinal tract. Recent data from our laboratory now show that the expression of these proteins in the epithelium is influenced by dietary factors.

Cytokines. An interesting example of a cytokine secreted by the epithelium is interleukin (IL)-8. This protein is small (8,000 D) but has a long half-life in vivo relative to other cytokines, making it a feasible candidate for long-lasting control over mucosal immune responses. IL-8 is a member of a superfamily of cytokines, the chemokines, which have chemotactic properties, recruiting as well as activating a number of immunologic cell types. It is a potent chemotactic factor for neutrophils and T lymphocytes and may be important in recruiting them into the gastrointestinal tract. Invasion by neutrophils, in particular, is a hallmark of Crohn's disease, a condition in which IL-8 production is enhanced.[169] IL-8 also stimulates the release of superoxide radicals in neutrophils as well as other potential mediators of damage in intestinal inflammation. Furthermore, it increases the permeability of the vascular endothelium to albumin, resulting in tissue edema. Its production in intestinal epithelial cells has been documented in response to bacterial invasion and by other agents, including phorbol-12-myristate 13 acetate (PMA) and IL-1.[170] Recent studies from our laboratory have shown unequivocally that the surface epithelium and its products can orchestrate the mucosal immune system of the gut. Macrophage inflammatory protein 2 (MIP-2) (mouse chemokine similar to human IL-8) transgenic mice were generated where the chemokine expression was confined to the small intestinal and colonic epithelium by the use of a fatty acid binding protein promoter.[171] The epithelium from the first generation of the founder showed effects on both neutrophil and lymphocyte recruitment. In the small intestine, where the fatty acid binding protein I promoter is active, the neutrophil recruitment, expressed as myeloperoxidase activity, was significantly greater. In the distal colon, where the promoter is inactive, there was no effect. These studies show for the first time that the epithelium can, through the release of chemokines, alter the mucosal immune function in vivo.

Further analysis of the immune system demonstrated that the small intestine has increased lymphocyte infiltration in addition to neutrophils. Lymphocyte numbers in the lamina propria are significantly increased ($p < .05$), and there was also a doubling of the number of intraepithelial lymphocytes. The increase in intraepithelial lymphocytes was attributable to an increase in both $\alpha\beta$ and $\gamma\delta$ lymphocyte populations. Interestingly, these cells express CXCR2, the receptor for MIP-2. These studies highlight the potential recruitment capacity of a single chemotactic activity; the in vivo situation, however, is likely to be more complex, with simultaneous alteration of various immune regulators.

Evidence is now emerging that expression of various epithelium-derived immune regulatory molecules is altered by dietary factors.[4,172] n-Butyrate is a short-chain fatty acid produced by the metabolism of normal intestinal bacteria whose levels in the intestine vary with diet. Newborn babies have very low butyrate levels in either the small or large intestine. However, with time, butyrate levels rise, reaching adult levels by 2 years of age. It has long been known that

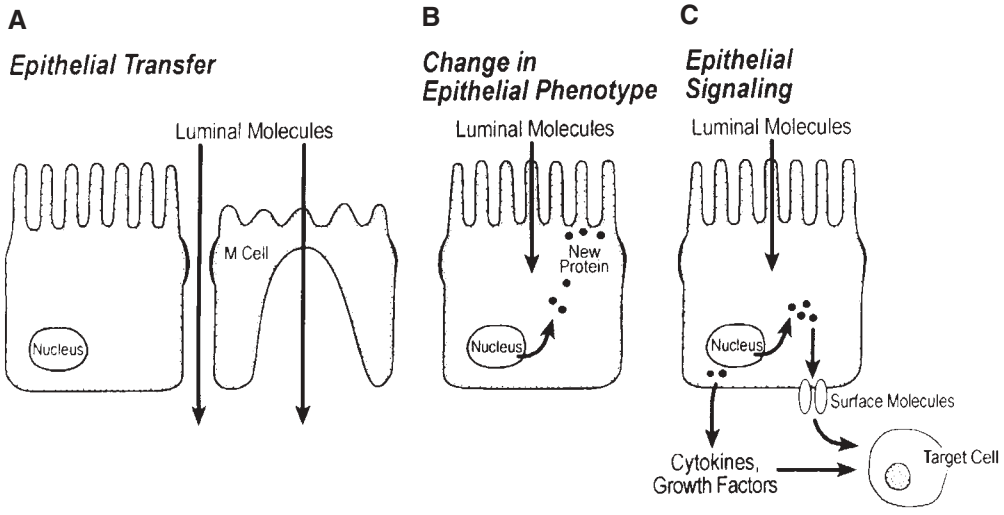

FIGURE 15-6 Possible interactions of molecules from the intestinal lumen with the epithelium. Traditionally, the epithelium has been seen as a selective barrier to molecules, admitting those required for energy intake or immunosurveillance and excluding others (*A*). However, nutrients can alter the phenotype of the epithelium to adapt to changing nutritional needs (*B*). When changes in the intestinal lumen induce new proteins that interact with mucosal immune cells, the epithelium can act as a membrane signaling information from the lumen to the immune system (*C*).

infants fed casein-based formulas produce large amounts of butyric acid and propionic acid in the stool, whereas the predominant fatty acid in breast-fed infants is acetic acid.[173] Furthermore, the bacterial flora (*Lactobacillus*) responsible for high acetate/butyrate production is inhibited by casein.[173] In addition, the amount of butyrate produced in the stool is altered by the type of fiber consumed in the diet.[174] Butyrate levels depend on the type of bacteria in the gut and how much substrate is available for butyrate production. Butyrate levels therefore reflect events in the intestinal lumen, and we hypothesized that their concentrations may alter cell signaling. We therefore examined its effects on IL-8 and *MCP-1* gene and protein expression.[175] We found that butyrate increased IL-8 secretion in enterocytes while simultaneously down-regulating another chemotactic cytokine, macrophage chemotactic protein 1 (MCP-1).[175] Further studies from our laboratory have defined a role for butyrate-induced histone acetylation in the regulation of chemokine gene expression.[175] Unlike IL-8, which attracts neutrophils, MCP-1 attracts macrophages and monocytes. It is constitutively secreted by the intestinal epithelium, whereas IL-8 is not.[176] These observations are consistent with events in the whole intestine in vivo, where, in healthy tissue, neutrophils are absent and macrophages abound. With increasing butyrate levels, IL-8 secretion is induced, but MCP-1 production is depressed. Such "chemokine switching" in response to butyrate may well alter the population of immunologic cells in the lamina propria. Thus, butyrate may affect both the number and types of cells in inflamed tissue through changes in chemokine production of epithelium during inflammation.

Antimicrobial Peptides. In recent years, a new family of endogenous epithelial cell–derived antimicrobial peptides have been identified (for a detailed review, see Diamond and Bevins[177] and Bevins and colleagues[178]). To date, mRNA expression of members of two families, the β-defensin and cathelicidin (LL-37), has been observed in enterocytes (the expression of α-defensin family is confined only to Paneth's cells). Several studies have shown dynamic changes in the expression of these peptides during infectious and inflammatory episodes, implicating them in the front line of host defense in the gastrointestinal tract.[179–181]

Class II MHC and Invariant Chain Expression. The initiation of an immune response to protein antigen normally requires the help of T lymphocytes. Activation of T cells, in turn, depends on the processing and presentation of peptides by an antigen-presenting cell (APC).[182] Class II MHC heterodimers (Ia in the rodent) are the molecules that present the processed exogenous antigen to the T cell receptor. In addition to classic APCs (dendritic cells, macrophages, B lymphocytes), a number of cell types express class II MHC (Ia antigen), including intestinal epithelial cells, and may function as APCs. In recent years, there has been increasing evidence that both the small intestinal and colonic epithelium may function as an APC.[183,184] The requirement for cell viability and an intact cytoskeleton suggests pinocytosis as a major mechanism for active antigen uptake by intestinal epithelial cells; however, passive diffusion and adsorption may also contribute to the process. Processing and presentation of exogenous antigen require an additional protein, the invariant chain (Ii).[185] Diet has a marked effect on the expression of class II MHC and its associated invariant (Ii) chain in the mouse intestinal epithelium. The expression of class II MHC and Ii mRNA is developmentally regulated in the epithelium (unlike its expression in the lamina propria, where it is expressed from before birth).[186] In addition, the timing of expression can be altered by delaying the age of weaning from mother's milk to normal chow.[187] Expression of class II MHC and Ii chain is apparent 3 to 4 days after weaning on chow. However, weaning onto an elemental diet (which contains chemically synthesized amino acids, simple sugars, and fats) did not induce the expression of class II MHC or invariant chain (Figure 15-7). Thus, the expression of these genes in the intestinal epithelium is influenced by dietary manipulation in vivo. The fact that elemental diets used in these experiments were the same as those administered therapeutically in Crohn's disease lends support to the idea that alterations in gene expression may be a significant tool in the treatment of disease (see below).

TABLE 15-3 Immunologically Relevant Genes Expressed by Intestinal Epithelial Cells

Gene	*Experimental System*	*Reference*
Cytokines		
IL-1β	Experimental colitis	184
IL-6	Isolated epithelium	185
	Rat IEC-6 cell line with IL-1	186
IL-8	Colon carcinoma cell lines	143
MIP-2	Rat IEC-6 cell line with IL-1	149
Acute-phase respondents		
	Colon carcinoma cell lines	187
Surface molecules		
Class II MHC	Sections of rat small intestine	188
Invariant chain	Freshly isolated mouse epithelial cells, IEC-6 cells	150
Growth factors		
IGF-I	Colon carcinoma cell lines	189
IGFBPs	Colon carcinoma cell lines	190

IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; IL = interleukin; MHC = major histocompatibility complex; MIP = macrophage inflammatory protein.

Insulin-Like Growth Factor Binding Proteins. Immune responses depend not only on the activation of T cells but also on the ability of these T cells to proliferate. Earlier sections of this chapter described the importance of IGF-I in growth. However, IGF-I is also an agent that affects cells of the immune system. IGF-I exerts a range of effects on T-cell physiology. The growth factor induced a marked increase in the gene and protein expression of both CD25 and IL-2 and modulated T-cell proliferation via both autocrine and paracrine mechanisms.[188] Treatment of adult mice with recombinant human IGF-I induces striking modifications in lymphocyte number and function.[189] Fourteen days of treatment with IGF resulted in increases in both CD4+ T cells and splenic B cells. Mitogenic responses of T and B cells were also enhanced, demonstrating that IGF-I increases lymphocyte numbers and activity. As discussed

earlier, IGFBPs modulate the actions of IGF-I. Because cultured intestinal epithelial cells secrete IGFBPs, it is possible that the epithelium can influence the proliferation of activated B cells by this means.[190,191] Furthermore, studies have shown that nutritional factors affect the production of IGFBPs in cell lines in vitro.[192] Therefore, not only may nutritional factors influence IGF/IGFBP secretion by the liver into the circulation, resulting in changes in growth of the whole individual, but nutrients may also affect the IGF/IGFBP system in the intestinal epithelium, leading to alterations in the proliferation of the local immune system.

Nutrient Recognition and Signal Transduction

The mechanisms whereby a nutrient (or other factor in the intestinal lumen altered by dietary change) results in changes in RNA transcription are not well understood (see Figure 15-1). It is likely that increases in transcription are the consequence of alterations binding nuclear proteins to the promoter of the particular gene, but the steps by which a cell recognizes a change in that nutrient will differ for every nutrient examined; so, too, will the mechanisms that transduce this signal into alterations of nuclear protein binding. In the enterocyte, we have seen the variety of mechanisms that might occur simply by appreciating the many factors that may alter when the diet is changed (see Figure 15-2). Different theoretic mechanisms of interaction exist between the lumen and epithelial cells. These mechanisms differ, depending on the exact luminal factor involved (see Figure 15-5). Small nutrients such as butyrate or galactose are likely to enter the cell and affect gene expression through their respective metabolic pathways. Growth factors and lactoferrin involve specific receptors on the surface of the epithelium, and large proteins may enter the cell and alter gene expression as they are sorted. Some complex entities may affect more than one pathway. Bacteria, for instance, may interact through all three pathways: they could influence enterocyte metabolism; they may produce factors or components of their cell walls (eg, endotoxin), which may interact with surface receptors; and the macromolecules from which they are composed may enter enterocyte compartments and be sorted inside the cell. Each pathway may influence aspects of nuclear function. In addition, indirect actions of cytokines produced from immune cells may also play a role.

Although sensing and signal transduction mechanisms (see Figure 15-1) in the epithelium require further investigation, there are some data on the mechanisms by which glucose regulates the expression of PK (in the liver) and insulin (in pancreatic islet cells). Three key questions relate to the effect of glucose on the expression of these two proteins: (1) What are the glucose metabolites that set in train the effects on transcription? (2) How is binding of nuclear proteins to gene promoter elements induced? (3) What is the sequence of DNA in the promoter that confers glucose sensitivity on the gene in question (the so-called nutrient response element)?

In practice, this last question is the easiest to answer because DNA sequences can be easily manipulated in the laboratory. Promoters linked to reporter genes allow researchers to directly measure promoter activity. This was first examined in the PK gene in response to glucose. The actual sequence in the PK promoter was determined by mutational analysis of the promoter and its effects on reporter activity. The glucose response elements in the PK gene and in the insulin I gene were discovered by this means. To determine the glucose response element in the PK gene promoter, promoter DNA sequences were transiently transfected into hepatocytes in culture and were also examined in transgenic mice.[193–196] Mutations induced into the DNA demonstrated a glucose response element occurring twice in the PK promoter. This motif is known as an E box because of its resemblance to a similar sequence in a promoter of the adenovirus, which had been given this name. This same DNA sequence also occurs in other genes that regulate glucose metabolism, most notably the fatty acid synthase gene, whose protein product catalyzes one of the later steps in the conversion of carbohydrate to fat, one that is up-regulated when glucose is abundant in the diet.

The rat insulin gene also contains an E box, which is termed the Far element. Paradoxically, this element does not confer glucose sensitivity to the insulin gene. This attribute is conferred by a sequence 10 bases away termed the FLAT element. We now understand some of the features of the signal transduction from nutrient to nuclear function in the insulin gene. MacFarlane and colleagues identified a nuclear factor, insulin upstream factor 1 (IUF-1), which binds to the insulin promoter.[197] IUF-1 binding was examined in vitro by assessing the degree of binding of nuclear extracts from cultured islet cells to

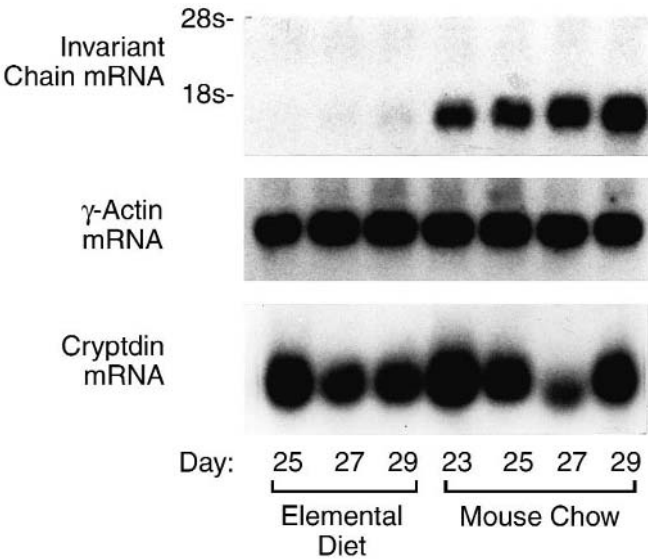

FIGURE 15-7 Dietary factors alter the expression of class II MHC and invariant chain expression in intestinal epithelial cells. Figure shows Northern blot of ribonucleic from epithelial cells taken from individual mice of a single split litter weaned at day 17 onto elemental diet or Purina mouse chow. The blot was probed with invariant chain complementary deoxyribonucleic acid (cDNA) and autoradiographed for 48 hours. Mice were examined at days 23, 25, 27, and 29. Blots were also probed with γ-actin and cryptdin cDNA to verify uniformity of enterocyte extraction. Reproduced from Sanderson et al.[187] mRNA = messenger ribonucleic acid.

radiolabeled promoter DNA. There was a high degree of IUF-1 binding in cells incubated with 20 mmol/L glucose, but this was abolished in cells incubated in 3 mmol/L glucose. In addition, this protein-DNA binding depended on the phosphorylation of IUF-1. Phosphorylation therefore alters a factor in the initiation of transcription of at least one glucose-sensitive gene. It is particularly interesting that phosphorylation is the signal that transduces glucose intake to induce insulin transcription because it is also phosphorylation that directly affects the activity of enzymes in the Embden-Meyerhof pathway. Thus, in this system, phosphorylation acts as a common transduction mechanism, responsible for both the quick and slow responses to glucose uptake.

The metabolites derived from nutrients responsible for the change in nutrient gene expression have not been elucidated in any system. Glucose-6-phosphate may possibly be the metabolite that activates the glucose response element in the fatty acid synthase and PK genes.[198] This was demonstrated by comparing the effects of the two glucose analogs, 2-deoxyglucose (2dG) and 3-O methylglucose (3OMeG). Neither analog can be metabolized. However, 2dG can be phosphorylated, but not 3OMeG; 2dG stimulated transcription, but 3OMeG did not. Therefore, only the phosphorylated sugar was able to stimulate the transduction mechanisms that resulted in transcription, which it did without further metabolism. Whether this phosphate bond provides the energy to phosphorylate a nuclear factor to bind to DNA is not known, but it is an interesting possibility.

CLINICAL AND THERAPEUTIC IMPLICATIONS OF NUTRIENT–GENE INTERACTIONS

The role of diet in diseases of many organs has become an area attracting attention from medical scientists and the general public. However, the relationship between dietary factors and the health of most organs has been difficult to examine, other than by using epidemiology.[199] Occasionally, data have emerged suggesting that particular diets benefit certain disease states. For example, renal failure was shown to be less progressive in rats whose protein intake had been restricted,[200] but even this has been difficult to substantiate in children.[201] Furthermore, it is not easy to see how the protein load has its effect. We have no knowledge of which cell types in the kidney may be affected, let alone how their phenotype may be altered by protein intake. On the other hand, in the small intestine, the relation between diet and gastrointestinal function is clearer.

In clinical practice, one of the most substantial changes in the content of the intestine occurs before and after parenteral nutrition. The effects of such changes have profound consequences for the small intestinal epithelium in human subjects (see Figure 15-6, B). Intestinal brush border hydrolase activity is diminished during parenteral feeding.[202] Moreover, the ability of the mucosa to form a barrier is compromised. Moore and colleagues studied 74 patients who had suffered abdominal trauma randomized to receive either enteral or parenteral nutrition.[203] Those fed parenterally had more episodes of infective complications (pneumonia and abdominal abscesses) than those fed enterally. Calorie and nitrogen intake was equivalent in the two groups. As it is thought that the main source of sepsis following trauma is the gastrointestinal tract, this study may be evidence that enteral feeding directly affects the ability of the injured patient to contain bacteria within the gastrointestinal lumen.

The effect of parenteral nutrition on the morphology of the intestine in animals has long been known.[204] Considerable attention has been paid to the question of which enteral components are responsible for maintaining normal bowel morphology and function. No clear answer has yet emerged. For example, Spector and colleagues observed that luminal infusion of 30% dextrose or 5% amino acids was effective in restoring intestinal weight, protein content, and DNA content after a period of intravenous alimentation.[205] Amino acids were more potent on a weight-for-weight basis or on a molar basis than dextrose. More recently, the changes in the intestine seen in animals fed via parenteral nutrition have been compared with the changes seen during weaning.[82] Intestinal length, mucosal mass, DNA, protein, and disaccharidase activities were significantly lower in animals sustained by intravenous nutrition when compared with normally weaned controls. However, restoration of luminal feeding resulted in a return to normal of the intestine in the total parenteral nutrition–fed group.

There are now many reports of the relationship of intestinal function to parenteral nutrition.[206] However, a study of the interaction between luminal content and the molecular control of intestinal cell protein synthesis is only just beginning, and this relationship is likely to provide the key to our understanding of how enteral feeds maintain a healthy epithelium.

It is also likely that epithelial signaling (see Figure 15-6, C) may have important therapeutic implications for diseased intestine. First, the contents of the intestinal lumen are directly amenable to therapeutic manipulation, whereas the environment that surrounds other, more internal organs is maintained in strict homeostasis by a plethora of mechanisms. Second, although we do not know exactly how the local environment surrounding the epithelial cell is changed by diet (see Figure 15-2), dietary manipulations are an important aspect of management of gastrointestinal disease states.

The activity of Crohn's disease is greatly influenced by altering the contents of the intestinal lumen. Inflammation subsides in patients who are fed parenterally and receive no oral nutrients and in those receiving elemental diets[207,208] (see "Enteral Products" in the Appendix). These chemically defined diets induce remission as effectively as high-dose oral corticosteroids in both adults and children.[209–211] The return of inflammatory changes to normal in the intestine has been documented indirectly by the use of markers of intestinal permeability and scanning of labeled neutrophils and directly by examining the mucosa at endoscopy with biopsies.[212–214]

It has been hypothesized that a reduction in antigen load in the intestine may underlie the efficacy of elemental

diets in Crohn's disease in a fashion similar to that in cow's milk–sensitive enteropathy and celiac disease.[210] However, the switch from a normal diet to an elemental diet alters many constituents of the intestinal milieu apart from food antigens (see Figure 15-2). In particular, bacterial populations (and therefore bacterial products) are profoundly altered by dietary alteration. Moreover, giving whole protein in the form of liquid diets (polymeric diets) is also an effective treatment for Crohn's disease.[215] Removal of protein antigen is therefore not essential for the efficacy of the formula diet. It is more likely that the diets are altering many factors in the local environment of the intestinal lumen (see Figure 15-2). The concept of genes in the epithelium signaling events to the mucosal immune system is a first step to understanding the basis of how such events may occur because it seeks to identify molecular pathways from the intestinal lumen through enterocytes to the mucosal immune system and other target cells beyond the epithelium. Certainly, this would be in keeping with data presented earlier (see Figure 15-7) showing that class II MHC and invariant chain expression in the epithelium are related to dietary factors. There was no expression in epithelial cells of the mice weaned onto an elemental diet,[187] and this diet was the same as that used in the treatment of Crohn's disease. Genes other than class II MHC, with common promoter elements, may also be altered by similar maneuvers and may be important in regulating intestinal inflammation.

CONCLUSIONS AND SPECULATION

Certain concepts have been laid down in this chapter that can be used as the basis for examining how dietary factors may affect the expression of genes in various cell types, including the intestinal epithelium. The essential components for an effective transition between nutrient and gene expression in cells have been documented. These components (see Figure 15-1) comprise a system of recognizing changes in factors as they interact with a cell (sensing) and a mechanism of converting these external molecule–cellular molecule interactions into changes in gene expression (signal transduction). It is not yet understood how these mechanisms are effected in the cell. This chapter has presented evidence that nutritional factors do indeed alter gene expression in cells, but it is likely that different molecular species are sensed by completely different mechanisms. In the case of the epithelial cell (see Figure 15-5), these sensing mechanisms can be at the cell surface or part of the internal mechanisms of the cell. It is also possible that special receptors exist on the surface of the cell and detect more complex external molecules, such as large proteins and oligosaccharides. The apical surface of mucosal epithelial cells expresses a number of molecules belonging to the immunoglobulin superfamily. Their function is at present unknown, but they have been identified because they form the attachments for invading viruses. One member of the immunoglobulin superfamily (intercellular adhesion molecule 1) allows rhinovirus attachment in nasal epithelium.[216,217] As the primary function of these molecules on the mucosal surface cannot be to serve as a conduit for viral infection, it is tempting to suggest that they and other similar molecules might play a role in the immunosurveillance of macromolecules in the gastrointestinal tract. Signaling through these molecules would require alterations in epithelial cell gene expression for this surveillance to be transmitted to the mucosal immune system. If antigens are recognized by epithelial cells of the gastrointestinal tract, it is possible that this information is correlated with information garnered from the previous penetration of similar antigens across the epithelium.[70]

Finally, this field of nutrient–gene interaction may have important therapeutic implications; the ability of the epithelium to interact with other immune cells makes it an active member of normal human defense.[218–222] This physiologic role may allow it to influence inflammatory reactions in pathologic situations. The opportunity exists through dietary means to manipulate the constituents of the lumen of the intestine by opening up a new vista for treatment of human disease. Genetic expression is now regarded as a central feature of human disease states, particularly those in which certain genes are defective. However, genetic influences also affect a much wider variety of diseases than those that are attributable to simple inherited gene mutations. The possibility that expression of genes can be modulated by means other than insertion of new DNA should be added to the armamentarium of the medical community. An understanding of how dietary factors may alter gene expression is an early step in this direction.

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CHAPTER 16

HUMORAL REGULATION OF GROWTH

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Hormones and nutrients interact to influence growth at all levels of biologic organization. Growth is often loosely defined to include all aspects of somatic enlargement and maturation. The principal impact of malnutrition on the growing child is to diminish or reverse weight gain. When malnutrition is of sufficient duration or intensity, statural growth is retarded, although under some unusual circumstances, malnutrition may selectively impair linear growth without a preceding or concomitant loss in weight.[1] The manifestations of malnutrition effects on growth are often subtle, frequently masquerading as social, ethnic, or racial characteristics. In a study of ethnically homogeneous conscripts in the Polish army, Bielicki and colleagues found that young men from large families, from the countryside, and from lower socioeconomic classes were smaller than their counterparts from smaller, urban, and more privileged families.[2] These authors concluded that the negative impact of these variables on stature could all be attributed to suboptimal nutrition. On a large scale, the effect of malnutrition is often so striking as to produce major population differences in stature that appear to be genetic. For instance, prior to World War II, native Japanese were smaller than Americans of European ancestry and smaller than Japanese Americans raised in the United States.[3] However, with the significant nutritional improvements that took place in Japan following World War II, these differences vanished.[4]

NUTRIENTS, HORMONES, AND GROWTH

Hormones and Growth Factors

Hormones are generally defined as the secretions of glands that specialize in their production; classic hormones, acting through an endocrine mode of regulation, therefore require conveyance through the circulation to alter the function of distant tissues. Their concentrations and association with binding proteins can be readily measured in the blood and other body fluids. Regulation occurs not only through changes in the concentration of the hormone but also in the numbers and cellular distribution of their peripheral receptors and in the systems of second messengers within the target cells that convey these signals to the genome or other cellular compartment. Each of these steps can be regulated by developmental programs and by the local milieu of nutrients and other hormones.

The body-wide endocrine system, however, is also an integrating system that is superimposed on multiple local regulatory systems that employ *paracrine* modes of regulation.[5] Paracrine control refers to the release by cells of soluble messengers that act on neighboring cells of another type. A circulation is not required because only physical proximity and the presence of receptors are required for effect. In 1980, Sporn and Todaro added the concept of *autocrine* control to include the substances that cells secrete to regulate their own growth.[6] Although autocrine control was initially thought to be a mode of growth control for neoplastic cells exclusively, autocrine control also characterizes the growth and function of many normal cells. Examples of autocrine control include the release of epidermal growth factor (EGF) by ulcerated gastrointestinal mucosa and release of transforming growth factor-α by normal intestinal epithelial cells.[7] As a consequence of the narrow range of action within the extracellular space of autocrine and paracrine growth factors, their roles in cellular regulation are much more difficult to document in clinical situations. It has recently emerged that proteolytic events at the cell surface are critical regulators of the accessibility of autocrine and paracrine factors to their receptors.[8] Multiple proteases associated with extracellular matrix or cell membranes are known to solubilize and activate growth factors from their cell surface–anchored, but biologically inactive, precursors.

It has been proposed that growth factors can exert biologic actions without release into the extracellular space. *Juxtacrine* control refers to the actions of growth factors that remain anchored to the plasma membranes of the cells that produced them; cell-to-cell contact brings them into contact with receptor-bearing target cells.[9] Finally, some growth-regulatory molecules can activate receptors on intracellular membranes, including those in the cytoplasm, nucleus, nucleolus, or mitochondrion, a mode of action called *intracrine* control.[10] In some instances, intracrine factors originate within their target cell; in other instances, they are internalized from the extracellular space.

Intracrine action appears to be critical for the regulation of the chicken ovalbumin gene.[11] In conjunction with the neuroendocrine mode of regulation, which makes use of axons to direct regulatory neurotransmitters to their target cells, the multiple systems of cellular regulation provide a diversity of regulatory options, each of which has relevance to an understanding of nutritional influences on growth. The characteristics of endocrine, paracrine, autocrine, juxtacrine, intracrine, and neuroendocrine modes of regulation are summarized in Table 16-1.

In distinction to the protein and steroid molecules that comprise the classic hormones of the endocrine system, peptide growth factors are the principal agents of the paracrine, autocrine, juxtacrine, and intracrine systems.[12] The distinction between hormones and growth factors is generally a functional one. There are instances in which a substance may be released from a gland into the circulation to act as a hormone at a distant site, whereas within a highly specialized tissue, the same substance might be locally secreted as a growth factor to influence the function of adjacent cells. In many instances, nature has retained the basic structure of successful regulatory molecules and, through a divergent evolution, has created new uses for them. The structural homology of insulin and the insulin-like growth factors (IGFs), which are discussed later in this chapter, illustrates how a substance with predominantly nutrient-transporting properties, which is found in even primitive unicellular organisms, has evolved to regulate highly differentiated functions. Illustrations will be provided of how, in many instances, hormones that circulate widely can produce highly individualized local effects by differentially regulating tissue-specific production of local growth factors.

Nutrients and the Growth of Cells

Holley was among the first to propose that the intracellular availability of nutrients is the ultimate regulator of cell growth.[13,14] He postulated that when cellular nutrition is adequate, mammalian cells require no additional extrinsic growth-promoting substances, and that hormones and growth factors regulate tissue growth ultimately by altering the availability of nutrients. In the laboratory, the growth of cells and tissues clearly requires the proper combinations of hormones and growth factors in addition to an adequate supply of nutrients. There is ample evidence that growth factors and hormones influence the transport and use of nutrients by cells.[15–19]

Hormones and nutrients interact in a delicate balance: hormones alter the nutritional requirements of cells, and, conversely, nutrients alter cellular hormonal requirements. McKeehan and McKeehan found that cultured human lung fibroblasts require lower concentrations of various minerals and substrates in the culture medium as the concentration of serum growth factors is increased.[20,21] Conversely, they found that adequate concentrations of nutrients reduce the need for growth factors, an interaction that has been systematically probed by Rizzino and colleagues and Wu and Sato.[22,23]

Although adequate supplies of nutrients are necessary to allow full manifestations of the effects signaled by hormones and growth factors, hormones influence cell growth by mechanisms other than changing their cellular nutritional status. Thyroid and steroid hormones, for example, can change cell function by directly influencing the transcription of target genes in the nucleus, although adequate "nutrition" in the form of high-energy phosphates and other low-molecular-weight substrates is required for full manifestation of the signal. In contrast, most polypeptide hormones and growth factors bind to cell-surface receptors, and their ability to influence the genome requires the initiation of a cascade of reactions that involve lipids, proteins, and ions as second messengers. Specific micronutrients, such as glutamine, allow the amplification of growth factor signaling and individually activate intracellular signaling kinases (eg, mitogen-activated protein kinases) in intestinal and liver cells.[24,25] Furthermore, there are amino acid response elements in the promotor of nutritionally important genes. One gene regulated by amino acid deprivation and the endoplasmic reticulin stress response is asparagine synthetase, which is a recognized target of antileukemic chemotherapy and is essential for maintenance of cell viability.[26]

TABLE 16-1 Modes of Cellular Regulation

Mode	*Agent*	*Source*	*Vehicle*	*Target*	*Modulators*
Endocrine	Hormone	Gland	Circulation	Heterologous tissue	Neurons Hormones Growth factors
Paracrine	Growth factor	Local site	Diffusion	Heterologous cell	Hormones Growth factors
Autocrine	Growth factor	Local site	Diffusion	Autologous cell	Hormones Growth factors
Juxtacrine	Growth factor precursor	Local site	Cell contact	Adjacent cell	Proteases
Intracrine	Hormone Growth factor Nutrient	Intracellular	Cytoplasm	Intracellular receptor	?
Neuroendocrine	Neurotransmitter Growth factor	Neuron	Axon	Heterologous tissue	Hormones Growth factors Neurons

Nutrients and the Growth of Tissues

The study of cellular proliferation in the laboratory culture dish can provide information on the hormonal and nutritional needs of dividing cells, but the growth and development of the organism as a whole require that the enlargement and maturation of each tissue occur at the appropriate rate and in the proper sequence.[27] As they can influence nutrient requirements of individual cells, hormones can also affect the nutrient needs of complex tissues as well as the supply of nutrients in the fluid milieu in which they are bathed. The effects of a given hormone on its various target tissues can be quite different: catabolic in one tissue, anabolic in another (Table 16-2). These effects are generally not without coordination as catabolism in one tissue can serve to increase the supply of nutrients to another tissue that is rendered anabolic by the same hormone. For example, under normal circumstances, anabolic hormones increase the protein content of both viscera and muscles.[28] In the nutrient-deficient state, however, anabolic agents such as growth hormone (GH) and androgens continue to preferentially support carcass protein (muscle) synthesis even at the expense of visceral protein. Androgens, for instance, diminish the rate of muscle breakdown in fasted guinea pigs while accelerating the loss of protein from the liver.[29] Similarly, the weight loss of food-restricted swine can be reduced by the administration of GH, but the effect is to preferentially retain muscle mass while depleting body fat.[30] Similar effects are seen in humans (see below) and have led to abuse of GH by competitive athletes. Conversely, an important adaptive response to long-standing malnutrition is a generalized inhibition of anabolic systems, such as those involving GH and androgens, to conserve essential body compartments.

Whereas anabolic hormones preferentially preserve muscle mass when nutrients are in short supply, catabolic hormones serve to protect the viscera. Brief exposure of rats to glucocorticoids or to thyroxine (T_4) increases the protein and glycogen content of the liver, whereas the protein content of muscle is depleted.[28] These effects are direct ones on hepatic uptake and synthetic processes and not merely the result of increased substrate availability from the carcass.[31] Even a prolonged exposure to glucocorticoids, which depletes both viscera and muscle, reduces visceral mass proportionally less than muscle.

Critical Periods in Tissue Growth

The ability of tissues to recover from a nutritional insult varies greatly at different times during development. The study of normal tissue growth has provided a model of normal tissue development that has been used to analyze the variable effects of malnutrition at different developmental stages. As the organ or tissue approaches its predetermined complement of cells, the organ grows by increasing both its cell number and the size of each cell. When the adult complement of cells is attained, cell division ceases and tissue growth results totally from enlargement of existing cells.[32] In the growing rat, Enesco and Leblond found the strictly proliferative phase to last until the seventeenth postnatal day, whereas after 34 to 48 days of life, tissue growth resulted solely from increases in cell size without an increase in new cells.[32] Between these two periods, tissue growth appeared to result from both cellular hyperplasia and hypertrophy.

Widdowson and McCance performed studies on growing animals that clearly established the existence of critical periods of sensitivity to the effects of malnutrition.[33–35] They manipulated the litter size and therefore the milk supply of rat pups during suckling and observed their subsequent growth. Rats that were nutritionally deprived during this period were small, and their growth could not be restored by institution of normal food intake.[36] The mechanism for this runting appears to be an irreversible effect of undernutrition on the number of cells. Similar mechanisms are likely to operate in some forms of intrauterine growth retardation (IUGR) in children, although the irreversibility of the growth deficit has come into question with the observation that GH treatment can accelerate growth in some small for gestational age children.[37]

Winick and Noble provided further evidence that the nutritional state of the neonatal period influences cell proliferation and consequently determines the ultimate size of the animal and its organs.[38] Food restriction in the first 21 days of life produced a subnormal complement of cells in most tissues. However, the size of the cells was normal. Adequate nutrition after weaning could not restore normal growth, presumably because of an irreplaceable deficit of cells. Food restriction between 21 and 42 days resulted in a comparable stunting of growth in most tissues, but the brain and lung were able to resume normal growth with the restoration of proper nourishment. In these tissues, the total adult cell number had already been attained, and mal-

Table 16-2 Actions of Hormones on Body Compartments

Hormone	*Protein*	*Carbohydrate*	*Fat*
Glucocorticoid	Breakdown in muscle, synthesis in viscera	Permissive for gluconeogenesis, glycogen synthesis	Redistribution
Insulin	Synthesis in muscle and liver	Glycogen synthesis in liver, glycolysis	Lipogenesis, inhibits lipolysis
Growth hormone	Synthesis in muscle	Insulin-like effects (acute), insulin antagonistic (chronic)	Lipolysis, inhibits lipogenesis
Thyroid hormone	Synthesis in liver, breakdown in muscle	Glycogenolysis, gluconeogenesis	Lipolysis
Androgen	Synthesis in muscle and viscera		

Adapted from Eisenstein AP and Singh SP.[289]

nutrition produced a reversible decrease in cell size. When malnutrition was induced between 65 and 86 days, almost all organs underwent a reversible decrease in cell size only.

Growing tissues are as sensitive to an excess of nutrients as to a shortage. When rat litter sizes were reduced to provide supranormal nutrition, the offspring were larger than normal and were found to have hypercellular organs.[39]

As it has evolved from studies such as these, the critical period hypothesis proposes that abnormal nutrition, either excessive or deficient, during the phase of tissue growth by cellular proliferation can increase or decrease the ultimate size of a tissue by enhancing or impairing cell division. These effects are irreversible because they bring the tissue into the phase of growth by cellular hypertrophy with an abnormal number of cells or abnormal organization. When nutritional surfeit or deficit occurs after establishment of the adult complement of cells, the net effect is a change in cell volume, but not in cell number, and is reversible by normalization of the nutrient supply. Because tissues mature at different rates, the long-term effects of nutritional variations occur most prominently in those tissues that are at a susceptible developmental period.[40] An important example of this principle of "programming" following an insult at a critical, sensitive period of early life is that mothers who are malnourished during pregnancy often have infants with IUGR, subsequent growth retardation, and, ultimately, disproportionately high rates of coronary heart disease, high blood pressure, and high cholesterol during adult life.[41] IUGR in girls has been linked to the development of hyperandrogenism, insulin resistance, and ovulatory dysfunction in adolescent years.[42–44]

Catch-Up Growth

It has long been documented that children have the capacity to accelerate their growth when recovering from a growth-impairing influence such as malnutrition or disease. At the complex level of organization that is required for statural growth, the ability of nutritionally deprived cells and tissues to be restored to functional health is reflected in the phenomenon of "catch-up growth," a term used by Prader and colleagues.[45] Subsequently, "catch-down" was coined to refer to the complementary process that follows removal of growth-accelerating influences, such as occurs with suppression of precocious puberty, restriction of food in obesity, or cessation of GH therapy in hypopituitary children.

Even under the most favorable circumstances, the accretion of height does not occur at a fixed rate but is developmentally regulated. Gender-specific, nutritional, and—in some cultures—seasonal influences are also superimposed. The period of most rapid postnatal growth in children occurs in the first months of life, when length increases by 14 to 22 cm per year. By the second birthday, the mean growth velocity has slowed to about 8 cm per year and to about 5 cm per year just before puberty. Then, under the influence of sex steroids (but involving the coordinated actions of GH, IGFs, thyroid hormones, and others), growth velocity nearly doubles before statural growth ceases as the epiphyses close.

After the second year of life and continuing throughout childhood, growth velocity is modulated to maintain stature at a constant position relative to the general population. The height percentile attained by about 2 years of age is maintained faithfully throughout childhood and correlates well with the height percentile in adulthood.[46] Statural growth along a predetermined percentile on a growth chart is often called canalization. Growth-retarding or growth-accelerating processes disrupt canalization and growth curves cross channels. With amelioration of the abnormal condition, a compensatory acceleration or deceleration occurs to restore the original growth channel (Figure 16-1).

In the first 2 years of life, catch-up growth can be a normal adaptation in children whose birth size is at variance with their genetic potential. Whereas statural growth from age 2 years to adulthood is primarily controlled by genetic influences, the determinants of body size during fetal life are largely determined by maternal and nutritional influences. The interval between birth and roughly 2 years of age is a preprogrammed period of catch-up or catch-down growth and is characterized by a shift of growth channels as maternal influences give way to genetically determined forces. It is essential for the clinician to be aware of these forces during this period because genetically programmed changes in growth velocity can be misconstrued as manifestations of disease.[47]

From a practical standpoint, for catch-up growth to be complete, the insult must be limited in duration and must not occur during certain vulnerable periods. Williams and

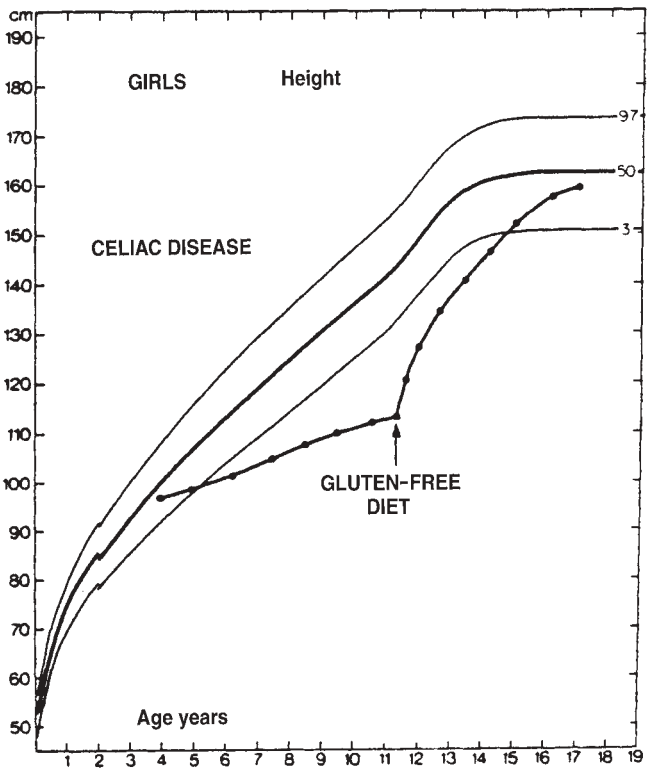

FIGURE 16-1 Catch-up growth in a girl with celiac disease. After 8 years of growth failure, she was placed on a gluten-free diet and exhibited striking catch-up growth. Note return to previous growth percentiles. Courtesy of J. M. Tanner.

coworkers noted that the degree of catch-up growth is generally muted if it begins when growth is normally decelerating.[48,49] Based on observations in birds and mammals, Wilson proposed that catch-up growth potential is modified by the nature of the insult, its severity, its duration, and the developmental state of the animal at the onset of the insult. For example, it had been assumed that GH deficiency and hypothyroidism were two conditions with the potential for essentially complete catch-up. However, the catch-up potential of hypothyroid children is diminished in proportion to the duration of the hypothyroidism before treatment.[50] Their subjects had been hypothyroid for approximately 5 years and had deficits from their predicted heights of 25 cm at the onset of therapy; however, at the conclusion of therapy, an average deficit of 7 cm remained (Figure 16-2). The magnitude of deficit between final height and predicted height was in proportion to the duration of hypothyroidism before treatment began. Similar conclusions resulted from studies of children with GH deficiency of long duration before treatment.[51] Incomplete catch-up growth has also been documented in children with acute nutritional insults, such as diarrhea, when they are superimposed on a background of chronic malnutrition.[52,53]

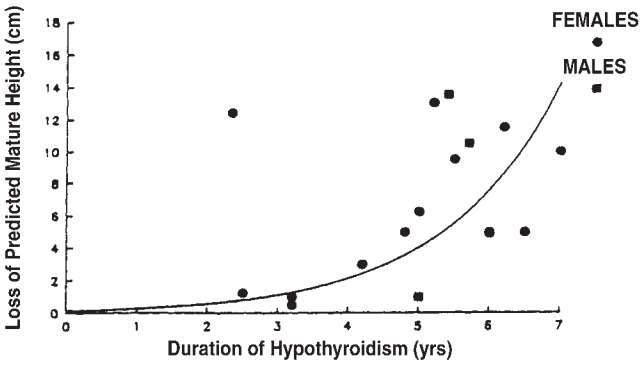

FIGURE 16-2 Loss of catch-up potential with long-standing hypothyroidism. Relationship between loss in adult height and duration of hypothyroidism before treatment in children. Loss of predicted height is predicted height at time of diagnosis minus actual mature height. Duration of hypothyroidism is chronologic age minus bone age at diagnosis. Reproduced from Rivkees S et al.[50]

In addition to its duration, the specific nature of the insult may be important in determining the extent of catch-up because some growth-arresting conditions appear to cause irreversible changes. Mosier found that cortisone-treated rats failed to regain normal body size after cessation of treatment, whereas rats that were comparably stunted by fasting resumed normal growth when refed.[54] Cartilage from the steroid-treated rats had increased numbers of dead and dying cells, altered cell morphology, and alterations in the matrix.[55]

It has been suggested that the catch-up growth of recovery from malnutrition in some experimental conditions is associated with an increase in the efficiency of energy use.[56] Fasted rats are capable of a fivefold increase in energy use efficiency for weight gain during recovery, perhaps by decreased thermogenesis.[57] The situation may be different in humans: children recovering from malnutrition often have increased appetite and caloric intake, suggesting to others that energy use is not efficient.[58] Some marasmic children do not begin to gain weight until 3 to 5 weeks of refeeding, despite an intake of more than 130 kcal/kg/day.[59]

Implied in the concept of catch-up or catch-down growth is an ability of the organism to constantly monitor its size and determine the extent of deviation from the intended size; to alter its velocity when unrestrained from the growth-perturbing influence; and, finally, to again modulate its altered velocity to prevent overshooting or undershooting the channel.[60–63] Williams stressed the theoretical importance of distinguishing between *catch-up* growth and *compensatory* growth.[63] He recognized that the former involved growth to attain a projected (and moving) statural target, whereas the latter involved the growth of a tissue or organ to restore actual lost mass. An example is the regeneration of liver following a partial hepatectomy.[64]

Two divergent, but not necessarily exclusive, models have been put forward to explain the ability of the organism to monitor body size and initiate catch-up. Tanner postulated the existence of a "sizostat" in the central nervous system (CNS) that maintained communication with the peripheral tissues.[65] Along the same lines, Leibel proposed that the concentration of a circulating hormone, such as insulin (or its ratio to other hormones or metabolites), might reflect the size of a body compartment, such as the adipose mass, by monitoring the number of insulin receptors on adipocytes.[66] With the isolation of leptin, the data to support a neuroendocrine control of weight regulation have been far stronger than those to support a neuroendocrine control of statural catch-up. The interactions between adipose mass and the CNS are discussed in the following section.

In contrast to a neuroendocrine mechanism of catch-up growth, Baron and colleagues focused on the growth plate as the key tissue in catch-up growth.[67] Their data showed that a unilateral growth-suppressing influence, accomplished by transient administration of glucocorticoids to a single growth plate, was accompanied by catch-up growth acceleration at that growth plate only, not systemically.[68] Although their model does not preclude the involvement of systemic hormones and the CNS, they proposed that growth-inhibiting conditions decrease proliferation of growth plate stem cells, thus conserving their proliferative potential. Catch-up growth results from a putative clock, or time tally to use Tanner's term, within the stem cell compartment.

Although it is likely that both systemic (neuroendocrine and endocrine) and local (paracrine, autocrine, and juxtacrine) signals will be implicated as critical regulators of the proliferation that occurs during catch-up or catch-down growth, there is little evidence to date that hormones and growth factors are significant mediators of the catch-up phenomenon. These data are extensively reviewed in reference.[69]

In this section, the interactions of nutrients and specific hormones are discussed as they pertain to normal growth, malnutrition, psychosocial growth failure, overnutrition, and growth acceleration.

GROWTH HORMONE, IGFS, AND INSULIN

Normal Growth

GH and IGFs in Normal Growth Pituitary GH (or somatotropin) is essential for normal, balanced somatic growth from childhood to normal adult stature. However, the mechanism by which this process is regulated is incompletely understood, especially in the fetus. The actions of GH are now known to involve a complex interaction among GH genes, GH receptors, somatomedins, or IGFs, IGF receptors, and IGF binding proteins (IGFBPs). In addition, the GH-somatomedin axis is entwined in a regulatory web that is strongly modulated by nutritional signals.

IGFs *and the* Somatomedin Hypothesis. With the advent of techniques for the culture of tissues and cells in the laboratory almost 50 years ago, it became evident that many of the biochemical events that had been attributed to GH in vivo could not be reproduced on isolated tissues studied in the laboratory. These included effects on chondrocyte proliferation and sulfate incorporation into glycosaminoglycans of growth plate cartilage. These observations led Salmon and Daughaday to propose the "somatomedin hypothesis": that the growth-promoting effects of GH are not direct ones on its target tissues but result indirectly from the actions of a mediator substance under GH control.[70,71] Initially called sulfation factor or thymidine factor, based on the assay system used to detect its presence, it was later determined that these two biologic activities resided in the same molecule, which was renamed somatomedin.[72] Other somatomedin species were initially distinguished, but somatomedin C was determined to be the GH mediator of serum.

IGFs were purified in parallel, but independent, studies to characterize the source of the insulin-like biologic activity of serum, only a small part of which derives from insulin itself. Two molecules were identified, IGF-I and IGF-II, the amino acid sequences of which were found to be remarkably similar to proinsulin.[73,74] Somatomedin C is identical to IGF-I, and current convention prefers the IGF terminology, although a number of IGF-I assays available from clinical reference laboratories retain the somatomedin C designation. The properties of IGF-I and IGF-II are contrasted in Table 16-3. Although the current nomenclature has the disadvantage of dissociating the IGFs from their regulatory link with GH, it does more firmly root these substances in the realm of nutritional control.

Initial iterations of the somatomedin hypothesis were inspired by endocrine models of growth control: liver was found to be a major producer of somatomedin activity, and the paradigm that evolved had the liver functioning as an endocrine gland under the control of pituitary GH to secrete somatomedins, whose ultimate target tissue was the growth plate. To further support an endocrine model, IGFs were found to feed back to the pituitary and inhibit the release of GH.

However, in the 1980s, it became clear that multiple tissues express messenger ribonucleic acid (mRNA) for IGFs and are involved in IGF production.[75,76] Most compelling was the observation that IGF-I mRNA is expressed in perichondrium and periosteum, suggesting that local production of IGFs in the epiphysis might account for the growth-stimulating effects of GH. Indeed, Isaksson and colleagues had shown that GH elicits an increase in both IGF-I mRNA and protein in rat epiphyses.[77] Based on analogy to the work of Green and colleagues on the role of GH in the differentiation of adipocytes, Isaakson and colleagues proposed that GH stimulates the differentiation of chondrocytes in the germinal zone of the growth plate; once the stem cells become chondrocytes, their proliferation would result from local (autocrine/paracrine) production of IGF-I.[77,78] However, inconsistencies remain among the data: GH- or GH receptor–deficient mice and humans have no paucity of differentiated chondrocytes, and growth plate chondrocytes can proliferate normally without IGF-I.[71] Nonetheless, the consensus is that locally generated IGFs in the epiphysis are the critical regulators of linear growth.

Table 16-3 Insulin-Like Growth Factors

Property	*IGF-I*	*IGF-II*
Synonyms	Somatomedin C, basic somatomedin	Multiplication stimulating activity (MSA), neutral somatomedin
Chromosome location	12	11
Molecular weight	7,649	7,471
Serum concentration	193 ± 58 ng/mL	647 ± 126 ng/mL
GH dependence of serum concentration	+++	+
Insulin-like actions	+	+++
Mitogenicity in cultured cells	+++	+
Developmental role	Postnatal	Fetal
Sensitivity to undernutrition	+++	+/–

GH = growth hormone.

The weakness of the original somatomedin hypothesis was most clearly illustrated by the creation of a liver-specific knockout of the IGF-I gene. Using Cre/loxP technology, Le Roith and colleagues produced mice with hepatic IGF-I mRNA levels reduced to less than 1% of normal, resulting in a 75% reduction in serum IGF-I.[79,80] Nonetheless, these mice lacking hepatic IGF-I grew normally, and "there were no phenotypic distinctions between the liver-specific IGF-1 gene-deleted animals and their wild-type littermates."[71] Although these studies do not confirm that bone-derived IGFs are the critical determinants of linear growth, they do support the contention that circulating IGFs are not critical to linear growth. As expected based on their markedly reduced serum IGF-I levels, the liver-specific IGF-I knockout animals had elevated concentrations of GH, leading LeRoith to speculate that the major role of circulating IGF-I might be to modulate GH secretion.

IGFBPs. In contrast to GH, which circulates in association with a fragment of the GH receptor called the GH binding protein, IGF concentrations in blood are maintained at relatively stable levels by serum binding proteins

that markedly delay IGF clearance. IGF binding in serum and other fluids resides in six different molecules, collectively known as the IGFBPs. The IGFBPs are summarized in Table 16-4.[81] The major IGF binding complex in serum consists of IGFBP-3 in association with the acid-labile subunit (ALS). IGFBP-5 can also interact with ALS and IGFs in the serum. Circulating IGFBP-3 concentrations, like those of IGF-I, are GH dependent. It is now clear that many, if not all, of the so-called somatomedin inhibitors identified in early bioassays of somatomedin activity, especially in conditions of malnutrition and disease, were actually IGFBPs.

All six proteins have higher affinity for both IGF-I and IGF-II than do IGF receptors. IGFBPs were initially proposed to function as IGF-sequestering agents, thus limiting the concentration of free IGFs. However, IGFBPs modify IGF actions in a variety of ways: they transport IGFs across vessel walls and capillary membranes, they regulate the concentration of IGFs in the vicinities of specific tissues and cell types, they control IGF interaction with cell-surface IGF receptors, and at least three of these molecules (IGFBP-1, -BP-3, and -BP-5) can augment IGF action. Baxter has proposed that a binary complex of a single IGFBP and IGF-I, which can leave the circulation rapidly, facilitates access of IGFs to their receptors, whereas a ternary complex consisting of IGF, IGFBP-3 (or -BP-5), and ALS cannot cross the endothelial barrier and remains in the circulation to sequester free IGF-I.[81] The implications of this on nutritional regulation of IGF action are discussed below. As noted in Table 16-4, serum concentrations of the three principal IGFBPs are profoundly influenced by nutritional signals (mediated by insulin) and by GH. IGF binding and action can also be modulated by post-translational modifications of the IGFBPs such as phosphorylation, proteolysis, and matrix association.[82] Three of the IGFBPs appear to be able to influence cell function independent of their role as an IGFBP. For example, IGFBP-3 can inhibit proliferation in cells that have no IGF receptors.[83] Specific cell-surface receptors for the IGFBPs have been proposed, and IGFBP-3 may have direct effects in the nucleus by interacting with the retinoid X receptor α, RXRα.[84]

GH, IGF, *and* IGFBP G*enes*. In humans, GH is encoded within a cluster of five structurally similar genes on the long arm of chromosome 17.[85] These genes include the so-called normal GH gene (*GH-N* or *GH-A*), a variant GH gene (*GH-V* or *GH-B*), and three genes for placental lactogen (chorionic somatomammotropin). Only GH-N is translated into GH in the pituitary gland, and the other four genes of the family are expressed in placenta. Two distinct forms of GH result from differential splicing of the mRNA that is transcribed from the *GH-N* gene. The predominant product is a single chain of 191 amino acids with a molecular weight of 22 kDA. The product of alternate splicing of the *GH-N* gene is 20 kDa GH, which results from a deletion of 15 amino acids and comprises about 10% of circulating GH. Clear evidence for a differential regulation of the secretion of these two GHs is lacking, although they may differ in some of their biologic actions.

Each of the IGFs is encoded by a separate gene, although alternative splicing of each of the genes and other post-transcriptional modifications result in multiple IGF mRNA species. The extent to which the modification of IGF gene transcripts is important in the regulation of IGF action is unclear. The IGFBPs as well arise from a gene superfamily that includes proteins whose function and relationship to IGF physiology are as yet undetermined.[86]

GH-IGF A*xis*: P*hysiologic* R*egulation*. Pituitary GH release is regulated by two principal hypothalamic peptides, one stimulatory (GH-releasing factor [GRF] or growth hormone–releasing hormone [GH-RH]) and one inhibitory somatostatin release inhibiting factor (SRIF) (Figure 16-3). Blood concentrations and patterns of GH secretion result from an interplay between these two substances on the somatotropes of the anterior pituitary. The hypothalamus receives rich innervation from higher centers in the brain, providing a mechanism by which even emotional influences can alter GH secretion (see discussion of psychosocial dwarfism later in this chapter). However, other modulating influences on GH release have been identified. Both free fatty acids and the orexigenic neuropeptide Y are known to directly inhibit GH secretion, whereas the fat-derived hormone leptin (see below) stimu-

Table 16-4 Insulin-Like Growth Factor–Binding Proteins

Property	*BP-1*	*BP-2*	*BP-3*	*BP-4*	*BP-5*	*BP-6*
Molecular weight	25,000	33,000	54,000	24,000	31,000	30,000
Chromosome location	7	2	7	17	5	12
Serum concentration (nM)	0.8–2.8	6.1–18.3	60.170	Present		Present
Tissue localization	Serum, amniotic fluid, kidney, reproductive tissues	Serum, CSF	Serum	Serum, CNS	Placenta, kidney, bone, thyroid	Serum, CSF
Regulation by GH	↓	↓	↑↑			↑
Regulation by insulin	↓↓	↓				
Proposed function	Transport of IGFs from vascular space; immediate early gene	Transport of IGFs from vascular space	Major component of 150 kDa serum IGF complex intravascular reservoir	Blocks IGF action in cells	Potentiates IGF action in cells	

CNS = central nervous system; CSF = cerebrospinal fluid; IGF = insulin-like growth factor.

lates GH release, perhaps by inhibiting secretion of neuropeptide Y.[87–91] Very recently, ghrelin has come to the fore as a potent regulator of GH secretion, food intake, and fat mass. Investigators studying a family of synthetic GH-releasing peptides identified a novel CNS receptor for these peptides and then identified ghrelin as its natural ligand.[92] Ghrelin is produced by hypothalamic neurons and by a highly specialized population of endocrine cells in the fundus of the stomach, where its secretion is suppressed by food intake. The model that is emerging ties stomach-produced ghrelin to the nocturnal stimulation of GH secretion, whereas hypothalamic ghrelin regulates food inake.[93]

IGFs feed back to inhibit GH secretion by the pituitary. IGF-I can stimulate the secretion of somatostatin by the hypothalamus and may directly inhibit GH synthesis.[94,95] It remains to be clarified whether IGFs of peripheral or hypothalamic origin are responsible for the inhibition of GH secretion, but the observations previously cited of enhanced GH secretion in the liver IGF-I knockout mouse suggest that circulating IGF-I is a prime regulator of GH secretion.[79]

In response to GH, but modified by other hormones and most critically by nutritional factors, multiple tissues in the body synthesize and secrete IGFs. Although the liver was the first tissue demonstrated to secrete IGFs and is the major producer of circulating IGFs, its primacy in the GH-IGF axis has been supplanted. Multiple cell types in virtually every tissue examined from both fetus and adult can synthesize IGFs. Thus, a model of IGF action has evolved that is primarily a paracrine one in which IGFs are produced practically everywhere and act on target cells in the vicinity of the producing cells. Thus, the function of the large quantities of circulating IGFs is not clear, but they may be more important for their insulin-like effects on metabolism than on their mitogenic effects.

GH *and* IGF *Concentrations in* Blood. Although it was believed that GH circulates in the blood free of binding proteins, it is now recognized that between 25 and 35% of circulating GH is loosely complexed to a 60 kDa glycoprotein referred to as the GH binding protein (GHBP).[96] This protein is identical to the extracellular domain of the GH receptor, but it is unclear whether in humans GHBP arises from alternative splicing of the GH receptor mRNA, as it does in the rat, or is shed from cell-surface receptors by peptidases. Changes in serum concentrations of GHBP reflect changes in the number of cell-surface GH receptors.[97] In contrast to the prolonged half-life of IGFs bound to the IBFBPs (more than 12 hours), the plasma half-life of GH is about 20 minutes.

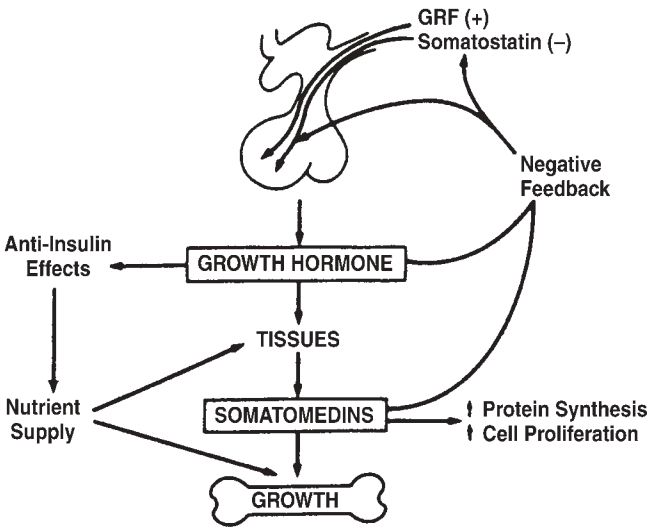

FIGURE 16-3 The growth hormone–somatomedin axis. (+) = stimulatory action; (–) = inhibitory action. GRF = growth hormone–releasing factor.

Normal GH secretion in humans is highly episodic. Blood concentrations are generally low or undetectable for much of the day and are interrupted by bursts of secretion that result in high concentrations for roughly 90 minutes before returning to the low baseline. This pattern is developmentally regulated.[98] The number and amplitude of secretory episodes are small in young children. Under the influence of gonadal steroids, both the frequency and amplitude increase dramatically and reach their highest levels during puberty, especially during sleep; they then gradually decline over the ensuing decades.

The combined concentration of IGF proteins in the blood is on the order of 750 µg/L or 100 nM. Although GH remains the predominant regulator of IGF production and IGFBPs the principal regulators of bioavailable IGFs, a number of other hormones influence IGF-I concentrations in blood. This peptide is low or nonexistent in fetal life, when IGF-II appears to be the predominant somatomedin. During fetal life, placental lactogen or the product of the *GH-V* gene is likely to be the major regulator of somatomedin production.[99] Prolactin, another GH-like hormone, can also stimulate the production of IGFs in cultured cells and probably in clinical conditions of prolactin excess. Blood levels of the IGFs remain low during infancy and early childhood but rise dramatically at puberty in response to increases in GH secretory activity. In addition, IGF-I concentrations are low in patients with hypothyroidism.[100] Clinically, IGF-I concentrations in blood have been shown to reliably mirror the total GH secretory activity. Thus, in older children and adults who are well nourished and do not have hypothyroidism, serum IGF-I measurements are more useful than random measurements of GH in diagnosing conditions of GH deficiency (hypopituitarism) and excess (gigantism or acromegaly). The marked influence of nutritional status on IGF production is discussed later in this chapter.

Direct versus Indirect Actions of* GH: A *Unifying Hypothesis? GH initiates a signal by binding to specific receptors on the surface of target cells. A single GH molecule contains two separate receptor-binding domains, which facilitate the formation of receptor homodimers on GH binding.[101] Receptor dimerization is a feature common to a number of growth factor receptors and appears to be a prerequisite for signaling. When activated by ligand, the GH receptor dimerizes and associates with a protein kinase called janus kinase 2 (JAK2). JAK2 then phosphorylates a family of proteins called signal transducers and activators of transcription (STATs). STAT proteins bind to deoxyribonucleic acid (DNA) in the nucleus and activate gene

transcription directly. The pathways of GH signal transduction are far more complex than JAK/STAT activation and also involve phosphorylation of the insulin receptor substrate proteins IRS-1 and IRS-2 and calcium fluxes, as well as the activation of the phosphatidylinositol kinase (PI-3 kinase) and protein kinase C pathways.[71]

The actions of GH in vivo have been categorized as either indirect (IGF mediated) or direct. The direct actions vary significantly depending on the duration of exposure. After short-term administration to GH-deficient individuals or to isolated GH-sensitive tissues in culture, GH has effects very much like those of insulin. They are rapid in onset, transient in duration, and not mediated through the actions of IGFs. They include the stimulation of glucose and amino acid transport and protein synthesis. GH also has inductive effects on a number of enzymes.

Chronic GH administration, in contrast, results in biochemical actions that appear antagonistic to insulin; blood sugar rises and fat mobilization and fatty acid oxidation occur. In fact, release of GH is one of the stress responses that the body uses to maintain euglycemia. In 20% of individuals with GH-secreting tumors, frank diabetes mellitus occurs.

The origins of these paradoxic "direct" actions are not clear but may reside in the structure of the GH molecule itself. The 20 kDa variant has been reported to have only one-fifth of the insulin-like activity of the 22 kDa GH molecule, while retaining normal growth-promoting and diabetogenic activity.[102,103] However, analysis of the biologic activities of both the 22 kDa and 20 kDa GH molecules in transgenic mice demonstrated largely overlapping activities with regard to linear growth and carbohydrate metabolism.[104]

The concept that IGFs can mediate the actions of GH in promoting linear growth has been validated by a number of studies that show that IGF-I injections increase tibial width and costal cartilage DNA synthesis in hypophysectomized rats to an extent that is comparable to that in GH-treated controls. In human newborn infants, umbilical cord plasma levels of IGF-I and leptin (see below) show a strong positive correlation with increasing birth weight and birth length.[105] Both IGF-I and leptin, which is secreted by both adipocytes and placenta, are important for fetal growth. The ability of IGF-I to stimulate linear growth in the absence of GH is strongly supported by studies demonstrating overgrowth in transgenic mice overexpressing IGF-I and in IGF-I-treated humans with Laron-type dwarfism, a condition that results from the hereditary absence of GH receptors.

There are major local effects of IGFs and EGF found in maternal breast milk. IGF-I, IGF-II, and a truncated form of IGF-I are also present in colostrum.[106] Importantly, intestinal IGFs are also produced by the mesenchymal cells within the lamina propria. Most of these effects are direct on the gut and do not generally affect somatic growth. Trophic effects have generally been observed in the distal bowel (ileum) more than the jejunum. In the piglet intestine, oral rhIGF-I increased small intestinal weight, protein, and DNA content and jejunal and ileal villus height.[107] Additionally, oral rhIGF-I has been shown to increase basal Na^+ absorption and the maximal rate of D-glucose and L-alanine absorption in newborn pigets.[108]

When intestinal cells are studied, IGFs are well-known stimulators of cell proliferation but also are potent stimulators of cell migration, a mechanism central to the healing of ulcers, villus damage in viral enteritis, and other lesions.[109] The mechanism by which migration/restitution is stimulated appears to be dependent on protein kinase C.[110] Other pathways are activated by IGF-1, including the PI-3 kinase pathway, c-Jun nuclear kinase, and mitogen-activated protein kinases.[111] Consequently, growth factors have been extensively investigated as therapeutic agents to enhance gut integrity and facilitate repair.

Orally administered growth factors have been found to exert trophic effects to the intestinal mucosa in experimental rotavirus enteritis and in rats with short-bowel syndrome.[112,113] In two studies, the combination of the primary metabolic fuel of the intestine, glutamine, with either GH or IGF-I resulted in a synergistic trophic response.[114,115] A synergistic trophic response of glutamine with transforming growth factor-α was seen after ischemia/reperfusion injury of the porcine intestine.[116]

In viral enteritis, exogenous growth factors have enhanced mucosal mass without reducing diarrheal output or increasing specific activities of jejunal disaccharidase enzymes.[112,117] In short-bowel syndrome and ischemic bowel disease, growth factors and the trophic amino acid L-glutamine have been shown to have synergistic effects.[115,118] These effects have not been translated into clinical therapy for diarrheal diseases to date.

Another disease for which enteral growth factor therapy has begun to be studied is short-bowel syndrome. In this condition, which is the leading cause of intestinal failure in newborns, the infant's bowel length limits absorption, leading to a prolonged dependence on parenteral nutrition and (eventually) to end-stage liver disease. In several studies, Donovan and colleagues treated newborn piglets that received 80% of required calories via parenteral nutrition with enteral IGF-I.[119] They found that enteral IGF-I augmented intestinal morphology and markedly increased disaccharidase activity in parenterally fed piglets over that observed with partial enteral nutrition alone. The mechanism by which lactase activity in the mucosa was so markedly increased appeared to be post-translational in nature.[120]

Transgenic mice overexpressing GH and IGF-I have shown increased body weight, as well as small bowel length and mass, and some notable differences between GH and IGF-I have altered the traditional concept that all effects of GH are mediated via IGF-I.[121] GH has much more profound effects on body mass compared to IGF-I (60% versus 23% increase), whereas IGF-I has much greater effects on bowel length (20% versus 44% increase), and IGF-I but not GH overexpression increases intestinal crypt cell proliferation while reducing crypt cell apoptosis. In further support, murine knockout models for IGF-I, the GH receptor, or both show that both factors have major independent effects on somatic growth (30 to 50%), whereas lack of functional expression of both growth fac-

tors profoundly affects growth. *Igf-1/ghr* double knockouts reach only 17% of the expected adult body weight.[122]

Insulin in Normal Growth The prominent influence of insulin on normal growth is best illustrated in disorders at the extremes of altered insulin secretion. Especially in the fetus, hyperinsulinemia produces somatic overgrowth. Hyperinsulinemic infants born of poorly controlled diabetic mothers exhibit visceromegaly, increased body fat, and increased length, whereas the hypoinsulinemic infant born with severe insulin resistance or pancreatic agenesis is small and depleted in body fat.[123] In postnatal life, poorly controlled diabetes mellitus can be associated with a striking growth failure, the so-called Mauriac syndrome.[124] The growth-promoting actions of insulin both in prenatal and postnatal life are complex and likely to result from both direct, largely metabolic effects mediated through the insulin receptor and indirect, predominantly mitogenic effects mediated through the structurally homologous IGF-I receptor.

Insulin Receptor–Mediated Actions of Insulin. High-affinity insulin receptors mediate the rapid biologic actions of insulin in stimulating the cellular transport of substrates and in the induction of enzymes that promote glycogen and fat synthesis and that inhibit gluconeogenesis, lipolysis, and ketogenesis.

An indirect consequence of insulin action appears to be the stimulation of IGF production. A number of clinical studies have shown that the depressed IGF concentration associated with poorly controlled diabetes mellitus can be returned to normal with insulin therapy.[125] Insulin appears to directly stimulate IGF production in whole liver, liver slices, or cultured hepatocytes.[126] Additionally, insulin may regulate IGF production by influencing the number of GH receptors on important IGF-producing tissues. In poorly controlled diabetes mellitus, there is a dramatic reduction in the number of somatogenic GH binding sites in liver. These can be restored to normal with insulin therapy.[127]

IGF Receptor–Mediated Actions of Insulin. In a few cell types, such as hepatocytes, certain teratocarcinoma cells, and mammary tumor cells, insulin appears to be directly mitogenic by binding to its own receptor at physiologic concentrations. However, some of the growth-promoting actions of insulin can be attributed to activation of IGF receptors. There are two principal IGF receptors, type I and type II. The insulin receptor and the type I IGF receptor are homologous "heterotetramers," consisting of two α and β subunits. Insulin or IGF binding to their respective α subunits activates a tyrosine kinase on the cytoplasmic portion of their respective β subunits, which, in turn, autophosphorylates the receptor and other cytoplasmic substrates that are essential for the actions of both insulin and IGF-I.[128] Both IGF-I and IGF-II can bind to and activate the insulin receptor, although with much lower affinity than insulin.

Crossover of IGF and insulin actions also occurs when type I IGF receptors are activated by insulin. Although type I receptors preferentially bind IGF-I, they can be activated by 10- to 100-fold excess concentrations of insulin, conditions that are achieved in some cases of hyperinsulinism, such as insulin-resistant states. Another level of overlap between IGF-I and insulin action is suggested by the finding that a single α, β subunit of the insulin receptor can associate with an α, β subunit of the type I IGF receptor, forming a hybrid tetramer.[129]

The type II IGF receptor is more enigmatic.[130] It preferentially binds IGF-II over IGF-I but is also the receptor that (at a different binding site) shuttles mannose-6-phosphate–containing extracellular proteins into lysosomes. The type II receptor does not contain an intracellular tyrosine kinase domain, and its role (if any) in intracellular signaling is unclear. Most of the actions of IGF-II are thought to be mediated through the type I IGF or insulin receptors. Type II IGF receptors do not bind insulin, but physiologic concentrations of insulin dramatically up-regulate the number of type II IGF receptors on adipocyte.[131]

Insulin Synergy with Other Growth Factors. One further mechanism by which insulin appears to influence cellular growth is to alter the cellular requirements for mitogenic signals from other growth factors. As discussed previously regarding the interactions of nutrients and hormones, growth factor signals frequently converge on common pathways within a cell so that low concentrations of two growth factors can amplify the actions of one another. In cultured hepatocytes, insulin can potentiate the mitogenic signal of EGF or of vasopressin,[132] and in the well-studied BALB/c 3T3 fibroblast, the presence of insulin or IGF-I strongly modulates the mitogenic actions of EGF and platelet-derived growth factor.

Malnutrition

Growth Hormone in Malnutrition ***Growth Hormone Levels in Malnutrition.*** In humans, experimental fasting and malnutrition generally result in elevated serum concentrations of GH. Studies of malnourished populations in different parts of the world have often led to conflicting conclusions, in part from differing criteria for malnutrition, from the inaccuracies inherent in characterizing complex GH secretory patterns from a single blood sample, and perhaps to some extent from confounding features such as infection.[133] The normal physiology of nutrient regulation of GH secretion is also complex; amino acids such as arginine stimulate GH release, whereas carbohydrates and fatty acids inhibit GH secretion. Clinical malnutrition results from a combination of dietary deficiencies that could be expected to have variable effects on GH release.

Recently, attention has turned to the effects of fasting on the pattern of GH release from the pituitary. As previously described, GH secretion in humans is episodic, and measurement of GH concentrations on random blood samples, as is typical of field studies, might be expected to give inconsistent results. Ho and coworkers performed frequent blood sampling (every 20 minutes) of fasted volunteers and uncovered an inherent pulsatility in GH secretion in humans that appears to be suppressed in the fed state, perhaps by the negative feedback of IGFs.[134] Over the course of a 5-day fast, those authors measured significant increases in GH pulse frequency, maximal pulse amplitude,

and 24-hour integrated concentration (Table 16-5). These changes coincided with a decline in concentrations of IGF-I and glucose and a rise in those of free fatty acids and acetoacetate. Subsequent studies led those authors to conclude that fasting-induced enhancement of GH secretion is mediated by an increase in GH-RH pulsatility and a decrease in somatostatin release.[135]

Serum GH concentrations are elevated in children with both kwashiorkor and marasmus but do not allow distinction between the two.[136–140] Becker and associates observed the magnitude of GH elevation to be inversely related to the severity of protein malnutrition, as judged by the serum albumin concentration.[136] In their subjects, GH concentrations fell after feeding a protein-rich diet for 36 to 72 hours. The critical role of protein in the refeeding diet was also demonstrated by Pimstone and colleagues, who found that refeeding with a high-carbohydrate, protein-free diet does not normalize GH concentrations.[140] When caloric deprivation predominates, the GH response appears to be variable; some groups have reported depressed GH concentrations and others have reported elevations.[141,142] In short-term malnutrition, the adaptive benefits of elevated GH concentrations are suggested by the known direct effects of GH to increase gluconeogenesis, lipolysis, and fatty acid oxidation. Elevated GH concentrations might be expected to increase glucose production initially, while shifting the organism to a lipolytic, protein-sparing state.

Whereas short-term protein-calorie malnutrition is associated with elevated GH concentrations, long-standing malnutrition results in depressed GH secretion. Beas and coworkers described a group of infants with low concentrations not only of GH but also of adrenal and thyroid hormones, suggesting generalized pituitary hypofunction.[143] An adaptive function of a hypopituitary state in reducing metabolic activity had previously been proposed by Mulinos and Pomerantz, who likened the malnourished state to a "pseudohypophysectomy."[144]

Clinical Uses of* GH *in Disease States. The adaptive changes in GH release that accompany malnutrition have prompted a number of studies on the possible uses of GH in promoting anabolism during recovery from operation or injury. Clemmons and coworkers determined the effects of GH injections on obese individuals subjected to hypocaloric diets.[145] Although dietary restriction produced comparable weight loss in subjects receiving GH and those receiving placebo, those treated with GH (0.1 mg/kg every 48 hours) had a significantly lower daily nitrogen deficit than controls. Similar findings were reported by Manson and Wilmore, who administered GH to volunteers receiving hypocaloric parenteral nutrition (Figure 16-4).[146] GH therapy decreased the rate of weight loss and increased nitrogen retention. In parenterally nourished patients recovering from gastrointestinal surgery, GH administration has resulted in sustained nitrogen retention, suggesting a possible role for this agent in promoting recovery from a variety of catabolic states.[147,148]

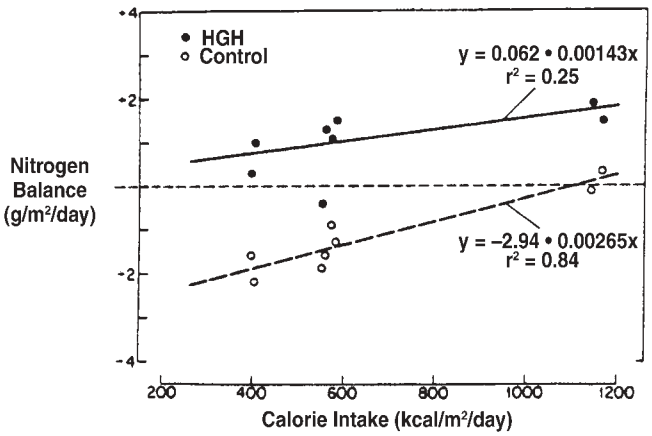

FIGURE 16-4 Positive nitrogen balance in growth hormone–treated subjects at all levels of hypocaloric calorie provision. Eight male subjects were exposed to various levels of hypocaloric intravenous feeding. Only adequate energy intake resulted in positive nitrogen balance in the controls (*open circles*), whereas growth hormone–treated subjects (*closed circles*) were in positive nitrogen balance at all levels of energy intake. Adapted from Manson J and Wilmore D.[146]

Unfortunately, a series of investigations in critically ill adults with multiorgan system failure in several placebo-controlled, masked trials found that high-dose recombinant human GH treatment produced a twofold increase in mortality, increased the length of stay in hospital, and prolonged the duration of mechanical ventilation.[149] Oddly, similar doses of GH administered to critically ill children with extensive body burns did not increase morbidity or mortality and reduced intravenous albumin and calcium requirements compared with placebo-treated children. There were increased hyperglycemic episodes and insulin requirements in the treated group, although these were not considered dangerous.[150]

In humans with several gastroenterologic conditions, exogenous GH administration has been shown to have beneficial effects. In cystic fibrosis, GH treatment improved growth rate (linear and ponderal) and—by as yet undetermined mechanisms—reduced pulmonary exacerbations.[151,152] In adults with Crohn's disease, a preliminary placebo-controlled trial of GH therapy for 4 months improved the Crohn's Disease Activity Index score significantly.[153] In these children, inflammatory bowel disease activity was not influenced, but 4-month treatment with GH improved fat-free body mass, decreased percent fat mass, and enhanced linear growth velocity.[154]

Table 16-5 Enhanced Pulsatility of Growth Hormone Release in Fasting

Measure of Pulsatility	*Day 0*	*Day 1*	*Day 5*
GH peaks (number/24 h)	5.8 ± 0.7	7.3 ± 0.6*	9.9 ± 0.7*
GH peak amplitude (ng/mL)	5.9 ± 1.1	13.1 ± 1.2*	12.3 ± 1.6*
24-hour IGHC (μg/mL/min)	2.8 ± 0.5	7.8 ± 1.1†	8.8 ± 0.8†

Frequent venous sampling of six adult male subjects was performed during a control fed day (day 0) and during the first (day 1) and fifth (day 5) days of a fast.
GH = growth hormone; IGHC = 24-hour integrated GH concentration.
*$p < .005$, compared with day 0.
†$p > .0009$.
Adapted from Ho et al.[134]

Substantial worldwide experimental support has emerged for GH treatment of infants born small for gestational age (a condition also called IUGR). IUGR reportedly is associated with subsequently high rates of coronary heart disease, high blood pressure, glucose intolerance, and high cholesterol.[155] Treatment with daily GH shots increased linear growth velocity in many studies, while delaying the onset of puberty and exhibiting few, if any, side effects.[156–160] However, treatment for years was required, higher doses were more effective, and younger children (3 to 5 years old) were more responsive to treatment.[161] Of major concern is the global scope of this problem with IUGR, however, because IUGR affects 20% of children in Malawi and 25% of children in Pakistan.[162,163] Clearly, ethical problems will arise as to which children can be treated with this expensive and long-term therapy.

IGFs and IGFBPs in Malnutrition **IGF B*ioactivity*, IGF I*nhibitors, and* IGFBP*s*.** Despite elevated GH levels in fasting or short-term malnutrition, the production of IGF-I is dramatically reduced in malnutrition. Studies using somatomedin bioassays were the first to indicate that serum IGF bioactivity falls with malnutrition. More recent data using highly specific radioimmunoassays indicate that the depressed bioactivity of serum from fasted or malnourished individuals results from a dramatic fall in IGF-I concentrations, minimal, if any, change in IGF-II concentrations, and changes in IGFBPs (Table 16-6).[164]

Measuring serum somatomedin bioactivity in a sulfation factor assay, Grant and associates were among the first to show a nutritional influence on somatomedin activity; they found low levels in the serum of malnourished South African children despite elevated GH concentrations.[165] Those authors found both hormones to return toward normal by the ninth day of refeeding. Similar results using somatomedin bioassays were forthcoming from other malnourished populations, including malnourished Thai and Nigerian infants and children and patients with celiac disease and anorexia nervosa.[166–170]

Bioassays of IGF activity in blood, although relatively nonspecific as to which of the two IGFs is being measured, allow the detection of physiologically important IGF inhibitors in serum. Much of the older data on somatomedin inhibitors can be attributed to changes in the concentration of known IGFBPs. Increased concentrations of inhibitors have been found in the serum of malnourished children and hypopituitary adults and in serum from starved, hypophysectomized, or diabetic rats.[166,171–174] Salmon and colleagues partially purified a 27 to 40 kDa, heat-labile inhibitor from fasted rat serum.[175] Recent studies have suggested that this inhibitor may be the serum binding protein IGFBP-1 (see Table 16-4).[176] Serum concentrations of BP-1 almost double with fasting and decrease after meals.[177] In addition, they are elevated in diabetes, consonant with the proposed role of insulin in the regulation of BP-1 production.[178] Phillips and associates have shown that concurrent with the fall in IGF activity of rat serum during fasting, total IGF inhibitor activity rises.[179] The IGF inhibitory activity of serum appears to be more nutritionally sensitive than the IGF activity itself. After 6 hours of refeeding, the IGF inhibitor activity had fallen significantly, but there was little change in IGF activity; both returned to normal with continued refeeding.

Table 16-6 Effects of Undernutrition on the GH-IGF Axis

Increased GH secretion
GH resistance in peripheral tissues
Decreased GH receptor mRNA
Decreased GH binding
Diminished postreceptor signaling (P)
Decreased somatomedin bioactivity
Decreased IGF-I production
Decreased IGF-I gene transcription
Diminished IGF-I mRNA stability (P)
Diminished IGF-I mRNA translation (P)
Normal IGF-II production
Increased IGFBP-1 production
Decreased IGFBP-3 production (P)
Increased IGF-I clearance
Increased IGF inhibitor production
Decreased tissue sensitivity to IGF-I

(P) indicates features more typical of protein deprivation or chronic malnutrition than of fasting.
GH = growth hormone; IGF = insulin-like growth factor; IGFBP = insulin-like growth facor binding protein; mRNA = messenger ribonucleic acid.

IGF-I *and* IGF-II *in* Malnutrition. As measured by specific radioimmunoassays, IGF-I concentrations drop dramatically with fasting in adult volunteers, whereas those of IGF-II do not.[164,180] Clemmons and colleagues found that fasting of overweight adult volunteers for 10 days produced a drop of IGF-I concentrations to hypopituitary levels; refeeding produced a return toward normal (Figure 16-5).[180] The decline in serum IGF-I correlated with nitrogen balance. In some physiologic circumstances, however, the fall in serum IGF-I concentrations becomes dissociated from the changes in nitrogen balance. Smith and coworkers studied six conditioned athletes and concluded that strenuous exercise, which produces negative caloric balance, causes as much of a fall in serum IGF-I as does comparable caloric restriction without exercise but a much lower nitrogen loss.[181]

In contrast to the apparent insensitivity of serum IGF-II to fasting in adults, Soliman and associates have documented depressed IGF-II concentrations in children with severe marasmus and marasmic kwashiorkor.[164,182] These returned to normal with refeeding. The magnitude of IGF-II depression was not nearly as great as that of IGF-I, and the IGF-II concentrations in sera of children who were underweight or had only kwashiorkor were not depressed. Thus, severe or long-lasting malnutrition in children may eventually depress IGF-II production, although IGF-I remains the more acutely sensitive to malnutrition.

***S*erum IGF-I *as an I*ndex *of* N*utritional* S*tatus*.** The striking correlation between (as yet unidentified) aspects of nutritional status and serum IGF-I concentrations has led some investigators to suggest that the latter might provide a highly sensitive and quantitative way of following nutritional status. Clemmons and colleagues found that IGF-I increased by 170% over 10 days in six malnourished

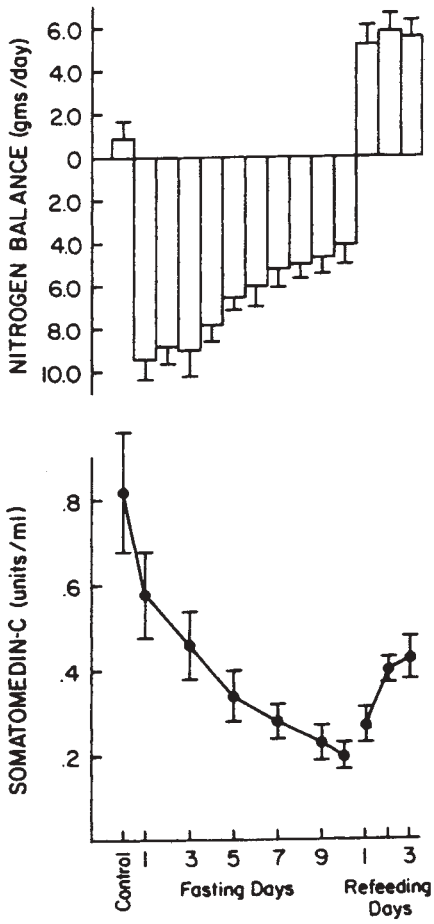

FIGURE 16-5 The effects of fasting on plasma somatomedin C (insulin-like growth factor I) and nitrogen balance. The subjects were seven males 20 to 70% above ideal body weight. During the control period, they were fed a 1,500 kcal diet for 3 days. Between days 4 and 13, they fasted, receiving only water, vitamins, and potassium chloride. Refeeding consisted of resumption of the control diet. Each point is the mean ± SEM. Adapted from Clemmons D et al. [180]

patients with gastrointestinal disorders that necessitated either total parenteral or tube feedings.[183] All patients were in positive nitrogen balance when first measured on the second day of refeeding. Other commonly used indices of nutritional status fell much less dramatically and normalized much more slowly: prealbumin by 21%, retinol binding protein by 18%, and transferrin by 10%. Unterman and coworkers came to similar conclusions when they compared IGF-I concentrations with other indices in 37 generally elderly hospitalized patients with a variety of neoplastic, gastrointestinal, and neurologic diseases.[184] The IGF-I was more depressed than albumin or transferrin in patients who had no reduction in either triceps skinfold thickness or midarm muscle circumference. In six patients given nutritional support, IGF-I concentrations rose by more than 70% in each patient, whereas the lymphocyte count and transferrin concentration rose in only four patients and albumin concentration in only one. Serum IGF-I measurements have also been suggested as a means to follow the progress of children and adolescents with chronic inflammatory bowel disease.[185] In a study of critically ill patients, serum concentrations of prealbumin, retinol binding protein, and transferrin levels were strongly correlated with levels of IGF-I, IGF-II, IGFBP-3, and ALS.[186]

***Mechanisms of* IGF *Regulation by* Nutrients.** A number of studies have attempted to determine the specific components of the refeeding diet that regulate IGF-I production in recovery from an acute fast. When normal-weight human volunteers were fasted for 5 days and then refed with a normal diet, a diet that was isocaloric but protein deficient, or a diet deficient in both protein and calories, Isley and associates concluded that intake of adequate quantities of both protein and calories is critical for the restoration of IGF-I after a fast.[187] They noted that even in the face of a protein-deficient diet, recovery of serum IGF-I concentrations was possible as long as the energy content was adequate. Animal studies have indicated that the roles played by protein and calorie intake in regulating serum IGF-I concentrations may be developmentally influenced. Prewitt and coworkers placed 3-week-old rats on diets in which the protein content was varied (5%, 10%, or 15% lactalbumin) at one of three levels of energy intake (100%, 75%, or 50% ad libitum).[188] After 2 weeks, protein intake played the major role in regulating IGF-I concentrations, whereas after 9 weeks, both protein and caloric intake were important.

The malnourished state is one of resistance to the effects of GH. As noted previously, GH secretion increases in the fasted state, whereas serum concentrations of IGF-I fall. Merimee and colleagues found that GH administered to fasted, GH-deficient subjects induced a minimal increase in serum IGF-I concentrations in comparison with the 10-fold increase in GH induced in normally fed, GH-deficient subjects.[189] Studies in fasted and diabetic rats have correlated the fall in serum IGF-I concentrations with a decline in the number of hepatic GH receptors, suggesting that a primary effect of malnutrition, perhaps mediated by decreased insulin concentrations, is to decrease GH receptors and consequently IGF-I production.[190–192] Indeed, fasting results in decreased GH receptor mRNA in the liver.[193,194] The situation may differ in protein-deprived rats, in whom a postreceptor defect in GH action has been suggested.[131] The net result of fasting is a decrease in the concentrations of IGF-I mRNA in the liver and other tissues.[193] This results from decreased transcription of the IGF-I gene, although the effects of protein deprivation may further influence IGF-I mRNA stability and also decrease the translation of IGF-I mRNA into peptide.[195]

The fasted or malnourished state is also one of resistance to the action of IGF-I. Thissen and associates showed that, in contrast to normally fed, hypophysectomized rats, an infusion of recombinant IGF-I into protein-restricted rats did not stimulate an increase in weight gain or linear growth, despite restoring normal serum concentrations.[196] Somewhat surprisingly, this nutritionally induced IGF-I resistance does not result from a decrease in IGF-I receptors at target tissues; instead, most tissues show increased IGF-I binding.[197]

IGFBPs in Malnutrition Among the IGFBPs, BP-3 is unique in its diurnal rhythm, which appears to be regu-

lated by food intake. IGFBP-1 is rapidly suppressed following a meal and acutely rises in response to hyperglycemia. In this context, IGFBP-1 may serve as a glucose counterregulatory hormone by further depressing free IGF concentrations in the hypoglycemic state. In addition to its regulation by nutrients, IGFBP-1 is stimulated by glucocorticoids and by cytokines such as tumor necrosis factor (TNF)-α and various interleukins. Nutritional status appears to also influence the phosphorylation status of IGFBP-1. Baxter postulated that increases in IGFBP-2, -BP-4, and -BP-6 during acute illness could serve to redistribute IGFs from ternary complexes in the serum to binary complexes in the extracellular space and make them more available to the tissues.[81]

Insulin in Malnutrition With fasting or protein-calorie malnutrition, plasma insulin concentrations are reduced, although, in some instances, high and normal levels have been reported.[182] Some of these discrepancies might be explained by the observations of Lunn and associates that in kwashiorkor, there is an early phase of hyperinsulinism that is followed by insulinopenia.[138] Diminished insulin release results in impaired tolerance to glucose or an amino acid load.[198] Pimstone and coworkers noted that the insulin response to oral glucose is abnormal in malnourished children but that intravenous glucose elicits a normal response, suggesting that deficiencies of glucagon or other insulinotropic factors are important in determining the response to malnutrition.[199] Those authors also demonstrated that the impaired insulin response to a glucose load in kwashiorkor could be ameliorated by the addition of potassium to the diet. The relationship of malnutrition and diabetes mellitus has been reviewed by Rao, who concluded that a malnourished condition can influence the diabetogenicity of other agents, including dietary toxins, drugs, and viruses, but does not directly cause diabetes.[200] In fact, initial presentation with dehydration and hypoglycemia (< 40 mg/dL) has been associated with a high mortality (42%) for children with diarrheal dehydration.[201]

Psychosocial Growth Failure

The interactions of nutritional and hormonal influences have been extensively studied in cases of "psychosocial growth failure" or "deprivation dwarfism," terms used to describe the growth failure that can accompany severe emotional deprivation. Early in this century, it was recognized that emotional deprivation could be associated with growth retardation in institutionalized children.[202] Subsequent studies revealed that such children need not be in an institutional setting and that an impoverished emotional environment in the home is sufficient. Affected children are observed to have a voracious appetite with bizarre eating and drinking behavior such as foraging, drinking from the toilet bowl, and gorging. In addition, delayed speech, foul-smelling stools, a protuberant abdomen, and characteristic neurologic postures have been described.[202,203]

Patton and Gardner speculated that emotional deprivation could produce growth retardation in a variety of ways, including failure of the caregiver to provide adequate nutrition, depression-induced anorexia in response to the emotional environment, altered gastrointestinal function, or changes in metabolism.[204] Considerable attention has been paid to whether the growth failure and endocrine-metabolic changes of psychosocial dwarfism are the result of emotional deprivation alone or are secondary to impaired caloric intake.

A large body of evidence suggests that a hypopituitary state can develop in some children with emotional deprivation. Talbot found significant malnutrition in a group of 51 children with growth failure of no identifiable etiology and postulated that they might have "functional hypopituitarism" as a means of adapting to limited caloric intake.[205] Twenty years later, Powell and colleagues studied emotionally deprived children and demonstrated diminished reserves of adrenocorticotropic hormone (ACTH) and GH, which were normalized when the affected children were removed from their adverse surroundings.[206,207] The authors found little evidence of caloric deprivation in their patients and suggested that psychic factors caused their hypopituitarism. Miller and colleagues demonstrated a loss of GH secretory episodes during a 6-hour period of blood sampling in four children with psychosocial deprivation.[208] In one child, GH secretion normalized after hospitalization and rehabilitation. Despite the apparent state of GH deficiency, attempts to induce growth in such children by administration of GH have been unsuccessful.[209,210]

Psychological factors were also invoked by Widdowson to explain her observations on the growth of children in two German orphanages after World War II.[211] Orphans under the care of a stern and forbidding supervisor who chose mealtimes to rebuke the children gained weight at about one-third the rate of children at another, more hospitable orphanage despite comparable food intake. When the supervisor of the first orphanage was transferred to the second, the pattern reversed, and the new children under her care gained weight poorly.

A countertheme to the hypothesis of a strictly emotional etiology of psychosocial growth failure has been the suggestion that underfeeding by caregivers is the primary cause of growth failure in these children. From their studies on emotionally deprived infants between 3 and 24 months of age, Whitten and colleagues observed dramatic weight gain in 11 of 13 children when the infants were given adequate nutrition in a hospital setting designed to reproduce the impoverished emotional ambience of their homes.[212] During a control period in which these children were fed equal amounts of food but also were given a high level of mothering care, their weight gain was no greater. Other studies have found elevated fasting levels of GH in a number of infants and children with emotional deprivation, leading to the speculation that these infants suffered from food deprivation as well as emotional deprivation.[213]

Contemporary dietary and health misconceptions have created a modern-day version of the growth-retarded child from a turn-of-the-century foundling house or war orphanage. Pugliese and colleagues described a group of 14 adolescents who presented with

short stature and malnutrition from self-imposed caloric restriction.[214] These children showed no evidence of overt psychiatric disease or anorexia nervosa but had restricted their food intake from a fear of obesity. Similar findings were reported in a group of younger children, 7 to 22 months of age, who presented with nutritional failure to thrive secondary to parental restriction of food arising from a fear of obesity, cardiovascular disease, or unhealthful eating habits.[215]

It is reasonable to propose from these somewhat disparate observations that the mechanisms involved in the growth failure associated with emotional deprivation form a spectrum (Figure 16-6). At one extreme are children in whom growth failure is nutritional in origin, whether from limited access to food, emotionally induced anorexia, or altered gastrointestinal function. In these children, endocrine alterations are adaptive and occur in response to malnutrition. At the other extreme of the spectrum are those children whose hormonal and metabolic alterations are emotionally induced. The growth failure of these children is probably mediated by hormone deficiencies rather than by inadequate nutrition. It would appear that many of the children with clinical features of psychosocial growth failure combine features of both extremes of the spectrum.

Overnutrition and Growth Acceleration

Just as a deficiency of nutrients can retard growth, so can nutritional surfeit accelerate growth. This is perhaps most pronounced in fetal life, when excessive glucose and other nutrients from conditions such as mild maternal diabetes can lead to significant overgrowth. A stimulatory influence of obesity on childhood growth appears to be the case as well. In the mid-1940s, Talbot noted that obese children tend to be tall, to have advanced skeletal maturation, and to excrete more ketosteroids than nonobese children.[216] Subsequent studies by Garn and others have confirmed a correlation between obesity and height throughout childhood.[217–220] In affluent societies, socioeconomic factors influence obesity, making correlation of the latter with adult height difficult. However, a recent study by Garn and associates in Central America indicated that the augmented stature associated with obesity in childhood persists into adulthood.[220]

In the fetus, insulin appears to play a critical role in the more commonly recognized overgrowth syndromes. Although obesity is associated with elevated circulating insulin concentrations, it is unlikely that insulin plays a direct role in the facilitation of growth because obese individuals are relatively insulin resistant and require high concentrations of insulin to maintain normal homeostasis.[221] A regulatory role for insulin in promoting growth, perhaps by stimulating appetite, has been suggested in a subgroup of children recovering from surgery for craniopharyngioma. These tumors compress the hypothalamus and often result in hypopituitarism, yet a significant number of patients are able to maintain normal growth velocities after surgery, despite a GH-deficient state. Bucher and colleagues compared a group of rapidly growing children with groups of normal- and slowly growing children after surgery for craniopharyngioma and found that those with supranormal growth rates were hyperphagic and had elevated insulin levels.[222] Comparable findings of hyperphagia, obesity, and hyperinsulinism have been made in animals with lesions in the ventromedial hypothalamus.[223]

There is a negative correlation between serum IGF-I concentrations and body fat.[224,225] It has been noted that the fall of plasma IGF-I concentrations is slower in fasted obese individuals than in normal subjects.[226] Underwood and colleagues studied the effects of overfeeding on IGF-I levels in GH-deficient subjects.[227] After 10 days of an

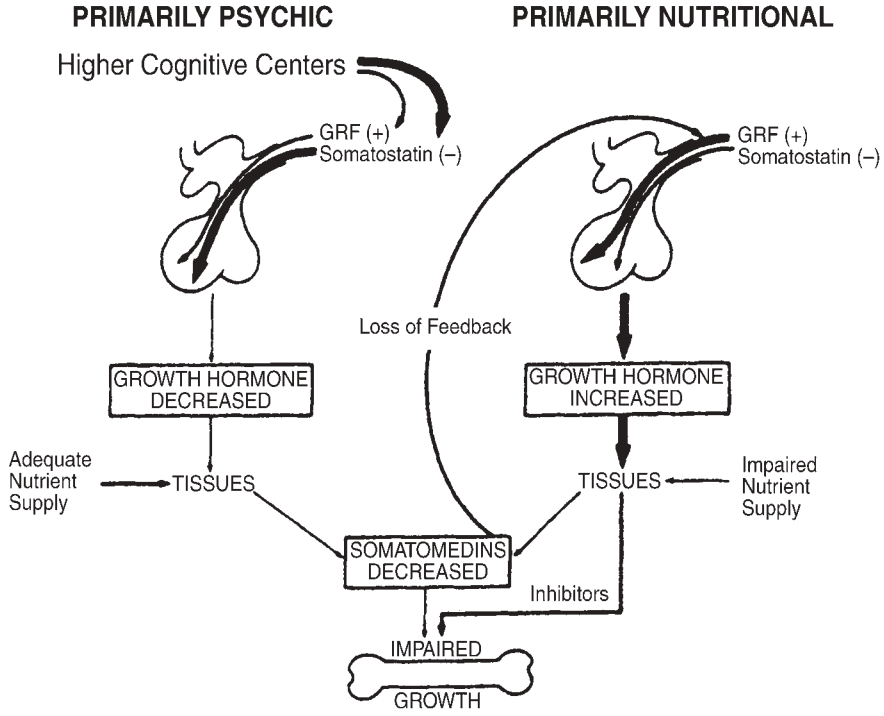

FIGURE 16-6 Psychosocial growth failure. Two possible mechanisms of psychosocial growth failure are proposed: primarily psychic (neuroendocrine) and nutritional. *Left*, Under largely psychological influences, pituitary growth hormone secretion is diminished in the face of normal nutrition. *Right*, When undernutrition predominates, the endocrine changes observed are adaptive ones. Somatomedin production is reduced, insulin-like growth factor binding proteins are increased, and growth hormone secretion is increased. GRF = growth hormone–releasing factor.

energy intake 50% above basal, those subjects experienced a significant increase in weight, nitrogen balance, fasting blood sugar, and insulin levels but no significant change in IGF-I concentrations. GH secretion may be altered in obesity, and GH release in response to pharmacologic stimuli is often blunted; however, pretreatment with beta-blocking drugs normalizes the secretory response, suggesting adequate GH reserves.[228]

Obesity as a Disorder of Humoral Signaling

Analogous to Tanner's proposed "sizostat" to monitor body size, recent studies have identified an "adipostat" factor by which the CNS monitors the peripheral adipose mass of the body and modulates appetite and thermogenesis accordingly.[65,229] The theoretic background for a central sensing mechanism of body fat stores was established by Kennedy 50 years ago.[230] A candidate adipose reporter substance is the product of the obese (*ob*) gene, mutation of which results in the genetically obese and diabetic *ob/ob* mouse; both the mouse gene and its human counterpart have been recently isolated.[231] Previous studies, in which the circulations of *ob/ob* mice had been crossed with normal mice, had suggested that *ob/ob* mice lack a bloodborne factor that might regulate adipose mass by suppressing appetite and increasing metabolic rate.[232] The *ob* gene sequence predicted a 16 kDa protein product that should be secreted from cells. Follow-up studies confirmed the expression of the *ob* gene in adipose tissue, the presence of ob protein in the circulation of normal mice, and increased ob levels in the plasma of the db strain of genetically obese diabetic mice.[233] Plasma levels of ob protein have been found to accurately reflect total body fat in mice fed high-fat diets.[234] Injections of ob protein (also called leptin) into *ob/ob* mice lower their food intake, body weight, percent body fat, and glucose concentrations while increasing their metabolic rate and body temperature.[233,235,236] However, the ob protein had no effect on obese *db/db* mice,[233] and normal mice fed high-fat diets became obese without decreasing their caloric intake despite elevated leptin levels, suggesting that genetic factors (the *db* gene product) and dietary components (lipids) may influence the actions of leptin in suppressing appetite.[234]

The model that has emerged proposes that adipocytes and placenta secrete leptin into the circulation, where it makes its way to the long form of the receptor in the CNS, in the hypothalamus (arcuate, paraventricular, lateral, ventromedial [VMN], and dorsomedial nuclei). The short form of the receptor is involved in leptin transport across the blood-brain barrier.[237] Nuclei neighboring the VMN are known to release appetite-stimulating substances such as neuropeptide Y, melanin-concentrating and -stimulating hormones, corticotropin-releasing hormone, galanin, glucagon-like peptide 1, neurotensin, and cocaine- and amphetamine-regulated transcript (CART), the suppression of which are downstream events of leptin receptor activation. Several of these, such as neuropeptide Y and CART, may mediate the effect of increased adipose mass in suppressing appetite.[237] Additionally, leptin activates the sympathetic nervous system, which impacts brown adipose tissues, kidney, hindlimb, and adrenal gland in rats, and induces uncoupling protein 1 (UCP-1) gene expression in brown adipose tissue and the homologue UCP-2 in white adipose tissue.[237,238] Activation of UCPs results in enhanced mitochondrial permeability, uncoupling of oxidative phosphorylation, and increased energy expenditure.

Acceleration of metabolism may involve the intermediacy of the β_3-adrenergic receptor, which can increase the generation of heat from the hydrolysis of fatty acids.[229] Genetic variation in the β_3-adrenergic receptor has been associated with both morbid obesity and insulin-resistant diabetes.[239–242] A third mechanism of obesity is modeled by the Zucker obese diabetic (*fa/fa*) rat, which also has a mutated leptin receptor. Transfection of normal but not *fa/fa* rats with leptin increased UCP expression and mitochondrial oxidative enzyme expression (eg, cartitine palmitoyltransferase 1 and acyl coenyzme A [CoA] oxidase). Leptin transfection reduced the expression of enzymes mediating fatty acid esterification (glycerol-3-phosphate acyltransferase and acetyl CoA carboxylase).[243] It has been shown that leptin acts in the brain to increase sympathetic stimulation of white and brown adipose tissues, which promotes their rate of fatty acid oxidation and reduces their fat content.[243] Human obesity certainly involves more genes than those of the ob protein and its receptor: to date, mutations in the *ob* gene are rarely detected in obese humans.

Just as leptin has been identified as the "satiety hormone," a recently identified hormone called ghrelin has been identified as an endogenous appetite stimulant.[244] Ghrelin, a 28–amino acid peptide named from "ghre," the proto-Indo-European root of "grow," was first identified as a GH secretagogue produced by gastric endocrine cells. Ghrelin is also produced by neurons in the hypothalamic arcuate nucleus, which is a critical region for feeding. Ghrelin levels vary diurnally, with sharp peaks before meals; its basal level and prandial peaks are sharply elevated by caloric restriction. Interestingly, extremely low ghrelin levels may explain why patients with gastric bypass surgery experience a paradoxical reduction of hunger between meals rather than a desire to eat more frequent small meals.[245] Ghrelin antagonists may be pharmacologically useful to treat obesity by mimicking the effects of gastric bypass surgery.

Mechanisms of Insulin Resistance

Obesity-related diabetes is characterized by increased hepatic glucose output and reduced glucose uptake in peripheral tissues. A key role for adipocytes in this condition has been proposed. Adipocytes secrete a number of cytokines and peptides that mediate insulin resistance, including leptin, TNF-α, adipocyte complement–related protein 30 kDa (Acrp30), interleukin (IL)-6, and resistin.[246] Acrp30 is unique in stimulating insulin sensitivity. Acrp30 is synthesized solely in adipocytes, where it is the most abundant gene transcript, and is secreted in serum. Administration to wild-type C57BL/6J and *ob/ob* mice lowers serum glucose levels while maintaining normal insulin levels. Acrp30 simultaneously accelerates fatty acid oxidation rates in muscle tissues.[246]

The cytokines TNF-α and IL-6 are produced by both immune cells and adipocytes, and levels of both are increased in obesity. TNF-α and IL-6 act to inhibit insulin-mediated tyrosine phosphorylation of the insulin receptor and the downstream mediator IRS-1. TNF-α additionally down-regulates the glucose transporter *GLUT4* expression. IL-6 increases hepatic triglyceride secretion, leading to an increase in circulating free fatty acids and increased insulin resistance.

A theory has emerged that "underleptinization" may also be responsible for the insulin resistance response of obese individuals. Leptin-deficient *ob/ob* mice and *db/db* mice lacking the leptin receptor have severe insulin resistance, reversible in the *ob/ob* mice by exogenous leptin. Hepatocytes treated with leptin exhibit decreased blood glucose and reduced insulin-stimulated tyrosine phosphorylation of the intracellular signal transducer IRS-1, which leads to decreased glucokinase activity, increased gluconeogenesis, and decreased glycogenolysis.[247]

Zhou's group has shown that diabetic rats with defective leptin receptors (Zucker diabetic fatty [ZDF] homozygous rats, also called *fa/fa* rats) have fatty infiltration of pancreatic beta cells with triglyceride. Heterozygous ZDF (fa/+) mice are lean and have only a small increase in beta cell triglyceride content; however, ZDF (fa/+) rats, when compared with control rats, have a diminished response to leptin, with partial loss of triglyceride content in pancreatic islets; the response is reduced compared with islets from normal rats. Furthermore, ZDF *fa/fa* rats have no significant proinsulin mRNA expression in response to either fatty acids or glucose, and heterozygous (fa/+) ZDF rats have a less-than-normal proinsulin mRNA response to fatty acid, providing a mechanism for reduced insulin output in obesity.[248]

Finally, resistin is an adipose tissue–derived peptide encoding a 114–amino acid polypeptide also called FIZZ1 and resistin 1α. Resistin serum levels are elevated in *ob/ob* and *db/db* mice and also in a diet-induced model of diabetes and obesity.[246] Thiazolidinedione ligands for the nuclear peroxisome proliferator activated receptors-γ receptor have been used to treat insulin resistance and function as antidiabetic drugs. These drugs induce adipocyte differentiation and facilitate increased fatty acid uptake into adipocytes as well as regulate genes related to insulin sensitivity.[249] Administration of antiresistin antibody to mice with diet-induced obesity and insulin resistance corrected blood glucose levels. A putative human homologue to resistin has been identified.

These exciting data establish new endocrine systems in the body and provide a framework for a new understanding of the relationship of adiposity to appetite and metabolism and possible mechanisms for intervention in the prevention of morbid obesity and diabetes.

THYROID HORMONES

Thyroid Hormones and Normal Growth

The actions of the thyroid hormones, like those of insulin, can be broadly separated into directly metabolic ones and those that result from thyroid induction of other genes that regulate cell growth and function. Increased oxygen consumption, heat production, and accelerated metabolism constitute the calorigenic effects of the thyroid hormones.[250] The mechanism by which thyroid hormones affect these actions is not clearly understood but probably does not involve an uncoupling of oxidative phosphorylation from respiration, as was originally postulated.[251] Unlike peptide hormones, which bind to cell membrane receptors and regulate cell function and gene transcription via second messengers, thyroid hormone receptors exist in the cytoplasm and directly regulate the transcription of other genes by binding to regulatory regions of DNA in the genome.[252] Many of the developmental effects of the thyroid hormones may result from induction of the genes for other hormones and growth factors, such as EGF and nerve growth factor.[253]

T_4 is the major hormone secreted by the thyroid, but it is deiodinated at its outer ring to produce triiodothyronine (T_3), which is the metabolically active hormone (Figure 16-7). Deiodination occurs both in the thyroid gland and at peripheral sites such as the liver, kidney, and brain. T_4 may also be deiodinated at its inner ring to form reverse T_3 (rT_3), which is metabolically inactive. Regulation of the relative activity of the inner and outer ring deiodinases to vary the concentrations of T_3, and rT_3 is a major control point in the thyroid economy. T_4 release from the thyroid is stimulated by thyroid-stimulating hormone (TSH; thyrotropin), which, in turn, is released from the anterior pituitary under the influence of the hypothalamic modulator thyrotropin-releasing hormone (TRH). Perhaps in conjunction with T_4, T_3 feeds back to inhibit TSH secretion.

The influence of thyroid hormones on growth occurs at many levels. Within the cell, they have profound effects on metabolic processes, including the induction of mitochondrial enzymes and an increase in Na,K-adenosine triphosphatase activity. Thyroid hormones influence the GH-IGF axis, as evidenced by the fact that hypothyroid rats have a diminished pituitary content of GH, low circulating GH levels, and depressed IGF levels.[253–256] T_3 has been shown to stimulate transcription of the GH gene.[257] In contrast to animal models, hypothyroid children do not consistently demonstrate subnormal GH release.[100,258,259] Furthermore, the growth-retarding effects of hypothyroidism in rats are not reversed by GH treatment. In addition to a GH-mediated influence on IGF secretion, thyroid hormones augment IGF-I actions on cartilage growth,[259] and their absence is evident at the growth plate cartilage by altered morphology.[260] In addition, some thyroid hormone actions on growth plate chondrocytes appear to be IGF mediated as the mitogenic actions of T_3 on cartilage growth can be blocked with an antibody to IGF-I. In contrast, the effects of T_3 on cartilage morphology and functional maturation do not appear to be IGF-mediated, direct ones.[261]

Thyroid Hormones and Malnutrition

Fasting and malnutrition induce a hypothyroid-like state characterized by a diminished rate of T_3 production and, consequently, a depressed heart rate and basal metabolic rate, as well as a diminished loss of nitrogen.[143,262,263] Con-

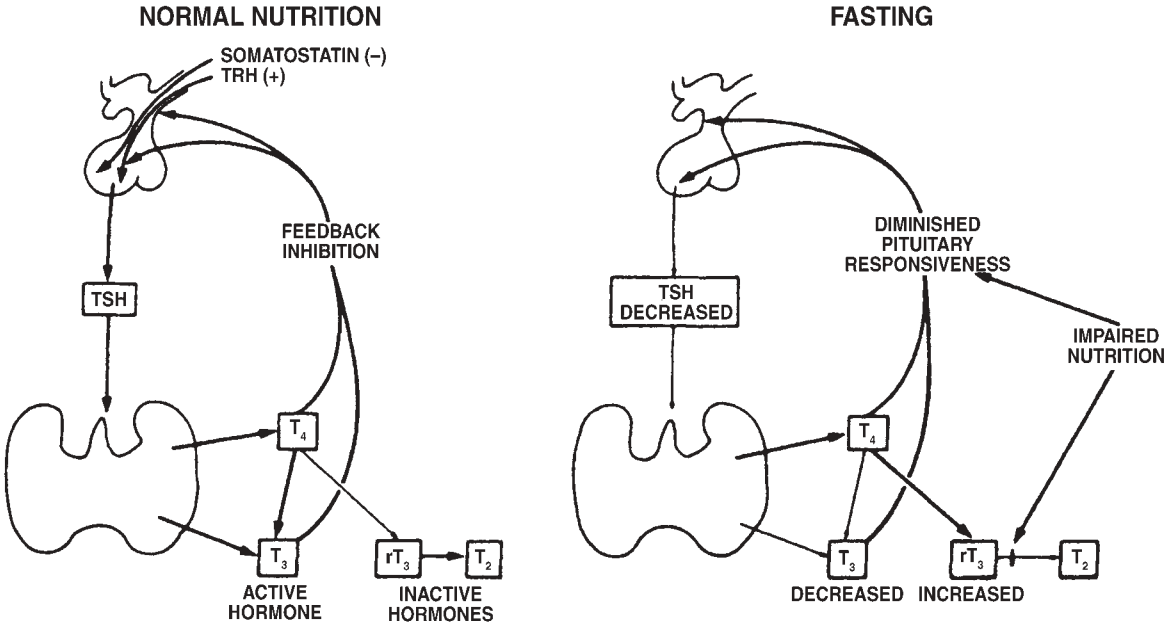

FIGURE 16-7 The pituitary-thyroid axis. *Left*, When nutrition is normal, thyroxine (T_4) is converted primarily to the calorigenic hormone triiodothyronine (T_3) in the thyroid and peripheral tissues. Levels of the inactive hormones—reverse T_3 (rT_3) and T_2—are relatively low. *Right*, After fasting, reverse T_3 concentrations rise primarily because of decreased degradation to T_2 and to some extent through preferential conversion of T_4 to rT_3. Fasting also diminishes the pituitary responsiveness to hypothalamic factors. Thyroid-stimulating hormone (TSH) levels do not rise as in other forms of hypothyroidism. (+) = stimulatory action; (–) = inhibitory action. TRH = thyrotropin-releasing hormone.

comitant with the fall in T_3 in malnutrition is a depression of sympathetic nervous system activity, as measured by norepinephrine secretion.[264] Within 48 hours of a fast, T_3 concentrations fall into the hypothyroid range, whereas concentrations of T_4 change little, and those of rT_3, the inactive metabolite of T_4, rise (see Figure 16-7). These changes result from a starvation-induced inhibition of the deiodination of T_4 to T_3, whereas the serum half-life of rT_3 is prolonged by preventing its deiodination to T_2. In addition, malnutrition also results in a diminished synthesis of the plasma thyroid-binding proteins, also leading to depressed thyroid hormone levels.

The low levels of thyroid hormones in the undernourished state are likely to be an adaptive mechanism meant to diminish the extent of catabolism. Danforth and Burger have shown that when T_3 is administered to fasting subjects sufficient to maintain T_3 levels in the normal range, nitrogen losses are accentuated.[251] Despite a low serum T_3, TSH secretion is not increased in fasting, and the TSH response to TRH is either normal or somewhat blunted.[263,265] The condition of depressed levels of metabolically active thyroid hormones without elevation in TSH in malnutrition or illness has often been called the "euthyroid sick syndrome."[266,267]

The depressed T_3 levels of the fasted state can be corrected by refeeding as little as 100 kcal of carbohydrate, whereas the protein or fat content of the diet does not significantly affect the recovery of T_3.[268] As little as 50 g of carbohydrate will prevent the effect of dietary restriction on serum T_3 levels.[86] As in those subjected to acute starvation, chronically malnourished children and adults have depressed serum T_3 and elevated rT_3 concentrations. However, the TSH concentrations are either normal or elevated in chronic malnutrition, and the TSH response to TRH is exaggerated.[139,187,269]

Thyroid Hormones and Overnutrition

Overnutrition results in changes in thyroid hormone metabolism that are predictably opposite to those seen in undernutrition. The resting metabolic rate is increased, as are T_3 levels, whereas rT_3 levels are decreased.[270] The mechanism for the changes in T_3 and rT_3 appears to be increased outer ring deiodination of T_4 in that overfeeding also results in an increased clearance of T_3. In contrast to the underfed state, it is not clear that the increased metabolic rate seen in overfeeding is associated with enhanced sympathetic nervous system activity because β-adrenergic blockade has no effect on the increased metabolic rate induced by overfeeding.[251]

The relationship between thyroid function and true obesity is minimal, despite popular opinion to the contrary. The weight gain seen in hypothyroidism is largely secondary to myxedema and fluid accumulation, and most of the metabolic effects of overfeeding on thyroid hormone levels occur independently of the degree of leanness or obesity of the subjects.

CORTISOL AND SEX STEROIDS

Cortisol in Intestinal Maturation

There is a striking maturation of absorptive function of the intestine following birth, with ample evidence to suggest that glucocorticoids regulate the process. Most of the data

on the regulation of gut maturation have been derived from studies in rats and other small mammals. Coincident with the period of weaning and, consequently, a decreasing reliance on lactose and other milk sugars for nourishment, there is a fall in the high activity of lactase in the small intestine and a rise in the activity of intestinal sucrase, maltase, and pancreatic amylase.[271] In addition, there is a loss in the abilities of the ileal and jejunal mucosa to take up macromolecules and to transport immunoglobulins. Delay of weaning has no significant effect on the timing of these changes. In contrast, deprivation of pituitary hormones by hypophysectomy in the newborn period elicits a marked delay.[272,273] These observations have led to studies of the role of pituitary-derived or pituitary-regulated hormones in the maturation of gut function.

The experimental data support roles for both glucocorticoids and thyroid hormones in intestinal maturation. Coincident with the enzymatic changes in the rat gut at the end of the second week of life, there is a prominent rise in circulating corticosterone. Breast milk might provide an additional source of glucocorticoids.[274] Glucocorticoid administration to preweanlings results in early maturation of intestinal enzymes such as sucrase[271] and of pancreatic amylase, bile acid synthesis, and transport phenomena such as bile salt absorption.[275] The dependence on glucocorticoids is not absolute, however, as adrenalectomy on day 9 of life does not prevent the appearance of sucrase or delay the maturation of sucrase to adult levels of activity.[271] A comparable role for thyroid hormones has also been suggested, although it appears that the ability of T_4 to induce maturation of the intestinal enzymes requires the presence of intact adrenal glands. Administration of T_4 to rats results in increased blood concentrations of corticosterone. Thus, the observed effects of T_4 may be through induction of glucocorticoids.[271]

Cortisol in Malnutrition

Reflecting metabolic stress, malnutrition in humans and laboratory animals results in elevated cortisol concentrations, with an abolition of the normal diurnal rhythm and a slowed clearance of exogenous cortisol.[276] Fasting also depresses production of cortisol-binding proteins, resulting in a further elevation of free glucocorticoids.[277] Despite the glucocorticoid excess, the adrenal glands remain suppressible with dexamethasone and responsive to ACTH in the malnourished state.

A prominent metabolic effect of cortisol is the diversion of substrates to the liver for protein synthesis. Rao and coworkers have demonstrated that infants with marasmus have higher cortisol levels than do infants with kwashiorkor and that the response of cortisol to ACTH is better preserved in marasmus.[278] Those authors postulated that the development of kwashiorkor is coincident with failure of the adrenal gland to secrete adequate cortisol to maintain normal protein levels. In rats, the biochemical manifestations of kwashiorkor resulting from a low-protein diet can be reversed by glucocorticoids.[279] As previously indicated, glucocorticoids have a deleterious effect on cartilage growth and act as IGF antagonists in somatomedin bioassays. In his studies on malnourished Nigerian children, Smith postulated that elevated cortisol, acting as an inhibitor of IGF action at the epiphyses, was a major contributor to the poor growth of his subjects.[168]

Reproductive Function in Malnutrition

The potent gonadal steroids testosterone and estradiol are primarily responsible for the establishment of reproductive fitness. Other, weaker androgenic hormones, however, which are produced by the gonads and adrenal glands of both sexes, are important in the maintenance of normal anabolism. These include androstenedione, dehydroepiandrosterone (DHEA), and its metabolite, DHEA sulfate. Whereas reproductive functions are expendable and potentially damaging during times of nutrient deficit, considerable attention has been paid to the importance of weaker androgenic hormones, or anabolic steroids, as possible therapeutic agents for the recovery from catabolic states.

In malnourished adults, hypogonadism often develops, and the secretion of sex steroids by the gonads decreases; in malnourished children, the onset of puberty is delayed.[280] Men suffering from chronic protein-calorie malnutrition often experience gonadal failure. In adults, nutrients appear to influence reproduction at both the hypothalamic and gonadal levels. In a group of Indian men suffering from malnutrition, Smith found low plasma testosterone and elevated gonadotropins, indicating impaired testicular function.[281] During recovery, these men continued to have elevated levels of luteinizing hormone and a subnormal release of testosterone to chorionic gonadotropin. In contrast, Klibanski found evidence for hypothalamic hypofunction when mildly obese men were fasted for 10 days.[282]

In addition to the effects of malnutrition in delaying puberty, a number of studies on young athletes have suggested a connection between body composition and reproductive fitness. In young female athletes and dancers who train extensively before puberty, menarche can be delayed by several years.[283] In some instances, the delay in menarche can be related directly to the duration of training prior to menarche: 5 months for every year of training.[284] These observations led Frisch and McArthur to propose that normal menstrual function depends on the attainment of at least 22% body fat.[285] This model, which has not been universally accepted, assumes that some aspect of body fat content signals permission for the secretion of gonadotropic hormones to trigger menstruation.[286] In light of the recent isolation of the adipocyte-derived product of the *ob* gene, leptin, this hypothesis may need to be revisited.

Anabolic Steroids as Therapeutic Agents in Catabolic Disease

Despite all attempts, it has been impossible to synthesize steroids with anabolic actions that are divorced from their androgenic (masculinizing) ones. Coupled with their anabolic effects, these hormones also have behavioral effects such as increased aggressiveness and an enhanced appetite. Like all androgens, synthetic anabolic steroids suppress gonadotropin production and result in a

lipogenic profile of cholesterol metabolism. High doses can alter liver function and result in hepatocellular carcinoma. Anabolic agents have been shown to decrease nitrogen loss after minor surgery but have had no consistent effect on weight gain in geriatric patients or in patients with chronic renal failure.[287–289]

There has been considerable popular attention in recent years to the use of anabolic steroids to increase performance in body building and other sports. Well-controlled studies in adult male athletes are few, and the results are conflicting.[290] Those whose performance stands to benefit the most from increased androgenic activity are those who produce relatively low levels of androgens endogenously: females, prepubertal children, and adolescents. These are the groups in whom additional adverse effects such as virilization, balding, sexual precocity, and premature closure of the epiphyses would be the most damaging. At this time, there appears to be no clear role for anabolic agents in the treatment of catabolic states. Their use in augmenting athletic performance entails significant medical risk.

SUMMARY AND CONCLUSIONS

The humoral controls on growth are highly sensitive to the nutritional milieu and are programmed to alter and even abort the body's developmental scheme as required during conditions of nutritional want or excess. The specific components of the diet that are monitored by the various nutritionally sensitive endocrine systems are still not known, although our understanding is growing as to how nutrients can alter the expression of specific genes that encode key regulatory hormones, growth factors, and enzymes. Nonetheless, a careful assessment of physical growth and maturation can serve as a sensitive and accurate index of nutritional status and disease, both for individuals and for whole populations.

The capacity of the growing organism to accommodate changes in the availability of nutrients by slowing or halting growth is a generally reversible process (catch-up), designed to permit adaptation to a changing nutrient supply. However, the ability to resume normal growth after the correction of metabolic insults is dependent on the nature of the insult, its duration, and the developmental phase of the organism during which it occurs. The damage incurred during certain susceptible periods of growth may be irreversible, perhaps owing to a reduction in the number or critical organization of the cells that make up key tissues. The mechanisms by which a tissue or organism can monitor its own size and correct discrepancies with its "intended" size are unknown. They probably involve coordination between mechanisms for catch-up that are extant in individual tissues and regulatory centers in the CNS; classic hormones probably do not play a key regulatory role.

Recent years have brought the discovery of new hormone systems with close ties to the nutritional status of the organism. The discoveries of leptin, an appetite suppressant produced by adipose tissue, and ghrelin, an appetite stimulant produced in the alimentary tract, shed new light on how the body monitors its nutritional status. Other adipocyte-secreted substances such as Acrp30 and resistin may mediate the insulin-resistant state of obesity. We have an abundance of candidate molecules to begin to elucidate the mechanisms involved in obesity and diabetes and to suggest therapeutic strategies against these disorders.

From our current vantage point, the metabolic changes of undernutrition are adaptive ones, designed to ensure survival until adequate reserves exist to permit growth and reproduction again. In some instances, however, morbidity may actually result from maladaptive endocrine changes. The development of kwashiorkor, for example, may result when the adrenal gland is no longer able to maintain adequate production of glucocorticoid hormones to facilitate withdrawal of proteins from structural stores, such as muscle.

A better understanding of the normal regulation of hormones and growth factors in conditions of altered nutrition has suggested new diagnostic and therapeutic approaches. Blood levels of IGF-I or some of its binding proteins may provide a more sensitive means of assessing nutritional status than many other currently employed tests. Administration of GH to individuals in catabolic states may hasten their recovery. Studies of anabolic steroid hormones in catabolic states have generally not been promising.

The future challenge is to better delineate the full spectrum of humoral and neuroendocrine changes that accompany nutritional alterations and to define those components of "nutrition" that are the actual signals that can regulate the production and actions of hormones and growth factors. The accelerated rate at which "new" hormone systems have been discovered illustrates the fact that we have not yet identified all of the relevant humoral control systems let alone understood them. The characterization of genes identified by the Human Genome Project may allow us to finally identify all of the critical components of the interface between nutrition and cellular control. At this time, the measurement of growth factors, their receptors, and their downstream signaling events within tissues is an invasive proposition and of little clinical practicality. When the physiology of these substances is better understood, however, the promise for therapeutic intervention will be great.

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CHAPTER 17

ENERGY METABOLISM AND REQUIREMENTS IN HEALTH AND DISEASE

Jean Louis Bresson, MD, Jean Rey, MD, FRCP

The interpretation of the changes in metabolic rate resulting from either malnutrition or disease finds its roots in the physiologic determinants of daily energy expenditure. The technical aspects of the measurement of energy expenditure and its obligate correlate, body composition, extend beyond the scope of this chapter and have been thoroughly reviewed in the literature.[1,2] Once raw data are available, many factors may confuse cross-sectional and, even more, age-related comparisons. The influence of body components, whether fat-free mass (FFM), fat mass (FM), or organ weight, should be considered first in an attempt to account for the wide differences in metabolic rate among infants, children, and adults. This is also relevant to a better understanding of the responses to underfeeding and malnutrition. Conversely, recent advances in the field of minor contributors to energy expenditure, such as the thermic effect of feeding or the thermic response to cold, may help us to understand how physiologic mechanisms may be turned into an energy-loosing machinery.

One of the most common findings in the sick child is a reduced food intake, which is widely accepted as the main, if not the only, cause of malnutrition. However, evidence accumulates suggesting that metabolic dysregulations may also participate and, in some instances, be primarily responsible for the nutritional deficit. This may be particularly true for proteins that, unlike fat, are not stored but make up functional or structural tissues. Nitrogen balance in the adult or net protein deposition in the growing child results from protein synthesis rates equal to or higher than protein breakdown, respectively. This equilibrium may be disrupted by the overproduction of peptides, otherwise playing a pivotal role in the regulation of the immune system. It results in a protracted increase in protein breakdown over protein synthesis. This mechanism is found in acute as well as chronic inflammatory syndromes and may lead to a severe protein malnutrition, despite apparently normal nutrient intakes. Consequently, underfeeding is clearly not the only factor in malnutrition. Furthermore, these protein losses are not easily controlled by classic dietary treatment and represent a pressing case for developing a specific pharmacologic approach.

PHYSIOLOGIC DETERMINANTS OF ENERGY EXPENDITURE

Basal Metabolic Rate

Comparisons between the rates of energy expended, or heat produced, by individual subjects require that the measurements should be free of the effects of any factor known to increase it. Failure to control for the effects of activity, feeding, and physical environment on metabolic rate would obviously result in spurious interindividual differences. Benedict proposed a set of standard conditions required to perform accurate measurements of the basal metabolic rate (BMR) in adults: the subject should be awake but in complete muscular repose both before and during the measurement, ideally performed in the morning before the patient rises; the subject should be in the postabsorptive state, normally accepted as 12 or more hours after the last meal, and should have received prior to the measurement a maintenance diet ensuring the stability of body weight; the subject should be in emotional repose and familiar with the measurement devices; in women, the measurement should not be made immediately before or during the menses; and ambient temperature should be set in the range of the subject's thermal neutrality to avoid any thermoregulatory effect on heat production.[3]

Obviously, these requirements may be impractical in infants and young children or in clinical settings. Metabolic rate measurement not performed in the postabsorptive state, but complying with the remaining conditions and usually termed resting metabolic rate (RMR), is about 15% higher than true BMR.[4] It should be pointed out that, even in adults, the conventional period of 12 hours after the last meal may not be a sufficient interval to guarantee

that the continuing effects of its metabolism are negligible.[5] Hence, BMR should not be viewed as a measure of the absolute minimal metabolism. Indeed, energy expenditure is about 8 to 12% lower during sleep than under basal conditions,[6] and oxygen consumption rate is then related to the stage of sleep.[7] As it is difficult to quantify the amount of work performed during spontaneous physical activity,[4] measurement of the sleeping metabolic rate (SMR) may be a convenient way to minimize its consequences on energy expenditure in young children. Thus, rather than defining a specific physiologic event, the set of standardized conditions chosen for metabolic rate measurements is primarily aimed at reducing the variance related to uncontrolled factors to increase the power of interindividual or intergroup comparisons. When the rigorous conditions listed by Benedict are fulfilled, repeated measures display a remarkably low level of intraindividual variations. For instance, the coefficient of variation (s/m) of replicate indirect calorimetry measurements amounts to about 2 to 4%, of which 2% could be accounted for by the variability related to the technique.[4]

The reproducibility of such measurements is high, even over a prolonged investigation.[8] Thus, the range of intraindividual variations in BMR becomes much narrower than the range of interindividual variations that one may observe in cross-sectional studies of normal adult populations. A threefold difference is usually found between the lower and higher BMR individual values, expressed in kcal or kJ/d.[9] Repeated measures confirm that these are true between-subject differences. Furthermore, BMR is about 15% lower in adult females than in adult males.[6] Many of these interindividual differences may be related to body build, as suggested by the significant correlations between BMR and body weight or height, or Quételet index (weight/height^2).[10] Multiple regression analysis indicates that FFM accounts for about 65 to 75% of BMR variance between subjects[6,11] and that FM, age, and sex together account for another 5%.[11] It is noteworthy that—exclusive of pregnancy—the contribution of FM to BMR variance is limited[6,11,12] or even negligible[4] and that BMR becomes comparable in males and females after adjusting for FFM and FM.[6] Thus, FFM, FM, age, and sex account for about 80% of the interindividual variability in BMR, and nearly all of the effect of these covariates is attributable to FFM (Figure 17-1).[13] However, differences between lower and higher individual metabolic rates still amount to about 600 kcal/day even after adjustment for these factors.[11] Further studies showed that family membership is another significant determinant of BMR.[14] In the Pima Indians, metabolic rate among families may vary by nearly 500 kcal/day, whereas the mean variation within families is only about 60 kcal/day.[13] In this population, FFM, age, sex, and family membership account for 94% of the variability in metabolic rate, with family membership contributing about 11%. Actually, a metabolic rate lower than that predicted by FFM, age, and sex at the beginning of the study turned out to be a major risk factor for body weight gain during the subsequent follow-up,[11] implying that obesity may result from an economy in energy expenses. These results emphasize the necessity to express metabolic rate in relation to FFM, its major constituent, rather than in relation to any other parameter such as crude body weight or body area.

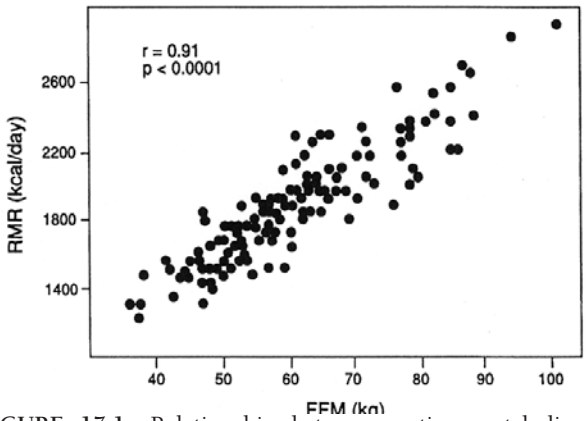

FIGURE 17-1 Relationship between resting metabolic rate (RMR) and fat-free mass (FFM) in 130 subjects. Adapted from Bogardus C et al.[13]

However, this mode of expression may still hamper interindividual comparisons in the pediatric population. During growth, RMR expressed either as kcal/kg body weight/day[15] or as kcal/kg FFM/day[16] follows a nonlinear increase, with slopes substantially higher in infants and young children than in adolescents and adults (Figure 17-2). After a steep increase in the days following birth,[17] RMR falls disproportionately to the rise in body weight or FFM, being about 67 kcal/kg FFM/day at 3 months, 46 kcal/kg FFM/day at 11 years, and 37 kcal/kg FFM/day at 13 years, compared with adult values of 28 kcal/kg FFM/day (Figure 17-3).[16] This suggests that the metabolic activity of FFM is changing as a whole,[18] or that the relative contribution of tissues with different metabolic rates to the composition of FFM is changing,[19,20] or both.

Holliday pointed out that the brain, heart, liver, and kidney together make up only 5 to 6% of the body weight but account for 60 to 70% of the BMR in the adult. Conversely, muscle mass, which makes up about 44% of the body weight, accounts for only 15 to 30% of BMR.[15] In contrast, the FFM of infants and young children comprises about 30%

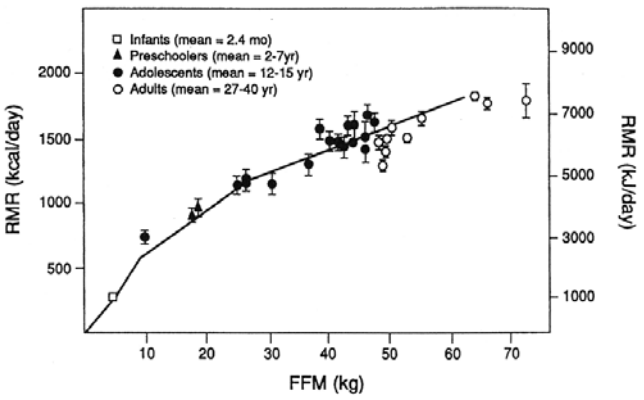

FIGURE 17-2 Relationship between resting metabolic rate (RMR) and fat-free mass (FFM) among different age groups. Adapted from Weinsier RL et al.[16]

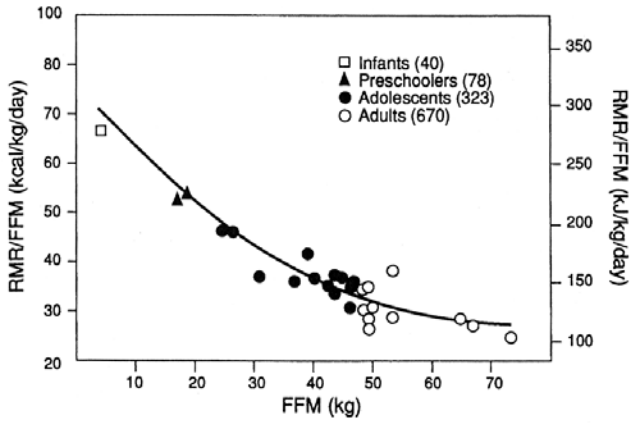

FIGURE 17-3 Relationship between resting metabolic rate (RMR) per unit fat-free mass (FFM) (RMR/FFM) to FFM among different age groups. Adapted from Weinsier RL et al.[16]

muscle and 20% other organs and that of adolescents averages 42% muscle and 8% other organs.[15] Therefore, the higher metabolic rate of infants and children in relation to FFM could be ascribed to a greater proportion of metabolically active nonmuscle organ mass and to a lesser proportion of less metabolically active muscle mass than in adults (Table 17-1).[15,16] This is exemplified by experiments carried out on pigs with different nutritional backgrounds.[21] The first group was fed to gain steadily 14 kg over 70 days. A second group was fed to gain 19 kg during the first 35 days (high-energy period) and to lose 5 kg during the second 35 days (low-energy period; group HL), and this pattern was reversed (low-energy period first) in a third group (LH). At the end of the 70-day experiment, all animals had achieved the same body weight, but the fasting metabolic rate of the LH group was 25 to 50% higher than that of the HL group and 13 to 40% higher than that of the first one. Furthermore, there was a significant correlation between fasting metabolic rate and organ weights.[21] The consequences of these observations are twofold. First, comparing the BMR to FFM ratio between two groups of subjects may be misleading when values of FFM are markedly different,[16] mainly because the ratio of the weight of organs (heart, liver, brain, spleen, and kidneys) to total FFM decreases as FFM increases.[22] Second, this raises the possibility that abnormal metabolic rates in disease states may be related to a change in the proportion of metabolically active organs to less active muscles. For instance, a reduction in muscle mass could account for the inverse relationship between RMR per kilogram of body weight and percent ideal body weight observed in patients with Crohn's disease.[23]

Differences in metabolic rate between young and mature animals have also been found in other mammalian species. These weight-related differences further extend to comparisons between mature animals of different species. For instance, mouse metabolic rate is about 5 times greater than human's and about 10 times that of the elephant.[24] Kleiber and Brody and Proctor proposed a generalization according to which RMR follows a metabolic power function corresponding to weight$^{0.75}$.[24,25] However, the mass coefficient is not the same in various species, ranging from 0.48 to 0.91, the mean value being 0.67 ± 0.03. As there is no definite value for either the intraspecific or interspecific mass exponents, any attempt to explain the Brody-Kleiber empiric relationship by a general physical principle is most likely to fail.[25] Actually, this statistical relationship may obscure rather than reveal biologically important changes. The relative proportion of metabolically active tissue may contribute to these differences as large mammals have a greater proportion of tissues with low metabolic activity, whereas smaller ones have a greater proportion of tissues with higher metabolic activity. However, Krebs showed that the rates of respiration of homologous tissues are affected by the size of the animal, although there is no strict parallelism between measured tissue oxygen consumption and the BMR of the animals.[26] A comparison between homeo- and poikilotherms might give a hint about a possible cause for this difference. The standard metabolic rate is sevenfold greater in the rat (a typical mammal) than in an ectothermic vertebrate (bearded dragon) of the same body size and at the same body temperature.[27]

This large difference in metabolism is also manifest at the cellular level. Rat hepatocytes respire fourfold faster than do hepatocytes from the lizard. The inner membrane of isolated rat liver mitochondria has a permeability that is four- to fivefold greater than the proton permeability of the lizard liver mitochondrial membrane.[27] Thus, the greater proton permeability of the mitochondrial inner membrane contributes to the greater metabolic rate of mammals. Actually, this is a major source of heat production (see below). Similarly, plasma membrane permeability to Na^+ and K^+ is higher in mammals than in ectothermic vertebrates, increasing the amount of energy devoted to active Na^+-K^+ exchange.[28] Thus, the activity of the Na^+-K^+-adenosine

TABLE 17-1 Relation between Basal Metabolic Rate (BMR) and Muscle and Organ Metabolic Rates with Age

Height (cm)	*Weight (kg)*	*BMR (kcal/d) A*	*Muscle MR (kcal/d) B*	*Organ MR (kcal/d) C*	*B/A*
60	5.5	300	21	279	7.0
80	11.0	590	45	545	7.6
110	19.0	830	117	713	14.0
140	31.0	1,160	204	956	17.6
160	50.0	1,480	373	1,107	25.2
180	70.0	1,800	500	1,300	27.7

Adapted from Blaxter K.[24]

triphosphatase (ATPase) accounts for about 20% of the total in vitro energy expenditure by mammalian tissues.[29] The use of ouabain to inhibit Na^+-K^+-ATPase in vivo leads to a 20 to 30% inhibition of resting oxygen consumption in guinea pigs[30] and to a 20 to 25% inhibition in mice,[31] supporting the idea that active Na^+-K^+ exchange is a significant determinant of resting energy expenditure. In humans, Na^+-K^+-ATPase activity may contribute 20 to 25% to BMR.[32] As in animals, Na^+-K^+-ATPase is subject to chronic control by thyroid hormones, and slight interindividual variations in free triiodothyronine (T_3) index among healthy adults would account for a between-subject difference in SMR of 142 kcal/day.[33] Furthermore, the magnitude of Na^+-K^+-ATPase-dependent energy expenditure in tissues appears to be related to the physiologic status and particularly to age. Muscle preparations from 7- to 21-day-old calves expend 26% more total aerobic energy in support of Na^+-K^+ transport than do the same muscles from 7-month-old calves.[29] Similarly, the Na^+-K^+-ATPase-dependent respiration of skeletal muscle preparations from 4-week-old lambs accounts for a 48% greater amount of energy than similar muscles from adult ewes. Also, energy consumption in support of active Na^+-K^+ exchange by the intercostal muscle from young lambs is 119% greater than for similar preparations taken from adults.[34] Comparable differences exist between hepatocytes obtained from 1- to 8-week-old lambs and from mature sheep.[35] In this latter case, the lower oxygen consumption of hepatocytes isolated from mature sheep is largely attributable (70 to 90%) to the decrease in the Na^+-K^+-ATPase-dependent component of respiration.

It is striking that in quiescent cultured animal cells exposed to mitogens, one of the first events to take place is a rapid, very large increase in the rate of Na^+ flow into the cells,[36] which, in turn, induces increased Na^+-K^+ pumping. Activation of Na^+-K^+-ATPase appears to be an early growth-related event, and it is tempting to speculate that increased energy expended on active Na^+-K^+ transport by young mammals is related to their higher growth rate.[34] Active ion transport is probably not the sole cause of this difference. Measurement of whole-body protein synthesis shows that the smaller mammals display the higher protein synthesis rates in relation to their body weight. Within-species comparisons also indicate that immature animals have higher protein turnover rates than adults. For instance, protein synthesis amounts to 6.7 ± 1.1 g/kg/day in term infants compared with 3.5 ± 0.6 g/kg/day in adult humans. Simultaneously, basal energy expenditure is 45.1 ± 4.6 and 23.6 ± 3.8 kcal/kg/day in newborns and adults, respectively.[37] Thus, a similar ratio of BMR to whole-body protein synthesis (6.7 to 6.9 kcal/g) applies to both healthy newborn and young adults, suggesting that the turnover of cellular constituents, including proteins, and energy expenditure change in parallel with maturation. Therefore, differences in BMR in relation to body weight or FFM during growth are not merely a matter of proportion between tissues with high or low metabolic rates but are also related to differences in the amount of work done by the cells in chemical syntheses and in maintaining membrane electrochemical gradients.[38]

Energy Cost of Growth

An estimate of the energy cost of growth can be obtained in groups of rapidly growing infants from the relationship between growth rate and metabolizable energy intake.[39] The slope of this linear relationship provides an estimate of the total amount of energy stored and expended for synthesis, and its intercept at zero growth indicates the amount of energy required for maintenance. It should be pointed out that maintenance requirement may be higher than BMR by 10% in premature infants[40] and 50% in children[41] as maintenance includes expenses for limited activity and feeding.[42] The energy cost of growth can also be estimated from the independent measurement of stored energy and energy expended for synthesis.[40] An indirect method for calculating the cost of tissue synthesis is to relate weight gain to energy expenditure, assuming that an increase in expenditure is directly related to the increase in cost of synthesis. Unfortunately, the result may be obscured by activity. A direct measurement of the cost of synthesis rests on the assumption that the thermic effect of feeding (ie, the increase in metabolic rate after the meal over the resting value in the postabsorptive state; thermic effect of feeding [TEF]) is largely accounted for by synthesis. This is supported by the positive correlation observed between weight gain and TEF in rapidly growing individuals.[42] However, the TEF may be grossly underestimated unless the interval between feeds is long enough to allow metabolic rate to return to postabsorptive levels.

Various estimates of the total cost of growth are in the range of 3 to 6 kcal/g of new tissue. A widely accepted figure in normal infants is 5 kcal/g.[40,41] Metabolic balance and body composition studies indicate that the average composition of weight gain is 28% fat and 16% protein during the first year of life.[43] Assuming crude energy contents of 9.25 kcal/g and 5.65 kcal/g for fat and protein, respectively, it is possible to estimate the amount of energy stored to about 3.5 kcal/g of body weight gain. In contrast, the cost of synthesis is about 1.5 kcal/g of body weight gain. Direct estimates of the amount of energy expended for synthesis usually provide figures in the range of 0.55 to 0.7 kcal/g.[40,44] This discrepancy may be related to an underestimation of the TEF as it is measured only 2 to 3 hours after the last meal. The so-called fasting metabolic rate used as a baseline is likely to be falsely high owing to the lasting effect of feeding. As the energy stored in weight gain represents about 70% of the total energy cost of growth, one can expect wide differences according to the composition of tissues laid down. For instance, it is possible to calculate that the total amount of energy required to deposit 1 g of protein is about 13.4 kcal/g and is 10.8 kcal/g for fat.[45] Thus, a weight gain comprising 16% protein and no fat would cost about 2.2 kcal/g. Conversely, a weight gain consisting of fat with no protein would cost about 9.7 kcal/g, assuming that adipose tissue may contain up to 90% lipids. These differences may account for the high cost of weight gain found in overfed adults. In these conditions, weight gain consists of about 70% fat and 30% fat-free tissue,[46] the theoretic cost of growth then amounting to ≈ 7 kcal/g. Similarly, the average cost of weight gain in patients with anorexia nervosa ranges from 5 to more than

7 kcal/g, suggesting either important changes in the composition of body weight gain during rehabilitation[47] or an important confounding effect of activity.[48]

The daily energy cost of growth will depend obviously on growth rate as well as on the composition of new tissue. Growth rate is highest during the first 3 months of life, reaching 30 to 35 g/day between birth and 8 weeks of age or a fractional growth rate of about 1%/day.[43] It decreases rapidly thereafter to 7 to 10 g/day at 1 year of age, or 0.07 to 0.09%/day, and to about 5 g/day (< 0.03%/day) by 5 years of age. Thus, the cost of growth represents a significant part of daily energy needs (≈ 33%) from birth to 4 months of age. Later, it decreases to about 7% between the ages of 4 and 12 months, 1.6% between 12 and 24 months, and 1% between 24 and 36 months. Thereafter, it is negligible compared to daily energy expenditure. Thus, on the basis of nutrient partition between growth and nongrowth, the 1- to 2-year-old child appears more like the adult than the small, rapidly growing infant.[49]

Thermic Effect of Feeding

It was recognized long ago that fed animals have substantially higher metabolic rates than fasted ones.[24] The effect of specific nutrients was investigated during the nineteenth century showing that the ingestion of proteins induces a greater increase in energy expenditure than carbohydrates or fat. The ingestion of a mixed meal also results in an increased metabolic rate above BMR. Energy expenditure may increase by up to 30% over BMR in response to large energy challenges,[50] a sizable change equivalent to 6 to 10% of the energy intake.[50] Unlike BMR, the TEF appears to be independent of weight, FFM, FM, and Quételet index.[50] In contrast, its duration and magnitude are linearly related to the energy intake,[50] which explains the greater effect of large meals.[51] Duration and magnitude of TEF are not significantly different when the same meal is ingested or directly delivered into the stomach.[52] However, the magnitude of the thermic effect is significantly greater if the same energy load is delivered in a short time rather than over several hours.[51,53] The route of administration of the nutrients, either intragastric or intravenous, does not seem to affect the magnitude of the response,[54] suggesting that the energy input of luminal digestion, fermentation, mechanical mixing, and nutrient absorption makes only a modest contribution to the TEF in normal subjects. Energy expenditure may still be significantly higher than postabsorptive levels by 5 to 8 hours after a large energy challenge.[50] Furthermore, the effect of the antecedent diet may significantly affect both sleeping and RMRs. For instance, RMR remains elevated by 12% 14 hours after the last meal during short-term overfeeding.[5] In these conditions, the TEF lasts not only for the whole day but also throughout the night until the following morning, when the effect is still apparent. There is also a strong indication that the TEF of one meal merges into the thermic effect of the next meal. Thus, the duration of the TEF should be carefully considered before attempting to determine either BMR or the effect of feeding, particularly in infants.

The composition of the meal bears some importance. In accordance with earlier work, the thermic response to a high-protein meal is greater than that to a high-carbohydrate one.[55] Similarly, the TEF is greater after a high-carbohydrate meal when compared with a high-fat[56] or mixed diet.[57] Thus, high-fat meals could be a risk factor for obesity in children.[58] However, the ingestion of a mixed meal elicits many simultaneous and complex events, and an experimental account of the thermic response to feeding could come only from a simplified model. The euglycemic-hyperinsulinemic insulin clamp offers several advantages in this regard.[59] It involves a single nutrient and bypasses absorption, allowing one to know precisely the rate of appearance of glucose within the body at any time. Combined with indirect calorimetry, it allows one to assess the effect of glucose infusion on glucose oxidation and storage as well as on energy expenditure. When different plasma insulin concentrations are achieved, together with glucose infusion rates appropriate for maintaining euglycemia, it is readily apparent that the increase in energy expenditure secondary to glucose administration is not related to an increase in its oxidation rate. In contrast, the increase in energy expenditure is closely related to the rate of glucose storage.[60] This is supported by studies in insulin-resistant patients showing that their blunted thermic response to glucose infusion is restored when glucose storage rate is matched to controls by further increasing insulin concentration.[61] Thus, in agreement with Flatt's proposal,[62] the TEF is primarily related to the cost of storage of the nutrients. According to the stoichiometry of these reactions, it is possible to calculate that the synthesis of glycogen costs about 4% of the energy of the glucose stored (0.15 kcal/g) and that this cost increases to 28% (1.05 kcal/g) when glucose is converted to fat. Conversely, the cost of triglyceride synthesis from absorbed fats amounts to about 2% of their energy content. Because of the many adenosine triphosphate (ATP)-consuming steps involved in the synthesis and breakdown of proteins, the cost of amino acid incorporation into proteins is estimated to be about 25% but might be as high as 55% of their energy content.[62] Indeed, comparing the thermic effect of high-protein and high-carbohydrate diets shows that the former results in a greater thermic response (+45%) than the latter. Simultaneously, the increase in protein turnover is twice as much with the high-protein diet as with the high-carbohydrate diet. The metabolic cost of protein synthesis would thus account for about 68 and 36% of the thermic effect of each diet, respectively, and the combined effect of increased protein synthesis and nitrogen excretion would account for 96% of the thermic effect of the high-protein diet.[55]

The cost of storage may not be the only component of the TEF. Indeed, the increase in energy expenditure related to glucose infusion is substantially higher than predicted from the amount of glucose stored.[60] The fact that overfeeding or the ingestion of a glucose-rich meal elicits an increase in sympathetic nervous system (SNS) outflow,[63] or in plasma noradrenaline concentration and turnover,[64,65] a known thermogenic hormone, suggests that the stimulation of the SNS is involved in the thermic

response to feeding. This is supported by the blunting of the glucose-induced increase in energy expenditure by β-adrenergic blockade during insulin clamps. As a result, the residual variation in metabolic rate becomes almost identical to the value predicted from the amount of glucose stored.[66] This implies that the TEF has two components. One is an obligatory component directly related to the intermediary storage of nutrients and accounts for about 60% of the response to feeding. The other is related to the stimulation of the SNS and represents about 30% of the increase in energy expenditure.[67] This partition is confirmed by the use of clonidine, a centrally acting α_2-adrenergic receptor agonist that inhibits SNS outflow. In association with the decreased SNS response to a carbohydrate-rich meal, TEF is blunted by 33%, a value similar to that obtained from peripheral β-adrenergic blockade during insulin clamps.[68] The effect of SNS activity on energy expenditure is not restricted to the hours following meals. Its inhibition by clonidine also decreases RMR. Although the reduction in RMR does not reach significance because of the small number of subjects, the authors aptly point out that a 6% decrease in BMR might account for a greater overall diminution in energy expenditure than the larger 33% blunting of TEF.[68] The contribution of SNS activity to energy expenditure in the postabsorptive state is further confirmed by the 8% reduction in BMR observed in response to a β-adrenergic antagonist that does not affect T_3 production, nadolol.[69] Furthermore, urinary noradrenaline excretion and muscle sympathetic nerve activity are significantly correlated to RMR adjusted for FFM, FM, and age in normal adults, implying that SNS activity is a physiologic determinant of energy expenditure.[70,71] A similar correlation between urinary noradrenaline excretion and oxygen consumption is observed in infants,[72] suggesting that the effects of SNS activity on energy expenditure extend to this age.

Therefore, the thermic effect of feeding involves a short-term meal-related component lasting for several hours and is accounted for by both nutrient storage (obligatory) and acute stimulation of the SNS (facultative). In rapidly growing infants, this short-term effect also reflects the cost of synthesis of new tissues as its magnitude is significantly correlated to growth rate.[42] However, the response to feeding also involves a longer-term component, which may affect BMR and SMR.

Thermogenesis

Heat production by living organisms is associated with respiration and concomitant oxidation of nutrients. According to the chemiosmotic hypothesis, the enthalpy of oxidation is transduced by the respiratory chain of the mitochondria into a proton gradient, which powers the ATP synthase.[73] However, the efficiency of the system characterized by the ratio of the amount of energy liberated to that recovered is far from one, even if it is higher than previously estimated from the standard-free energy of ATP, $\Delta G^{0'}$.[1] Attempts to directly evaluate this efficiency in humans indicate that about 65% of the energy liberated may be recovered under the form of ATP.[74] Thus, a minimum of 35% is lost as heat, and nutrient oxidation at the level of mitochondrial respiration appears as the primary heat-releasing process. This is consistent with the significant relationship existing between body temperature and BMR or SMR.[75] However, basal heat production may be insufficient to maintain the core temperature within a narrow range of variation, particularly when heat exchange is increased by a low ambient temperature. Extra heat production can be generated by recruiting metabolic processes that do not produce any net work. Isometric muscular contraction, as during malignant hyperthermia, is a major heat-generating process. Similarly, shivering increases oxygen consumption,[76] and because no external work is performed, the energy appears as heat.

There is some evidence in adult humans that heat production may be increased by other means. For instance, BMR or 24-hour energy expenditure increases significantly (6 to 11%) in response to an ambient temperature drop from 28°C to 20°C to 22°C, without any overt sign of shivering or any correlation with activity.[77] Similarly, the metabolic rate of full-term infants increases in response to an ambient temperature lowering from 32°C to 23°C. This increase is not correlated with activity and occurs in the absence of shivering. In these conditions, the infants' response is dramatic, amounting to a 100% increase in energy expenditure,[78,79] which suggests that a nonshivering thermogenesis is operative. In the rat, the early stage of cold adaptation is associated with shivering. However, shivering disappears with acclimatization, and a nonshivering heat source eventually takes over all of the duties of heat production.[80] It is now well established that cold exposure results in a marked increase in sympathetic activity, largely responsible for the elevated metabolic rate of the rats.[81] The dominant role in nonshivering thermogenesis has been ascribed to brown adipose tissue (BAT), even in adult animals.[82] BAT stimulation is achieved through β-adrenergic receptors, among which is a new type of receptor with pharmacologic properties differing from either β_1 or β_2, thus termed β_3.[83] BAT's prominent characteristic is the synthesis of a specific, 32,000 Da protein, known as uncoupling protein 1 (UCP-1 ; reviewed in Pecqueur and colleagues[84]), located in the inner mitochondrial membrane and acting as a proton conductance pathway. UCP-1 dissipates the proton gradient created by respiration, thus bypassing ATP synthase. In turn, the dissipation of the proton gradient causes a dramatic increase in the mitochondrial respiratory rate. On β-adrenergic stimulation, BAT substantially increases its respiration. As mitochondrial respiration and phosphorylation are uncoupled, ATP generation accounts for much less than 10% of oxygen consumption,[85] and the enthalpy of oxidation of the nutrients is essentially dissipated as heat, making BAT a tissue specialized in thermogenesis. Acute cold exposure leads to a rapid and pronounced elevation of the level of the messenger ribonucleic acid (mRNA) coding for UCP-1, and UCP-1 synthesis is evident within 15 minutes.[86] In contrast, hypothyroid rats are unable to maintain a normal body temperature when placed at 4°C, despite increased

noradrenaline turnover rates.[87] The response of UCP mRNA to adrenergic stimulation in hypothyroid brown adipocytes is readily restored by thyroxine (T_4) through mechanisms requiring its intracellular conversion to T_3.[88] For a full UCP-1 response to cold, near-saturation of the nuclear T_3 receptor is required.[88] BAT contains a type II 5′deiodinase (5′D-II), which locally generates T_3 and allows it to reach a very high level of receptor occupancy despite the low physiologic plasma T_3 levels.[89] Indeed, T_4 appears to be a much more efficient source of T_3 for BAT than plasma T_3 when the 5′D-II is activated. Conversely, iopanoic acid, an inhibitor of 5′D-II, abolishes the T_4-induced restoration of both UCP-1 response and normothermia in hypothyroid rats.[88] In turn, 5′-II activity is stimulated by SNS,[90] and nuclear T_3 receptors are nearly saturated within 4 hours of cold exposure.[89] Thus, SNS, through cyclic adenosine monophosphate (cAMP) generation, and thyroid hormones act synergistically on BAT. T_3 affects the *UCP-1* gene expression at a transcriptional[91] and post-transcriptional level.[92] However, this effect of T_3 is not sufficient to elevate UCP-1 mRNA cellular content in the absence of significant levels of transcription, explaining why T_3 cannot increase UCP-1 mRNA in vivo in the absence of adrenergic stimulation.[93] Thus, T_3 amplifies the effects of the adrenergic stimulation on UCP-1 gene expression, allowing BAT to reach its full thermogenic capacity. Conversely, pretreatment of rats with corticosterone abolishes the UCP-1 mRNA response to noradrenaline and cold by inhibiting *UCP-1* gene expression.[94] Interestingly, this effect is antagonized by the action of the corticotropin-releasing hormone (CRH; under feedback control by glucocorticoid) on the central nervous system, stimulating SNS outflow[95] and leading to an increased expression of UCP-1.[96] The simultaneous expression of several proteins (UCP, 5′D-II, and β_3-adrenoreceptors) appears to characterize functionally active BAT, although only UCP-1 is tissue specific.

The first attempts to settle the controversy about the presence or absence of BAT in humans involved the characterization of UCP-1. This protein was first reported in human fat depots from patients with pheochromocytoma.[97] It was subsequently isolated from newborn brown fat.[98] Later, UCP-1 was found in humans at all ages, but its content was highest in children.[99] Since then, the human *UCP-1* gene has been cloned. Its sequence is 80% homologous to rat UCP-1, both at the nucleotidic and amino acid levels.[100] Both UCP-1 and UCP-1 mRNA are present in infants and in an unexpected number of adult patients, UCP-1 mRNA being detected in the periadrenal adipose tissue of all of the subjects studied.[101] UCP-1 transcripts are abundant in an infant's perirenal fat but are low in quantity in subcutaneous depots.[102] Full-term newborn interscapular UCP-1 content is equal to, or even higher than, the level found in 3-week-old mice acclimatized at 20°C. In contrast, ATPase content is low in infant BAT, similar to that found in animal BAT mitochondria, compared with heart and liver mitochondria.[103] The specific content of UCP-1 in infant BAT increases twofold between 25 and 32 weeks of gestation and remains nearly constant thereafter.[103] Infant BAT also expresses 5′D-II. Strikingly, 5′D-II content follows the same pattern as UCP-1 and achieves levels comparable to 5′D-II activities found in animals stimulated during the neonatal period by exposure to cold or increased cAMP levels.[103] Moreover, β_3-adrenoreceptor mRNA content in children and adults parallels that of UCP-1 mRNA.[102] This coexpression of UCP-1, 5′D-II, and β_3-adrenoreceptor strongly suggests that functional BAT exists in humans from birth to old age. Measurements performed in vitro on isolated cell preparations as well as in vivo suggest that the heat-dissipating capacity of BAT is in the range of 300 W/kg of tissue.[104] Thus, 16 g of BAT would be sufficient to account for the 25 to 30 W/m^2 increase in energy expenditure observed in newborns exposed at 23°C.[79] This would represent about 2% of the adipose tissue mass of newborns or a figure similar to the amount of BAT found in adult rats acclimated to cold.[82] Adrenaline-mediated thermogenesis also occurs in human muscle,[105] even if its mechanism is still uncertain. Similarly, it was recently shown that T_3 administration to normal adults results in a significant increase in the activity of muscle tricarboxylic acid (TCA) cycle, without any change in the rate of ATP synthesis.[106] The disproportionate increase in TCA cycle flux compared with ATP synthesis suggests that T_3 induces an increase in muscle thermogenesis by promoting mitochondrial energy uncoupling. This might be achieved through an increase in UCP-3 protein expression, which is specific to skeletal muscle and upregulated by thyroid hormones. In this regard, it is noteworthy that the biochemical properties of muscle (ie, fast-twitch versus slow oxidative fibers) account for part of the interindividual variability in SMR and 24-hour energy expenditure in the adult.[107,108] However, the respective contributions of BAT and muscle to the overall thermogenic response are difficult to ascertain. Some studies in adults suggest that a ≈ 700 g BAT would contribute 25% to adrenaline-induced thermogenesis, whereas the ≈ 34 kg muscle mass would account for 50% of the thermic response.[109] Despite the uncertainties about its effectors, the reality of a β-sympathetically mediated thermogenesis is now recognized in humans.[71,110]

24-Hour Energy Expenditure

BMR represents a major determinant of 24-hour energy expenditure, amounting to about 60% of 24-hour energy expenditure in sedentary adults.[111] This corresponds to a 1.6 24-hour energy expenditure to BMR ratio, also named physical activity level (PAL). Actually, a PAL of 1.35 is considered the lowest value compatible with long-term maintenance in adults, other than the completely chair- or bed-bound. A PAL range of 1.55 to 1.65 represents the average of the so-called sedentary lifestyle. Data also suggest that activities do not have to be obviously strenuous for relatively high PAL values to be achieved. PAL values vary from about 1.6 to 1.7 in boys and girls between 1 year of age and adolescence (Appendix, Table A-12).[112] Indirect estimates suggest that the energy cost of spontaneous activity represents only 5 to 10% of 24-hour energy expenditure in premature infants[44]) but amounts to 20 to 26% of 24-hour energy expenditure between 1 and 4 months of

age[113] and up to 50% in 8- to 12-year-old children. A mean PAL value of 1.5 was reported in 10- to 13-year-old boys and girls. In this latter case, the variability of the 24-hour energy expenditure to BMR ratio is quite large, reflecting important individual differences in the amount of energy expended for activity (range 1.20 to 1.87).[114] Nonexercise activity may also significantly affect energy balance and may be—independent of volitional exercise—an important mediator of resistance to fat gain.[115] This suggests that components other than BMR and the energy cost of activity contribute modestly to the 24-hour energy expenditure of normal infants and children. However, an increase in the energy expended by these minor components (SNS activity and thermogenesis) may significantly contribute to the alteration of energy balance in disease states.

EFFECTS OF UNDERFEEDING AND MALNUTRITION

Effects on Energy Expenditure

Underfeeding healthy or obese adults results in a consistent 20 to 30% reduction in BMR and 24-hour energy expenditure expressed either in absolute terms or related to body weight, body surface area, body weight to the 0.73 power,[116] or FFM.[117] It should be pointed out that this effect has important implications for the clinical management of obesity as this compensatory change opposes the maintenance of a body weight that is different from the usual weight.[117] The decrease in BMR is rapid during the first weeks and then proceeds at a slower rate.[116,118] Thus, the initial, rapid decrease in BMR is not entirely accounted for by a corresponding loss of metabolically active tissue.[116] An analysis of fasting and semistarvation studies suggests that about 25 to 30% of the short-term decrease in BMR may be independent of the loss in lean body mass, indicating either a change in the composition of FFM or an alteration of cellular metabolism.[118] The dramatic effect of refeeding on BMR, which returns to normal within a few days without a parallel increase in body weight,[116] further supports the hypothesis that the decrease in metabolic rate during acute dietary restriction is of larger magnitude than that of tissue losses. A down-regulation of BMR might be related to the decrease in noradrenaline appearance rate[65,119] and in thyroid hormones[65,120,121] in response to fasting or semistarvation. This possibility is supported by the prevention or the reversal of the metabolic response to acute energy restriction by replacement with either levodopa or T_3.[120,121] The enhancement of the thermic response to adrenaline infusion by prior starvation is consistent with a reduction in SNS activity.[122] A decrease in SNS outflow might also explain the significant reduction in the energy cost of glucose storage observed after underfeeding normal adults for 7 days.[123] Similarly, it might account for the absence of any increase in the metabolic rate of undernourished patients exposed to mild cold. As their thermic response to adrenaline is conserved, the defect in cold-induced thermogenesis following weight loss cannot be ascribed to a decrease in tissue responsiveness. In these patients, the thermic response to mild cold is fully restored after weight gain.[124] Similar functional defects are apparent in children. Malnourished infants switched from 28°C to 24°C respond with a progressive fall in central temperature. When recovered, these infants increase their BMR by 20% in response to temperature lowering and are able to maintain their body temperature within the normal range without shivering.[125] A decrease in skeletal muscle respiration proportional to the change in BMR in malnourished infants further supports a decrease in cellular metabolism.[126] However, metabolic rate measurements in chronically undernourished children may provide results that apparently conflict with those observed during acute energy restriction in adults.

Surprisingly, BMR may be approximately normal relative to body weight and may even appear higher in those infants who are the most wasted.[127] Similar results are obtained in chronically undernourished adults. BMR related to body weight appears higher in the undernourished than in the controls, although, in absolute terms, it is significantly lower.[128] Body cell mass is reduced even in moderate deficiency, but muscle mass seems to decrease linearly with the increasing severity of undernutrition, whereas visceral cell mass shows limited changes. For instance, body fat and body cell mass are reduced by 29%, whereas muscle mass is decreased by 41% in severe undernutrition.[129] This is in general agreement with animal experiments, although a larger range in the weight change of some organs in response to nutritional manipulations may be observed.[130] Thus, taking into account the respective metabolic rate of tissues,[14] it is not surprising that BMR related to body cell mass or FFM may appear falsely high in some cases of severe malnutrition. This increase in metabolic rate related to FFM or body weight does not preclude an overall depression of tissue metabolism.[127,131] In infants, protein turnover, synthesis, and breakdown rates are significantly lower (≈ 40%) before than after recovery from malnutrition.[132] Diminished substrate cycling is observed in adults during short-term underfeeding, and the resulting decrease in both protein turnover and glucose cycling may account for about 35% of the reduction in 24-hour energy expenditure.[133] Conversely, the malnourished infants' increase in energy expenditure in response to dietary treatment is an early event,[127] concurrent with a dramatic increase in growth rate[42] and in protein turnover,[132] suggesting that it may not be entirely accounted for by the change in body composition. Fasting metabolic rate (related to body weight) during rapid growth is equal to, or even higher than,[127,131] the recovered values, a fact that further strengthens this possibility. Another way to look at the reality of metabolic rate down-regulation would be to measure the cost of growth, which might be decreased by a higher metabolic efficiency. Although an overall increase in food efficiency may exist during the early period of catch-up growth,[42] the cost of growth during recovery from malnutrition generally appears similar to that of the normal infant.[134] However, longitudinal studies may easily overlook any enhancement in metabolic efficiency if it is short-lived.[135]

Effects on Substrate Use

The classic studies of starvation showed that endogenous glucose production amounts to about 180 g/day after a few days fast, of which 80% is oxidized by the brain.[136] The bulk of gluconeogenic precursor is provided by body proteins.[136] After 5 or 6 weeks of starvation, ketone bodies have replaced glucose as the predominant fuel for brain metabolism,[137] and glucose production has decreased to about 86 g/day, of which about 50% comes from recycled lactate and pyruvate.[138] Thus, fasting endogenous glucose production relies on gluconeogenesis much earlier than previously expected,[139] and both decrease as peripheral glucose uptake diminishes. The reduced demand in gluconeogenic precursors is paralleled by a significant reduction in protein breakdown, which favors sparing of tissue proteins.[140] In parallel, there is a state of insulin resistance at both the hepatic and peripheral levels, which is restored after refeeding.[141] From the beginning, fat is the predominant fuel, the respiratory quotient falling to 0.70 by the fourth day of fasting.[136] Observations made in malnourished children are consistent with these results. Protein contributes little to total energy expenses.[142] The average daily amount of glucose oxidized is also lower, and glucose oxidation decreases more rapidly in response to fasting before recovery than after recovery,[142] which does not demonstrate, but is suggestive of, a reduction in glucose production.[136] It is striking that the reduction in urinary nitrogen output, which occurs in lean, starving adults, is proportionate to the simultaneous decrease in metabolic rate, suggesting that protein sparing may result from the general reduction in fuel use rather than from a specific fat-related mechanism.[143] In any case, protein sparing cannot be effective unless free fatty acids are available in sufficient amounts to cover energy expenditure; hence, fat stores are not depleted.[143]

Therefore, underfeeding results in a significant decrease in metabolic rate related to tissue loss and, to a lesser extent, to a reduction in the activity of the remaining tissues. This reduction in metabolic rate can be viewed as an attempt to save energy in the face of reduced intakes. However, such an economy goes far beyond the physiologic range of adaptation as it is obtained at the expense of growth and body composition. Furthermore, its only flexibility depends on the use of remaining functional tissues as a source of substrates. Thus, any interfering increase in energy demand may entirely jeopardize this precarious balance.

EFFECTS OF DISEASE STATES

The compromise achieved by malnourished infants may be imperiled in two obvious ways. The first one would be to increase energy expenditure, for example, through fever. The other one would be to disrupt the adaptation of protein metabolism by a selective increase in protein breakdown, leading to a rapid net loss of nitrogen.

Effects on Protein Metabolism

It has been known for a long time that urinary nitrogen output is dramatically increased during infection and trauma, in sharp contrast to what is observed during malnutrition. In vivo studies reveal that this is accounted for by a disproportionate increase in protein breakdown over synthesis.[144,145] However, infusion of counterregulatory hormones to healthy adults falls short of reproducing the massive 20 to 40 g/day nitrogen losses observed after trauma or thermal injury, although it does induce plasma hormone elevations typical of severe stress.[146] In contrast, peptides isolated from the plasma of patients with sepsis or trauma are able to specifically induce a dramatic increase in protein breakdown without affecting synthesis.[147,148] This specific effect on protein breakdown is reproduced in vitro by incubating muscle biopsies with the culture medium of activated macrophages, suggesting that cytokines are involved.[149] Cytokines are a large family of cellular regulators that include interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), and others. They play a pivotal role in the immune system, but their effects extend far beyond the immune cells. Each cytokine may interact with different cell types, thus exhibiting pleiotropic functions in different target cells.[150] Conversely, many different cytokines may exert the same biologic actions, a property known as redundancy. Administration of recombinant tumor necrosis factor (rTNF) or recombinant interleukin-1α (rIL-1α) to animals results in accelerated muscle proteolysis.[151,152] Chronic administration of either rTNF or rIL-1α induces muscle wasting.[151,153] Furthermore, there is a synergistic effect between TNF and IL-1 on the stimulation of proteolysis.[151] In contrast to earlier expectations, the effect of cytokines on protein breakdown is only partially abolished by inhibitors of prostaglandin E_2 synthesis.[154] Moreover, proteolysis in response to rIL-1α is not mediated by glucocorticoids.[152] In humans, administration of rTNF also results in a dose-dependent rise in the amino acid efflux from muscle,[155] confirming the central role of cytokines in disease-related protein losses. In children, rates of protein synthesis and breakdown increase markedly in response to infection. However, breakdown increases more than synthesis, leading to a net loss of nitrogen.[156] Although malnutrition blunts the response to infection, infected malnourished children have protein turnover rates twice as high as uninfected ones, the relative increase in protein breakdown resulting in a negative protein balance.[156] Increased protein breakdown was first noted in sepsis or trauma patients, but a significant change may also be observed in response to much less severe conditions, such as vaccinations,[157,158] suggesting that even mild infections are likely to offset the fragile equilibrium of undernourished children.

It should be pointed out that protein metabolism imbalance per se (ie, protein breakdown rates greater than synthesis) results in a net protein loss and thus may lead to protein deficiency.[144] Growth failure in Crohn's disease might be accounted for by such a mechanism. Growth failure is often associated with Crohn's disease[159] and may even precede symptoms. These patients have a short stature, but, in most cases, their body weight is close to the expected weight for height.[160] Obviously, their FFM is significantly lower than in age-matched controls.[161] As

growth hormone (GH) secretion is normal,[162] a search for nutritional deficiencies was undertaken. A reduction in energy intakes is noted in some reports,[163] but not all,[164,166] whereas protein intakes appear consistently within the ranges of Recommended Dietary Allowances.[163,164] Furthermore, energy losses in the feces are not different from those of normal children,[160,164] and intestinal protein losses are only slightly increased over control values.[160,164] When measured, energy expenditure related to FFM is comparable to results in matched controls.[161,165] Despite the lack of evidence in favor of nutritional deficiencies, energy supplements do result in a significant increase in growth rate,[164,166] suggesting that a nutritional deficiency is indeed responsible for growth failure in Crohn's disease. That such a deficiency could not be ascribed to an overt imbalance between intakes and needs suggests that it might result from an abnormal use of available substrates. Indeed, abnormal protein turnover rates are consistently found in these patients.[167,168] Moreover, alterations in protein metabolism are correlated with the intensity of the inflammatory syndrome[167,168] and are consistent with an increased production of TNF-α and IL-1.[169] Besides the dramatic effect of energy supplements, another line of evidence points toward a nutritional deficiency in Crohn's disease. The plasma concentration of insulin-like growth factor I (IGF-I) is significantly depressed in these patients and further correlates with growth rates.[170] Reduced plasma IGF-I concentrations, despite normal or increased circulating GH levels, are a trait of malnutrition, and measurements of IGF-I levels have been proposed as a highly efficient way of monitoring nutritional rehabilitation.[171] Of particular interest is the fact that plasma IGF-I concentration is closely correlated with protein balance in both animals and humans.[171,172] In the rat, IGF-I level is also correlated with protein intake.[173] Furthermore, low fasting IGF-I concentrations cannot be restored to normal levels by refeeding protein-free diets.[172] This is related to the direct modulation of IGF-I expression by essential amino acid availability, independently of insulin and glucocorticoid contributions.[174] Likewise, IGF-I levels in infected malnourished children are sensitive to dietary protein alterations.[175] High-protein diets result in higher IGF-I levels and improved growth rates,[175] despite the possible direct effect of some cytokines on IGF-1 expression.[176] Therefore, the decrease in IGF-I levels in Crohn's disease pinpoints the critical importance of protein metabolism in growth failure. Indeed, nutritional supplementation results in elevated IGF-I concentrations and increased growth rates.[170] Food supplements induce a significant increase in protein synthesis, which results in an increase in protein balance.[161] In contrast, nutritional support does not seem to affect the elevated breakdown rates.[167] The favorable effect of the nutritional supplements could then be accounted for by the specific induction of protein synthesis by amino acids.[177] Therefore, growth failure in Crohn's disease may be primarily related to an abnormal use of substrates, owing to an imbalance between protein synthesis and breakdown rates, the latter being specifically increased by the associated inflammatory syndrome. Reduction in food intake would exaggerate the protein debt only by further reducing the synthesis-to-breakdown ratio, whereas nutritional support compensates for the increased breakdown rates by promoting protein synthesis. Findings in rheumatoid arthritis (RA) are also consistent with a dominant effect of inflammatory syndromes on protein metabolism. RA is associated with a chronic inflammatory syndrome involving local cytokine production.[178] The immunologic response occurs in affected joints and can also be observed and monitored in peripheral blood. The circulating level of some cytokines (IL-6) is significantly correlated to the commonly used markers of inflammatory syndromes, indicating that it is related to disease activity.[179] The measurement of ^{40}K and total-body water in RA patients shows that their body cell mass (BCM) is decreased by 13% compared with controls. In addition, there is a strong dose response between RA severity and the amount of BCM adjusted for stature: the more severe the RA, the lower the BCM.[180] This difference in BCM is important in two regards: it amounts to about one-third of what is thought to be a survivable loss, and it occurs in patients with energy and protein intakes comparable to those of controls. Surprisingly, the FM measured by dual-energy x-ray absorptiometry is not very different in RA adult patients and in controls.[180,181] This last observation suggests that the covert nutritional deficiency responsible for the decrease in BCM in adults is not primarily related to energy imbalance. Alternatively, the increase in protein breakdown rates observed in these situations might account for the preferential loss in FFM,[182] particularly in muscle.[183]

A comparable increase in protein breakdown may be induced by ammonium chloride infusion to healthy volunteers,[184] an effect also found in chronic renal failure (CRF). For instance, proteolysis may be increased in children with CRF by up to threefold in relation to metabolic acidosis.[185] In contrast to cytokine-mediated protein breakdown, net proteolysis is related to changes in plasma cortisol levels, suggesting that it plays an important role in protein metabolism during metabolic acidosis.[186] It should be pointed out that the acidosis-induced increase in net proteolysis may be quite deleterious to infants and children with inherited diseases of amino acid metabolism.

Therefore, the disruption of protein metabolism regulation in the favor of breakdown, by cytokine overproduction during chronic inflammatory syndromes or by some glucocorticoid-mediated mechanisms during CRF, might well constitute an entry into severe malnutrition, independent of decreased food consumption.

Effects on Energy Expenditure and Energy Substrate Use

Obviously, fever is a common event in children. It is also an efficient way to increase energy expenditure. DuBois emphasized the striking similarity between fevers of greatly different origins by showing that metabolic rate has a much closer relationship with body temperature than with the nature of diseases. This relationship indicates that metabolic rate increases by an average 13% for each 1°C above normal temperature.[76] A comparable relationship is

found in children, resting energy expenditure increasing by about 12% for each 1°C above normal temperature.[187] For instance, during acute malaria, the mean increment in RMR is about 30%.[187,188] This would amount to a 1,200 kcal/day expenditure in a 5-year-old child, or to a 250 to 300 g/day weight loss, should the child not eat.[187] It is noteworthy that the increase in RMR for each degree of increase in temperature is positively correlated to the expected weight for height, suggesting that undernutrition blunts the RMR response to fever.[187] Although the rise in metabolic rate was first related to shivering,[76] there is some evidence that other mechanisms are operative. An endotoxin bolus delivered to healthy volunteers induces a significant pyrogenic response (+2°C in body temperature) within 90 minutes, maximal at 180 minutes, and sustained for more than 6 hours. Total-body oxygen consumption is increased by 28% at 2 hours, when body temperature is about half-maximal, and remains elevated at 6 hours. Coordinately, splanchnic oxygen consumption is increased by 64% at 2 hours and is still increased by 47% at 4 hours.[189] The increase in splanchnic oxygen extraction represents ≈ 80% of the increase in whole-body oxygen consumption at 2 hours, suggesting that shivering is not the major source of heat production at this time, although body temperature is still rising. This interpretation is consistent with the absence of increase in leg oxygen extraction at 2 hours.[189]

Both the traditional pharmacologic approach and the recent gene knockout technology stress the importance of cytokines in the development of this thermic response. However, some discrepancies persist, which may be related to cytokine redundancy and to the models used. For instance, IL-1β and IL-1 type 1 receptor knockout mice challenged with a low or high dose of lipopolysaccharide (LPS) display a thermic response similar to wild-type mice, whereas the fever, anorexia, and weight loss resulting from turpentine injection are completely abolished.[190] Similarly, the significant increase in plasma IL-6 levels observed in wild-type mice injected with turpentine is virtually absent in the IL-1β knockout mice.[191] Injection of turpentine into IL-6 knockout mice also fails to induce fever, anorexia, and weight loss.[192] All of these data support the direct implication of IL-1β and IL-6, but also TNF-α, in the induction of fever and sickness behaviors. The thermic response to LPS depends on prostaglandin synthesis as it is blocked by indomethacin, as well as by cyclooxygenase 2 or prostaglandin receptor gene disruption.[193,194] Prostaglandin receptor (subtype EP3) knockout mice fail to mount a febrile response to LPS, IL-1β, and prostaglandin E_2. The pyrogenic effect of IL-1β may also be inhibited by pretreatment with either a receptor antagonist or a monoclonal antibody to CRH.

In parallel to their effects on energy expenditure, ILs affect food intake. Chronic administration of IL-1 to rats causes persistent inhibition of feeding.[195] Strikingly, this effect is not obtained in fish oil–fed rats.[196] Anorexia induced by IL-1 is mediated by CRF,[196] melanocortin 3/4 receptors,[197] and, to a lesser extent, by prostaglandins.[198] Thus, CRF seems to modulate both aspects of energy balance regulation in the rat, that is, food intake and energy expenditure. CRF effect on energy expenditure is mediated by a stimulation of SNS outflow, as reflected by a dramatic increase in the secretion of both adrenaline and noradrenaline,[95,199] explaining that the increase in body temperature and oxygen consumption induced by experimental inflammatory syndromes may be significantly reduced by β-adrenoreceptor blockade.[200,201] Urocortin, a member of the CRF family, also increases leptin and affects mitochondrial UCPs.[202] The chronic administration of IL-1β thus induces a sustained rise in body temperature and a reduction in food intake. The simultaneous increase in energy expenditure and decrease in energy intake result in a significant reduction in body weight gain of the experimental rats compared with controls, indicating that low levels of IL-1β release, maintained over periods of several days, could be responsible for changes in energy balance during chronic infection or inflammation.[203]

Chronic cytokine overproduction also affects energy expenditure in humans. In RA, for instance, RMR adjusted for body cell mass is about 12% higher than in adult controls. Furthermore, there is a positive correlation between cytokine production and the increase in RMR, cytokine production and body cell mass accounting for about 20 and 50% of RMR variability, respectively.[180] RMR adjusted for FFM is increased by about 20% in children with systemic juvenile rheumatoid arthritis (JRA) compared with controls. As a result, they are stunted and their FFM is reduced. Oligo and polyarticular JRA children still display an 8% increase in RMR over controls.[204] Similarly, RMR is increased in stable, cystic fibrosis (CF) patients by 10 to 25% above control values,[205,206] a change that is not accounted for by the increase in the oxygen cost of breathing.[205] There is a positive relationship between RMR and TNF-α levels[207] and adrenaline levels, TNF-α accounting for about 27% of RMR variability. Contrary to RA patients, who have a significant reduction in FFM but a relatively conserved FM, in CF patients, FFM and FM are both significantly reduced.[208] Thus, besides the dramatic thermic response to infectious disease or injury, cytokines may also mediate lower-magnitude increases in metabolic rate, which might lead to a progressive depletion of energy stores if sustained for weeks or months.

Infection also induces important changes in the production or use of energy substrates. Infected patients present glucose intolerance, irrespective of the severity of the infection and of the infective agent.[209] There is a significant increase in endogenous glucose production, which is not suppressible by glucose infusion and partially accounts for the increase in plasma glucose concentration. [210] The stimulation of hepatic glucose production is principally mediated by increased levels of catecholamines and an increased glucagon-to-insulin ratio.[211] Although whole-body glucose turnover is increased, insulin ability to stimulate glucose uptake is reduced. Indeed, peripheral glucose use is impaired when compared with controls.[212,213] It is noteworthy that marked insulin resistance is present in previously healthy individuals with uncomplicated viral infections.[214] Insulin resistance is readily apparent 4 hours

after the administration of LPS to healthy volunteers.[215] The increase in glucose turnover and the peripheral insulin resistance may be partially accounted for by a sustained β_2 stimulation[216] and by the increase in free fatty acid appearance rate in infected humans and animals,[211,212] an increase related to adrenergic stimulation.[211] However, cytokines, particularly TNF-α, also contribute to insulin resistance by a direct effect on the insulin signaling cascade[217] and by increasing free fatty acid appearance rate by a stimulation of adipose tissue lipolysis[218] and a simultaneous reduction in adipocyte lipoprotein lipase activity.[219] When compared with healthy controls, fat oxidation is increased in septic patients and falls by a much lesser percentage in response to glucose and insulin.[212] Indeed, at the end of an insulin clamp, fat oxidation still contributes about 58% to the metabolic rate in the septic patients, whereas it amounts to only 23% in controls.[212] Moreover, fat oxidation rate appears to be positively related to the severity of sepsis. Despite an increase in glucose turnover, fat thus appears as a preferred calorie source during sepsis.[220] Endotoxin administration to humans induces an increase in adrenaline and cortisol levels, whereas glucagon and insulin do not change.[189] Simultaneously, there is a significant rise in free fatty acid levels. Splanchnic glucose output is also increased, and a progressive hyperglycemia ensues. The reduction in glucose use, like that observed in sepsis, is related to impaired nonoxidative glucose disposal and not abnormal glucose oxidation.[215] Increases in plasma glucose, free fatty acid turnover (126%), and fat oxidation (60%) and similar variations in hormone concentrations follow the injection of rTNF to human volunteers, further supporting the role of cytokines in the development of the metabolic response to acute infection or injury.[221] It is interesting that an increase in both free fatty acid and glycerol concentrations is also observed in CF patients despite a reduction in FM, suggesting that chronic inflammatory syndromes may result in changes in the pattern of substrate use qualitatively comparable to those observed during acute infection.

ENERGY REQUIREMENTS IN DISEASE

ENERGY

The Food and Agricultural Organization of the World Health Organization (FAO/WHO) has published detailed estimates for energy requirements in infants and children of various ages.[222] In the adult, baseline energy needs, that is, energy needed to cover the metabolic response to food and the energy cost of minor activities, are assumed to be equal to 1.35 × BMR, and the time spent sleeping is equal to BMR. This is considered a survival requirement and is of practical value only for estimating the short-term needs of inactive and dependent individuals. Otherwise, estimates should include the energy cost of various occupational activities. However, it is not possible to specify with any confidence the allowance that should be made for a desirable level of physical activity in infants and children. Thus, energy requirements from birth to 10 years have been derived from the observed intakes of healthy children growing normally.[190] Beyond 10 years, calculations are based on published BMR measurements, incremented for the cost of growth and for a cost of activity assumed to be about 1.6 × BMR.[190] Free-living measurements of 24-hour energy expenditure corrected for the energy deposited during growth show that estimated energy requirements are substantially higher than total energy expenditure.[223] Furthermore, calculated energy expenditure also exceeds the energy intakes of 10- to 17-year-old children and adolescents.[223] Clearly, the difficulties encountered in achieving an accurate prediction of the energy needs in healthy infants and children would make unrealistic any such attempt in sick children as the issue is further confused by the contradictory effects of underfeeding and disease on energy expenditure. Then the only option left is to try to identify some agreement about the range of variations in metabolic rate induced by diseases.

Studies in children with acute measles-associated underfeeding suggest that negative energy balance is related to a dramatic reduction in gross energy intake concomitant with a sustained level of energy expenditure. Metabolic rate after recovery is not significantly different from the values obtained during acute infection, although an average 20% increase would have been expected from the presence of fever.[224] The surprising stability of metabolic rate during acute infection might be accounted for by the balanced effects of underfeeding and infection. In any case, maintenance energy requirement (MER) determined at zero energy balance is 64 kcal/kg/day,[224] a figure similar to the MER of thriving immature infants.[39] In these infants, the safe level of energy intake is estimated to be between 91 and 100 kcal/kg/day, or about 1.5 × RMR,[224] compared with the 81 to 87 kcal/kg/day free-living 24-hour energy expenditure of normal infants,[223] or the average 103 kcal/kg/day estimated energy requirements for the same age group.[190] It is further possible to evaluate the consequences of sepsis and trauma on energy expenditure. Earlier measurements in adults indicated 20 to 50% increases in metabolic rate in response to severe infection or multiple trauma. Studies performed in critically ill patients without malnutrition indicate that the mean increase in fasting metabolic rate ranges between 5%[225] and 14 to 18% over predicted values.[226] This is consistent with reports comparing septic patients with matched controls and showing a 15 to 19% increase in fasting metabolic rate over normal values.[227] Comparable estimates are obtained in traumatized children. RMR peaks at 3 days after injury, representing an 8% increase over predicted values or a 14% increase over replicate measurements obtained after discharge.[228] After surgery, the mean increase in RMR over baseline reaches about 15%. In these conditions, RMR peaks at 4 hours postoperatively and returns to baseline levels by 12 hours, thus resulting in a modest overall change in metabolic rate. Furthermore, the increase in RMR is related to the nature of the surgical procedure, the maximal rise being about 5% for minor surgery and 19% for major operations.[229] A similar trend toward decreasing estimates is observed regarding the energy expenses following burn injury. RMR in burned infants is independent of burn size and of the time elapsed between burn injury and mea-

surements. Indeed, these two factors account for only 24 and 21% of the variation in RMR above predicted values, which primarily depends on body size.[230] Furthermore, β-adrenergic blockade induces a substantial decrease in RMR in severely burned children.[201] As a result, the amount of energy required to achieve energy balance may be much lower than previously estimated. Actually, caloric delivery in excess of 1.2 × RMR might only result in increased fat mass without changes in lean body mass.[231] A comparable re-evaluation of the change in metabolic rate resulting from severe head injury suggests that patients who are properly taken care of have a lower than expected increase in RMR.[232] Therefore, it is likely that an energy intake equivalent to 1.5 × BMR would meet the requirements of most septic, traumatized, or burned infants and children. That increases in RMR after trauma, sepsis, or burn injuries are somewhat comparable is consistent with the existence of common mediators. Although the increase in energy expenditure resulting from disease appears to be substantially lower than previously estimated, applying equations that were originally developed for healthy, nonhospitalized individuals to predict the energy requirements of critically ill children could result in significant errors and may lead to provision of inappropriate nutritional support.[233]

Energy Substrates and Amino Acids

Energy intake should provide glucose and fat in amounts adapted to insulin resistance and to the preferential oxidation of lipids.[234,235] Physiologic considerations also suggest that the amount of glucose infused to malnourished, uninfected patients be limited. In adults, glucose oxidation levels off at about 4 mg/kg/minute in response to increasing glucose infusion rates.[236] A similar limitation exists in 6-month-old infants, with a maximal oxidative glucose disposal rate of 12 mg/kg/minute.[237] Furthermore, this maximal oxidative disposal decreases in parallel to energy expenditure with age, amounting to about 9 mg/kg/minute at 6 years and about 6 mg/kg/minute at 10 years.[237] In the uninfected infant, glucose infusion in excess of the maximal oxidative glucose disposal rate results only in inhibiting fat oxidation, whether of endogenous or exogenous origin,[237] and may adversely affect protein metabolism and net protein deposition.[238] Thus, expecting some benefit from high glucose intakes in infected infants seems hazardous. On the contrary, glucose intakes should be lower because of the glucose intolerance. Indeed, the insulin resistance–related decrease in peripheral glucose uptake is accounted for by impaired nonoxidative glucose disposal and not by abnormal glucose oxidation.[215] Glucose intakes in the range of the physiologic endogenous glucose production of the corresponding age range are sufficient to meet the needs of glucose-requiring tissues.[239] In these conditions, the clearance of intravenous emulsions and their oxidation are enhanced in septic patients,[234] and there is no more difference in the efficiency of glucose and fat to promote nitrogen balance.[225] The other goal is to equilibrate the increased proteolysis by promoting protein synthesis. In the healthy adult, protein synthesis is primarily regulated by amino acid inflow.[177] Similarly, amino acid infusion decreases net nitrogen losses in septic patients; the higher the amino acid intake, the more rapid the effect.[240] In burned infants and toddlers, amino acid intakes in the range of 2.5 to 3 g/kg/day efficiently support recovery.[241]

The Inflammatory Syndrome: A Case for a Pharmacologic Approach

Providing nutrients may not be enough in many of these situations. Nutritional support should be aimed at avoiding unnecessary increases in metabolic rate or, better, at controlling the disease-induced increase in energy expenditure. Obviously, attention should be given to ambient temperature and humidity, particularly in infants and burn patients. Furthermore, the use of inhibitors of either cytokine expression or cyclooxygenase, as well as of blockers of SNS peripheral effects, should be considered. As glucocorticoids suppress the production and action of several cytokines as well as the production of prostaglandins, it appeared warranted to test their effects in vivo in septic patients. The results are disappointing and do not support their use in sepsis, probably because corticoids could be administered only after cytokine release.[242] The use of molecules (antibodies or receptor analogs) directed against cytokines or modulating inflammation seems to offer interesting possibilities.[243,244] Another way to curb the inflammatory response is to interfere with signal transduction in target cells through inhibitors of the cyclooxygenase. Indeed, pretreatment with ibuprofen results in the complete suppression of fever, tachycardia, and an increase in stress hormones after endotoxin injection compared with the subjects who were not pretreated, despite an identical rise in TNF in both groups.[245] Similarly, the use of β-adrenergic receptor antagonists may substantially diminish energy expenditure.[201] If these dispositions may reduce metabolic rate, in many cases, they will have little effect on the accelerated protein breakdown.

A pharmacologic intervention would be even more pressing when nutrition support fails to prevent protein losses, as is still the case in sepsis or during cancer cachexia. Animal models confirm that protein wasting is not accounted for by the effects of underfeeding in these situations,[154] thus requiring an approach other than dietary therapy. Besides their effect-boosting proteolysis, glucocorticoids have an inhibitory effect on protein synthesis,[246] which could further exaggerate cytokine-induced protein losses. Unfortunately, cyclooxygenase inhibitors seem to have only a partial and transient effect.[154] One remaining possibility is to directly inhibit cytokine production by new agents. Pretreatment with pentoxifylline inhibits TNF secretion and partially suppresses anorexia, weight loss, and muscle protein wasting in septic rats,[247] although fever, myalgia, and increased cortisol levels are unaffected in pretreated, endotoxin-injected humans.[248] However, these molecules are effective when administered prior to endotoxin or TNF injection, but little is known about their efficacy as therapeutic agents.

The other possibility is to antagonize the effects of cytokines on protein metabolism. Recombinant growth hormone (rGH) administered to postoperative patients

induces a dramatic change in nitrogen balance, despite low energy intakes.[249] Furthermore, rGH treatment is able to reverse net whole-body and skeletal muscle protein catabolism in cancer patients.[250] This positive effect has been confirmed in severe sepsis and in patients with human immunodeficiency virus–related wasting. Similarly, rIGF-I infusion to rTNF-treated animals preserves its anabolic action and induces a significant reduction in net protein losses in the face of high TNF levels.[251] It is noteworthy that decreased IGF-I levels, a common finding in acutely ill patients, may enhance protein catabolism. The protein anabolic effects of both rGH and rIGF-I may be substantially increased by using both agents simultaneously,[252] a synergy that might prevent acquired GH resistance. Although recombinant hormones are not the only agents favoring net protein synthesis, available evidence suggests that they are the best candidates to date for improving the nutritional therapy of protein-wasting inflammatory syndromes through direct pharmacologic intervention. Indeed, preliminary studies suggest that rGH treatment improves growth and clinical conditions of cystic fibrosis patients,[253] increases linear growth and lean body mass in patients with Crohn's disease,[254] may even result in a significant decrease in the Crohn's Disease Activity Index,[255] and, by and large, has substantial anabolic effects on whole-body protein and bone metabolisms in children on chronic steroid therapy.[256]

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CHAPTER 18

GASTROINTESTINAL DEVELOPMENT: IMPLICATIONS FOR INFANT FEEDING

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The survival and prognosis of the prematurely born human infant are dependent on a successful transition from the intrauterine to the extrauterine environment. This is largely a consequence of the maturation of sufficient gastrointestinal function to provide for adequate nutrition. However, the gastrointestinal tract of the premature infant and, to some extent, of the full-term infant might be unprepared to provide the requisite absorptive function. Postnatally, the developing gastrointestinal tract is uniquely adapted to the absorption of breast milk and its nutrient components; exclusion of foreign antigens, pathogens, and some xenobiotics; adaptation to the intestinal microflora; and, with the kidney, maintenance of water balance. In the full-term infant, these processes are integrated and support normal growth and development. In the preterm infant, and under conditions of clinical disease, maturational processes can be impaired; nutritional support must then be achieved by either enteral tube or intravenous feeding.

Detailed descriptions of the morphogenesis of the human gastrointestinal tract are available in standard texts. More extensive discussion of the regulation of the development of the gastrointestinal tract is provided in several reviews.[1–3] This chapter focuses on those processes that are of relevance to successful infant feeding.

The anatomic and morphologic development of the human gastrointestinal tract and liver are summarized in Table 18-1. These data indicate that maturation of form and function occurs in a genetically regulated sequence. Many essential mechanisms are mature at birth, but some, such as bilirubin conjugation and excretion, and hepatic drug metabolism, are completed only in the early postnatal period. Others develop later in the postnatal period, including

- esophageal sphincter function and motility
- gastric acid and intrinsic factor secretion
- gastric motility
- intestinal glucose absorption
- vitamin B_{12} and bile salt absorption
- synthesis of bile acids and the expansion of the bile acid pool
- secretory response to bacterial toxins

Pancreatic exocrine function is completed after approximately 6 months of age; endocrine function, characterized by insulin release after feeding, is also delayed, but not quite as long. The process of development prepares the infant for extrauterine existence and is initially integrated with the composition of breast milk.

MOLECULAR MECHANISMS OF DEVELOPMENT

The epithelium of the gastrointestinal tract is derived from the endoderm, one of three embryonic germ layers that originate during gastrulation of the embryo. Studies in model organisms such as *C. aenorhabditis elegans*, *Drosophila*, *Xenopus*, zebrafish, and mice have identified some of the critical molecular regulators of endoderm formation.[4–6] Analysis of null mice has demonstrated that transcription factors of the HNF3β and GATA families are required for initial formation of the endoderm. Recently, the transcription factor sox-17 has also been shown to be critical for the early development of endoderm in mice.[7]

Formation and regionalization of the gut tube depend on interactions between the endoderm and mesoderm.[8] The mechanisms that mediate epithelial and mesenchymal interactions during intestinal development are beginning to be identified. The signaling protein sonic hedgehog (Shh) is expressed in the endoderm at the earliest stages of gut development. Shh has been shown to induce Bmp-4, a member of the transforming growth factor (TGF-β) superfamily, and members of the *HOX* gene family, determining the regionalization of the chick gut.[9] Expression of Bmp has also been implicated in formation of the pyloric sphincter.[10] Analysis of chick and mouse development has demonstrated that expression patterns of *HOX* genes are correlated with emerging boundaries between different parts of the gastrointestinal tract.[11,12] Generation of null alleles has produced developmental abnormalities in specific regions.[13–17] Signaling via

TABLE 18-1 Developmental Milestones in the Human Fetus

Event	*Time of First Expression*
Gastrulation	Week 3
Gut tube largely closed	Week 4
Liver and pancreas buds	Week 4
Growth of intestine into umbilical cord	Week 7
Intestinal villus formation	Week 8
Retraction of intestine into abdominal cavity	Week 10
Organ formation complete	Week 12
Parietal cells detectable, pancreatic islets appear, bile secretion, intestinal enzymes detectable	Week 12
Swallowing detectable	Week 16, 17
Mature motility	Week 36

the hedgehog and Bmp pathways not only delineates boundaries between organs but also determines the concentric tissue organization in the organs.[18,19]

Recent work has confirmed the role of Shh in mammalian gastrointestinal tract development. Shh null mice develop foregut malformations, including esophageal atresia, tracheoesophageal fistula, and other abnormalities.[20] Furthermore, the transcription factors Gli2 and Gli3, which are transducers of Shh signaling, also are required. Mice in which Gli3 expression is reduced on a Gli2 null background display esophageal atresia and tracheoesophageal fistula.[21] It has also been demonstrated that mutant mice that lack Gli2 or Gli3 exhibit imperforate anus with rectourethral fistula and anal stenosis.[22] The patterning role is apparently completed by midgestation in mice because hedgehog antibody blocking experiments initiated at embryonic day 12.5 did not affect intestinal morphology. However, crypt proliferation and lipid metabolism were disrupted, indicating additional roles for Shh at later stages of development.[23]

Although the same or related signaling molecules mediate development along the gastrointestinal tract, differences in the pattern of inducing signals and possibly receptor expression patterns lead to regionalization. Microarray analysis of gene expression profiles demonstrates that the organs of the gastrointestinal tract display distinct patterns. Furthermore, the analysis identified common regulatory elements, including those for HNF1 and GATA factors, in the 5′ flanking region of genes expressed in different regions.[24] Combination of these approaches should provide a deeper understanding of the regulation of gastrointestinal development.

ESOPHAGUS

Morphogenesis and Differentiation

The esophagus can be identified as a distinct structure early in embryogenesis (4 weeks) and elongates during subsequent development relatively more rapidly than the fetus as a whole.[25] At 10 weeks gestation, ciliated columnar epithelium appears in the esophagus. Stratified squamous epithelium replaces it at around 20 to 25 weeks, a process that begins in the midesophagus and proceeds both caudad and cephalad.[26]

Hitchcock and colleagues have studied the esophageal musculature and innervation of the esophagus in fetuses of 8 to 20 weeks gestation and in infants 22 to 161 weeks of age.[27] The circular muscle is present at 8 weeks, but the longitudinal muscle does not become apparent until approximately 13 weeks gestation. In fetuses, the thickness of the muscularis externa increases linearly from 8 weeks to term (40 weeks), and then growth slows postnatally.

Neurons can be recognized concomitantly with circular muscle at 8 weeks gestation. The density of neurons peaks at 16 to 20 weeks, falls rapidly in the second trimester of pregnancy, and is reduced further toward adult levels during infancy. Numbers of ganglion cells and nerve fibers in the myenteric plexus are also maximal at 16 to 20 weeks. Their density falls with increasing gestational age to 30 weeks, when it becomes constant, despite further esophageal growth.[27]

Functional Implications

Fetal swallowing can be detected as early as 11 weeks gestation, with sucking movements seen between 18 and 20 weeks.[28] The swallowing of amniotic fluid begins very slowly, at a few milliliters per day, and increases to 450 mL per day in the third trimester.[25] In animal models, fetal swallowing defects have been correlated with failure of growth of the gastrointestinal tract, as well as with ultrastructural abnormalities.[29,30] Careful studies are not available in human fetuses; however, human infants with esophageal atresia appear to have normal gastrointestinal function after correction of their lesions.[31] The significance of morphologic changes in animals as a consequence of the exclusion of growth factors from the fetal luminal environment during development remains to be delineated.

Postnatal Development

The development of esophageal function in premature infants has been studied by several groups. It is clear from this research that maturation of esophageal motility progresses in an orderly fashion postnatally.[28,32,33] How much of this information is of direct relevance to the fetus in utero is not known. Specifically, whether reduced lower esophageal sphincter pressure, simultaneous contractions and noncoordinated peristalsis, and frequent transient lower esophageal sphincter relaxations, characteristic of the youngest preterm infants, represent merely delayed development or confer some specific adaptive advantage to the third-trimester human fetus remains to be determined.[28] In preterm infants of approximately 28 weeks gestation, the resting pressure of the lower esophageal sphincter is only 4 mm Hg. However, it rises to adult values (15 to 45 mm Hg) by 40 weeks (Figure 18-1).[32]

STOMACH

Morphogenesis

The morphologic and histologic development of the stomach is complete at term. Prenatal ultrasound examinations

have shown that the fetal stomach grows in a linear fashion from 13 to 39 weeks gestation and that the characteristic anatomic features (greater curvature, lesser curvature, fundus, body, and pylorus) can be identified by 14 weeks. Abnormal images can identify the presence of congenital anomalies. Failure to delineate the fetal stomach ultrasonographically in the second trimester indicates esophageal atresia, and an enlarged fetal stomach can herald the presence of gastric outlet obstruction or duodenal atresia.[34]

Detailed studies of the development of the mouse stomach from Karam and Leblond have established that the epithelial cells of the gastric pits arise from stem cells located in the neck region. As these stem cells divide, they produce cell populations that move upward and populations that move downward.[35] Parietal cell lineage ablation experiments suggest that the balance between parietal, pit, and zymogen cells is maintained by interactions among the cell lineages.[36] It has been demonstrated that gastrin is an important factor in the differentiation of the parietal cells, which are reduced in numbers in transgenic mice bearing either a gastrin receptor knockout or a gastrin knockout.[37,38]

Postnatal Acid Secretion

It is known that parietal cell mass is the controlling variable in the production of gastric acid and intrinsic factor in infants and children, as well as in adults, and that parietal cell mass increases with fetal weight and age.[25,39] In the first 24 to 48 hours after birth, the acid secretory response of full-term infants is relatively resistant to pentagastrin.[40–43] The intragastric pH level remains at approximately 5.5 to 7.0. Increases in gastrin responsiveness occur over the first week of life in both premature and full-term infants. Basal and pentagastrin-stimulated acid secretion double from the first to fourth week of life in preterm infants, as found previously in full-term infants.[25,44]

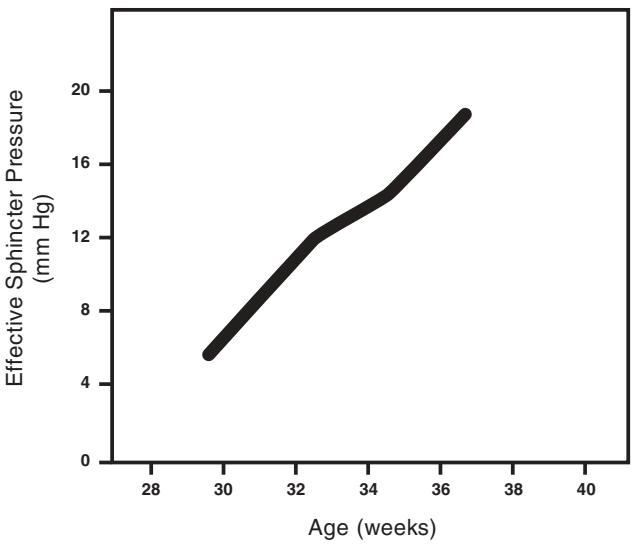

FIGURE 18-1 Lower esophageal sphincter pressure increases with gestational age in premature infants. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; drawn from data in Newell S et al.[32]

The full-term neonatal mean serum gastrin concentration is significantly elevated to levels greater than 135 pg/mL; occasional newborns have levels greater than 200 pg/mL, and some have levels greater than 500 pg/mL.[42] In contrast to these data, Harada and colleagues have shown that the newborn stomach can respond to a glucose-containing protein hydrolysate formula by increasing proton secretion twofold over that seen with glucose alone.[45] The discrepancy between this neonatal response to formula and the previously described resistance to pentagastrin requires clarification.

During the first week of postnatal life, increases in gastrin responsiveness occur. Maximal acid output is approximately at the same level as it is in children and adults by 24 weeks of life (Figure 18-2).

Intrinsic Factor

In the parietal cell, there is an interesting dissociation between the early expression of intrinsic factor and its relatively delayed secretion.[25] In studies of 8- to 29-week-old fetuses and neonates, intrinsic factor can be identified from 11 weeks onward at the base of the gastric glands in the pylorus and corpus of the stomach.[46] Secretion of intrinsic factor, however, is delayed and is correlated in a linear fashion with the capacity for hydrogen ion secretion.[39]

Both haptocorrin (R protein) and intrinsic factor have been identified in fetal gastric extracts from 18 to 25 weeks gestation, and the ontogeny of the intrinsic factor receptor (IFr) has been described.[47] The IFr has been noted throughout the small intestine and colon in 10- to 23-week-old fetuses and becomes restricted predominantly to the distal small intestine in 25-week-old fetuses.[47] This pattern strongly suggests that the proximal-to-distal gradient of IFr expression is developmentally regulated; the mechanisms responsible require further elucidation. From a functional point of view, the early expression of all components of the vitamin B_{12} entry pathway demonstrates the potential for uptake of the receptor-IF-B_{12} complex during fetal life.

A number of genetic defects in the complex mechanism for vitamin B_{12} uptake that result in symptoms early in postnatal life have been described. A juvenile form of pernicious anemia has been reported in a number of children presenting with megaloblastic anemia and developmental delay.[48] It is attributable to the absence of functional intrinsic factor, despite normal gastric acidity and mucosal morphology. A complementary DNA for intrinsic factor of both rats and humans has been cloned, and the intrinsic factor gene has been localized to chromosome 11.[49] Nevertheless, the genetic defect, which is inherited in an autosomal recessive manner, remains unidentified. Grasbeck and colleagues[50] and Imerslünd[51] independently described a syndrome consistent with an autosomal recessive selective malabsorption of vitamin B_{12}.[51] The problem lies in the transport mechanism of the intrinsic factor-Cbl complex at the level of the ileal enterocyte. Studies indicate that the disease is the result of mutation in the gene encoding the endocytic receptor cubulin.[52]

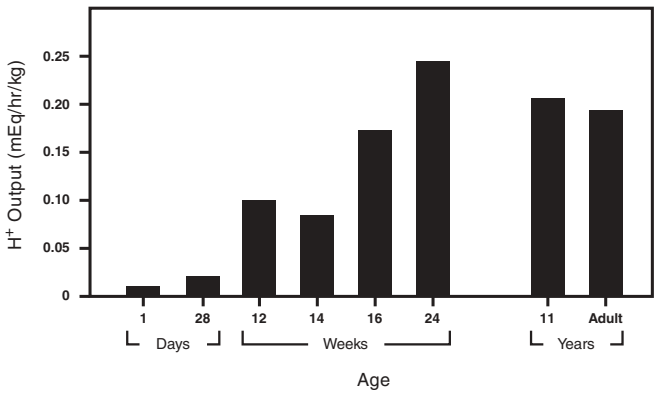

FIGURE 18-2 Maximal gastric acid secretion at birth is low and matures during the first 4 postnatal months. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; adapted from data in Grand RJ et al.[25]

Gastric Lipase

Human gastric lipase has been shown to be expressed as early as 11 weeks gestation in a fundic location and reaches adult levels by 3 months postnatally.[53] Human gastric lipase has been cloned.[54] The enzyme consists of a 379–amino acid polypeptide with a molecular mass of approximately 43 kDa (unglycosylated) and demonstrates close amino acid homology to rat lingual lipase but is unrelated to porcine pancreatic lipase. Lingual lipase plays an important role in preduodenal fat digestion in the rat, but its involvement in lipolysis in the human is now considered to be minimal.[53,55] Lingual lipase activity represents less than 0.015% of total gastric lipase activity. Detailed topographic activity mapping of gastric lipase has been performed by DiPalma and colleagues.[56] Even in the youngest subjects studied (3 months of age), gastric lipase was found only in the body of the stomach; only 5% of the fundic value was found in the antrum. Interestingly, considerable pepsin activity was identified, which did not vary with age. The levels of pepsin and lipase activities are identical in young infants and adults, indicating early complete maturation of these enzymes.[57]

Lipid comprises 40 to 50% of the total calories of human milk, and it is well known that preterm and full-term neonates have relative pancreatic insufficiency and a diminished bile acid pool compared with children and adults.[25] Accordingly, preduodenal lipolysis assumes a critical role in lipid digestion in infants.[58–61] Bile salt-stimulated lipase (BSSL) activity in human milk is capable of initiating lipolysis and yields three fatty acid moieties and glycerol when triglyceride is the substrate and the reaction is complete. Combined with gastric lipase, milk BSSL facilitates lipid hydrolysis and either prepares intraluminal lipid for further cleavage by pancreatic lipases or bypasses the need for these enzymes.[62] Milk BSSL activity decreases with the length of the gestation period, being higher in the milk of mothers delivering preterm than in those delivering at term.[63] This pattern reflects the adaptive capacity of the fetal-maternal dyad to protect neonatal nutritional status.[64,65]

Motility

The characteristics of in utero gastric motility are unknown, but data are available from very low birth weight preterm infants from 26 to 35 weeks gestation.[66] In these infants, antral motor activity was similar in preterm and term infants, although the preterm group had fewer antral clusters coordinated with duodenal clusters than term infants did. The functional implications of these patterns can be found in studies of gastric emptying of human milk and formula. Emptying half-time doubled when newborns of 28 to 34 weeks gestation were compared with full-term neonates independent of feeding.[67] When newborns of 32 to 39 weeks gestation were compared, increasing the caloric density of feedings decreased the rate of gastric emptying, as in adults, indicating that appropriate control mechanisms were already developed.[28] There are no effects of posture, temperature, or volume of feedings on the rates of gastric emptying. Isocaloric feeds of different osmolarity produce comparable rates of gastric emptying.[68,69] Dietary fat does not delay gastric emptying in the preterm infant, whether the lipid is of long or medium chain length.[68–70]

LIVER

Morphogenesis

The liver diverticulum emerges from the most caudal portion of the foregut just distal to the stomach at about the fourth week of gestation. It is first detectable as a thickening of the ventral duodenum. Hepatogenesis is initiated through an instructive induction of ventral foregut endoderm by cardiac mesoderm. A series of elegant experiments has identified a number of signaling pathways involved in the complex process of development of the liver.[3] The immediate signal is provided by fibroblast growth factors from the cardiac mesoderm that bind to specific receptors in the endoderm.[71] After formation of the liver bud, hepatocyte growth factor is required for continued hepatocyte proliferation.[72] The hepatic diverticulum grows into the septum transversum and gives rise to the liver cords, which become the hepatocytes. During this process, a combination of signals from the cells of the septum transversum, including Bmp, is necessary for liver development.[73] Endothelial precursor cells provide another critical factor for hepatogenesis.[74] Secretion of bile into the duodenum begins during the fourth month of gestation.

Biochemical Differentiation

A vast number of hepatic enzymes undergo developmental regulation during the ontogeny of hepatic function. These are beyond the scope of this chapter. Nevertheless, they have distinctive patterns that are relevant. These are shown in Figure 18-3.

Postnatal Function

The newborn depends upon the liver, gastrointestinal tract, and kidney for the excretion of bilirubin and its metabolites. Serum levels of bilirubin peak between 60 and 120 hours after birth (Figure 18-4). By 10 days of age, most

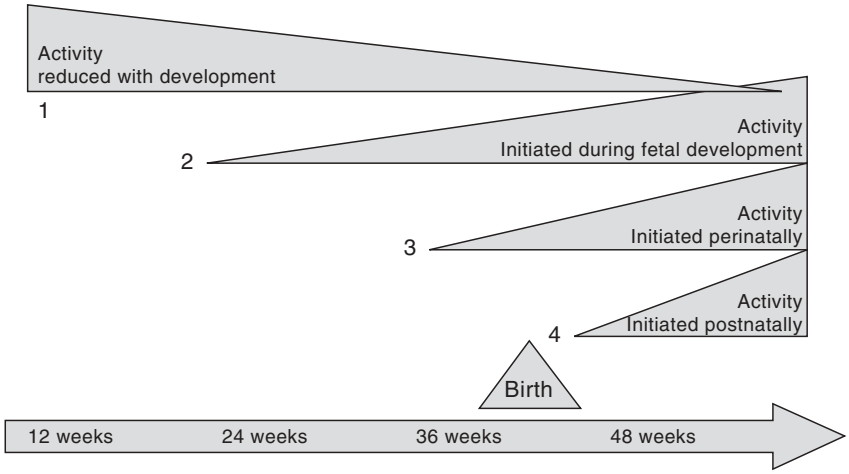

FIGURE 18-3 The quantitative pattern of enzymes in fetal human liver is significantly different from that of adult liver. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; data adapted from Greengard O. Pediatr Res 1977;11:669–76.

babies have serum bilirubin levels comparable to those of adults. The change in bilirubin concentration results from changes in metabolic pathways. There is a dramatic increase in bilirubin production, coupled with immature levels of hepatic bilirubin-uridine diphosphate (UDP) glucuronosyltransferase activity, which conjugates bilirubin and facilitates its excretion by the kidney. In addition, the hepatic uptake of bilirubin is delayed at birth and thereafter rises slowly.

The full-term infant maintains a cholic acid pool half the size of that of the adult (Figure 18-5). After birth, the cholic acid pool size increases dramatically with maturation. In the premature infant, the pool is approximately one-sixth the level it reaches in adults.[58,61,75]

PANCREAS

Morphogenesis

Morphogenesis of the human pancreas begins at about 30 days gestation. Formation of the pancreas is initiated by the emergence of dorsal and ventral pancreatic buds on opposite sides of the foregut. As these epithelial buds enlarge, a treelike ductal system develops by growth and branching. As the gut tube grows and rotates, the two pancreatic buds come together and fuse at about the seventh week of gestation. Individual endocrine cells are identifiable initially, with islets becoming established later. The molecular basis of this process is under intense study, and a number of key regulators have been identified. The homeotic gene *PDX* is essential for initiation of pancreatic development. A single-nucleotide deletion in the human gene results in pancreatic agenesis.[76] Suppression of Shh expression in the dorsal endoderm determines the location of the dorsal pancreatic bud.[77] A more detailed description of current understanding of the molecular mechanisms is presented by Slack[78] and Kim and Hebrok.[2] At approximately 20 weeks gestation, enzyme activity is detectable in the exocrine pancreas, and secretion begins at around the fifth month, with each enzyme developing in an individual pattern.[79]

Postnatal Development

Maturation of secretory function occurs during the first few postnatal months,[79,80] and the magnitude of the increase in specific activity of each pancreatic enzyme is somewhat different. For example, amylase activity in response to cholecystokinin and secretin challenge rises several hundred-fold after the first month of life (Figure 18-6). A 10-fold rise can be achieved by 1 month of age by increasing the quantity of ingested starch. Marked increases in secretory capacity are also found for proteases, lipase, fluid, and bicarbonate.[81] Delayed maturation of pancreatic function permits contact of intact intraluminal macromolecules with enterocytes, a potentially important adaptive response.[82]

SMALL INTESTINE

Morphogenesis and Differentiation

The ontogeny of the small intestine can be thought of as proceeding through three successive phases: morphogenesis and cell proliferation, cell differentiation, and cellular and functional maturation.[83] By 13 weeks gestation,

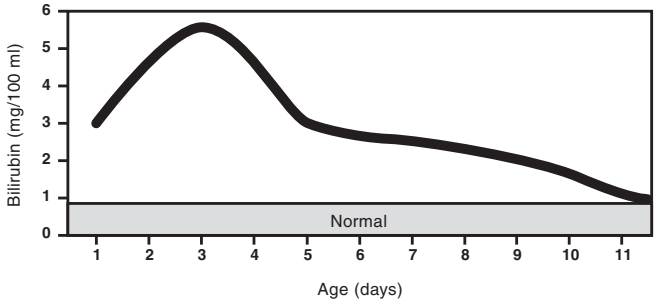

FIGURE 18-4 Physiologic jaundice in the newborn is characterized by a rise in serum unconjugated bilirubin concentration. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick.

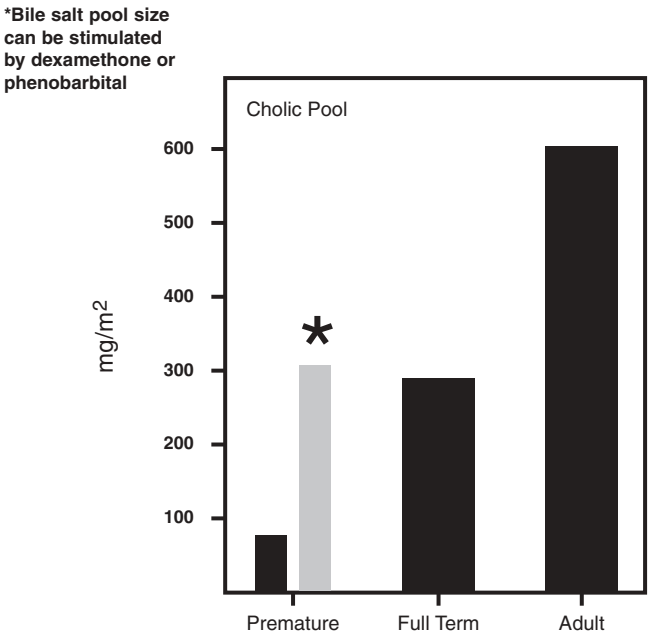

FIGURE 18-5 Cholic acid pool size is lower in premature infants than in full-term neonates or adults. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; data adapted from Watkins JB et al. Gastroenterology 1975;69: 706–13.

organogenesis of the intestine is complete.[84] Organ morphogenesis is well described in standard texts and will not be considered in detail. The major milestones are indicated in Table 18-1. New data on the process and regulation of cellular differentiation are described.

It is well established that, by morphologic and biochemical criteria, the human fetal intestine is more mature at term than that of commonly examined mammalian models. In contrast to the well-studied rodents, development of the human intestine is largely completed well before birth, at approximately the end of the first trimester of pregnancy, and by week 22, the absorptive epithelial cells resemble those of the adult intestine. Human absorptive cells at midgestation resemble those of the 5- to 15-day suckling rat, whereas the proximal human absorptive cells at 22 weeks resemble those of the weaned rat.[85]

The process of morphogenesis occurs in human fetal intestine very much as it does in the rat.[85] Mucosal remodeling and villus formation proceed in a cranial–caudal direction beginning at 9 to 10 weeks. The earliest indication is the appearance of subepithelial aggregations of mesenchymal cells associated with projections into the central lumen of the overlying stratified epithelium. Studies of mouse platelet-derived growth factor (PDGF) and PDGF receptor knockouts suggest the presence of an organizing center in the mesoderm of the nascent villi that might regulate their formation.[86] Distinctive junctional complexes appear between cells in the deeper layers of the stratified epithelium during the period of villus formation. Within the mesenchymal invaginations, smooth muscle cells and blood vessels appear as development progresses. Smooth muscle–specific protein markers have been reported in the human fetal jejunum as early as 8 weeks.[87]

There are few data on human intestinal muscle development. The available information has been reviewed by McHugh.[88] Apparent abnormalities of muscle morphogenesis in children have been reported.[89] Columnar epithelium initially lines only the apices of the developing villi but appears along the sides as the villi mature. After 10 weeks, only the intervillus epithelium remains stratified. In all levels of the stratified epithelium, mitotic figures are abundant. Occasional mitoses are seen on villi until 16 weeks, but by 10 to 12 weeks, most mitotic figures are restricted to the intervillus regions and developing crypts.

Crypts first appear as solid cords of epithelial cells but by 12 weeks display a small lumen lined by undifferentiated simple columnar cells. Between 17 and 20 weeks, the first indications of muscularis mucosa develop near the base of the crypts.[84] Little information is available on mechanisms of vascularization. Analysis of mice with a targeted gene disruption has demonstrated that a chemokine receptor is necessary for normal vascularization of the gastrointestinal tract.[90] Prior to villus formation at 9 to 10 weeks, the stratified epithelium contains undifferentiated absorptive cells, goblet cells, and enteroendocrine cells. Paneth cells are observed at the base of developing crypts at 11 to 12 weeks.

All other epithelial cell types known to occur in adult human intestine appear by the beginning of the second trimester.[84] By 12 weeks, 13 morphologically distinct types of enteroendocrine cells are identifiable.[84] In addition to the four major cell lineages, M cells, unique cells restricted to domes of epithelium overlying lymphoid follicles of maturing Peyer's patches, are present by 17 weeks.[84] Available data indicate that M cells arise from the same intestinal stem cells as the other lineages.[91] Caveolated or tuft cells are identified by 16 weeks gestation.

Because they cannot be identified prospectively, little is known about development of stem cells. At an as yet unidentified time, a small number of stem cells become established just above the base of the crypts. Whether the

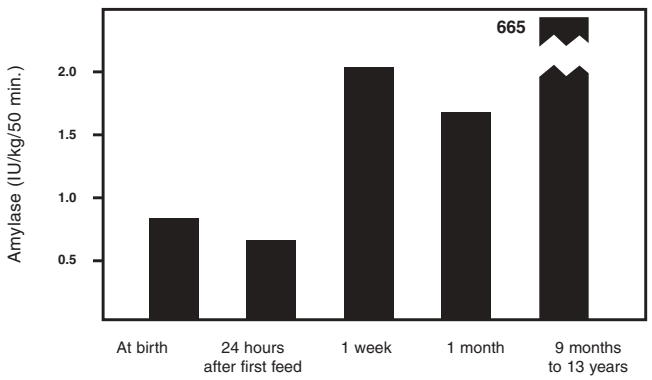

FIGURE 18-6 Pancreatic secretory function increases between infancy and childhood. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; data from Zoppi G et al. Pediatr Res 1972;6:880–6; and Hadorn B et al. J Pediatr 1968;73:39–50.

establishment of stem cells is determined by crypt formation or whether the location of stem cells directs crypt formation is unknown. In mice, expression of the transcription factor Tcf-4 is essential for maintenance of the stem cell compartment in the small intestine.[92]

The stem cells produce a transit cell population, which after additional divisions, gives rise to all of the cell lineages.[93,94] Recent experiments have identified several critical transcription factors involved in the differentiation of intestinal stem cells. Yang and colleagues demonstrated that the transcription factor Math1 is required for differentiation of stem cells into the goblet, enteroendocrine, and Paneth cell lineages but not into absorptive cells. Their data suggest that members of the Notch signaling pathway are involved in cell lineage determination.[95] Hes1 is also required for enteroendocrine cell formation in the stomach and pancreas, as well as in the small intestine. Although required for goblet cell formation in the colon, KLF4 is not required for goblet cells in the small intestine.[96] In contrast to the effects of lineage ablation in the stomach, ablation of the Paneth cell lineage in small intestine did not affect the other cell lineages.[97]

Intestinal Length

Intestinal growth in utero occurs at different rates as gestation advances. It is most rapid during the third trimester and then slows during the remainder of childhood and adolescent growth. The overall increase in length of the small intestine from the fourth to the fortieth week of gestation is approximately 1,000-fold, and, in general, the small intestine is slightly more than three times the crown–heel length of the infant or the standing height of the child or adult (Figure 18-7).

Functional Differentiation

The most extensively characterized measure of human fetal intestinal function is the activity of enzymes located on the microvillus membrane of the enterocyte.[25] Available human development data are largely descriptive; with a few exceptions, little is known of regulatory mechanisms. The regulatory regions of sucrase-isomaltase (*SI*) have been compared in rodents and humans. Three identified regulatory sites are completely conserved in humans and mice.[98] There are, however, significant differences in patterns of expression. In human intestine, SI is first detectable following intestinal morphogenesis in the first trimester of pregnancy, whereas the rodent enzyme does not appear until weaning.[99] Lactase-phlorizin hydrolase (LPH) is first detectable with intestinal morphogenesis in both human and rodent intestine. In humans, LPH remains low until shortly before birth, whereas in rodents, expression increases dramatically until reaching a peak several days after birth.[100]

Most of the enzymes measured in human fetal intestine begin to be detectable shortly after the period of morphogenesis and rise with gestational age. Proximal–distal differences in level of expression are established early. Thus, there are basic similarities in patterns of expression, as well as significant differences between human enzyme expression and the patterns in other mammals. Although important distinctions do exist, this comparison is somewhat misleading because rodents are born at a more immature stage and undergo some of the enzymatic maturation postnatally that occurs in humans prior to birth.

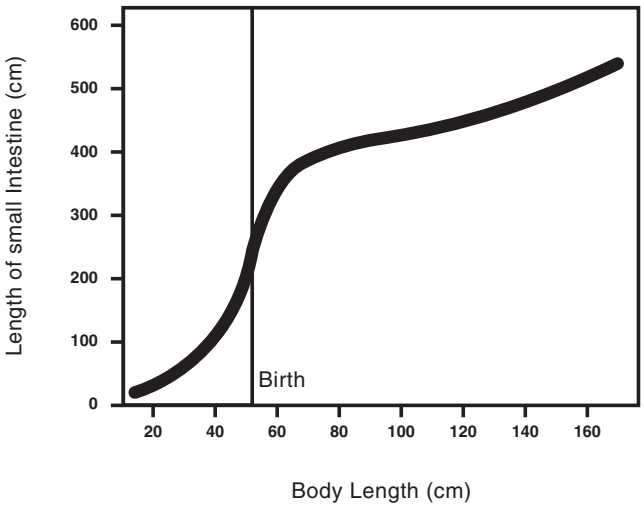

FIGURE 18-7 Intestinal elongation is rapid in utero and continues more slowly through puberty. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; data from Underhill BML. BMJ 1955;2:1243–6; Siebert JR. Am J Dis Child 1980;134:5993–5; and Weaver LT. In Walker WA, et al, editors. Pediatric gastrointestinal disease. 2nd ed. St Louis (MO): Mosby, 1996; p. 9–30.

Disaccharidases. Lacroix and colleagues correlated enzyme activity and morphogenesis in the fetal human intestine.[101] They found that SI and LPH activities were first detectable concurrent with the appearance of duodenal villi, suggesting that enzyme expression is initiated simultaneously with enterocyte formation. Immunofluorescence studies of SI confirmed that the enzyme appeared concurrent with villus formation and enterocyte maturation.[102]

Lactase-Phlorizin Hydrolase. The human *LPH* gene, located on chromosome 2q22, comprises 17 exons and covers about 70 kb, giving rise to a messenger ribonucleic acid (mRNA) of about 6 kb that encodes 1,927 amino acids.[103] The nascent protein is heavily glycosylated so that the final translation product is about 220 kDa. This high-molecular-mass glycoprotein undergoes two cleavage events and is then inserted into the microvillus membrane of the enterocyte as a mature enzyme of approximately 160 kDa.[104]

At 8 to 9 weeks, LPH is detectable in the proximal but not the distal intestine; later, up to 14 weeks, no clear-cut gradient was seen.[101] A slight jejunal peak of LPH was reported at 22 to 24 weeks by Antonowicz and Lebenthal, with the peak becoming more pronounced toward term.[105] Skovbjerg demonstrated that LPH in the human fetal small intestine is expressed at the highest level in the jejunum, with decreased activity in the proximal and distal intestine.[106] Little difference was found in jejunal LPH mRNA levels from 9 to 18 weeks gestation, but levels were considerably lower than in adult jejunum, consistent with reported measurements of

enzyme activity.[107] Villa and colleagues found a correlation between LPH enzyme activity and mRNA levels in human fetal jejunum, both at 14 to 20 weeks, when levels were low, and in a sample from a 37-week-old fetus with elevated LPH, consistent with regulation of LPH activity at the level of transcription (Figure 18-8).[108]

In agreement with previous results, they also demonstrated that hydrocortisone treatment elevated LPH activity in explants. However, they did not find a significant elevation of LPH mRNA, suggesting that corticoids do not directly regulate transcription, consistent with the lack of a glucocorticoid binding site in the first kb of the human LPH 5′ flanking region.[103] The mechanism of corticoid-induced LPH elevation and its possible role in the late-gestation surge in LPH level thus remains unresolved. Data from adult humans indicate that LPH expression is predominantly regulated by transcriptional mechanisms, although other mechanisms also play a role.[107,109–111]

It has recently been established that the proximal promoter of LPH is regulated by the combinatorial action of Cdx-2, HNF1, and GATA factors.[112–114] In addition, *HOXC11* binds to the CE-LPH element and activates pig LPH expression.[115] Analysis of the distal 5′ flanking region in transgenic mice indicates that additional distal elements are required for correct developmental and organ-specific expression.[116]

Postnatal Development

In most of the human population, a decrease in lactase activity occurs at about 5 years of age, leading to low levels in adulthood. In contrast, a minority of the human population, especially those of Northern European extraction and a few other racial groups, retains high levels of activity throughout adult life (Figure 18-9).[117] Lactase persistence is inherited as an autosomal dominant trait.[118,119] A reduction in lactase expression coincident with weaning is the general mammalian pattern. Although the primary mechanism of this decline is decreased LPH transcription, a small number of individuals with lactase nonpersistence have an abnormality in the intracellular processing of newly synthesized lactase protein.[120]

Hydrolysis of lactose to glucose and galactose on the microvillus membrane of the intestinal absorptive cells has been considered the rate-limiting step for the overall process of lactose absorption.[121] Uptake of these monosaccharides is accomplished by the sodium-dependent glucose carrier (SGLT-1; see below). When lactose is not absorbed by the small bowel, it passes rapidly into the colon as a consequence of the osmolality of the intraluminal disaccharide. In the colon, lactose is converted to short-chain fatty acids and gas (hydrogen, methane, CO_2) by bacterial flora, producing acetate, butyrate, and propionate. The short-chain fatty acids are absorbed by the colonic mucosa, and this route salvages malabsorbed lactose for energy use. This is the mechanism by which the newborn colon also salvages lactose, and the adult with low intestinal lactase activity can adapt to persistent lactose ingestion.[117] This fermentative process not only conserves nutritionally important carbohydrate but also serves as the basis of the lactose breath hydrogen test.

The results from investigations of methods for increasing maturation of intestinal lactase remain equivocal. In premature infants, trials suggest a beneficial effect of milk compared with formula feeding in stimulating an increase in the low levels of LPH in the immature intestine.[122] On the other hand, a recent study concluded that feeding low-lactose milk to premature infants improved feeding tolerance.[123]

Congenital lactase deficiency is a very rare disorder. A study in a group of Finnish patients with congenital lactase deficiency indicated a separate gene on chromosome 2 near *LPH* but distinct from it.[124] Genetic analysis in subjects with high and low lactase levels has identified several patterns of single-nucleotide polymorphisms, but whether they have functional importance in lactase expression or are simply markers remains unclear.[125] A recent report identified a single-base polymorphism 13 kb away from the *LPH* coding region that had a 100% correlation with adult lactase nonpersistence.[126] The authors suggest that the polymorphism could be functionally important in *LPH* regulation and that it might prove useful as a diagnostic tool.

Sucrase-Isomaltase The SI gene, located on chromosome 3, encodes a polypeptide of 1,827 amino acids.[127] The final form of the protein inserted into the microvillus membrane is heavily glycosylated, such that the molecular mass is around 245 kDa. Once it is inserted into the microvillus membrane, the 245 kDa form is cleaved by pancreatic proteases into its mature form, a dimeric enzyme complex in which sucrase (approximately 130

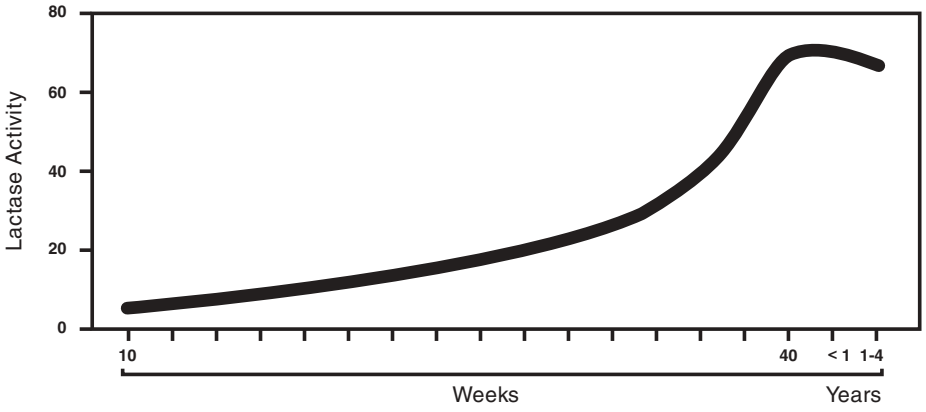

FIGURE 18-8 Small intestinal lactase activity reaches maximal levels at the end of gestation. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; data from Antonowicz I et al. Gastroenterology 1974;67: 51–8.

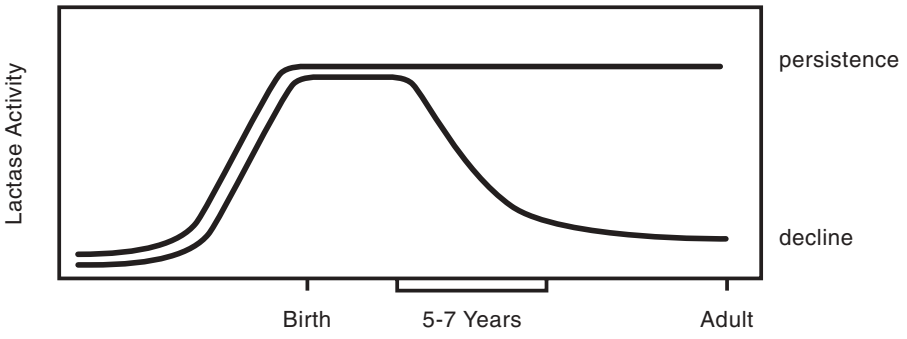

FIGURE 18-9 The genetic background of the individual determines the mature levels of lactase activity. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick.

kDa) is noncovalently linked to isomaltase (approximately 145 kDa) anchored to the microvillus membrane by a small hydrophobic anchor sequence.[128]

Similar to LPH, the proximal–distal expression of fetal SI at the earliest stages also reflects progressive proximal to distal intestinal maturation.[101] By 10 weeks, the typical pattern of a peak of activity in the midintestine is established. Over the remainder of gestation, SI levels show only a small increase.[101,105] Using polymerase chain reaction–based detection, Wang and colleagues reported SI mRNA levels to be essentially the same in fetal intestine from 9 to 18 weeks and in adult intestine.[107] Fetal SI protein from 15 to 30 weeks gestation was present in the pro-SI form, but after 30 weeks, most of the enzyme consisted of sucrase and isomaltase subunits.[129] The appearance of the subunits coincided with the beginning of enteropeptidase activity, which activates pancreatic proteases known to cleave pro-SI, at 26 weeks.[105,130]

These authors confirmed that fetal SI differs in electrophoretic mobility and lectin binding from the adult form, indicating differing carbohydrate compositions of the glycoproteins,[129] as also described by Auricchio.[131] They further showed that fetal human colon expressed the fetal form of SI until 30 weeks. A high level of SI mRNA was detected in fetal colon at 10 to 12 weeks gestation.[107] Sebastio and colleagues reported a correlation of SI mRNA and enzyme activity in human fetal intestine, indicating control at the level of transcription or mRNA stability.[132] The importance of transcriptional regulation has been well established in rodent models.[98,99,133,134]

SI deficiency is an autosomal recessive disorder characterized by undetectable levels of intestinal sucrase activity and reduced isomaltase activity. Whereas intestinal histology might show minor villous atrophy with associated malnutrition,[135] most patients with SI deficiency have normal villus architecture. The biochemical defects identified indicate that the deficiency state arises from varying allelic mutations of the *SI* gene.[136,137] At least seven different defects have been identified[136,138]:

- arrest of prosucrase-isomaltase in the rough endoplasmic reticulum (RER)
- arrest and degradation of prosucrase-isomaltase in the Golgi apparatus
- catalytically altered enzyme in the microvillus membrane and partial missorting to the basolateral membrane
- missorting to the basolateral membrane and accumulation in the RER
- intracellular loss of the sucrase subunit and expression of the isomaltase subunit at the microvillus membrane
- cleavage and secretion of the mutant sucrase
- absent immunoreactive protein

Thus, most genetic defects seem to reflect mutations in the gene, leading to changes in the primary amino acid sequence of SI.[137] The resulting mutant proteins display a broad variety of aberrant intracellular sorting or premature degradation.

SI deficiency presents at different ages.[135,139] In infancy, symptoms can occur when sucrose is introduced into the diet, with diarrhea, secondary malabsorption, and failure to thrive. In young children, chronic diarrhea can occur immediately or months after the introduction of sucrose. Because most infant formulas do not have sucrose as the primary carbohydrate, malnutrition is less commonly associated with SI deficiency.

Maltase-Glucoamylase. The third major intestinal microvillus membrane disaccharidase is maltase-glucoamylase, which hydrolyzes glucose units from the nonreducing ends of starch and dextran molecules. Less structural and functional information is available for maltase-glucoamylase than for the other disaccharidases. In the human fetal intestine, maltase activity reaches most of its normal postnatal level by week 28 of gestation, as does SI.[105] In premature infants, higher activities of glucoamylase in the colon than in the proximal intestine have been reported.[140] At the age of 1 month, glucoamylase activity is comparable to the activity in young adults.[141]

The human enzyme was recently cloned by Nichols and colleagues. A single gene located on chromosome 7 produces a 6.5 kb mRNA, which encodes a protein of approximately 210 kDa. Previous studies had demonstrated that the protein is heavily glycosylated.[142,143] The glycosylated protein forms a dimeric structure with an apparent mass of 335 kDa. Two identical catalytic sites characteristic of a family of hydrolases were identified. Although the proteins are only 59% homologous, the 6–amino acid sequence incorporating the active site aspartic acid residue in glucoamylase is identical to the active site sequences of SI, indicating that enzymatic specificity is attributable to the surrounding protein structure. In addition to the intestine,

maltase-glucoamylase transcripts were identified in granulocytes and kidney, where glucoamylase activity has been reported.[144] Little is currently known about the molecular regulation of glucoamylase expression.

Alkaline Phosphatase Brush-border alkaline phosphatase activity is detectable in fetal duodenum as early as 7 weeks gestation. It remains at low levels until 14 weeks, when it increases nearly fourfold, although it remains less than one-quarter of adult levels.[101,145] Human intestinal alkaline phosphatase is one of three isoforms, transcribed from different genes. Fetal intestinal alkaline phosphatase differs from the adult form.[146–148] Tryptic digests suggested different fetal and adult enzymes,[149] whereas sequencing of the adult and fetal forms indicates that the proteins are the same[150] but could differ in glycosylation or processing.

Peptidases Auricchio and colleagues measured the activities of five brush-border peptidases in human fetal intestine and found levels of three to be higher than those in children, whereas one was lower.[151] Cell fractionation demonstrated that all of the enzymes were predominantly microvillar rather than intracellular. There was little proximal–distal gradient, with a slight trend toward higher distal activity. The authors concluded that the full-term and preterm intestine, possibly with a few exceptions, should be able to digest peptides. As with SI, several of the peptidases were expressed as fetal forms, differing from the adult in carbohydrate composition.[152] Concurrent with villus formation, aminopeptidase was first detected at 8 weeks and increased by 14 weeks to levels comparable to those in adult intestine, when the distal segment had the highest activity.[101]

Other Enzymes Development of lysosomal enzymes was extensively analyzed by Antonowicz and colleagues, and few new human data are available.[153] There were indications of measurable enzyme activity before observable lysosomes, but Moxey and Trier reported lysosomal bodies in 9- to 10-week-old fetal intestine,[154] consistent with the initial time of appearance of lysosomal enzyme activity reported by Antonowicz and colleagues.[153]

Enterokinase Enterokinase plays a critical role in the initiation of protein digestion, activating proteolytic zymogens in the gastrointestinal tract. Antonowicz and Lebenthal were first able to detect significant levels of duodenal enterokinase activity at week 26 of gestation.[105] Activity increased gradually until term, when it was approximately one-quarter the level found in 1 year olds. Fetal duodenal activities were greater than jejunal or ileal, although much more pronounced peaks in duodenum occurred at 1 and 4 years of age. Although well-differentiated zymogen granules were detectable in the fetal pancreas by 20 weeks, tryptic activity in meconium rose markedly only after 28 weeks, suggesting that activation by enterokinase is an important determinant of tryptic activity in the fetal intestine.[105]

Transport

Hexose Transporters Hexose transport across the epithelium is one of the key functions of the small intestine. Many years ago, glucose uptake in fetal intestine was demonstrated to be present by 11 to 19 weeks gestation (reviewed by Grand and colleagues[25]). The morphologic and molecular basis of the development of human intestinal transport has been elucidated little further. The major hexose transporters in adult human intestine are the apical Na^+-coupled glucose transporter SGLT-1, the facultative glucose transporter GLUT-2 (located on the basal membrane), and GLUT-5, a high-affinity, facultative fructose transporter, located on the apical membrane of the enterocyte. Mutation of the gene encoding SGLT-1 has been shown to be responsible for glucose-galactose malabsorption, which can result in fatal diarrhea of newborn infants.[155] The disorder is inherited as an autosomal recessive trait and is attributable to the inability to absorb hexoses via SGLT-1, whereas digestion of lactose, sucrose, and maltose, as well as absorption of fructose and xylose, occurs normally.[156]

In 17- to 20-week human fetal jejunum and ileum, Malo and Berteloot demonstrated that a proximal–distal gradient of Na^+-dependent glucose transport was already established.[157] Malo presented evidence for two Na^+-dependent glucose transporters that differed in kinetic properties, as well as substrate and inhibitor specificities.[158] The relation of these fetal Na^+-dependent glucose transporters to SGLT-1 remains unclear. GLUT-5 protein has been identified immunologically on the apical membrane of human fetal small intestine, but not colon, at 16 to 25 weeks.[159] There is immunologic evidence that GLUT-2 and GLUT-5 proteins are present in fetal rat intestine prior to villus formation.[160] Rat Na^+K^+-adenosine triphosphatase has been shown to become localized to the lateral membranes in polarized cells anchored to a basal lamina as a single-layer epithelium forms, but is distributed throughout the plasma membrane of enterocytes in the stratified epithelium prior to villus morphogenesis.[161] Although likely to be similar to that in rodent models, development of transporter protein localization has not been correlated with human intestinal morphogenesis.

Glucose Absorptive Capacity in the Neonate Age-dependent increases in the rate of glucose transport continue through the first few months and up to a few years of age. Infants less than 21 months of age demonstrate a plateau in glucose absorption at approximately 0.16 g/cm/hour when studied with intraluminal perfusion techniques providing 10 g/hour. By comparison, even at sixfold higher perfusion rates, glucose absorption in adults has not reached plateau, although it has increased eightfold (Figure 18-10). These data strongly suggest that the number of glucose carriers per enterocyte increases developmentally, although the number of cells per unit area of intestine also increases. The apparent Michaelis constant (K_m) for glucose absorption in infants is 5.8 mM, compared with 20 mM or greater for adults. From a clinical point of view, these findings could explain the propensity of infants to develop loose stools or diarrhea with the ingestion of large volumes of sweetened drinks such apple juice.[162]

Amino Acid Transporters In the enterocyte microvillus membrane, at least six different amino acid transport systems have been identified.[163] Malo has characterized these

using brush-border vesicles from human fetal intestine of 17 to 20 weeks gestation.[164] Of the transport systems studied (neutral, acidic, basic, and imino classes), all were functional, and a proximal–distal gradient of transport capacity was already established by this stage of development, shortly after villus and crypt formation.

Transporter Defects

Cystic fibrosis transmembrane conductance regulator (CFTR), which functions mainly as a chloride channel, begins to be expressed in both small intestine and colon by 18 weeks gestation.[165] Mutations in CFTR represent the molecular basis of cystic fibrosis.[166]

Primary Bile Acid Malabsorption

The increasing molecular data on ileal bile acid uptake are consistent with the hypothesis of a defect in the ileal sodium-dependent transporter as a cause of chronic diarrhea, particularly if onset is early in life. The human ileal Na^+/bile acid cotransporter gene (*SLC10A2*) was cloned and used for single-stranded conformational polymorphism analysis to find possible causative mutations in a family with primary bile acid malabsorption. Mutations were identified and shown to inhibit bile acid transporter function in transfected COS cells, thus correlating mutations in a bile acid transporter with primary bile acid malabsorption.[167] Infants and children with this disorder manifest watery diarrhea, malabsorption syndrome, reduced plasma cholesterol levels, and failure to thrive.

Congenital Chloride Diarrhea

Congenital chloride diarrhea (CCD) is inherited as an autosomal recessive trait. The gene was localized to chromosome 7q31 proximal to the CFTR.[168,169] A candidate gene known as *DRA* (down-regulated in adenoma) because of its reduced expression in colonic adenoma was identified in this position. The product of this gene is expressed in the brush border of normal ileum and colonic epithelial cells.[168] *DRA* encodes a transporter with properties of Cl^-/OH^- exchange.[170] Twenty different mutations of the *DRA* gene have been identified in patients with CCD.[168]

One of the features of CCD is the fetal onset of diarrhea as evidenced by the development of maternal hydramnios.[171,172] Other clinical features can include prematurity, absence of meconium, hyperbilirubinemia, abdominal distention, and failure to thrive. Radiographic studies of newborns reveal fluid-filled intestinal loops with or without ascites, again pointing to the intrauterine onset of the disease.

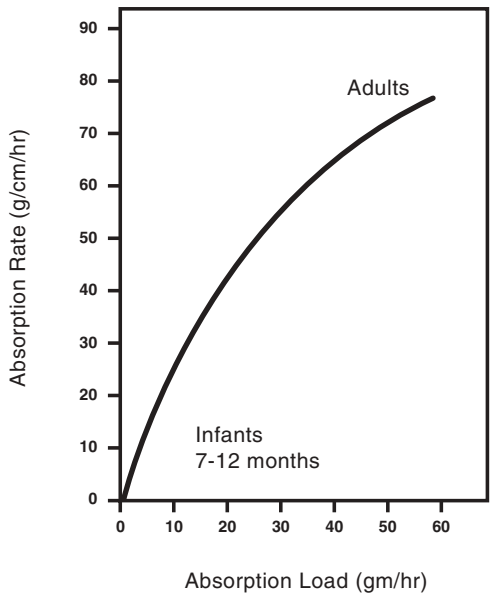

FIGURE 18-10 Glucose absorptive capacity in the neonate is lower than in children or adults. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; data from Mobassaleh M et al.[162]

Congenital Sodium Diarrhea

Four reports have described neonatal watery diarrhea ascribed to a defect in Na^+ reabsorption in the small intestine.[173–176] Several Na^+/H^+ exchanger isoforms have been cloned to date,[177,178] in particular *NHE3*, which appears to be an epithelial brush-border exchanger, confined to the intestine and kidney. However, multifocal linkage analysis of patients excludes *NHE1*, *-2*, *-3*, and *-5* as potential genes for CSD based on their chromosomal location.[176]

Lipid Digestion. Human fetal intestine at 14 to 20 weeks-gestation studied in organ culture has an increasing capacity to elaborate lipoprotein fractions, including chylomicrons, very-low-density lipoproteins, and high-density lipoproteins.[179,180] Furthermore, release of lipoproteins is modulated by both epidermal growth factor (EGF) and insulin.[179,181]

In studies of apolipoprotein B (apo B) synthesis, Glickman and colleagues found that fetal intestine synthesized only apo B-100 at 11 weeks but both apo B-48 and apo B-100 at 16 weeks, with apo B-48 predominant in mature intestine.[182] It is known that mature intestine synthesizes only apo B-48 as a result of mRNA editing. In accordance with these data, Teng and colleagues have demonstrated that the apo B mRNA editing function is developmentally regulated in the human fetus.[183]

Abetalipoproteinemia is an autosomal recessive disease characterized by the virtual absence of apo B and apo B–containing lipoproteins in plasma of affected subjects. Triglycerides accumulate in the cytoplasm of hepatocytes and enterocytes secondary to abolished secretion. Abetalipoproteinemia is not the result of defective apo B synthesis,[184–186] as initially contended, and there is no genetic linkage between the disorder and the apo B gene.[187] The phenotype is linked to a defect in the microsomal triglyceride transfer protein (MTP), a neutral lipid transfer heterodimeric enzyme composed of protein disulfide-isomerase (PDI), a ubiquitous multifunctional resident endoplasmic reticulum protein, and a unique subunit (97 kDa) that confers lipid transfer activity to the complex.

Genetic studies have been undertaken in subjects carrying the abetalipoproteinemia phenotype.[188,189] All were carriers of a homozygous or compound heterozygous

mutation on both alleles. Most subjects demonstrated a truncated form of the MTP large subunit (97 kDa), impeding its interaction with PDI and rendering the complex nonfunctional in its role of shuttling lipids between membranes of the endoplasmic reticulum.[190] The clinical expression of this disorder depends on the age of onset. Symptoms of malabsorption and failure to thrive secondary to steatorrhea are the hallmarks of early onset in infancy and childhood.[191] Poor growth can precede overt gastrointestinal symptoms, and affected children are frequently thought to have celiac disease.

Ontogeny of Motility

The innervation of the gastrointestinal tract in utero is accompanied by functional activity of increasing complexity. The first studies to measure intestinal transit in humans used amniography; aboral transport of contrast did not occur in the intestinal tract of fetuses younger than 30 weeks gestation (reviewed by Grand and colleagues[25]). With increasing gestational age, increasing aboral transit and rate of propagation developed. Subsequent studies of gastrointestinal motility in premature infants have been performed using intraluminal catheters and have been reviewed in detail elsewhere.[28] The data reveal no regular periodicity or rhythmicity in the youngest infants studied (25 weeks). Further development occurs during the next 15 weeks, so that by term, mature motor patterns are well established. Responses to feeding vary considerably among preterm infants; in general, intestinal motility studies can predict feeding intolerance.[192] For example, the rate of feeding can determine the rate of intestinal motility. Slow infusions of preterm-infant formula led to an increase in duodenal motor activity, whereas rapid bolus feedings were associated with a reduction in duodenal motor activity (Figure 18-11).[193]

The release of gastrointestinal hormones is a characteristic response to enteral feeding in humans. Even in preterm infants of approximately 33.5 weeks gestation, some gastrointestinal hormones are responsive to feeding (enteroglucagon and gastrin) within the first 2 days of life, whereas others (motilin, gastric inhibitory polypeptide, and pancreatic polypeptide) are not responsive until after 6 days of age. The plasma enteroglucagon concentration strongly correlates with the volume of milk ingested in milliliters per kilogram of body weight. Even a small intake of 15 mL/kg is associated with a threefold rise in hormone secretion. At 125 mL/kg, a maximal response is achieved; this is a volume likely to be consumed by an average-sized, breast-fed infant. Volumes as high as 250 mL/kg do not stimulate further increases in enteroglucagon concentration (Figure 18-12).[194] Seventy-five percent of the maximal rise is obtained with approximately 50 mL/kg, giving rise to the concept of "minimal enteral feeding." This hypothesis holds that intestinal maturation can be stimulated by providing regular, small-volume feedings. The adaptive value of such a regimen and the maturation of intestinal function potentially achieved have not been rigorously studied.

COLON

Morphogenesis and Differentiation

A striking characteristic of the developing fetal colon is its initial similarity to the small intestine. The development of the colon is marked by three important cytodifferentiative stages: the appearance (from about 8 to 10 weeks) of a primitive stratified epithelium, similar to that found in the early development of the small intestine; the conversion of this epithelium to a villus architecture with developing crypts (at about 12 to 14 weeks); and the remodeling of the

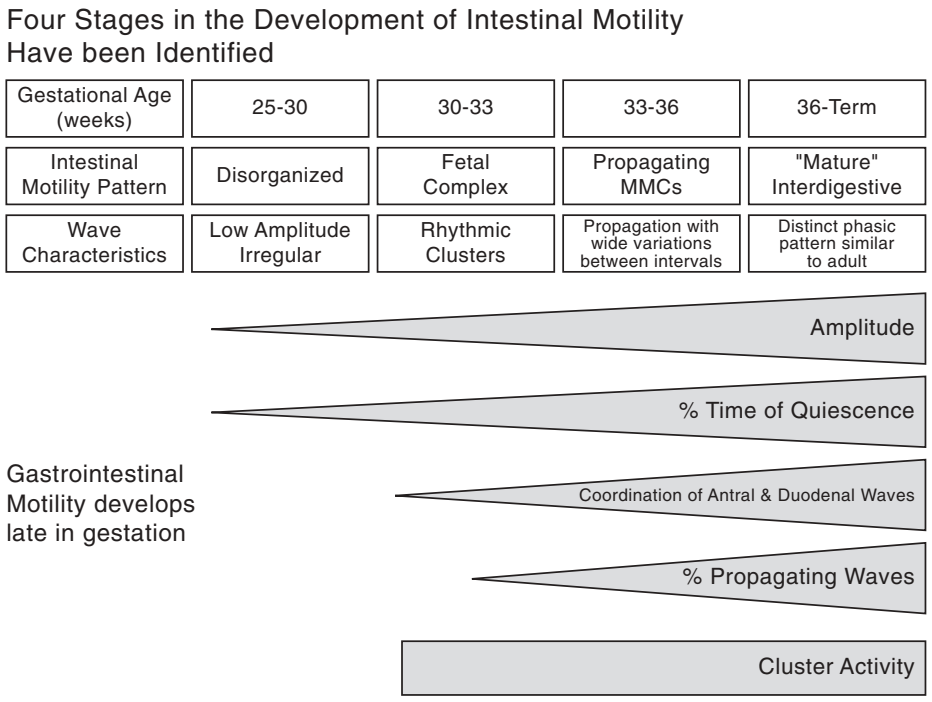

FIGURE 18-11 Four stages in the development of intestinal motility have been identified. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick; redrawn from Dumont CR, Rudolph CD. Gastroenterol Clin North Am 1994;23:655–71.

epithelium at around 30 weeks gestation, when villi disappear and the adult-type crypt epithelium is established. Immunostaining for smooth muscle β-actin was detectable in the muscularis propria at 8 weeks gestation and in the muscularis mucosae at 15 weeks.[195] The apical surface of columnar colonocytes displays enterocyte-like microvilli,[196] and glycogen stores are abundant.[197] The quantity of intracellular glycogen, as well as the number of glycogen-positive cells identified by periodic acid–Schiff staining, decreases from 13 weeks onward. From 30 to 36 weeks, very few glycogen-positive cells are found in fetal colon.[197] During malignant transformation, glycogen expression reappears and is a prominent feature of cell lines derived from human colonic adenocarcinomas.[198]

Arsenault and Menard studied the kinetics and topography of cell proliferation in explanted fetal colon from 8 to 18 weeks gestation. Cell proliferation occurred abundantly throughout the stratified epithelium. As villi formed, labeled cells were found principally in the intervillus region. At later stages, proliferation was limited to the crypts.[199] In vitro, EGF, but not hydrocortisone, altered colonic cell proliferation.[200]

Concurrent with the presence of villus morphology, the colonic epithelial cells express differentiation markers similar to those in small intestinal enterocytes. Lacroix and colleagues showed that SI was detectable at 8 weeks in fetal colon, increased 10-fold as villus architecture emerged at 11 to 12 weeks, peaked at 20 to 28 weeks, and then decreased rapidly to barely detectable levels at term.[196] Lactase was not detected in these studies, whereas alkaline phosphatase and aminopeptidase followed a pattern generally similar to that of SI.[196] Analysis of isolated fetal colonic epithelial cells demonstrated low levels of the disaccharidases typical of small intestine.[201] In addition, the fetal human colon during the second trimester can synthesize and process lipids, phospholipids, and apolipoproteins.[202,203] Data on functional development of the human colon remain sparse. Examination of premature infants suggests that sodium transport develops in the last trimester,[204] whereas anion exchange mechanisms remain immature until the end of the first year of life.[205]

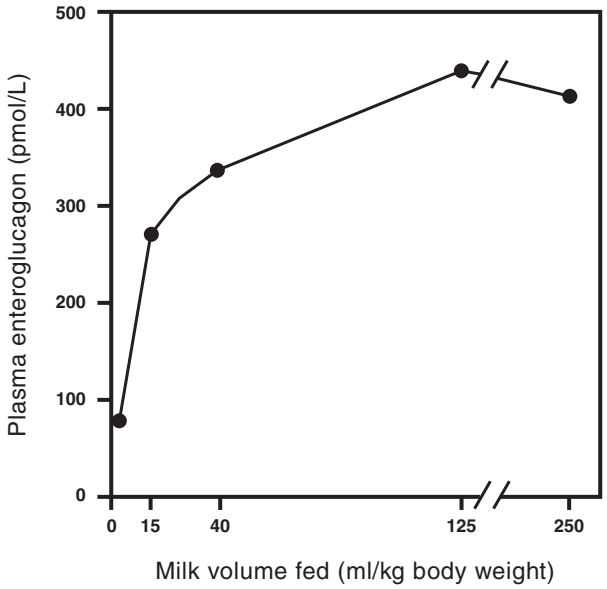

FIGURE 18-12 Gastrointestinal hormone secretion is stimulated after feeding in the newborn. Reproduced from the American Gastroenterological Association Undergraduate Teaching Project, Unit 35, Development of the Human Gastrointestinal System, with permission of the publisher and Milner-Fenwick.

CONCLUSIONS

At term, the human gastrointestinal tract exhibits essential structural and functional maturity. However, some key functions mature postnatally, including lower esophageal sphincter pressure and esophageal motility, gastric acid secretion, pancreatic secretion, some hepatic functions (such as bilirubin conjugation, hepatic drug metabolism, and bile acid synthesis), gastrointestinal motility, and the colonic bacterial fermentative pathway for salvage of carbohydrate not absorbed in the small intestine. Genetically induced alterations in the transporters and carriers that mediate the absorptive process can lead to important pediatric diseases. Further understanding of the genetic regulation of gastrointestinal function should yield insights into the pathogenesis and treatment of many such disorders.

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CHAPTER 19

IMMUNOPHYSIOLOGY AND NUTRITION OF THE GUT

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The gastrointestinal tract is the largest lymphoid organ in the body, containing an estimated 70 to 80% of the body's immunoglobulin (Ig)-producing cells.[1] It constitutes a vast surface area—400 m^2 in the adult—which daily encounters and processes a host of nutrients and antigens.[2] This system is closely linked with the immune systems of other mucosal surfaces, and together they comprise what is known as the common mucosal immune system.

Gastrointestinal immune function of human infants is immature and remains so for the first several months of life. There are several different aspects to this immaturity, including increased intestinal permeability to macromolecules, impaired oral tolerance, decreased production of secretory IgA (S-IgA), variable production of antibody to foreign proteins, and immaturity of antigen-presenting cells (APCs) and the T-helper 1 (Th1) subset of immune cells.

Studies of the intestinal uptake of macromolecules in humans and animals suggest that increased amounts of undigested molecules are taken up by the newborn compared with the adult.[3–7] This increased intestinal permeability may be protective because it allows absorption of maternal Igs from breast milk, thereby enhancing passive immunity.[8] On the other hand, it may be one of the mechanisms underlying the increased incidence of food allergies in the young infant.[9] In addition to increased permeability, the neonatal Fc receptor FcRn, expressed on the brush border of intestinal epithelial cells (IECs), aids in the transfer of passive immunity by internalizing maternal IgG.[10]

There appears to be a defect in oral tolerance in the first months of life. Miller and colleagues fed 10 neonatal rats myelin basic protein (MBP).[11] Rather than inducing tolerance, as it does in older rats, MBP feeding actually amplified subsequent immune responses to intravenously injected MBP. In human infants, administration of cow's milk–containing formula in the first 3 days of life followed by breast-feeding results in elevated IgG to β-lactoglobulin, casein, and bovine serum albumin (BSA) for up to 2 years of age compared with exclusively breast-fed infants.[12] Defective oral tolerances in the neonatal period may be antigen dependent, however. In nonobese diabetic mice, oral administration of insulin in the neonatal period suppresses the subsequent development of diabetes.[13] One factor contributing to defective oral tolerance in the neonatal period may be the deficiency of S-IgA lining the intestinal tract early in life, a deficiency that is compensated for by the provision of S-IgA in breast milk.[14,15] The production of S-IgA may contribute to oral tolerance by suppressing IgG production and dampening systemic immune responses.

In contrast to oral tolerance, neonates have increased systemic tolerance to antigen compared with older children and adults, a phenomenon known as "neonatal tolerance."[16] In addition to a decrease in T cell receptor diversity and density owing to a delay in the induction of terminal deoxynucleotidyl transferase,[17] this phenomenon appears to be attributable to a relative defect in costimulatory signals provided by neonatal APCs. Neonatal tolerance can be reversed by coculture of T cells with adult APCs or adjuvant.[18] Neonatal T cells also produce relatively low levels of the Th1 cytokines interferon (IFN)-γ and tumor necrosis factor (TNF)-α, a phenomenon that may contribute not only to tolerance but also to increased susceptibility to allergies.[19,20] This defect can also be reversed by the addition of interleukin (IL)-12, a cytokine produced by mature APCs.[21]

In premature infants, failure to produce antibodies may also contribute to impaired immunity. Rieger and Rothberg fed BSA to human newborns at different gestational ages and followed the development of anti-BSA antibodies in serum.[22] Infants born at less than 35 weeks gestation did not produce anti-BSA antibodies, whereas four of five infants born at greater than 35 weeks did. However, factors other than gestational age may be important in the development of humoral immunity. Animals raised in a germ-free environment show a striking absence of antibody-producing cells in the intestine.[23,24] Thus, age plus antigenic exposure appears to regulate the development of a normal intestinal immune response.

As the intestinal immune system matures, two functional compartments become apparent: (1) the inductive arm of the immune system composed of Peyer's patches, IgA-secreting plasmocytes, and lamina propria lymphocytes and (2) the effector arm composed of intestinal

epithelial cells, mast cells, eosinophils, macrophages, and dendritic cells. The different cell types in these two functional compartments secrete and respond to various mediators, including cytokines, adhesion molecules, growth factors, nitric oxide, prostaglandins, neurotransmitters, and hormones. These mediators are responsible for intracellular communication and the elaboration of an effective immune response.

This chapter is divided into two parts. The first part gives an overview of gastrointestinal immunology and is organized according to the different cell types participating in an immune response. The second part of the chapter addresses the interactions of different types of dietary nutrients with immunity in general and gastrointestinal immunity in particular. Where possible, it builds on concepts presented in the first part.

INTESTINAL MUCOSA

Epithelium

Intestinal Epithelial Cells IECs are highly versatile cells that have absorptive, secretory, barrier, and immune functions. The role of IECs or enterocytes as APCs has been recognized for some time.[25,26] These cells begin to express class II major histocompatibility complex (MHC) molecules shortly after birth in response to intraluminal antigenic stimulation.[26] For this reason, a state of "physiologic inflammation" has been proposed to exist in the healthy human intestine.[27]

Although IECs express class II MHC molecules, they differ from classic APCs. First, their interactions with both intraepithelial lymphocytes (IELs) and lamina propria lymphocytes involve nonclassic MHC class I–like molecules.[28–31] The intestinal nonclassic MHC class 1b molecules, CD1d, MHC class I chain-related gene A (*MICA*), the neonatal Fc receptor (FcRn), and histocompatibility leukocyte antigens (HLAs) E, F, and G are nonpolymorphic and have most likely evolved to present lipid antigens to evolutionarily conserved ligands on CD8+ T cells and natural killer (NK) cells.[32] In addition, thymic leukemia antigen, glycoprotein 180, E-cadherin, the class II invariant chain-chondroitin sulfate, and leukocyte function–associated antigen 3 can provide costimulation to IELs.[33–37] Another difference between IECs and classic APCs is their ability to present lipid and peptide but not protein antigens in a transporter-associated antigen-processing–independent manner, suggesting an intracellular antigen processing system that may share features of class I and II antigen-processing systems but may differ from both.[38] IECs were at one time thought to lack expression of costimulatory molecules present on classic APCs. However, recent data indicate that CD86 is expressed on IECs.[39]

In common with other cells of the innate immune system, IECs express toll-like receptors (TLRs). A major task of the innate immune system is to distinguish a large number of pathogens from self by recognizing unique molecules on pathogens that are not found in higher eukaryotes. These foreign molecules are called pathogen-associated molecular patterns (PAMPs) and include lipopolysaccharide (LPS) (a glycoplipid endotoxin of gram-negative bacteria), peptidoglycan (PGN) (a component of gram-positive bacteria), and unmethylated cytosine p guarine dinucleotide (CpG) dinucleotides from bacterial deoxyribonucleic acid (DNA). TLRs are part of a wider family of pattern recognition receptors. Different TLRs respond to distinct PAMPs. For example, TLR2 recognizes PGN on gram-positive bacteria, TLR4 recognizes LPS on gram-negative bacteria, and TLR9 recognizes bacterial and, possibly, host DNA.[40–42]

Although TLR-mediated signaling pathways have not been completely elucidated, it is apparent that TLR2, TLR4, and other TLRs share a common signaling cascade. The major signaling target of TLRs is the transcription factor NF-κB. Interaction of PAMPs with TLRs stimulates the adaptor molecule MyD88, which activates the IL-1 receptor–associated kinase. As a result, TNF receptor–associated factor 6 is recruited. Stimulation of these proximal signaling molecules activates the MAP kinase pathway or I-κB kinase (IKK). Activation of IKK causes I-κB phosphorylation, ubiquitination, and degradation by the proteasome, leading to NF-κB release from I-κB and its nuclear translocation (Figure 19-1).[43]

IECs express several TLRs, including TLR2, TLR3, TLR4, and TLR5.[44,45] These TLRs play an important role in innate immune responses to gastrointestinal infection. LPSs from *Helicobacter pylori* elicit proinflammatory reactions of the gastric mucosa by stimulating the TLR4 cascade in pit cells.[46] In addition, flagellin, a flagella component of *Salmonella*, activates TLR5-mediated immune responses in the intestinal epithelium.[45]

Nod2/CARD15 is a different but related pattern recognition receptor expressed on innate immune cells that was recently detected on IEC.[47] Nod2 is a leucine-rich intracellular receptor for LPS that also activates NF-κB. Nod2 is likely to play an important role in intestinal immunity because inactivating mutations have been linked to genetic susceptibility to inflammatory bowel disease.[48]

IECs have been shown to secrete cytokines and chemokines as well as present antigens and recognize pathogens. This enables them to participate directly in host defense and to recruit neutrophils to sites of inflammation. In vitro studies of IECs have demonstrated production of IL-8 in response to gastrointestinal pathogens and to stimulation by the proinflammatory agents IL-1, TNF-β, IFN-γ, or LPS.[49,50] IL-8 is an important mediator of neutrophil recruitment and adhesion in inflammatory conditions. Fractalkine is a CX3C chemokine expressed by IECs. Interestingly, IELs express the fractalkine receptor, suggesting a role for fracktalkine in IEL homing and/or activation.[51] CCL25 (thymus-expressed chemokine) is expressed on small IECs. It regulates the localization of small intestinal lymphocytes through interactions with its lymphocyte receptor, CCR9, and plays a major role in attracting IgA antibody-secreting cells to the intestine.[52] Enterocytes have also been shown to secrete the chemokines GRO-α, GRO-β, GRO-γ, extractable nuclear antigen 78, membrane cofactor protein 1, macrophage inflammatory protein 1 (MIP-1), regulated upon activation, normally T-expressed,

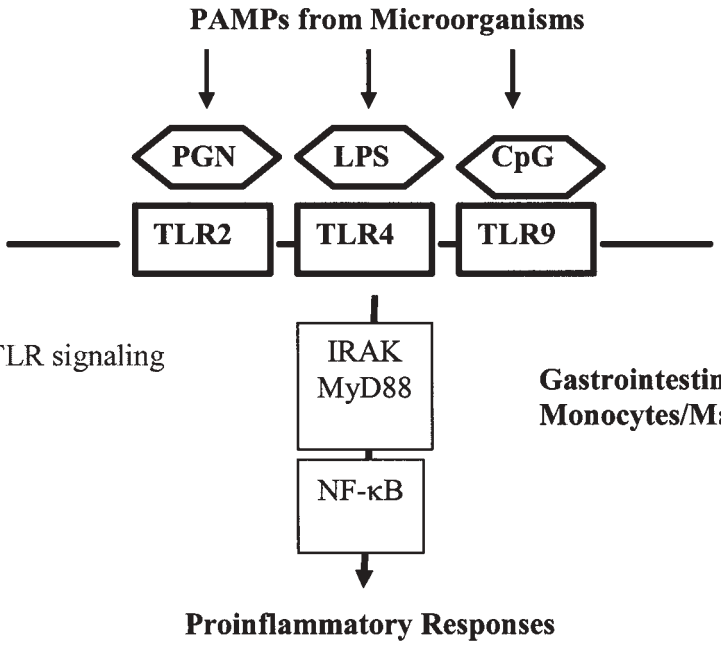

FIGURE 19-1 Pathogen-associated molecular patterns (PAMPs) such as peptidoglycan (PGN), liposaccharides (LPS), and cytosine p guarine dinucleotide (CpG) from bacteria interact with toll-like receptors (TLR) to release interleukin-1 receptor–associated kinase (IRAK), an adaptor molecule (MyD88), and transcription factor κB (NF-κB) to stimulate inflammation.

and presumably secreted (RANTES), and eotaxin and the cytokines IL-1, IL-5, IL-6, transforming growth factor (TGF)-α, transforming growth factor (TGF)-β, IL-1, and IL-10 in animal and human studies (Table 19-1).[53–56]

One of the most interesting potential roles for IECs is a thymopoietic role in the differentiation of IELs. IECs have been found to induce T cell receptor rearrangement and T-cell development from hematopoietic precursors in vitro just as thymic epithelial cells do.[57–59]

A related putative role for IEC is the regulation of CD8+ expression on IELs. Experimental data provide two interesting clues about this process. First, in bone marrow transplant models in animals, although donor cells are for the most part CD4+ cells, it is donor CD8+ cells that populate the host intestinal epithelium.[60] Second, coculture of peripheral blood lymphocytes with IECs leads to the induction of CD8+ cells.[61,62] In situations of inflammation, however, the reverse occurs with repopulation of the intestinal epithelium by CD4+ cells.[63] The molecular mechanisms governing these phenomena most likely involve the CD8 specificity of classic and nonclassic MHC class I molecules expressed on IECs.

Another important function of IECs is the creation of an effective epithelial barrier. The barrier consists of epithelial cells and the tight and adherens junctions between them as well as the mucin and S-IgA layer above the cells. Tight junctions have been shown to be fine-tuned, selectively permeable pores that are regulated both by changes in the epithelial cell cytoskeleton and by the secretion of cytokines, growth factors, and hormones in the local microenvironment.[64,65] Tight and adherens junctions are made up of a network of proteins including zona occludens 1, 2, and 3; membrane-associated guanylate kinase-related 1 (MAGI-1); occludin; junctional adhesion molecule (JAM); E-cadherin, α- and β-catenin; and members of the claudin family that are anchored to the actin cytoskeleton.[66] Tight junction permeability is regulated by members of the Par family, protein kinase C family, myosin light-chain kinase, and CDC42.[67] In addition, IFN-γ and TNF-α are known to increase intestinal epithelial permeability by increasing the leakiness of tight junctions. This leads to increased antigen uptake and increased mucosal inflammation, but it also enables the body to mount an effective secretory response and flush harmful antigens out of the gut lumen.[68] Mast cell products such as oxidants, nitric oxide, platelet-activating factor (PAF), and histamine have also been shown to increase epithelial permeability.[69,70]

Finally, enterocytes are important in the secretion of dimeric S-IgA. S-IgA plays a key role in host defense against enteric pathogens. It acts by blocking antigen bind-

TABLE 19-1 Chemokines and Cytokines Expressed by Intestinal Epithelial Cells

Proinflammatory	*Regulatory*	*Anti-inflammatory*
Fractalkine	Interleukin (IL)-7	IL-10
Granulocyte-macrophage colony-stimulating factor	IL-15	Prostaglandin E_2
	IL-18	Transforming growth factor β
IL-1	CCL9 (thymus-expressed chemokine)	
IL-8		
IL-18		
IP-10		
MIG		
MIP-2α		
MIP-3α		
Membrane cofactor protein 2		
RANTES		
Tumor necrosis factor α		

MIG = manokine induced by interferon-γ; MIP = macrophage inflammatory protein; RANTES = regulated upon activation, normally T-expressed, and presumably secreted.

ing to receptors on enterocytes.[71] IgA does not appear to neutralize antigen by activation of the complement system and/or recruitment of neutrophils; thus, compared with other immunoglobulins, it is anti-inflammatory.[72] Recently, S-IgA has been shown to be internalized by immature dendritic cells, and it may inhibit their maturation.[73] S-IgA production is sensitive to host malnutrition, which may result in impairment in the function of both B and T cells.[74] Decreased S-IgA is one of the factors that predisposes malnourished individuals to enteric infection.[75]

There are two subclasses of IgA: IgA1 and IgA2. IgA1 predominates in bone marrow, spleen, tonsils, and serum.[76,77] In mucosal tissues, the amount of IgA1 and IgA2 is approximately equal.[78] Within the mucosal immune system, IgA2 tends to predominate in the colon, whereas IgA1 predominates in oral, gastric, and proximal duodenal secretions.[76,77] Several bacterial pathogens such as *Haemophilus influenzae*, *Neisseria meningitides*, *Neisseria gonorrhoeae*, and *Bacteroides* species produce proteases specific for human IgA1, aiding in their evasion of host defenses.[79]

Intestinal Epithelial Lymphocytes Interspersed among the IECs of the intestine are specialized IELs. IELs originate in the bone marrow, migrate to Peyer's patch, and recirculate to mucosal sites (Figure 19-2). Approximately one in five cells in the jejunal epithelium is an IEL, decreasing to 1 in 20 in the colon.[80] The exact role of IELs in gastrointestinal host defense has not been completely established. However, they are unique in at least five ways. First, the majority of IELs (85 to 95%) are T cells of the suppressor/cytotoxic CD8+ phenotype.[81–84] This is in marked contrast to peripheral blood lymphocytes and lamina propria lymphocytes, which are predominantly CD4+ helper T cells. Second, the majority of IEL (as well as lamina propria lymphocytes) express T-cell activation markers not normally found on peripheral blood cells, including the αEβ7 integrin, a very late activation antigen that is the ligand for E-cadherin on IECs.[85,86] Third, despite their apparently activated state, IELs proliferate in response to mitogens but not in response to specific antigens.[87,88] In addition, they proliferate sluggishly in response to activation of CD3 T cell receptor complexes but briskly in response to CD2 ligation, suggesting an alternative activation pathway.[80,89] Fourth, a significant proportion of IELs in humans lack the CD5 molecule and express an α-α CD8 molecule, a characteristic shared by extrathymically derived cells.[87,90,91] Finally, the proportion of IELs bearing the γΔ T cell receptor (5 to 30%) is significantly higher than that observed in peripheral blood, where less than 5% have the γΔ T cell receptor.[85,92–95] Some of the implications of these unique features of IELs are discussed below.

For a long time, it was suspected that the suppressor function of CD8+ IELs could explain the lack of immune responsiveness to intraluminal antigens. Recently, the CD-α subset of IELs has been shown to mediate tolerance and to participate in dampening of inflammatory responses.[96,97] Specific molecules present on the surface of IECs or secreted from IECs enhance the production and functioning of α-α IELs, including TL (thymus leukemia) antigen, IL-2, IL-7, IL-15, and glycoprotein 180.[33,34,98]

IELs are capable of producing a variety of cytokines, including IFN-γ, TNF-α, IL-2, IL-3, IL-6, TGF-β,[80,99,100] and possibly IL-5 (Table 19-2).[101] This pattern of cytokine production may be important in the regulation of neighboring epithelial cells. For instance, IFN-γ has been shown to induce class II MHC molecule expression[102] and to stimulate polymeric Ig receptors on IECs.[103]

TGF-β is an important regulator of IEC growth and repair.[104,105] Whereas IFN-γ has been shown to increase intestinal permeability,[106] TGF-β decreases it.[107] TGF-β has immunosuppressive properties and may play a significant role in oral tolerance.[108] Weiner and colleagues examined oral tolerance to MBP as a therapeutic intervention in an experimental animal model of multiple sclerosis.[109] These investigators found that the secretion of TGF-β by T cells in both Peyer's patch and in the target organ (in this case, the brain) follows oral feeding of antigen and accompanies recovery from autoimmune disease. [101] TGF-β can induce a switch from inflammatory Th1 cells to the less inflammatory Th2 cells.[110] This may be another factor contributing to oral tolerance and overall down-regulation of immune responsiveness in the gut.

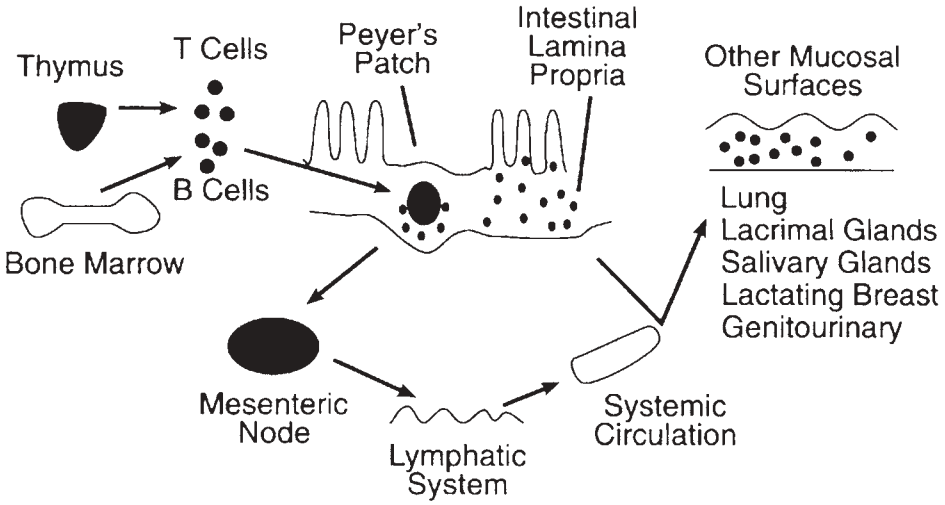

FIGURE 19-2 Intestinal lymphocytes originate in the bone marrow or thymus, migrate to Peyer's patches, and recirculate (home) to the mucosa of the intestine and other organs.

Table 19-2 Source and Effects of Cytokines in the Human Intestine

Cytokine	*Source*	*Effects*
IL-1	Macrophages Epithelial cells Endothelial cells Fibroblasts	Activates CD4+ cells, NK cells Attracts neutrophils and macrophages Increases expression of intracellular adhesion molecules (ICAM), fever
IL-2	T cells (LPL and IEL)	Induces proliferation and differentiation of antigen-stimulated T cells Induces proliferation and Ig secretion of activated B cells Activates NK cells
IL-3	CD4+ T cells Mast cells	Induces growth and differentiation of basophils
IL-4	T cells Mast cells B cells Macrophages Basophils	Induces differentiation of Ig-A-committed B cells Induces isotype switching to IgG- and IgE-producing cells in uncommitted B cells
IL-5	T cells Mast cells	Stimulates growth, differentiation, and activation of eosinophils
IL-6	T cells Macrophages Fibroblasts Endothelial cells	Induces growth and differentiation of B cells and T cells
IL-7	Unknown in gut	Activates γ-δ T cells
IL-8	T cells Fibroblasts Endothelial cells Epithelial cells Neutrophils	Induces adhesion of neutrophils to endothelial cells Activates neutrophils to secrete lysosomal enzymes
IL-10	T cells B cells Macrophages	Suppresses macrophages including production of inflammatory cytokines Enhances B cell proliferation and Ig secretion
IL-12	B cells Macrophages	Stimulates the differentiation of Th1 cells from uncommitted T cells Stimulates growth of T and NK cells
IL-13	T cells	Inhibits inflammatory cytokine production by macrophages Stimulates B cell growth and differentiation
SCF	Endothelial cells Fibroblasts	Stimulates the proliferation and maturation of mast cells
TGF-α	Macrophages Epithelial cells	Induces angiogenesis, epithelial development Induces proliferation of fibroblasts
TGF-β	T cells Fibroblasts Epithelial cells	Promotes epithelial repair Induces IgA production by uncommitted B cells Inhibits growth of mature cells Stimulates extracellular matrix production May mediate oral tolerance
TNF-α	Neutrophils Lymphocytes Endothelial cells NK cells Smooth muscle cells	Activates neutrophils and macrophages, mesenchymal and epithelial cells Causes apoptosis
IFN-γ	T cells NK cells	Modulates class II MHC expression Antiviral activity Stimulates macrophages

IEL = intraepithelial lymphocyte; IFN = interferon; Ig = immunoglobulin; IL = interleukin; MHC = major histocompatibility complex; NK = natural killer; SCF = stem cell factor; TGF = transforming growth factor; TNF = tumor necrosis factor.

In addition to cytotoxicity and cytokine secretion, IELs may play an important role in tumor surveillance. Cepek and colleagues, as well as others, have shown that IELs bind with high affinity to human colon cancer cell lines via their αEβ7 integrin receptors.[111] IELs express Fas ligand and are spontaneously cytolytic to Fas-expressing host-derived tumor cells in vitro.[112] IELs also induce apoptosis of infected and senescent IECs through the secretion of IFN-γ and TNF-α, thereby potentially reducing the risk of carcinogenesis.[113]

One of the paradoxes of gastrointestinal immunology is the observation that IELs and lamina propria lymphocytes

exist in a highly activated state as a result of continual exposure to intraluminal antigen but do not provoke either a local or a systemic immune response under normal circumstances. As mentioned earlier, the existence of a subset of suppressor or "regulatory" CD8 α-α T cells has been demonstrated. In addition, the secretion of anti-inflammatory cytokines such as IL-4 and IL-10 by Th2 cells in the lamina propria, assisted by the secretion of TGF-β by IELs and IECs, may serve to dampen the local immune response. Finally, a subset of regulatory CD4+ T cells that express the activation marker CD25 was first described in mice and has recently been shown to play a potentially significant role in the human gastrointestinal tract.[114]

Another concept central to the understanding of this paradox is the concept of T-cell anergy.[115] For T-cell activation to occur, the T cell receptor needs to bind to antigen complexed to an MHC molecule on an APC; costimulatory molecules on the surface of the T cell and the APC must interact to produce a second signal (Figure 19-3). Two of the most well characterized and important of these costimulatory molecules are CD28 and its inhibitory partner CTLA-4, expressed constitutively on 95% of CD4+ and 50% of CD8+ T cells, and B7 (CD80 and CD86), expressed on activated monocytes, dendritic cells, and activated B cells.[116–119] In the absence of B7 costimulation, T-cell anergy can result.[119] Sanderson and colleagues examined B7 (CD80) messenger ribonucleic acid (mRNA) in rat IECs and found that even when epithelial cells were stimulated with IFN-γ, B7 mRNA expression remained very low compared with that of spleen cells.[120] Paucity of B7 expression by IECs could help to explain the anergy of IELs. Deficient costimulation does not automatically translate into a quiescent immune system, however. Recent data indicate that absence of CD80 can potentiate cytotoxic CD8 T-cell responses.[121] Further, engagement of CD28 may be necessary for the subsequent expression of its inhibitor CTLA-4, an important component of regulatory T cells.[117]

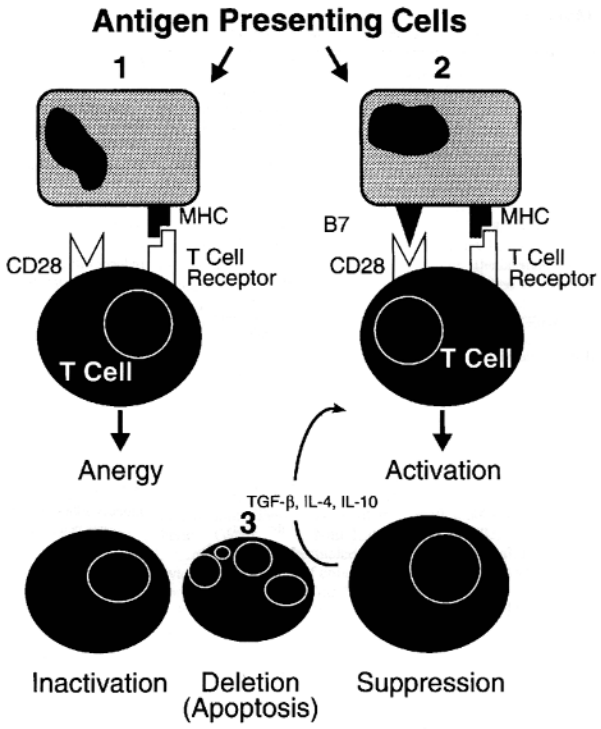

FIGURE 19-3 Immune down-regulation in the gastrointestinal tract may be mediated by (1) T-cell anergy, (2) T-cell apoptosis, or (3) the production of anti-inflammatory cytokines (transforming growth factor β [TGF-β], interleukin [IL]-4, IL-10). MHC = major histocompatibility complex.

A corollary to the concept of anergy is the concept of apoptosis or programmed cell death.[122,123] Apoptosis refers to cellular suicide characterized by internucleosomal DNA fragmentation by proteases known as caspases. Sometimes the lack of a second signal and/or exposure to noxious agents results not in anergy but in apoptosis.[124] This is one of the mechanisms by which clonal deletion of self-reactive lymphocytes occurs in the thymus.[125,126] Lamina propria T cells are known to be particularly susceptible to apoptosis, in part owing to lower levels of FLIP, an inhibitor of caspase 8.[127]

In the gastrointestinal mucosa, regulatory T cells, T-cell anergy, T-cell apoptosis, and anti-inflammatory cytokine production may all contribute to the down-regulation of the local immune system (see Figure 19-3). Conversely, release from the tight control afforded by these mechanisms may occur in conditions such as inflammatory bowel disease.

T cells bearing a T cell receptor with γ and Δ chains comprise a significant minority of all IELs and probably a majority of extrathymically derived IELs.[80] Despite a profusion of studies, the precise role of γΔ T cells in the gastrointestinal tract remains a mystery. Their predilection for epithelial surfaces throughout the body makes a role in the regulation and/or defense of epithelial cells likely.[128] Mice deficient in γΔ T cells have reduced epithelial cell turnover and decreased MHC class II expression.[129] Like other IELs, they have been shown to have a cytotoxic function[130] and to secrete IFN-γ.[99–101] Their likely role in combating infectious disease is supported by the observation that increased numbers of γΔ T cells are observed at sites of infection with certain *Listeria* and *Trypanosoma* species, mycobacteria, influenza virus, *Leishmania*, leprosy, and schistosomiasis.[100,131–138] Further, γΔ T cell–deficient mice are more susceptible to *Yersinia* infection.[139]

The relative oligoclonality of γΔ T cells in the intestinal tract suggests that they may recognize only a limited number of antigens.[140] Studies of γΔ T cells from other parts of the body have shown that these cells can recognize and bind mycobacterial and other heat shock proteins.[141] Heat shock proteins are proteins secreted by cells stressed by heat and other noxious agents, which are highly conserved across species.

In terms of activation, γΔ T cells are the least reactive IELs.[99,142,143] Further, γΔ T cells appear to be much less dependent on intraluminal antigenic stimulation than αβ T cells; they increase only modestly following birth, unlike αβ T cells, and they exist in germ-free mice.[88,144] Recent gene expression studies reveal, however, that γΔ T cells constitutively express high levels of both cytotoxicity genes and inhibitory signaling genes, suggesting that these cells are primed for rapid activation when

released from inhibition by signals, which are still as yet poorly understood.[139] In celiac disease, both αβ and γΔ T cells are significantly increased. However, the withdrawal of gluten from the diet leads to a rapid reduction in αβ IELs, whereas γΔ cells persist despite the removal of antigen.[80] This finding, coupled with the presence of γΔ cells in granulomata and granulomatous tissue,[131,138] suggests a potential role in healing.

The extrathymic origin of most γΔ T cells may have a functional significance. Most autoreactive T cell clones are deleted in the thymus. In the gut epithelium, some extrathymically derived αβ and γΔ autoreactive T cell clones exist that spontaneously secrete IL-2 in vitro.[31] As discussed earlier, these T cells are normally under stringent control by the local immune system and are anergic. Under special circumstances, however, such as the luminal presence of an exogenous superantigen like staphylococcal enterotoxin, these autoreactive T cells may be released from anergy and participate in the elimination of damaged epithelial cells.[57,145,146]

Lamina Propria

T Lymphocytes. Lamina propria (LP) T cells are Peyer's patch–derived T cells, which differentiate chiefly into CD4 Th cells under the influence of the local microenvironment.[147,148] Oral immunization with antigen appears to induce Th2 cells in the lamina propria.[149,150] Th2 cells can be distinguished from Th1 cells by their pattern of cytokine secretion, as can be noted in Table 19-3. Th1 cells secrete the proinflammatory cytokines IL-2, IFN-γ, and TNF-β, needed for microbial killing; Th2 cells secrete the less inflammatory cytokines, IL-4, IL-5, IL-6, IL-10, and IL-13, needed for B-cell help.[151] Under the influence of TGF-β, IL-4, IL-5, and IL-6 secreted by lamina propria Th2 cells, IgA-committed B cells undergo terminal differentiation into IgA-secreting plasma cells.[152–154]

LP T cells that have been primed with antigen in the Peyer's patches and mesenteric lymph nodes home back to the intestine by means of the integrin α4β7, which binds to the mucosal addressin cell adhesion molecule (MadCAM) on vascular endothelial cells.[155]

Table 19-3 Cytokine Secretion by T Helper 1 and T Helper 2 Cells

Cytokine	*T Helper 1 Cells*	*T Helper 2 Cells*
TNF-β	+	–
INF-γ	+	–
IL-2	+	–
IL-3	+	–
IL-4	–	+
IL-5	–	+
IL-6	–	+
IL-10	–	+
IL-13	–	+

IFN = interferon; IL = interleukin; TNF = tumor necrosis factor.

B Lymphocytes. It was noted earlier that S-IgA is important in intestinal host defense. The B lymphocytes of the lamina propria are important in the production of polymeric IgA as opposed to the monomeric IgA characteristic of serum IgA, which is produced in the bone marrow.[79,156,157] The IgA molecule consists of two heavy (α) and two light (K or Δ) polypeptide chains linked by disulfide chains. Polymeric IgA comprises polymers and tetramers of this molecule.[79,158] In addition, polymeric IgA contains a unique J chain, which may play a role in polymerization.[156,157] Polymeric IgA, with its J chain, is secreted from plasma cells in the intestinal lamina propria and binds to the polymeric Ig receptor on the basolateral side of IEC (Figure 19-4). The polymeric Ig receptor is composed of an Ig-like molecule known as secretory component with a transmembrane domain and a cytoplasmic tail.[158–160] Following binding, the IgA molecule with the secretory component attached is endocytosed, transported across the IEC, and secreted at the apical end into the intestinal lumen as S-IgA.[161]

Although secretory and serum IgA are normally two separate compartments of the immune system, the liver pro-

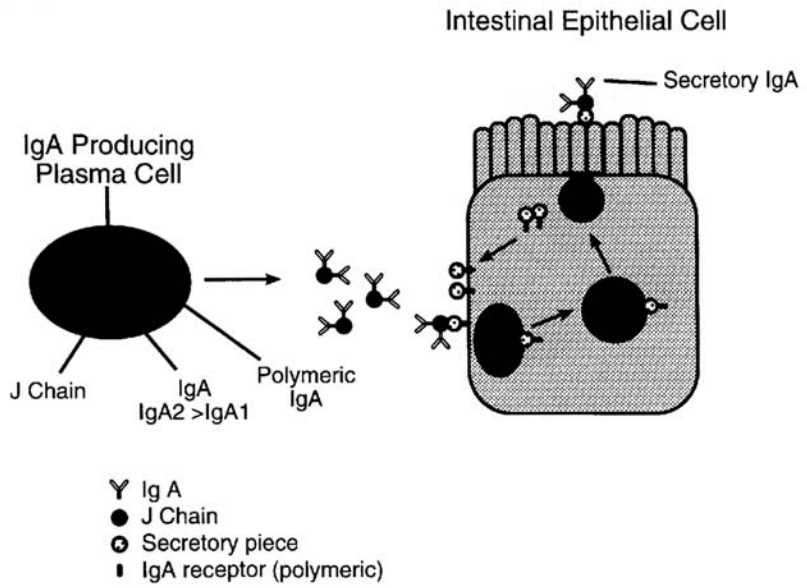

FIGURE 19-4 Secretory immunoglobulin A (IgA) is produced by IgA plasma cells in the lamina propria and is then transported to the mucosal surface by intestinal epithelial cells.

vides an interface between these two systems. Hepatocytes can bind monomeric and polymeric IgA via a sialoglycoprotein receptor (ASGP-R), which is distinct from the secretory component receptor.[162] Following binding, both serum and S-IgA may either be degraded via a lysosomal pathway or secreted into bile.[163, 164] Not only serum IgA but also bacterial antigens bound to IgA can be removed from the circulation via this mechanism.[165] Thus, hepatobiliary transport of serum IgA and immune complexes may provide a means of down-regulating systemic immune responses in a process known as "immune exclusion."[166]

Other Mucosal Cells

Mast Cells Stem cell precursors of mast cells migrate from the bone marrow preferentially to sites that border the external environment, such as the skin, respiratory mucosa, and gastrointestinal tract. Once in the skin or epithelium and under the influence of the local microenvironment, stem cells differentiate into mature mast cells. Mature mast cells are primarily involved in allergic, IgE-mediated reaction. They also play an accessory role in non–IgE-mediated immune and inflammatory responses.

There are two distinct classes of mast cells: mucosal mast cells and connective tissue mast cells, or mast cells present in the submucosa.[167] The most important growth factor for human mast cells appears to be stem cell factor, which is abundantly expressed by fibroblasts. It binds with high affinity to the c-kit receptor expressed on the mast cell membrane.[168,169] Other cytokines such as IL-3, IL-4, IL-9, IL-10, TGF-β, and nerve growth factor may play an auxiliary role in mast cell development.[168,170] The functional differences between mucosal mast cells and connective tissue mast cells are still being investigated.

Mast cells contain high-affinity receptors for the Fc portion of IgE known as Fc RI receptors. Interaction of antigen bound to IgE with these receptors results in mast cell degranulation and the release of mast cell mediators. These mediators include histamine, superoxide, leukotrienes, prostaglandins, and PAF. Many of these substances participate in type I hypersensitivity reactions with which mast cells are classically linked. Activated mast cells also release proteases such as tryptase and chymase from granules stored in the cytoplasm. These proteases cleave a wide variety of substrates, including kininogens, fibrinogen, angiotensin I, vasoactive intestinal peptide, substance P, and matrix metalloproteinases 1, 3, and 9. A wide variety of proteinase inhibitors, including secretory leukocyte proteinase inhibitor, α_1-antitrypsin, and α_1-antichymotrypsin, serve to keep this process tightly regulated. Collectively, this substrate profile supports a role for mast cells in vascular permeability, tissue and vascular remodeling, neurogenic inflammation, and allergic reactions.[168,171,172]

Mast cells also play a role in neutrophil recruitment to the intestine. In a study using murine mast cells, Ansel and colleagues showed that substance P selectively activates TNF-α mRNA expression.[173] Both substance P and mast cell–derived TNF have been shown to stimulate the expression of endothelial leukocyte adhesion molecule 1, an adhesion molecule involved in lymphocyte transmigration into tissue.[174,175]

As mentioned earlier, mast cells are important regulators of IEC permeability. Mast cell–derived histamine, nitric oxide, and TNF-α have been shown to increase epithelial permeability and induce chloride secretion. These substances have also been implicated in antibacterial innate immune responses and allergic reactions to foods.[176–178] Mast cells also mediate stress-induced increases in intestinal permeability that may play a role in irritable bowel syndrome by activating the proteinase activated receptor 2.[179]

Finally, mast cells may play a role in gastrointestinal defense against parasitic infections. An increase in both IgE and mucosal mast cells has been associated with intestinal parasitic infection in animals.[180,181] Mice with a targeted deletion of the mucosal mast cell–specific granule chymase, mouse mast cell protease 1, showed delayed expulsion of the nematode *Trichinella spiralis*.[182]

Eosinophils Eosinophils are derived from bone marrow granulocyte precursors. They are found in small numbers in the circulation but are mainly tissue-dwelling cells. Like mast cells, eosinophils are found mainly in tissues that are at the interface between the internal and external environment, including the lamina propria of the stomach, ileum, lungs, and uterus. Also like mast cells, eosinophils have been associated with allergic reactions and parasitic infection.

Eosinophils home to the gut in response to the chemokine eotaxin and mature under the influence of the cytokines IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF).[183–185] Other chemotactic factors involved in eosinophil recruitment include the eotaxin receptor CCR3; the adhesion molecules intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM); the integrins α4β7 and CD11/CD18; IL-5, leukotriene B_4, PAF, and C5.[185–190]

Once in tissue, eosinophilic degranulation can be induced by binding of Igs and PAF to IgG, IgA, IgE, Fc, and PAF receptors on the surface of eosinophils.[191–193] Eosinophilic granules contain a number of proteins that have neurotoxic, antihelminthic, and antibacterial properties. These include major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil peroxidase. In addition, eosinophils produce leukotrienes, leukotrienes C_4 and D_4, and several cytokines, including IL-3, GM-CSF, TGF-α, and TGF-β.[194–196]

Eosinophils have been implicated in host defense against intestinal parasitic infection. However, it has been shown that in mice infected with some parasites, the elimination of tissue eosinophilia with monoclonal antibody to IL-5 or genetic deletion of IL-5 had no effect on the clinical course of the infection.[197,198] In contrast, nematodes are largely susceptible to IL-5-mediated immunity.[199] Eotaxin may be necessary for containment of larval infection, whereas IL-5 may be important for expulsion of adult worms.[200]

Eosinophilia has been found in several gastrointestinal diseases, including eosinophilic gastroenteritis, cow's milk allergy, and Crohn's disease. The role of eosinophils in the

pathophysiology of these disorders has not been clearly established. For example, despite marked attenuation of eosinophilia in IL-5 mice with experimental colitis, tissue pathology and clinical course remained unchanged.[201] Eosinophilic gastroenteritis is an uncommon disorder characterized by eosinophilic infiltration of the gastric and small intestinal mucosa with subsequent inflammation, edema, and protein-losing enteropathy. Some cases have been shown to be related to specific food allergens and may respond to elimination diets, whereas others have been linked to inhaled allergens.[202,203]

Macrophages and Dendritic Cells There are at least two types of nonlymphocyte monocytes in the intestinal mucosa: macrophages and dendritic cells. Macrophages predominate in the epithelium and lamina propria, where they are involved in phagocytosis of apoptotic cells as well as antigen presentation. Their effects on the mucosal immune system depend heavily on the nature of the stimulus. They may play a proinflammatory role in response to bacterial stimuli and produce IL-12, TNF-α, and IL-6, or they may play an anti-inflammatory role after ingesting neighboring apoptotic cells and secrete anti-inflammatory cytokines such as IL-10 and TGF-β or the anti-inflammatory prostaglandin E_2.[204–206] Dendritic cells predominate in Peyer's patches, where they are involved in antigen presentation and stimulation of naive T cells. The presence of dendritic cells and macrophages appears to be necessary for optimal production of antibody by plasma cells.[207]

A profusion of research on intestinal dendritic cell biology in recent years has revealed the existence of several subclasses of dendritic cells in the intestine and the mesenteric lymph nodes. Immature dendritic cells have an activated endocytic pathway primed for uptake of antigen. They express the surface antigens CD11c, CD1a, and CCR6 and reside immediately underneath the follicle-associated epithelium in Peyer's patches in close proximity to epithelial cells expressing CCL20, the ligand for CCR6+.[208,209] Recently, dendritic cells have been shown to sample luminal antigens directly by interdigitating through epithelial tight junctions. Expression of tight junction–associated molecules on dendritic cells enables them to sample antigen without disrupting epithelial cell permeability.[210]

Dendritic cells mature in response to danger signals from bacterial antigens such as flagellin and LPS. Mature dendritic cells are CD11c+, CD83, DEC-205+, and CCR7+. They express the costimulatory molecules MHC class II, CD80, and CD86 and do not effectively phagocytose antigen. They also can secrete high levels of IL-12, which stimulates IFN-γ production in nearby Th1 cells.[208,209]

Dendritic cells can, in some instances, modulate tolerance in the intestinal mucosa. Two subsets of mature dendritic cells have been identified in Peyer's patches and mesenteric lymph nodes in rodents. Both subsets express MHC class II, OX62, CD11c, and CD80. One subset is CD4+ and OX41/SIRP alpha+ and consists of strong APCs. The other subset is CD4– and OX41/SIRP alpha– and contains remnants of phagocytosed apoptotic epithelial cells in their cytoplasm. These cells are weak APCs and may serve to down-regulate intestinal immune responses. Administration of intravenous LPS causes a rapid shift from OX41– to OX41+ dendritic cells in mesenteric lymph nodes.[211]

Peyer's Patches

Peyer's patches are collections of lymphoid follicles located in the terminal ileum, appendix, and colon. Their function is to recognize and absorb macromolecular antigens and to initiate antigen-specific mucosal immune responses; they accomplish this task largely through the induction of IgA-committed B cells. The Peyer's patches develop early in fetal life.[212] Postnatal antigenic stimulation is necessary to activate lymphoid follicles, however. The size and number of lymphoid follicles increase up to puberty, after which there is a decline.[213]

Recent studies in knockout mice have elucidated the key signaling molecules involved in the formation of Peyer's patches. Mice deficient in the IL-7 receptor, lymphotoxin-α and lymphotoxin-β, the lymphotoxin-β receptor CXCR5, and the transcription factor Id2 all fail to develop Peyer's patches.[214–219] The IL-7 receptor may up-regulate lymphotoxin signaling, which, in turn, stimulates expression of the adhesion molecules VCAM and ICAM in the organizing center of the patch.[220] Id2 appears to be necessary for the transcription of lymphotoxin. CXCR5-expressing cells are mainly B lymphocytes, which appear to be necessary for the organization of the dome epithelium and the formation of M cells, as shown by the severe reduction in follicular associated epithelium (FAE) and M cell size and number in B cell–deficient mice.[221]

Peyer's patches consist of three distinct regions: (1) an overlying dome (also known as follicle-associated) epithelium, (2) a B cell zone or germinal center, and (3) a parafollicular T cell zone.

Dome Epithelium The dome epithelium contains specialized cells known as M cells (Figure 19-5). M cells are so called because of the presence of microfolds on their luminal surface, which can be distinguished by electron microscopy from the longer, more slender, more abundant microvilli on the surface of neighboring epithelial cells.[222] The lack of microvilli and membrane-associated hydrolases is consistent with the M cell's lack of absorptive and digestive capability. The absence of a thick, protective brush border glycocalyx and goblet cells in the dome epithelium contributes to the M cell's increased accessibility to microorganisms. Because of their increased exposure to the luminal antigens, M cells have evolved to more efficiently bind and endocytose antigens and transport them to macrophages, dendritic cells, B cells, and T cells in the follicles below.[221]

How M cells recognize luminal antigen is not completely understood. These cells have been shown to adhere to and/or take up various pathogens, including the RDEC-1 strain of *Escherichia coli*, *Vibrio cholerae*, *Shigella flexneri*, poliovirus, *Salmonella typhi*, reovirus, *Campylobacter jejuni*, and mycobacteria.[223–228] In contrast, most normal gut flora are taken up little if at all. One clue to the selec-

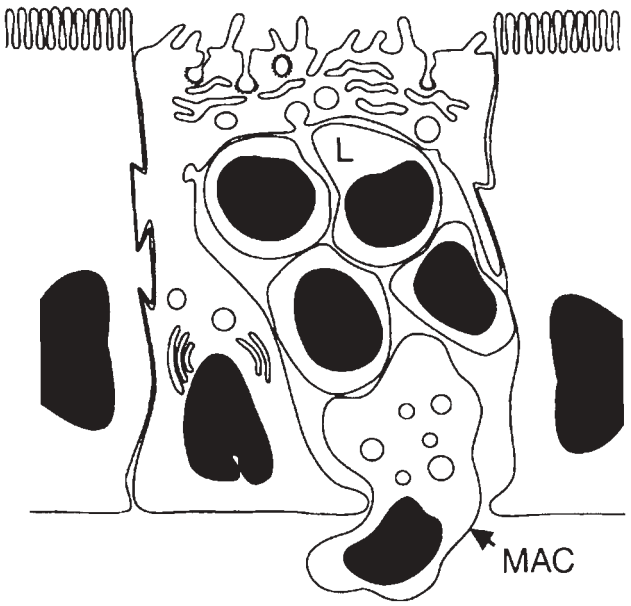

FIGURE 19-5 Diagram of an M cell. The M-cell basolateral surface is modified to form an intraepithelial packet into which lymphocytes (L) and macrophages (MAC) migrate. Antigens, microorganisms, and particles that adhere to the M-cell apical membrane are efficiently endocytosed and transported into the packet, and hence into underlying mucosal lymphoid tissue.

tive uptake of foreign antigen is the finding that there are Fc receptors for Ig on M cells and that S-IgA adheres preferentially to the apical surface of rabbit and mouse M cells.[229–231] Hence, binding of antigen-specific IgA and/or IgA-antigen complexes may prime the M cell for endocytosis of antigen.[232,233] Additionally, M cells in mice and rabbits have been shown to selectively bind sugar-specific lectins distinct from lectins bound by other enterocytes, indicating specificity of glycoconjugates on the M cell apical membrane.[234, 235] In humans, the sialyl Lewis A antigen distinguishes M cells from other IEC types.[236]

Until recently, the search for specific receptors on M cells that bind intraluminal bacteria had been fruitless. Now M cells have been shown to internalize human immunodeficiency virus (HIV) via two receptors, lactosyl cerebroside and CXCR4.[237]

B Cell Zone

Following isotype switching, IgA-committed B cells as well as primed naive T cells and dendritic cells emigrate out of Peyer's patches into mesenteric lymph nodes and travel through the abdominal and thoracic lymphatic systems into the systemic circulation (see Figure 19-2). They rapidly leave the systemic circulation and migrate to mucosal tissue (salivary, lacrimal, bronchial, mammary) until they finally return to the intestinal lamina propria near their germinal centers of origin. This process is known as homing.[238] It succeeds in educating the systemic and mucosal immune system about orally ingested antigens. Through this process, breast milk cells confer immunity to dietary and enteric bacterial antigens.[239]

The molecular mechanisms of homing are now well understood. Specialized receptor molecules on lymphocytes, known as "homing receptors," direct lymphocytes to specific tissue sites.[240] At their destination, lymphocytes recognize and bind to tissue-specific adhesion molecules on vascular endothelium, known as "vascular addressins."[241] Vascular addressins are expressed on high endothelial venules (HEVs), specialized endothelial cells in postcapillary venules. Ligation of homing receptors to vascular addressins permits the migration of lymphocytes from the circulation into tissue (Figure 19-6).

In the gastrointestinal tract, a tissue-specific lymphocyte homing receptor, known as the $\alpha 4\beta 7$ integrin or lymphocyte Peyer's patch HEV adhesion molecule (LPAM-1), has been characterized.[242] It has been shown to bind to MAdCAM 1, a vascular addressin expressed in Peyer's patches, the lamina propria of the small and large intestine, and the lactating mammary gland. Other lymphocyte adhesion molecules of the integrin and selectin family bind gut mucosal cells with less specificity but may assume an important role in inflammatory conditions. Successful experimental attempts to block gut inflammation in animals by blocking the adhesion molecules $\alpha 4$ and $\beta 7$ integrins with monoclonal antibodies have shown therapeutic promise.[243,244]

Parafollicular T Cells

The majority of Peyer's patch T cells are CD4+ Th cells located in the interfollicular zones around the germinal center.[147] One of the major functions of these cells may be to help the germinal center B cells with the process of isotope switching from immature IgM-bearing cells to IgA-committed cells.[245] Dendritic cells also participate in this process.[246]

Cytokines secreted by Peyer's patch Th cells have been shown to regulate different steps in IgA production. TGF-β is a major switch factor in isotype switching.[247] It induces IgA production in B cells by inducing the binding of downstream transcription factors, Smad, AML, and ets, to promoter elements upstream of the IgA1 and IgA2 switch regions.[248,249] The interaction of costimulatory molecules on the surface of B cells and T cells, such as CD40 and CD40 ligand, may also be required for isotype switching.[250] TGF-β secreted by B cells may be a downstream effector of CD40 ligation.[251] Recent data implicate activation-induced cytidine deminase, a member of the cytidine deaminase family that is induced by TGF-β, IL-4, and CD40 ligand stimulation of B cells in isotype switching. This gene appears to regulate DNA repair genes that carry out the final steps of class switch recombination.[252,253] Once isotype switching has occurred, IL-4, IL-5, IL-6, and IL-10 all can amplify the production of S-IgA in IgA-committed cells (Table 19-2; see also Chaper 6).[254,255]

NUTRITION

An increasingly large number of dietary components have been found to alter immune function. Dietary factors

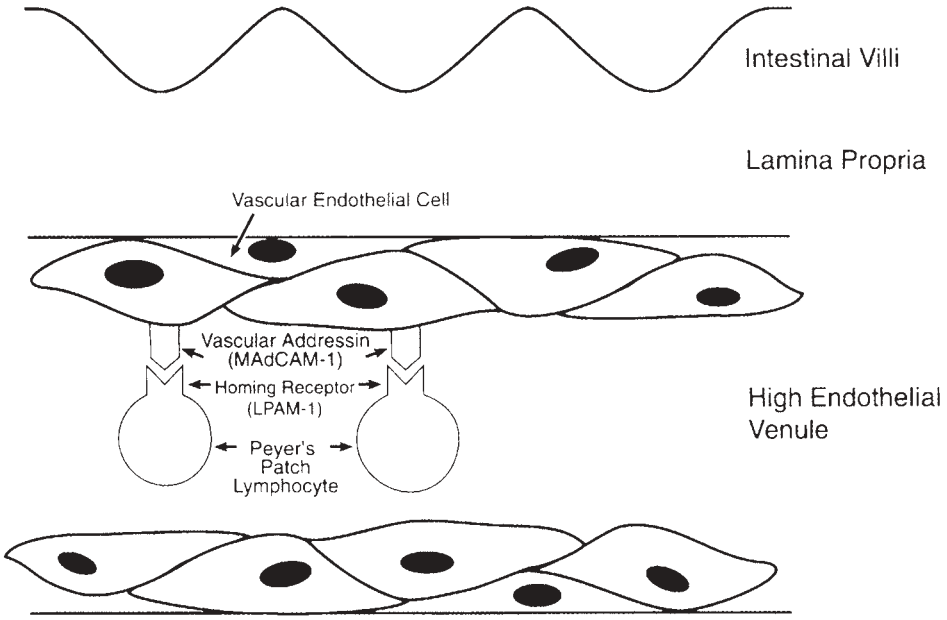

FIGURE 19-6 Homing receptor and vascular addressin interactions in the gastrointestinal tract: PP lymphocytes in the circulation attach to vascular addressins on vascular endothelial cells in high endothelial venules in the lamina propria and then transmigrate into the lamina propria.

known to influence outcome by producing a pharmacologic effect rather than correcting or preventing a simple deficiency include proteins, glutamine, arginine, lipids, nucleotides, vitamins, and the metals zinc, copper, and iron.[256] Nutritional therapy using disease-specific formulations or supplements is an old idea now assuming increasing importance (see Table 19-4; see also Chapter 6).

MALNUTRITION

Malnutrition is not a discrete, all-or-none phenomenon but rather an entity that spans an entire spectrum, ranging from subclinical malnutrition to lethal nutritional deficiency states. It is now recognized that a pure deficiency of a single nutrient rarely occurs. Vitamin and mineral deficiencies accompany those of protein and calories, and, more importantly, there are interactions among these deficiencies. Protein-calorie malnutrition (PCM) may be classified as primary or secondary. Classically, children with primary malnutrition have an inadequate nutrient intake. Secondary malnutrition is present when nutrient intake appears adequate, but nutrient needs and/or losses are excessive as a result of a primary disease state. Malnutri-

Table 19-4 Comparison of Formula Products with Potential Immune-Enhancing Qualities[1]

	*Alitra Q**	*Crucial*†	*Immun-Aid*‡	*Impact*§[2]	*Perative**	*Replete*†[3]	*Vivonex TEN*§	*Vivonex Plus*§
Cal/cc	1.0	1.5	1.0	1.0	1.3	1.0	1.0	1.0
Protein (g/L)	52.5	62.5	37	56	66.6	62.5	38	45
Fat (g/L)	15.5	67.6	22	28	37.4	34	2.8	6.6
Carbohydrate (g/L)	165	135	120	130	177.2	113.2	205	190
Immunonutrients added								
Glutamine (g/L)	14.2	7.2	9.0	11.8	—	5.6	4.9	10.0
Arginine (mg/L)	4.5	15.0	15.4	14.0	8.1	2.4	3.0	5.0
L-Carnitine (g/L)	0.10	0.15	0.10	—	0.130	0.10	—	0.10
Taurine (g/L)	0.20	0.15	0.20	—	0.130	0.10	—	0.20
Molybdenum (µg/L)	110	220	76	200	130	220	50	139
Selenium (µg/L)	50	100	100	100	61	100	50	55.6
Chromium (µg/L)	74	140	76	100	87	140	16.67	83.3
Zinc (mg/L)	17.7	36	26	15	19.5	24	10	12.5
Vitamin C (mg/L)	200	1000	60	80	260	340	60	67
Vitamin A (IU/L)	3,998	15,000	2,666	6,700	8,666	7,332	2,500	4,167
Other nutients	—	ω-3 fatty acids	ω-3 fatty acids	ω-3 fatty acids	—	ω-3 fatty acids	Branched-chain	Branched-chain
	—	—	Nucleotides	Nucleotides	—	ω-6 fatty acids	amino acids	amino acids
	—	—	Branched-chain Amino acids	Ntructured lipids	—	—	—	—
Osmolality (mOsm/kg)	575	490	460	375	385	290	630	650
Availability	Powder	Liquid	Powder	Liquid	Liquid	Liquid	Powder	Powder

[1]Manufacturers: *Ross Labs, Columbus, OH; †Clintec Nutrition Co., Deerfield, IL; ‡Kendall McGaw, Irvine, CA; §Sandoz Nutrition Co., Minneapolis, MN.
[2]Impact with fiber is also available.
[3]Replete with fiber is also available.

tion may also be categorized as marasmus (nonedematous PEM), kwashiorkor (edematous PEM), or marasmus-kwashiorkor. Children who have been completely starved develop marasmus. They lack dietary protein, calories, vitamins, and minerals and ultimately develop the clinical picture of starvation. Marasmus generally develops over several weeks or months, whereas kwashiorkor often develops acutely, often in the context of infection.

Malnutrition varies in severity. Gomez and coworkers developed criteria for defining first-, second-, and third-degree malnutrition by comparing the gender, weight, and age of a child against locally derived growth standards.[257] Later, Waterlow stressed the importance of determining a child's deficit in weight-for-height ratio and height for age using the 50th percentile of the Harvard Standards.[258] Children with deficits in weight for height are considered to have evidence of acute malnutrition.[259] Those with height-for-age deficits suffer from chronic malnutrition (and/or chronic inflammation) and are considered to be growth retarded. Children may be both acutely and chronically malnourished. Therefore, it is important to underscore that the severity (first, second, or third degree) and chronicity of the undernourished state, as well as the presence or absence of infection, all interact to affect gastrointestinal immunity.

The intestinal mucosa atrophies in severe PCM, especially of the kwashiorkor type, resulting in the blunting of villi and an increase in antigen uptake.[260–263] Patients with kwashiorkor tend to have the most severe intestinal morphologic changes, the greatest disruption of gastrointestinal function, and probably the greatest impairment of gastrointestinal immunity. In contrast to this, patients with marasmus in many instances have what appears to be a normal intestine with minimal dysfunction.

The pathogenesis of villous atrophy is still under investigation. Two types of villous atrophy have been described. The first type is characterized by increased loss of mature enterocytes, via either shedding or apoptosis, which stimulates crypt hyperplasia.[264] Apoptosis leading to villous atrophy may be attributable to TNF-α, Fas–Fas ligand interactions, as well as perforin and antibody-mediated cytotoxicity by lymphocytes and monocytes in the intestinal mucosa.[265,266] Conversely, villous atrophy may commence with crypt hyperplasia, which, in turn, leads to premature sloughing of mature enterocytes.[267] Whichever the causative sequence, villous atrophy has been associated with the presence of activated T cells and may be cytokine mediated.[267,268] The fact that kwashiorkor, more often than marasmus, has been associated with infection and, hence, an increased production of inflammatory cytokines[269] may help to explain its preferential association with villous atrophy. An additional factor contributing to mucosal atrophy may be the withdrawal of growth factors such as insulin-like growth factor I (IGF-I); levels of IGF-I are sensitive to changes in host nutritional status. Finally, polyamine synthesis from dietary amino acids by ornithine decarboxylase is needed for normal mucosal maturation.[270] Deficient synthesis of polyamines during periods of starvation and stress may also contribute to mucosal atrophy.

Animal studies have helped to separate the individual effects of malnutrition and diarrhea on the intestinal tract in a way that is not possible in the human situation. A series of studies by Castillo and colleagues revealed that in infant rats deprived of intraluminal nutrients, intestinal length, weight, protein, and DNA were decreased.[271] After refeeding, these same variables increased at a supranormal rate.[272] Thus, "catch-up" growth is possible for the intestine just as it is for the infant itself. Studies of malnourished children provide somewhat subjective and semiquantitative data concerning intestinal morphology. Several reports indicate that in children with malnutrition and persistent diarrhea, the clinical severity and prognosis do not necessarily correlate with the degree of small intestinal mucosal damage.[273–275] Nutritional rehabilitation via the enteral route can be shown to produce a demonstrable increase in small intestinal crypt cell proliferative activity in children with persistent diarrhea.[276] Certain dietary components, such as glutamine, appear to be particularly important in reversing atrophy.[277] It is now widely accepted that children with acute diarrhea should be fed solid food throughout the course of their illness whenever possible to minimize weight loss and promote intestinal recovery.

In addition to inducing villous atrophy, malnutrition can hamper the mucosal immune system's ability to clear microbial infection. Several pathways play a role in the immune suppression associated with nutritional deprivation. Malnourished piglets have prolonged excretion of intestinal prostaglandin E_2 during rotavirus infection associated with prolonged diarrhea.[278] In mice, caloric restriction leads to an increase in the proportion of naive, CD45RA+ T cells to memory, CD45 RO+ T cells in the mesenteric lymph nodes, which may contribute to local immune suppression.[279] A similar shift in T cell subsets has been seen in malnourished humans.[280] Protein-restricted mice have a defect in mesenteric lymph node IL-4 production that has been associated with prolonged survival of intestinal nematodes.[281] Recently, leptin, a hormone linked to obesity in mice, has been shown to reverse starvation-induced immunosuppression in malnourished mice, even in the absence of refeeding, by stimulating Th1 immune responses (see Chapter 20).[282]

Total Parenteral Nutrition

Total parenteral nutrition (TPN) is also associated with atrophy of the intestinal mucosa and increased infectious complications.[283,284] Several studies have evaluated the effects of TPN on intestinal immune function and intestinal bacterial translocation. In one study, Wistar rats underwent central vein cannulation and were randomized to isocaloric feeding of a regular diet plus saline infusion or TPN and no enteral feedings for 7 days. Bacteria-positive mesenteric lymph nodes were found in 17% (2 of 12) of the regular diet–fed rats but in 77% (10 of 13) of TPN-fed rats ($p < .05$). In addition, *Candida albicans* phagocytosis was significantly decreased in the TPN group compared with the regular diet group. Impaired macrophage function was reversed by small oral feedings.[285] More recent studies

have elucidated some of the mechanisms leading to the villous atrophy and increased susceptibility to infection observed in TPN-nourished animals. In mice, TPN resulted in decreased T and B cell numbers in the intestinal mucosa within 2 days of initiation and to a decreased lamina propria CD4+-to-CD8+ ratio within 4 days. IgA levels in both the gastrointestinal and respiratory tracts were decreased by day 3 of TPN.[286] In addition, mice maintained on TPN had decreased levels of IL-4 and IL-10 and increased levels of the adhesion molecule ICAM compared with enterally fed mice. These changes were reversible when TPN was supplemented with either glutamine or the neuropeptide bombesin.[287] Finally, at 6 hours, endotoxin-treated fasted mice had significantly higher levels of gut apoptosis related to increased intestinal caspase 3 activation compared with endotoxin-treated, enterally fed mice.[288] These data suggest that apoptosis might contribute to the villous atrophy seen in TPN-nourished children.

Although available data support use of the enteral route for nutritional supplementation whenever possible, interestingly, a meta-analysis of studies conducted with patients being fed parenterally failed to document an increased mortality rate in patients maintained on TPN.[289]

Selected Nutrients

Glutamine Glutamine is a nonessential amino acid and the most abundant amino acid in the body.[290] However, during catabolic states, plasma levels of glutamine drop dramatically, suggesting a "conditionally essential" role for this amino acid in periods of stress.[291] Glutamine has been identified as an extremely important fuel not only for enterocytes but also for lymphocytes and macrophages, lending support to its role in the immune response.[292]

Many studies have examined the effects of glutamine on intestinal structure and function, and many excellent reviews are available.[293,294] O'Dwyer and collaborators compared the effects of TPN devoid of glutamine with TPN enriched with glutamine on the intestine of male Wistar rats.[295] Intestinal samples were taken for measurements of jejunal weight, DNA, protein, mucosal thickness, and villous height. The authors also measured nitrogen retention. They found that glutamine-enriched TPN protected the animals from atrophy of the intestinal mucosa. It also improved nitrogen retention during intravenous feeding.[295] There is other evidence to support the concept of glutamine's trophic effect on the intestine. Reducing plasma glutamine concentrations to undetectable levels by glutaminase infusion in animals causes intestinal atrophy, ulceration, and necrosis.[296] Intestinal atrophy associated with malnutrition is prevented with enteral glutamine supplementation.[277]

In humans, glutamine has been shown to decrease proinflammatory cytokine production (IL-6, TNF-α, and IL-8) while increasing production of IL-2 and IFN-γ in vitro.[294,297] Some placebo-controlled, double-blind trials of glutamine supplementation in critically ill patients have reported reductions in infectious complications, whereas others have not.[294,298–300]

Arginine Arginine is a dibasic amino acid, best known as an intermediate in the urea cycle, although it also serves as a precursor for a number of biologically significant compounds such as nitric oxide and growth hormone. It is generally considered a nonessential amino acid because, under normal conditions, requirements for the amino acid are met through tissue synthesis. However, it has been stated that arginine is "essential to the traumatized host and may have tissue-specific properties which influence components of the immune system."[301]

Arginine enhances immune function by increasing lymphocyte and monocyte proliferation, cytotoxicity, and phagocytosis and promotes nitrogen retention.[302] Diets given to burned guinea pigs when supplemented with arginine at a level of 2% of energy intake have been associated with increased survival and apparent augmentation of cell-mediated immunity.[303] Daly and collaborators studied the effect of supplemental arginine or isonitrogenous glycine in 30 cancer patients undergoing major surgery.[304] Nitrogen balance was measured daily, and immune parameters were determined before and after the surgery. Mean age, degree of preoperative weight loss, disease state, and calorie and nitrogen intake were similar for the groups studied. The authors noted that mean daily nitrogen balance was similar for the arginine- and glycine-supplemented groups. However, supplemental arginine increased mean CD4+ T cells on postoperative days 1 and 7 compared with the glycine-supplemented group. The authors concluded that arginine may benefit surgical patients who are at increased risk of infection.[304]

Madden and associates reported that survival was increased by arginine supplementation given orally before sepsis or started intravenously after cecal ligation and puncture in rats.[305] Supplemental arginine was shown to improve wound healing and immune response in 36 healthy, human volunteers.[306] However, Ronnenberg and colleagues found that arginine supplementation in a purified amino acid diet (30 g/kg diet) did not enhance mitogen-stimulated proliferation or alter IL-2 production by splenocytes of healthy young and aged rats.[307]

The importance of arginine in modulating the immune system remains somewhat controversial. A recent meta-analysis of 22 randomized trials with a total of 2,419 patients compared the use of immunomodulatory formulas, most of which contained supplemental arginine, and standard enteral formulas in surgical and critically ill patients. The use of commercial formulas with high arginine content was associated with fewer infectious complications. Benefits were most marked in surgical patients. Of note, however, was a disturbing trend toward increased mortality in septic and critically ill patients supplemented with immunomodulatory formulas.[308] In some of these studies, the cause of increased mortality was from respiratory failure.[302] In summary, arginine supplementation appears to be of benefit to uninfected, postoperative patients, but its safety has yet to be established in critically ill, infected patients.

Lipids The lipid composition of monocytes, macrophages, lymphocytes, and polymorphonuclear cells reflects

the fatty acid composition of the diet.[309] These cells synthesize all of the nonessential fatty acids of cellular lipids but require the essential omega-6 fatty acid α-linoleic acid, its products arachidonic acid, the downstream 2-series prostaglandins (eg, E_2) and thromboxanes, and 4-series leukotrienes (eg, LTB_4); and the essential omega-3 fatty acid linolenic acid and its downstream 3 series and 5 series eicosanoid products (eg, LTB_3 and LTB_5).

Omega-6 fatty acids are incorporated into cell membranes and stimulate the inflammatory arachidonic acid pathway. This results in the production of prostaglandin E_2, as well as the proinflammatory leukotrienes B_4, C_4, and D_4. In addition, omega-6 fatty acids may increase the production of the proinflammatory cytokines TNF-α, IL-1, and IL-6.[310] These substances are important in host defense against infection. Indeed, in a study of burned mice challenged with *Pseudomonas aeruginosa*, survival was significantly higher in animals fed a 40% safflower oil (omega-6) diet than in animals fed a 40% fish oil (omega-3) diet.[311]

Sometimes the host inflammatory response to trauma or infection proves more devastating than the initial insult itself. In this cast, exploiting the anti-inflammatory properties of certain types of lipids may have therapeutic benefit. The role of arachidonic acid metabolites and of proinflammatory cytokines has been studied in the pathogenesis of atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, and, most recently, acquired immune deficiency syndrome (AIDS). In these disorders, omega-3 fatty acids and the omega-6 fatty acids α- and γ-linolenic acid compete with arachidonic acid, dampen the inflammatory response, and may have some therapeutic benefit.[312–316] Both omega-3 fatty acids and linolenic acids have been shown to decrease the production of the proinflammatory cytokines TNF-α, IL-1, and IL-6.[310] Fish oil, comprising eicosapentaenoic and docosahexaenoic acids, has been shown to reverse mucosal atrophy.[317] Whereas in low doses, omega-3 fatty acids are anti-inflammatory, at high doses, they may be immunosuppressive. In an animal study, Chang and colleagues demonstrated increased mortality in *Salmonella*-infected mice fed a 20% fish oil diet.[318] Clearly, caution needs to be exercised in the use and dosing of these agents in patients with significant infection.

Quantity of dietary lipid may be as important as type of dietary lipid in determining immune outcomes. Laboratory animals fed high-fat diets have decreased lymphocyte proliferation and NK cell activity compared with animals fed low-fat diets.[319]

Nucleotides Recent studies have suggested a role for dietary nucleotides as semi-essential nutrients.[320] Among their diverse roles, they serve as precursors for nucleic acid synthesis, participate in energy transfer reactions, and function as coenzymes. The endogenous supply of nucleotides is maintained both through de novo synthesis in tissue and through the salvage pathway in which precursors (purine and pyrimidine bases and nucleosides) are converted to nucleotides. Dietary purines and pyrimidines in nucleic acids are absorbed mainly in the form of nucleosides and bases. Gastrointestinal and liver tissues metabolize dietary nucleotides extensively prior to their entry into the systemic circulation. Certain tissues, including lymphocytes, may have a limited capacity for the de novo and salvage synthesis of nucleotides. Thus, it has been suggested that dietary nucleotides may optimize the function of immune cells by providing an exogenous supply. In one study, 37 healthy term infants were evaluated.[321] They were either breast-fed or fed SMA™ formula supplemented with 33 mg nucleotides/L or standard SMA formula. At 2 months of age, NK cell percent cytotoxicity was significantly higher in the breast-fed and nucleotide-supplemented groups compared with the unsupplemented group. IL-2 production by stimulated mononuclear cells at 2 months of age was higher in the nucleotide groups compared with the group fed the same formula without nucleotides. Rate of growth and incidence and severity of infections did not differ significantly among the dietary groups. The authors concluded that nucleotides may be a component of human milk that contributes to the enhanced immunity of breast-fed infants.[321]

Dietary nucleotides also contribute to humoral immunity and antibody production. A controlled, randomized, blinded, multicenter trial of 311 infants was conducted. Infants were assigned to one of three groups: milk-based control formula, milk-based control formula with nucleotides, and breast-fed infants supplemented with a cow's milk–based formula with iron. At the end of 12 months, the nucleotide-supplemented groups had significantly higher *Haemophilus influenzae* type B and diphtheria antibody titers than the formula control group. Breast-fed infants had significantly higher polio antibody titers than either the nucleotide-supplemented group or the formula controls.[322]

Vitamin A The importance of vitamin A in sustaining an adequate immune response has been recognized since as early as 1925, when Wolbach and Howe showed that rats fed diets deficient in vitamin A developed thymic atrophy.[323] Since that time, deficiencies in vitamin A have been linked in vivo and in vitro with various immune abnormalities, including a decreased number of CD4 cells,[324] impaired lymphocyte proliferation,[325] decreased antibody response to immunization,[326] decreased resistance to infection,[327,328] and increased susceptibility to certain cancers.[329,330] Indirect evidence of vitamin A's critical role in immunity has come from the achievement of a 20 to 50% reduction in childhood mortality in parts of the world where large-scale supplementation programs have been implemented.[331]

In the gastrointestinal tract, vitamin A deficiency is both a cause and a consequence of diarrheal disease. Diarrheal diseases may cause vitamin A deficiency by several mechanisms. First, steatorrhea can lead to a generalized loss of fat-soluble vitamins. Second, damage to the brush border may inhibit the function of brush border retinyl esterases, which contribute to the intestinal absorption of vitamin A.[332] Finally, if diarrheal disease is accompanied by PEM, vitamin A deficiency may be further aggravated by a decrease in retinol-binding protein as well as abnormalities in conjugated bile acids, which contribute to the digestion, absorption, and transport of dietary vitamin A.[333]

Conversely, vitamin A deficiency may predispose a child to diarrhea for several reasons. Data from animal studies indicate that vitamin A deficiency can cause goblet cell depletion, abnormal villous architecture, and villous atrophy.[334–336] In addition, hypersecretion and impaired colonic responsiveness to aldosterone have been observed.[337] When a cohort of vitamin A–deficient children from Indonesia was followed, a significant decrease in mortality from diarrheal disease and respiratory tract infections was noted in children given vitamin A supplementation.[338] A later study in Indonesian children showed, however, that vitamin A supplementation of well-nourished children was actually detrimental, with a trend toward increased incidence of diarrheal and respiratory illnesses seen.[339]

The mechanisms underlying the immunologic effects of vitamin A on the gastrointestinal tract are being elucidated. A study by Carman and colleagues examined cytokine production in vitamin A–deficient mice infected with intestinal *T. spiralis*.[340] Mesenteric lymph nodes of deficient mice produced substantially more IFN-γ and substantially less IL-2, IL-4, and IL-5 than controls. The authors concluded that this alteration in cytokine production may help to explain the poor response to tetanus toxoid (as well as hypoeosinophilia) observed in vitamin A–deficient mice.[340]

In a related series of findings, vitamin A has been shown to play an important role in the induction of S-IgA responses. Cui and colleagues studied children with viral pneumonia supplemented with high doses of vitamin A (250,000 IU/kg/day) or control doses of vitamin A (4,000 IU/kg/day) given before and during infection. Although there was no difference in disease severity between the two groups, vitamin A–supplemented children had significantly higher salivary IgA concentrations and higher IL-10 levels but lower serum IgG concentrations and lower IFN-γ levels than controls.[341] Thus, although vitamin A supplementation can improve some immunologic parameters (IgA), it can suppress IFN-γ, which is an important component of antiviral immune responses.

Vitamin C The immunologic effects of vitamin C are multiple. Ascorbic acid is an important antioxidant that scavenges free radicals (harmful oxygen derivatives such as the hydroxyl radical, superoxide, and hydrogen peroxide) under conditions of inflammation or stress. However, under certain conditions, such as the presence of free iron, ascorbic acid can act as a pro-oxidant agent.[342] It is capable of lipid peroxidation of cell membranes, and it is by this mechanism that it may act, together with TGF-β, to stimulate collagen synthesis.[343] Its in vitro antiviral properties have been extensively studied.[344–346] In vivo, vitamin C supplementation has been shown to enhance T-lymphocyte proliferation in response to mitogens and to viral infection.[347] There are also reports of improved neutrophil chemotaxis and improved phagocytic function of macrophages in supplemented patients.[348,349] Attempts to alter the clinical course of virally infected children with vitamin C supplementation have been disappointing,[350] although vitamin C supplementation may prevent the onset of certain viral infections.[351] Vitamin C may affect gastrointestinal immunity indirectly by influencing the absorption of micronutrients. For instance, it enhances the absorption of dietary iron[352] but inhibits copper uptake.[353]

There has been a good deal of research interest recently regarding the role of vitamin C in *Helicobacter pylori* infection and in the prevention of gastric cancer. Several studies have shown that gastric juice ascorbic acid levels are lower in patients with *H. pylori* infection and return to normal following eradication of the bacteria.[354,355] A study by Ruiz and colleagues has shown that serum and gastric juice levels of vitamin C are lower in adult patients with chronic atrophic gastritis or intestinal metaplasia than in patients with normal mucosa or ulcer disease.[356] Recently, Zhang and colleagues showed that vitamin C inhibits gastric cancer cell growth in vitro when administered at concentrations normally present in gastric juice but not at lower concentrations seen in individuals infected with *H. pylori*.[357]

Vitamin E α-Tocopherol or vitamin E is a fat-soluble, free radical scavenger that is incorporated in cell membranes and inhibits lipid peroxidation. Clinically, vitamin E deficiency is associated with a demyelinating neuropathy and hemolytic anemia. Children with cholestatic liver disease and children with chronic fat malabsorption are at risk for deficiencies of vitamin E. Vitamin E supplementation has been shown to result in an increase in the CD4-to-CD8 ratio, an increase in lymphocyte proliferation, and a decrease in prostaglandin E_2 synthesis.[358,359] Vitamin E augments IL-2 production in both animals and humans.[360,361] Vitamin E supplementation has been shown to prevent cancer in humans; one mechanism may be through the suppression of vascular endothelial growth factor, a major mediator of tumor angiogenesis.[362]

In the gastrointestinal tract, vitamin E deficiency in animals renders absorptive mucosa secretory and thereby contributes to the pathogenesis of diarrheal disease. Its effects on secretion may be mediated by damage to enteric neurons, particularly those that transmit 5-hydroxytryptamine.[363] Empey and colleagues studied the effects of ionizing radiation on rats pretreated with vitamin E or misoprostol (a prostaglandin E_1 analogue).[364] Only the vitamin E–treated rats were protected from radiation-induced changes in absorption. Finally, in a rat model of inflammatory colitis induced by trinitrobenzene sulfonic acid, oral vitamin E supplementation was shown to reduce macroscopic mucosal damage.[365]

Vitamin B_{12} The association of vitamin B_{12} or cobalamin deficiency with pernicious anemia, atrophic gastritis, and ileal disease is well known. Recently, however, the spectrum of clinical illness associated with vitamin B_{12} deficiency has grown. Vitamin B_{12} deficiency is relatively common in the healthy elderly and in AIDS patients.[366,367] In a study of 98 adults with vitamin B_{12} deficiency, a significantly increased number were infected with *H. pylori*.[368] These findings have not been confirmed in children. Children who are strict vegetarians or neonates whose mothers are strict vegetarians are at risk for vitamin B_{12} deficiency, as are children with Crohn's disease.[369,370]

In the gastrointestinal tract, dietary cobalamin enters the stomach bound to food proteins. Gastric acid appears to be necessary to cleave the food-cobalamin complexes so that cobalamin can then bind to intrinsic factor secreted in the stomach. Intrinsic factor–cobalamin complexes traverse the small intestine, where they bind to a specific receptor known as cubilin, present in the epithelium of kidney and intestine but located principally in the ileum.[371] Transcobalamin II is a protein constitutively expressed in the small intestinal villi that binds free cobalamin after uptake of cobalamin–intrinsic factor complexes and transports it into the microcirculation and thence the portal blood.[372] Either decreased gastric acid production or mutations in cubilin or transcobalamin II may be the initiating event in cases of vitamin B_{12} deficiency syndrome.

Vitamin B_{12} may affect immune function in a variety of ways. In patients with pernicious anemia, vitamin B_{12} supplementation leads to an increase in CD8 numbers.[373] In cobalamin-deficient adults, serum TNF-α responses were significantly higher and epidermal growth factor levels lower than in iron-deficient or healthy control subjects.[374] In cobalamin-deficient mice, IgG, IgM, C3, and IFN-γ levels are lower but IgE, CD4+ T cell, and IL-10 levels are higher, suggesting the induction of a Th2 response.[375] Animal data from our laboratory suggest that supplementation with vitamin B_{12} improves survival in septic animals and that it does so largely by sequestering nitric oxide.[376]

Trace Elements Deficiencies of zinc, copper, and iron adversely affect immune function. A lethal mutation in Holstein-Fresian cattle was shown to be responsible for decreased zinc absorption and failure of the thymus to develop normally.[377] Later, Prasad and colleagues showed that human zinc deficiency was associated with dwarfism, hypogonadism, abnormal taste sensation, diarrhea, and an increased susceptibility to infection.[378] Dietary zinc deficiency induces thymic atrophy and loss of Th cell function.[379,380] Zinc deficiency leads to decreased DNA binding of the transcription factor NF-κB and decreased IL-2 and IFN-γ production as well as increased susceptibility of lymphocytes to apoptosis.[381] Children with chronic diarrheal disease as well as those on TPN are at risk for zinc deficiency and may require supplementation. Zinc supplementation leads to mucosal regeneration, increased activity of brush border enzymes, and higher levels of secretory antibodies and augments catch-up growth by increasing levels of IGF-I, which permit catch-up growth.[382]

Although copper deficiency in humans is rare, lower total-body levels of this trace mineral have been associated with an increased incidence of infection and impaired cell-mediated immunity.[383,384] The Menkes' kinky-hair syndrome is an X chromosome–linked inborn error of metabolism owing to a mutation in the copper adenosine triphosphatase, alpha polypeptide gene that leads to copper deficiency. This condition results in increased infections, and death is often caused by bronchopneumonia.[385] Copper deficiency has been linked to defects in the respiratory burst in macrophages and an attenuation of LPS-induced cytokine production.[386] Copper has been shown to play an important role in wound healing by stimulating the expression of matrix metalloproteinases and vascular endothelial growth factor.[387,388] The corollary is, however, that copper may play a role in tumor angiogenesis as well.[389]

Iron deficiency is associated with increased susceptibility to infection.[390,391] However, excessive iron intake appears to be linked to oxidative stress and to more infections as well.[392] Iron may help in combating infection by up-regulating IL-1 production.[393] Iron may predispose to infection by nourishing certain species of bacteria[394] or by inhibiting the induction of nitric oxide synthase.[395]

Intestinal transport of dietary iron is a tightly regulated process so as to avoid the deleterious effects of either iron excess or iron deficiency. Two iron transporters belonging to the natural resistance–associated protein (Nramp) family play an important role in intestinal iron homeostasis. Nramp2 is a protein that localizes to the cell membrane and to recycling endosomes of the intestinal brush border and governs the transferrin-independent intestinal absorption of iron.[396] Nramp1 is a phagosome-associated protein that pumps iron out of the phagosome, presumably to be able to prevent the prolonged survival of intracellular bacteria.[397] Polymorphisms in these genes have been linked to increased susceptibility to infection with intracellular pathogens and possibly to Crohn's disease susceptibility.[398–400] Taken together, these data point to an important role for iron in mucosal immunity.

FUTURE DIRECTIONS

Despite a proliferation of research in the field of gastrointestinal immunology in the last 10 years and the continuing evolution of knowledge regarding nutrition and immunity, the interactions of dietary nutrients and enteric flora with the immunologically active cells functioning in the gastrointestinal tract are only beginning to be elucidated. A recent review article by Bach and an accompanying editorial by Weiss discussed early environment and the development of immune-mediated disease.[401,402]

There has been an epidemic of both autoimmune diseases (in which the immune response is dominated by Th1 cells, such as type 1 diabetes, Crohn's disease, and multiple sclerosis) and allergic diseases (in which the immune response is dominated by Th2 cells, such as asthma, allergic rhinitis, and atopic dermatitis). One theory proposed to explain this increase in the prevalence of autoimmune and allergic diseases is that it results from a decrease in the prevalence of childhood infection. Bach detailed a number of potential mechanisms by which the decrease in the frequency of childhood infections might influence the frequency of autoimmune diseases. The first is that the decrease in antigenic stimulation related to the decrease in the frequency of childhood infections has resulted in a decrease in the levels of regulatory cytokines—specifically, IL-10 and possibly TGF-β. CD25-positive T cells and other regulatory T cells produce IL-10 and TGF-β and act to down-regulate Th1-mediated responses and Th2 responses.[402]

Environmental cofactors may also be important. Endotoxin is a hitchhiker that can attach itself to particulate air

pollutants that might potentiate the immune effects of endotoxin. The levels of heat shock protein and 1,3-β-glucan, the latter an immunostimulatory cell-wall component of fungi, yeast, and plants, correlate with levels of endotoxin in house dust. A final environmental cofactor may be the presence in bacterial DNA of greater numbers of unmethylated cytidine-phosphate-guanosine sequences than are present in mammalian DNA. These sequences are sensed by TLR9, which interacts with TLR4 and may potentiate immune stimuli when activated by LPS.[402]

Finally, genetics is an additional determinant of the response in any given person. Case-control association studies have suggested that a TT polymorphism in the promoter region of CD14, the receptor that binds LPS, is associated with higher levels of soluble CD14 in peripheral blood and, in persons with allergies, with lower serum IgE levels and decreased sensitization to allergens.[402] We need to clarify and extend this so-called hygiene hypothesis concerning asthma and other allergic and autoimmune disorders.[401]

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CHAPTER 20

MALNUTRITION AND HOST DEFENSES

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This at least I clearly know: that bread has different effects in the human body according as it is fine or coarse, made of wheat winnowed or unwinnowed, mixed with much or little water, knead much or not at all, baked thoroughly or underbaked and a thousand other differences besides. . . . If one fails to consider these points or having considered does not understand them, how can he know anything about human disease?[1]
—Hippocrates (460–377 BC)

The vital importance of nutrition in host defense has been recognized from the time of Hippocrates,[1] long before the development of the germ theory of infection in the nineteenth century.[2] In contrast, immunology is modern, perhaps traceable in origin to Metchnikoff and the cell theory,[3] but dating in its present form to the 1960s.[4] The fundamental relationship between malnutrition and immunity was initially described by Smythe and colleagues as a thymolymphatic deficiency caused by protein-calorie malnutrition (PCM).[5] Current investigations also describe the thymus as the "barometer of malnutrition," [6] are identifying how specific nutrient deficiencies such as zinc correlate with clinical malnutrition and impaired thymic function,[7–9] and furthermore seek to know how critical molecular processes may be affected.[10]

The selective sensitivity of the thymus to nutritional injury is specifically important in the formative phases of the fetal and neonatal immune system. Recent studies suggest that prenatal nutrition and growth during the first year of life may predict thymic function in adolescence.[11] Related studies in the mouse have shown that perinatal zinc deficiency is associated with decreased immune function in later life.[10,12] It is generally accepted that age-related changes in immune response appear to stem from programmed involution of the thymus.[13] However, both reversal of thymic involution in the mouse and induction of thymulin secretion from human thymic epithelial cells have been obtained with zinc treatment,[14] suggesting that specific nutrients may act as regulatory elements by modulating cellular programs. The potential significance of early nutrition for adaptive immune response in general is also indicated by studies of mucosal immune response to antigens, such as the work of Harrod and colleagues, who have shown that experimental priming at birth ensured both a stronger and a more lasting immune response toward potential pathogens.[15]

Current thinking about the fundamental nature of immune response places major emphasis on the microenvironment. Innate immune cells such as natural killer (NK) cells and NK T cells, monocytes, and dendritic cells influence the pattern of cytokine produced by the adaptive immune system, in part by directly secreting their cytokine products into the microenvironment.[16] Neonates and infants must rely primarily on innate immunity, although some components of innate immunity are not as functional in young children as in adults.[17] Pathogens such as parasitic infections or viruses may easily compromise these resources, and if malnutrition is present, the overall development and expression of immune response are significantly impaired.[18,19] A critical hypothesis is that conditionally essential nutrient requirements may be associated with key stages of development. Settings in which conditional nutrient requirements have already been identified include surgical stress in which glutamine and arginine are required for immune recovery[20–22] and conditions of rapid growth in which the impact of dietary nucleotides can be observed.[23] Fundamental questions for the future are likely to focus on the role of host genes as well, for example, those regulating iron uptake[24,25] or cytokine and cytokine receptor gene polymorphisms.[26] The importance of host genetic polymorphisms has already been reported for infections such as tuberculosis in which malnutrition is an important risk factor.[27,28]

Host defense requires energy expenditure, and this rapidly becomes compromised in the malnourished or chronically infected host. Infections trigger initiation of the acute-phase response, affecting nutrient metabolism and modulating cytokine pathways.[29–31] The mechanisms through which nutrients affect immune functions frequently include modulation of the cytokine response and are reflected in changes in the overall cytokine pattern. Cytokines are produced in response to triggering events such as infection and cancer but are also induced in

response to a wide range of stress signals, including nutrient deprivation.[32,33] Cytokine response is essential for host defense but, if uncontrolled, can also lead to the extreme state of septic shock, causing loss of lean tissue and body fat.[34,35] To a lesser degree, some of the observed effects of malnutrition may also involve concurrent subclinical and generalized infectious processes, particularly from opportunistic pathogens acting through mediators common to the acute-phase response,[36] as illustrated in Figure 20-1. Examples include the effects of nutrient alteration on host immune response associated with human immunodeficiency virus (HIV) infection or parasitic infections.[37,38]

In this discussion, effort will be made to distinguish indirect nutrient effects, which are general and apply to all tissues, from direct actions in which lymphoid tissues and immune response are affected either disproportionately or specifically.[39] Similarly, the mechanism of nutrient action may differ according to setting and concentration. Pharmacologic use of nutrients may have immunomodulatory effects different from those exerted by smaller amounts given to achieve physiologic repletion to normal levels (see Chapter 59, "Specific Diets"). These differences may explain why supplementation above normal levels may sometimes be associated with a decline of immune response that could not have been predicted from studies of repletion.[40,41] The impact of any supplementation is also affected by conditions in the host. Presence of infection, underlying illness, or immune deficiency may also affect response to nutrient administration, and correlations observed in these settings between immune response and nutrient level may not hold true in the healthy host.

Primary nutrient deficiency occurring in children as a single entity is usually the result of poverty, lack of adequate supply, or other environmental factors.[42,43] Rare innate occurrences include the genetic defect of zinc metabolism, acrodermatitis enteropathica,[44,45] and defects of copper in Menkes' syndrome or Wilson's disease.[46,47] However, deficient intake of essential nutrient requirements may easily be caused by altered metabolism in association with an underlying congenital condition, disease, or acute illness and can also lead to malnutrition and impaired host defense. Although malnutrition is often considered as mainly an issue for underdeveloped countries, suboptimal nutrition is relatively common in children throughout the world and is a significant cause of susceptibility to infection.[48] In the changing social conditions of childhood in general and increasingly fragmented family life, knowledge of how nutrients may affect the development of immune response will have greater critical importance for preventive efforts to support future host defense against new pathogens.

MICROENVIRONMENT AND NEONATAL IMMUNE RESPONSE

The effect of nutrients on immune response can depend on the site of action, for example, the gut-associated lymphoid tissue (GALT), thymus, spleen, regional lymph nodes, or immune cells of the circulating blood (see Chapter 19, "Immunophysiology and Nutrition of the Gut").[49,50] The same nutrient may have a different mechanism of action at various sites. For example, zinc may potentiate T helper type 1 (Th1) response systemically and T helper type 2 (Th2) responses at the level of GALT.[30,51] Responses are also affected by other host factors, including the presence of infection or other illness, stage of life, age, and antigenic history.[52–54] With the principal exception of thymulin, the zinc-dependent hormone, hormonal changes have not been taken into account in studies of immune development. However, current evidence suggests that endocrine factors affect both innate and adaptive immune response.[55,56]

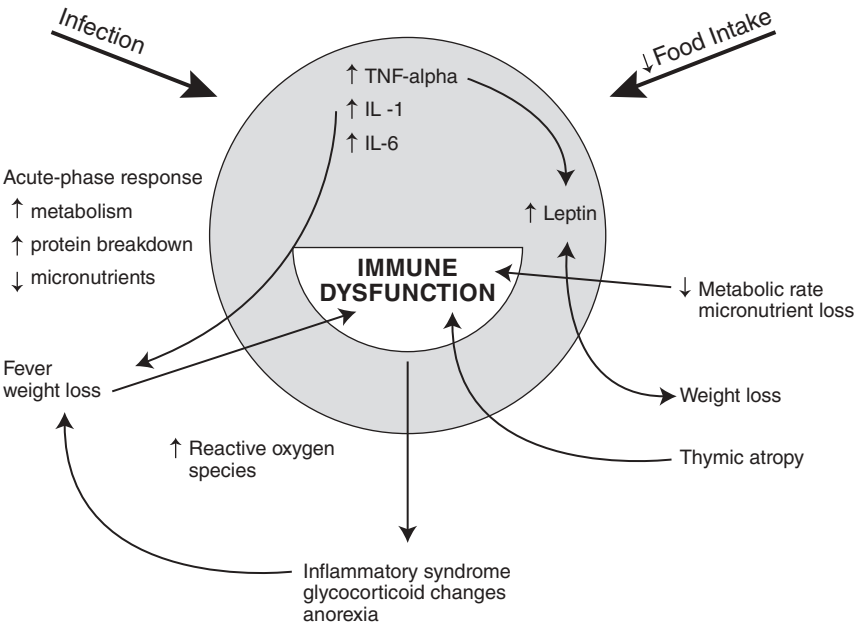

FIGURE 20-1 Illustrates some of the key interactions that lead to altered immune response in the malnourished host during infectious exposure. IL = interleukin; TNF = tumor necrosis factor.

The immune system has, until recently, been thought of as two essentially separate innate and adaptive systems responding to the evolving needs of the organism in defense against pathogens. The innate system that mediates an immediate immune reaction that is independent of specific antigens has developed to recognize microbial "nonself" through identification of conserved microbial products, pathogen-associated molecular patterns, and to know "self" by means of specific gene products. Thus, in addition to unique microbial motifs, infected or pathologically altered self can be identified as missing or altered self.[57,58] Adaptive immunity has been divided conceptually according to cell type and origin as the response of bone marrow–derived B cells belonging to the humoral immune system and thymus-derived T cells of the cellular immune system. Through antigen encounter, polyclonal T cell responses become refined to a more restricted T cell repertoire in a process that resembles the affinity maturation of B cells. Differentiation of cell function and cell–cell interactions, however, is significantly determined by the local microenvironment, for example, in the liver, immune cells such as natural T cells, which have distinct cytokine secretion patterns affecting host response to antigen.[59] Thymus-independent T-cell differentiation is also dominant in the gastrointestinal tract, as mediated by such cells as the intraepithelial lymphocyte.[60]

Micronutrients, trace elements, and vitamins present in the local environment have important regulatory effects on adaptive immune cell function. Specific nutrients such as zinc support a Th1 cytokine response in which interleukin (IL)-2 and interferon (IFN)-γ are produced, whereas other nutrients, such as vitamin A, typically support secretion of Th2 cytokines, including IL-4, IL-5, and IL-10.[30,61] Therefore, the overall effect of the microenvironment is to drive immune response toward either a Th1 or a Th2 response (Figure 20–2; see also Chapter 6, "Trace Elements").

Many nutrients interact with other immune regulatory molecules to influence immune response. Examples include the reported counterregulatory effect of vitamin E on prostaglandin E_2 (PGE_2) suppression of a cyclic adenosine monophosphate (AMP) response element binding (CREB) protein.[62] Mechanisms of nutrient action often involve several pathways and produce a range of phenotypic effects. For example, in the mouse, vitamin B_{12} (cobalamin) deficiency reduces levels of C3, immunoglobulin (Ig)M, and IgG and increases levels of IgE through causing a shift from Th1 to Th2 response.[63] Increased CD8+ T cell number and NK cell activity, as well as megaloblastic anemia, characterize human vitamin B_{12} deficiency.[64] Vitamins A and D have been intensively studied as critical regulators of gene expression for both growth and immune development. Vitamin A deficiency impedes retinol-dependent signals during embryonic development, and vitamin A supplementation enhances Th2 response to viruses such as influenza.[65,66] Vitamin D acts as a nuclear receptor for target genes and also has a regulatory influence on immune cell differentiation (see Chapter 7, "Vitamins").[67–69]

Nutrient deficiencies may have an indelible effect during critical periods of early development by exerting an imprinting effect on the fundamental program of future development. This concept, advanced by Dobbing,[70] is supported by the discovery of interactions between neonatal nutritional status and blood pressure or cognitive ability.[71,72] McDade and colleagues have now shown that prenatal undernutrition reflected in intrauterine growth retardation leads to reduced thymopoietin production.[11] The study reported that adolescents who were small for gestational age (SGA) at birth had lower thymopoietin levels when compared with control adolescents who were appropriate for gestational age (AGA) at birth. In both groups, thymopoietin level during adolescence correlated with growth in length during the first year of life.

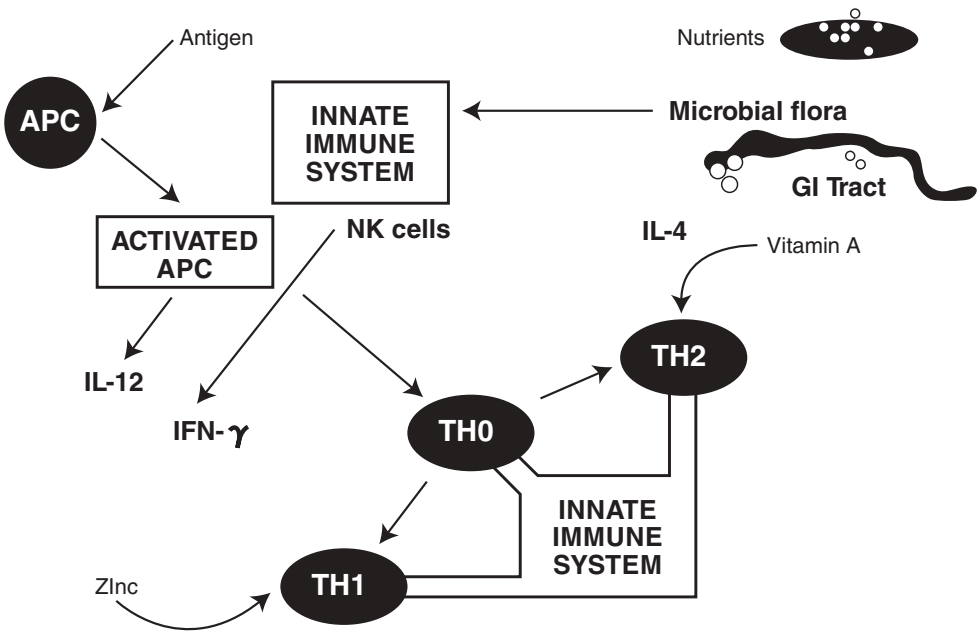

FIGURE 20-2 Indicates the role of nutrients in how the microenvironment influences the production of cytokines by the adaptive immune system. APC = antigen-presenting cell; GI = gastrointestinal; IFN = interferon; IL = interleukin; NK = natural killer; Th = T helper.

In general, impairment of cell-mediated immunity and reduction in phagocyte function are characteristic of low birth weight infants[19,73,74] Complement deficiencies are also an important cause of susceptibility to infections.[75] The development of cytokine response is crucial for the differentiation of adaptive immunity in this period.[76] Low birth weight AGA infants respond well to some immunogens such as bacille Calmette-Guérin (BCG) with respect to proliferative response to antigen, IL-2 production in vitro, and skin test response to purified protein derivative (PPD) in vivo.[77] Low birth weight infants also tolerate and respond to immunization with diphtheria-tetanus-pertussis (DTP) but do not respond effectively to *Haemophilus influenzae* type B.[78,79] Further, maternally acquired passive immunity, assessed as geometric mean antibody to viruses and to bacteria, is reduced.[80] The low birth weight infant is hypogammaglobulinemic and susceptible to nosocomial infections, but intravenous immune gammaglobulin is largely ineffective in reducing these infections.[81] Importantly, studies have also shown that the immune response of the premature infant is also affected by routine blood transfusion to replace blood drawn for clinical monitoring.[82]

A growing general concern is that nutrient intake may be suboptimal because the diseases of prematurity impose an additional metabolic burden.[83] Assessment of selenium and zinc has shown that levels are low, even when intake follows current guidelines.[84,85] Protein and lipid intake may need to be increased.[86,87] Because the development of the gut and the immune system occurs interactively, it is likely that nutrients may foster normal tolerant immune response toward food antigens. Supplementation with dietary nucleotides has been suggested as a means of beneficially affecting the growth of the gut in the premature infant through influencing intestinal permeability and absorption of macromolecules, thus affecting antibody response toward β-lactoglobulin and α-casein.[88,89] Martinez-Augustin and colleagues have found that IgG antibodies against the main antigenic proteins in cow's milk were generally higher when nucleotide supplementation was provided.[90] This difference reached significance for antibody to β-lactoglobulin at 30 days of life when gut closure had occurred. Studies by this group also suggest that IgA and IgM humoral immune response are enhanced by nucleotide supplementation.

The neonate requires micronutrients such as iron, zinc, and selenium as well as an energy-dense diet. Vitamin A is crucial for development of normal immune response and for development of epithelialization in the lung (see Chapters 6 and 7). Thus, Shenai and colleagues have shown that airway infection in the mechanically ventilated very low birth weight infant was associated with reduced plasma vitamin A.[91] Human milk normally provides bioavailable micronutrients such as zinc, as well as secretory immunoglobulin and growth factors.[92] Curiously, some maternal milk may be lacking in zinc despite normal levels in serum, and in such cases, babies may develop a condition that is phenotypically identical to acrodermatitis enteropathica.[93] Low levels of fatty acids, such as docosahexaenoic acid (DHA), in maternal milk have been found to correlate directly with low levels in malnourished children.[94] DHA is critical for visual acuity, affects postnatal brain growth,[95] and also influences immune response through inhibitory effects on the IL-2 pathway.[96] The significance of this for host defense and maturation of the immune system requires further study.

Secretory IgA antibodies in milk reactive against antigens in the maternal gut can be protective against gastrointestinal disease.[97] Recent studies show that bioactive immune mediators in milk such as transforming growth factor (TGF)-β and soluble CD14, the bacterial pattern recognition receptor, are likely to be key elements in tempering neonatal immune response.[98,99] Maternal malnutrition is associated with a decline in total milk IgA, C3, and C4 and may affect passively transferred antimicrobial defense.[100] Studies suggest that milk antibody levels are to some degree conserved, even when maternal nutrition is inadequate.[101] Maternal milk may also be important in influencing the gradual shift in immune polarity in the neonate from Th2-type pattern systemically and a Th1-type response in the GALT toward the adult pattern in which inflammatory immune response is up-regulated in the periphery and Th2 response predominates in the gut.

Changes in mucosal development occur in the neonatal period in the context of major shifts in enteral intake, microbial exposure, and immune cell maturation. Weaning is a time of enhanced risk of malnutrition and therefore of increased vulnerability to infections. Normal intestinal growth is sharply enhanced at weaning, and this is mediated through T-cell activation by food substances and microbial antigens and involves transient, localized inflammatory response. Recent studies have shown that this is accompanied by increased expression of the IL-2 receptor and expansion of α/β T-cell receptor–positive (TCR)+ cells.[102]

HOST DEFENSE IN PROTEIN-CALORIE MALNUTRITION

PCM may involve energy deficiency, protein deficiency, and vitamin and mineral deprivation (see Chapter 6). If prolonged, PCM produces wasting and stunting. PCM (or protein-energy malnutrition) encompasses a range of protein-energy deficiency states, from marasmus to marasmic kwashiorkor. Protein insufficiency alone, with or without infection, causes edema associated with hepatomegaly from fatty infiltration of the liver. The manifestations of clinical malnutrition are related to type, severity, and duration of nutritional impairment and may be subclinical, reversible, or irreversible depending on the availability of treatment, presence of other diseases or complicating disorders, and the degree of damage. A wide range of effects is observed that affect many organ systems and specific tissues, requiring integrated clinical management.[103–108] According to the severity and features at presentation, PCM is defined as marasmus, characterized by a chronic wasting condition, or kwashiorkor, which is distinguished by edema and anemia. A mixture of features of both con-

ditions and gradations of expression are frequently observed among malnourished children. Recent studies show that growth faltering actually begins very early, underscoring the need for rapid evaluation.[109]

The effect of nutrient deficiency on immune response and host defense has been primarily studied in PCM and in micronutrient deficiencies. Undernutrition, especially PCM, is clearly associated with increased susceptibility to infections and with greater morbidity from infections.[18,110] However, the proximate cause of reduced host defense and increased mortality from acute respiratory infections observed in the malnourished child is often related to a combination of factors rather than to a single factor.[111]

Both marasmus and kwashiorkor are characterized by reduced antioxidant activity, an important component of host defense. Tatli and colleagues have described reduced red cell glutathione and increased lipid peroxidation in children with marasmus,[112] whereas Reid and colleagues observed decreased erythrocyte glutathione synthesis in kwashiorkor.[113] Although the basis of edema in kwashiorkor is unclear, this is probably linked to increased levels of inflammatory cytokines, specifically IL-6 and C-reactive protein, and to the action of the soluble receptors of tumor necrosis factor (TNF).[114]

Primary malnutrition is associated with atrophy of lymphoid organs and profound immune malfunction leading to susceptibility to pathogens, reactivation of viral infections, and development of opportunistic infections.[115,116] The effect of malnutrition on T-cell maturation and thymic function is particularly important in children in whom the adaptive immune response is forming. Malnutrition leads directly to thymic involution,[8] revealing the thymus gland as the barometer of malnutrition in children.[6] As suggested by studies comparing AGA and SGA babies, prenatal undernutrition may be generally linked with thymic function in adolescence.[11] Congenital thymic absence, DiGeorge's syndrome, is associated with recurrent infections, which can be fatal. Other developmental anomalies that stem from chromosome 22q11 deletions comprising the CATCH-22 (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia) group of disorders may also have clinically significant immune deficiency in association with reduced thymic function.[117] A zinc finger gene, *ZNF74*, has been identified in the commonly deleted region.[118] Nutritionally caused thymic involution is very similar to congenital thymic aplasia in terms of effects on immune function and host defense.[8]

Lymphocyte development and differentiation are directly affected by malnutrition as a consequence of thymic deficiency. When T cells from children with severe PCM were compared with those from well-nourished children, immature differentiation was directly associated with thymic involution as measured by echoradiography.[7] Although regrowth of the thymus took longer than restoration of normal body weight when children were fed, this could be significantly hastened by the addition of zinc supplementation.[8] Thymic involution can also occur secondary to infections caused by malnutrition because the thymus is extraordinarily susceptible to stress depletion.[13]

Experimental studies show that the thymus is unusually vulnerable to programmed cell death. Studies in the genetically wasted mouse wst/wst suggest that the central abnormality may be a high or premature rate of spontaneous apoptosis in the thymocyte population.[119] Possibly related effects have been observed in rats rendered magnesium deficient by diet. In these studies, Malpuech-Brugere and colleagues found acceleration of thymic involution and apoptosis.[120] In these studies, magnesium deficiency caused enhanced inflammation and susceptibility to peroxidation in association with increased apoptosis. Recent studies by Hoffman-Goetz reported that artificial rearing without maternal factors is associated with reduced thymic cell number and weight compared with maternal rearing of rat pups.[121] These studies suggest involvement of the hypothalamic-pituitary-adrenal axis in thymic homeostasis.

Reported immunologic abnormalities in severely malnourished infants and children have been primarily related to the cellular immune system. Relatively fewer changes in overall immunoglobulin levels have been found, although IgA1 and IgA2 tend to be higher.[122] Rikimaru and colleagues undertook a systematic evaluation of lymphocyte subpopulations and immunoglobulins among normal children and children with kwashiorkor, marasmus, and marasmic kwashiorkor in Ghana.[123] IgA and C4 were higher, whereas C3 and relative B cell percentage were lower in the severely malnourished groups.

Serum levels of immunoglobulins do not predict specific de novo antibody response, and specific studies suggest that malnutrition affects some immunogens more than others. Stunting appears to be strongly associated with decreased IgG antibody response to measles.[124] Decreased C3, decreased TNF-α, and IL-6 response to lipopolysaccharide stimulation in vitro are also characteristic of malnourished children.[125,126]

Protein deprivation alone may cause reduced phagocytic activity and impaired IL-1 and IL-6 production, while sparing monocyte antigen interaction.[127] Experimental studies in the rat have suggested that low dietary protein affects the gut immune system at several levels, including mucosal IgA, secretory component, the number of IgA-containing cells, and the level of IgG. These studies were conducted in the absence of caloric restriction and could be reversed by refeeding.[128] However, the effects of a single-grain diet such as maize may also be related to metabolites of dietary constituents rather than to nutrient absence. Current thinking suggests that the high level of linoleic acid in maize in the absence of other polyunsaturated fatty acids in the diet may cause increased production of PGE_2, leading to down-regulation of Th1 cytokine production.[129]

Some of the effects of PCM might involve endocrine interaction with the immune system. Zamboni and colleagues observed high basal growth hormone (GH) levels but reduced GH receptors in malnourished children.[130] Recent studies have shown that serum leptin levels and insulin-like growth factor I (IGF-I) are reduced in both marasmus and kwashiorkor, suggesting that nutrient deprivation leads to decreased fat mass, insulin, and possibly

IGF-I, suppressing leptin, which may, in turn, stimulate the hypothalamic-pituitary-adrenal axis to increase cortisol and GH secretion.[131] Related studies have shown that GH could be used therapeutically to restore somatic and muscle growth in an experimental model of PCM.[132] In controls, an enriched diet promoted fat deposition alone. Thymic atrophy in malnutrition leads to loss of cortical CD4+ T cells. Fasting triggers this process in the genetically deleted leptin-deficient ob/ob mouse but can be counteracted by leptin administration.[133] Correlation between serum corticosterone level and thymic atrophy has been shown in a murine model of protein malnutrition.[134] Refeeding reversed this effect. These studies suggest that increases in serum corticosterone observed in PCM could also trigger apoptosis, contributing to the loss of differentiated T cells.

Although the effects of infection and malnutrition on immune response are interactive, the impact of each on immune response is also independent. A recent examination by Mishra and colleagues of graded PCM in children at risk for *Mycobacterium tuberculosis* infection included study of response to a skin test anergy panel, including PPD.[135] Impaired cellular immunity was found in all grades of malnutrition with the exception of response to PPD in grade I. Weight loss is a common presenting symptom in children with active *M. tuberculosis* infection. A recent study in adults has shown that before treatment, both leptin and TNF-α levels were elevated and intercorrelated. Although changes in body mass index (BMI) were proportional to change in leptin during treatment and weight gain was achieved early in the course of antibiotic treatment, there was no correlation between BMI and leptin before or after treatment. TNF-α levels did not change. Post-treatment leptin and TNF levels did not correlate. Thus, the underlying deregulation of leptin and TNF-α, which promoted wasting, continued to linger.[136]

PCM seriously impairs immune response to some vaccines, such as BCG. Although BCG does not prevent *M. tuberculosis* infection, immunization in endemic environments may inhibit development of invasive disease.[137] However, this protection may be largely ineffective in children with PCM, as shown in a study of immunized malnourished children who did not respond to tuberculin after immunization, became infected, and went on to develop disseminated disease. The control group of well-nourished children was skin test responsive and had a modified disease expression with greater localization and reduced hematogenous spread.[138] In contrast to the impaired reaction of malnourished children to BCG, immune response to other vaccines may be conserved. For example, seroprotection was achieved even in malnourished children with hepatitis B vaccine, although the observed frequency of protective response was reduced compared with that of healthy infants.[139]

Paradoxically, response to some pathogens may appear to be improved in some states of malnutrition. Genton and colleagues assessed incidence of malaria in children of Papua, New Guinea, and found that increased height for weight at baseline predicted incidence of malaria during the year of study, whereas lymphocyte response to malarial antigens was lower among these wasted children.[140] However, malarial incidence was not different among well-nourished compared with malnourished children when the stunted children were included in the analysis. Further, cytokine production toward malarial antigens was actually greater among the malnourished but not wasted children, suggesting that a favorable cytokine regulatory shift might be the basis of improved response. Although stunting may be considered an adaptive host response to prolonged nutrient deprivation, the stress response is negatively affected, and this would likely have a detrimental effect on immune response in acute infection.[141]

Increased incidence of infections is common in PCM. A large longitudinal study carried out over 1 year among undernourished rural Bangladeshi children has shown that wasting and skin test anergy indicating immune deficiency were linked to acute upper respiratory infections.[142] Some infections may also be pivotal in enhancing risk of malnutrition in children. Dale and colleagues have shown that *Helicobacter pylori* infection, common among Gambian children, is strongly associated with other enteric infections and chronic malnutrition in the postweaning period.[143]

MICRONUTRIENTS AND IMMUNE FUNCTION

Current studies suggest that much of the enhanced susceptibility to infections observed in PCM may be directly related to micronutrient insufficiency (see Chapters 6 and 19). This association was first recognized by Good and colleagues, who proposed that deficiency of certain key trace elements, especially zinc, might be the direct cause of immune deficiency in the malnourished host.[144] Iron, copper, and zinc deficiencies are the most common trace element nutrient deficits in North America (see Chapter 6). Selenium deficiency, like that of iodine, affects parts of the world with low levels in soil. Micronutrients are often deficient in generalized infections such as chronic viral illnesses and may directly cause impaired immune response.[145]

Low dietary intake of antioxidant nutrients can also influence response to infections and may lead to an unopposed inflammatory state. For example, *H. pylori* can lead to chronic gastritis caused by activated phagocytes. Nair and colleagues observed that patients with gastritis and peptic ulcer disease characteristically have a low level of antioxidants in both serum and mucosa whether or not *H. pylori* infection was detected.[146] Relevant studies in a mouse model have shown that treatment with antioxidants led to reduced gastric inflammation and to lowered bacterial load. Bennedsen and colleagues observed a shift from a Th1-type immune response to a mixed Th1/ Th2 response, which was dominated by IL-4 and IFN-γ production.[147]

Micronutrients have a crucial impact on immune response, both through antioxidant effects and through modulation of cytokine expression. Trace elements and vitamins perform antioxidant functions through participation in enzyme-catalyzed reactions. These reactions are essential to offset potential oxidative damage caused by free radical formation. Three antioxidant enzymes, the copper, zinc, and manganese superoxide dismutases,

require trace metals for biologic activity. In addition, micronutrients are pivotal regulators of cytokine production. Parenteral nutrient preparations may not provide adequate levels of micronutrients such as vitamin E and selenium, causing antioxidant deficiency, which may lead to lipid peroxidation, a measure of oxidative stress.[148] Table 20-1 summarizes the role of key micronutrients in regulation of immune response. The implications and significance of these functions for the development of immune response to pathogens are outlined below.

Iron

Although low iron is the most common nutrient deficiency, controversy concerning iron supplementation continues because of the possibility that iron supplementation may promote bacterial growth.[149] However, iron deficiency causes spontaneous cytokine production.[150] Iron deficiency has been implicated in chronic mucocutaneous candidiasis, and iron supplementation may support recovery from candidal infection secondary to primary immune deficiency.[151] TNF-α is a regulator of iron metabolism and has a role in the pathogenesis of the anemia of inflammation. Both iron and inflammatory cytokines regulate hepatic secretion of ferritin, which is an acute-phase protein.[152] Increased TNF-α and IL-1β production in response to lipopolysaccharide in vitro is seen in the iron deficiency anemia of infancy. Iron supplementation corrected this hyper-response.[153] Interestingly, intracellular growth of *M. tuberculosis* in the monocyte can be inhibited by iron.[154] Iron deficiency is associated with adaptive immune defects. Impaired mitogenic lymphocyte response and depressed delayed-type hypersensitivity (DTH) can be seen.[155] In a group of children with iron deficiency, almost 60% were found to have IgG subclass deficiencies. Pneumococcal polysaccharide-specific IgG1 and IgG2 were lower in these children than in healthy peers.[155]

Genetic control of iron uptake and metabolism has recently been elucidated by the discovery of the gene for hereditary hemochromatosis (HH), an autosomal recessive disorder of increased gastrointestinal iron uptake.[24] The normal gene product of *HFE*, a nonclassic gene of the major histocompatibility complex (MHC) homologous to MHC class I, regulates the metabolism and distribution of iron through affecting the binding of transferrin-bound iron to the transferrin receptor.[156] Although the incidence of HH is closely linked with homozygosity for one *HFE* mutation, the severity of disease expression is not directly associated with either gene mutation.[157,158] Recent studies indicate that a defined T cell phenotype associated with low numbers of CD8+ T lymphocytes in the peripheral circulation is linked with high iron stores.[159] Chronic, therapeutic red blood cell blood transfusion causes iron overload analogous to that of HH in β-thalassemia, a severe, congenital anemia. An analogous low CD8+ T cell phenotype has recently been observed in a large subgroup of β-thalassemia patients. The expression of this immune phenotype was independent of age and therefore did not reflect cumulative transfusion history, indicating a possible link between the immune system and response to iron.[160]

Zinc

Zinc is the most extensively studied micronutrient in relation to immune response. Secondary zinc deficiency may be a significant complication of gut disturbances such as regional enteritis, celiac disease, and diarrhea, as well as the more widely recognized settings of IgA deficiency, fetal alcohol syndrome, and the hyperzincuria of sickle cell disease. Zinc is essential for the development of normal immune function.[161] Deficiency affects the pattern of cytokine production, thymic hormone activity, and lymphopoiesis.[10,162] Nutritional replenishment with zinc-fortified formula can lead to increased DTH response, mononuclear response to PHA, and salivary IgA levels in both non–zinc-deficient and zinc-deficient marasmic infants.[163] After 1 month of zinc supplements, hemodialysis patients had increased serum zinc and B cell percentage compared with patients who received placebo, and their antibody levels to multivalent influenza vaccine were higher.[164] In a seminal investigation in which zinc deficiency was induced by diet-alone induction deficiency in healthy adult volunteers, Prasad observed decreased total CD4+ cells, ratio of naive-to-memory CD4+ cells, and Th1 cytokines,[165] and these conditions were reversed with zinc repletion.[165]

Zinc deficiency may occur as a genetically based defect of absorption in acrodermatitis enteropathica, which presents in infancy as skin lesions (acute dermatitis or hyperkeratotic plaques), diarrhea, alopecia, and increased incidence of infections caused by severe immune deficiency.[44] Although untreated disease can lead to fatal infections, all of the symptoms can be resolved with zinc therapy.[166] Zinc deficiency can also arise from malabsorption syndromes, excessive loss through hyperexcretion as in sickle cell anemia, through fluid loss, or from low intake. When zinc levels are reduced temporarily in a wide range of conditions such as prematurity, intravenous hyperalimentation, artificial feeding, and gastrointestinal disturbances, the effects on immunity range from severe thymic atrophy and profound lymphopenia to anergy in DTH skin testing to recall antigens and loss of NK cell activity.[167–169] Studies of acquired mild or marginal zinc deficiency in chronic diseases, such β-thalassemia and epidermolysis bullosa, have also shown that even modest zinc depletion is associated with significant immune impairment.[170] Zinc-fortified formulae have been used to improve both linear growth and immunocompetence, as shown by improved DTH, enhanced lymphoproliferative responses, and increased salivary IgA in severely malnourished infants.[163]

The mechanisms of zinc action include regulation of cysteine-rich intestinal protein (CRIP), a zinc finger protein for which metallothioneine serves as a source of zinc. CRIP-deficient transgenic mice show altered cytokine profiles.[171] Experimental dietary zinc deficiency leads to critical genetic changes at several levels, including the gastrointestinal tract, where differential display has shown that zinc deficiency is associated with increased expression genes coding for peptide hormones that affect fluid exchange.[51] In an experimental model of zinc deficiency using HuT-78, a human malignant T lymphoblastoid cell

TABLE 20-1 Regulatory Effects of Micronutrients on Immune Response

Nutrient	*Target Cell*	*Effect*	*Mechanism*
Zinc	T cells, NK cells, B cells	Deficiency promotes infection, impairs immune response, ↓ lymphopoiesis Required for biologic activity of thymulin Essential for antioxidant enzyme activity	Deficiency causes cytokine shifts Deficiency causes glucocorticoid mediated T-cell apoptosis Promotes Th1 response in periphery Promotes Th2 response in GALT Zinc is a T cell mitogen
Iron	T cells, monocytes	Iron deficiency causes ↓ T-cell function and cytotoxic activity Iron excess can promote bacterial growth, but iron also ↓ intracellular growth of mycobacteria	Promotes Th2 response Interacts with TNF-α Excess may suppress IFN-γ production, proliferation of T cells Excess may promote lipid peroxidation
Copper	Monocytes, T cells, neutrophils	Increases antigen presentation Deficiency leads to infections Deficiency ↓ proliferation, phagocyte activity	Modulation of MHC class II expression Affects selenoglutathione peroxidase activity Affects IL-2 receptor secretion Regulates NF-κ
Selenium	Monocytes	Deficiency suppresses antigen presentation Supplementation ↑ proliferaton, cytotoxic activity	Modulation of MHC class II expression Affects IL-2 induction Regulates NF-κB
Magnesium		Deficiency promotes neuropeptide activity SP, calcitonin gene–related peptide Thymic involution	Apoptosis leads to thymic involution SP leads to cytokine activation: IL-2, -4, -5, -10, -12, and -13 and IFN-γ and inflammatory processes
Vitamin A	T cells, NK cells, B cells promote Th2 response	Deficiency causes infections, mortality from infections, ↓ NK activity Supplementation improves gut integrity at weaning Repletion reduces morbidity, mortality from infections	Promotes Th2 cytokine and IgA production Affects keratin and mucin expression IL-2 receptor beta, IFN regulatory factor, transcription factor mRNA Affects IL-12 and IL-10 production
Betacarotene	T cells	Antioxidant/anti-inflammatory effects Low-carotenoid diet reduces T cell function	Increased production of IFN-γ and IL-4
Vitamin C	Phagocytes	Promotes phagocytic function Reduces incidence of colds associated with heavy physical stress	Increases IFN-γ response Regulates NF-κB May inhibit T-cell apoptosis
Vitamin D 1,25-dihydroxy-vitamin D_3	T cells, B cells, monocyte/macrophage/dendritic cells	Vitamin D_3 affects differentiation, maturation, and function of cells Vitamin D_3 suppresses autoimmune disease in animal models Experimental suppression of transplant rejection	Functions through a nuclear receptor, vitamin D receptor that binds to response elements in target genes (many) Modulates MHC class II Affects differentiation of monocytes Regulates cytokine secretion Transcriptional modulator of IFN-γ gene
Vitamin E	T and B cells, monocytes	Enhances response to vaccine Improves skin test response	Modulates cyclic AMP response element binding proteins Affects prostaglandin production

AMP = adenosine monophosphate; GALT = gut-associated lymphoid tissue; IFN = interferon; Ig = immunoglobulin; IL = interleukin; MHC = major histocompatibility complex; mRNA = messenger ribonucleic acid; NK = natural killer; NF = nuclear factor; SP = substance P; Th = T helper; TNF = tumor necrosis factor.

line, slower cell growth with cells remaining in S phase and not entering mitosis was detected. This was likely owing to decreased messenger ribonucleic acid production of IL-2, IL-2 receptor antagonist, and impaired NF-κB nuclear binding.[165] Zinc deficiency can promote the survival of intestinal parasites through impaired IL-4 production, leading to reduced IgE and IgG.[172] Thus, zinc deficiency may affect the Th1-type response systemically and the Th2-type response at the level of GALT in response to the regulatory influence of local conditions.

Copper

Because zinc competes with copper for gastrointestinal uptake, increased zinc intake may sometimes induce copper deficiency, causing neutropenia.[173] Copper deficiency can also impair immune response. In genetic copper deficiency, Menkes' syndrome, death is often related to intractable infections.[174] Reduced copper affects growth of lymphoid cell lines leading to reduced activity of the antioxidant enzyme superoxide dismutase and increased cellular damage associated with impaired mitochondrial

activity and calcium efflux, thereby affecting the cell membrane.[175] Copper also interacts with iron because ceruloplasmin, which contains most of the plasma copper, is a ferroxidase. Ceruloplasmin facilitates release of tissue iron into plasma by oxidizing ferrous iron into ferric iron, which is then bound to transferrin for delivery to the bone marrow for hematopoiesis. High intake of iron, zinc, and manganese can interfere with copper absorption; these interactions may also have an impact on immune response.[176] Although copper is an essential nutrient, clinical copper deficiency is rare. However, short-term dietary depletion in volunteers achieved by means of a low-copper diet was found to cause reduced immune cell proliferative response and diminished IL-2 receptor secretion in response to activation in vitro.[177]

Selenium

Selenium is a key part of the antioxidant enzyme glutathione peroxidase, which maintains the redox state of a cell and catalyzes the conversion of peroxides to nontoxic alcohol. Selenoproteins are an important component of the antioxidant host defense system.[178] Selenium affects neutrophil function and has a role in the initiation of leukocyte adherence to endothelium.[179] A nutrient intervention study has demonstrated an overall survival benefit from supplementation with betacarotene, vitamin E, and selenium among subjects in a region of China with increased stomach cancer incidence, generally low micronutrient intake, and selenium-deficient soil.[180] This benefit was primarily attributable to lowered mortality from stomach cancer. A study of selenium supplementation in healthy volunteers has reported an increase in both proliferative response and cytotoxic effector cell activity.[181,182] Reduced immune response in patients on parenteral nutrition secondary to voluntary selenium depletion has been shown to improve following selenium repletion.[183] A relationship between low selenium level and deficient immune response is observed in children with HIV infection.[184] Selenium supplements did enhance IL-2 production and improve Th cell function in this setting.[185]

Antioxidant Vitamins

The antioxidant vitamins E, C, and A and the precursor of vitamin A, betacarotene, are cofactors in immune response (see Chapter 7). Plasma vitamin E levels are observed to correlate significantly with proliferative response of both T and B lymphocytes in vitro and with resistance to infection.[186] Selenium and vitamin E interact in the development of antioxidant host defense because vitamin E is the major lipid-soluble antioxidant in serum and cellular membranes. Vitamin E appears to influence T-cell function through effects on PGE_2.[187] New studies show that the mechanism of action involves the CREB proteins. Vitamin E appears to enhance CREB2 protein expression and to down-modulate the effect of PGE_2 on CREB1 expression.[62] Murine studies show that deficiency of either vitamin E or selenium may lead to a change in the viral phenotype of coxsackievirus B from nonvirulent to virulent.[188]

Vitamin C supplementation may lead to increased levels of plasma glutathione levels.[189] Vitamin C has been successfully used to treat recurrent furunculosis and was found to restore deficient neutrophil function.[190] Vitamin C appears to lower the incidence of colds among persons under acute physical stress who were prone to upper respiratory tract infection.[191] Ascorbic acid has been shown to suppress HIV viral replication activated by cytokines.[192,193] A recent study indicates that ascorbic acid may inhibit T-cell apoptosis.[194]

Carotenoids have significant effects on immune function and appear to enhance host defense against tumor development.[195] Some studies have shown that betacarotene supplementation affects human immune cells.[196] A low-carotenoid diet may reduce T lymphocyte function.[197] One report suggests the possibility that differences in the physical location of carotenoids in lymphocyte subsets might be the basis of some functional effects.[198]

Although vitamin A is not a particularly efficient oxygen quencher, this micronutrient is emerging as a critical cofactor in host defense. Vitamin A is important for mucosal and epithelial growth. Deficiency of vitamin A can lead to impaired T-cell responses to mitogens and antigens both in vivo and in vitro and is closely associated with risk of infections.[166,199] Vitamin A deficiency may have a promoting effect on measles, *Rotavirus*-associated diarrhea, and progression of HIV infection.[200] Effects on the immune system include reduced antibody response, impaired NK cell activity, and decreased IFN production in the rat.[201,202] Supplementation appears to enhance the development of the humoral immune response.[203]

The causes of human vitamin A deficiency include altered metabolism, either through increased use or increased loss, as suggested by a study of Peruvian children in which diarrhea and low serum retinol were closely linked.[204] Another study in which vitamin A supplementation was given to children in China to prevent diarrhea and respiratory disease showed a reduction in incidence of both conditions that was greater than twofold in the treated compared with the untreated control group of children.[205]

Semba and colleagues have proposed that vitamin A works specifically through support of Th2 cytokine induction.[206] In Lewis rats, low vitamin A intake was associated with decreased ratio of CD4+-to-CD8+ cells and decreased IL-2 production.[207] Pharmacologic levels of vitamin A were able to reverse the effect of protein deprivation in mice, including decline of IgA, IL-4, and IL-5 production, and also to enhance response to immunization.[208] Vitamin A is critical for differentiation of many tissues acting through association with cellular cytoplasmic proteins and nuclear receptors.[65] The effects of vitamin A deficiency can be profound in fetal life, leading to numerous embryonic abnormalities, for example, renal malformations. The vitamin A signal is transduced by nuclear retinoic acid receptors allowing vitamin A control of epithelial mesenchymal interactions.[66]

Vitamin A supplementation studies have largely addressed the potential for support of antibody response. Given a placebo-controlled trial to study the effect of vitamin A supplements, Bangladeshi infants were randomized

to receive either vitamin A or placebo with each of the three DPT/poliovirus vaccine live oral immunizations. Compared with the placebo group, infants who received vitamin A supplementation and also achieved normal retinol levels were more likely to exhibit positive cell-mediated immunity in DTH testing.[209] Similary, children with mild vitamin A deficiency who were asymptomatic or who had mild xerophthalmia showed significantly higher IgG and IgG1 responses to tetanus immunization after vitamin A supplementation.[210,211] On the other hand, higher tetanus titers were not observed in a different group of children given vitamin A with each DPT immunization, although diphtheria titers were increased.[212]

Vitamin A has been used to enhance response to viral vaccines. Concomitant administration of vitamin A along with measles vaccine improved seroconversion rates in some studies.[213] Other investigators found no improvement except among malnourished infants.[214] Reduced secretory IgA and response to measles and polio vaccines associated with vitamin A deficiency have been successfully treated with supplementation.[215] Interestingly, the potential efficacy of vitamin A supplementation has been examined in conjunction with influenza vaccination in children with HIV infection. In these studies, there was no impact on response to influenza. However, the anticipated increment in HIV viral load after immunization was blunted.[216]

MALNUTRITION AND CHRONIC INFECTION

Impaired host defense in the malnourished often leads to a failure to respond optimally to childhood immunization and increased susceptibility to infectious pathogens. Poor response to immunization may be attributable to an inability to develop appropriate humoral and cell-mediated responses to foreign antigens and/or an inability to maintain the capacity for such responses. The extent of this parameter immune deficiency is suggested by a 70% rate of cutaneous skin test anergy in one study of children with marasmus, marasmic kwashiorkor, and kwashiorkor.[217]

Chronic undernutrition often occurs in environments with a high prevalence of enteropathogens in water, which leads to compromised mucosal immunity, which is especially dangerous for infants and children. During fetal and early neonatal life, the development of gut mucosal immune defense may be easily compromised by undernutrition and lead to susceptibility to severe infection.[110] Chronic infection commonly involves malabsorption and malnutrition that is associated with altered cytokine patterns affecting both regional and systemic or immune response and alters metabolism and growth.[36,37]

Nutrient metabolism provides an essential stimulus for the induction, differentiation, and maintenance of the mucosal immune system,[218] which is compromised by prolonged illness and reduced dietary intake. Lack of enteral dietary intake impairs mucosal IgA and secretory component production, the number of IgA-containing cells, and the level of IgG, as shown in recent studies.[49,219] The enteral route of nutritional intake promotes mucosal growth.[220] Loss of this stimulation is associated with immune suppression. Current studies show that provision of glutamine, arginine, certain combinations of n-3 polyunsaturated fatty acids, and dietary nucleotides are critical for recovery of mucosal immune function.[221]

The catabolic state imposes a strict requirement for normally nonessential amino acids, specifically arginine and glutamine. These must be supplied acutely to promote cellular proliferation in the gut and T-cell production and to protect against the development of host defense against infection, as well as to restore nitrogen balance. Glutamine use is highly increased in proliferating immune cells, and reduced availability directly limits immune response.[22] Glutamine stimulates a Th2-type cytokine response, leading to increased IL-4 production and an increase in mucosal IgA level,[222] which improves both GALT and respiratory tract immunity. Arginine has a similar function and, in experimental studies, modulated monocyte production of TNF-α.[223]

Nutrient Deficiency and HIV Infection

Weight loss is a common occurrence in chronic viral illness. Infection-induced malnutrition, as discussed above, is primarily cytokine mediated and occurs through the initiation of the acute-phase response. Fever, cellular hypermetabolism, and various endocrine and metabolic changes eventually lead to catabolism and gluconeogenesis. These are accompanied by multiple effects on metals and minerals such as fluxes of iron and zinc and cause losses of nitrogen, potassium, magnesium, phosphate, zinc, and vitamins. This process is accompanied by retention of salt and water. Malnutrition may occur early during the asymptomatic phase of HIV infection, especially in children,[224–226] in whom growth failure may be a presenting symptom.[37] Malnutrition in the late stages of acquired immune deficiency syndrome (AIDS), in the absence or failure of effective antiretroviral treatment, is closely linked to poor survival and to lower CD4+ T-cell level.[227] Response to intravenous nutrition is not impaired in the early stages of disease, and repletion of body mass through parenteral nutrition is effective in patients who have malabsorption without serious ongoing systemic disease.[228]

Trace elements and micronutrient levels are fundamentally significant for the HIV+ host response as a consequence of the need for enhanced antioxidant defense. Reactive oxygen species generated through either HIV replication or host response can damage tissues and can also up-regulate genes involved in the inflammatory response. One of these, NF-κB, is an important regulator of HIV replication.[229] Several studies have shown that micronutrient impairment is causally associated with the course of HIV infection and that there is a crucial impact on immune function.[230–233]

One key factor is iron status. The anemia of HIV infection is characterized by iron deficiency, poor erythropoietin response, reduced number of red cell progenitor colonies, and other abnormalities of reticuloendothelial iron metabolism.[234] Both iron deficiency and iron overload may affect

erythropoietin function through differential effects on Th function and cytokine patterns.[235] Whereas iron deficiency secondary to malabsorption is common in HIV infection,[236] iron overload also occurs frequently and is reflected in high serum ferritin and red cell ferritin.[237] The cytokines that mediate these effects include TNF-α, a powerful activator of NF-κB, which, in turn, is a critical activator of HIV replication. HIV replication leads to production of HIV tat protein, which further shifts the cellular milieu toward a pro-oxidative state by down-regulating the manganese-dependent superoxide dismutase.[238] Interestingly, iron chelation can be effective in blocking HIV replication.[239] The presence of oxidative stress in HIV infection has also been shown as increased lipid peroxidation.[240] This appears to be directly linked to reduction in levels of antioxidant trace elements and vitamins. Recent studies in HIV-infected persons support this connection showing that vitamin E and C supplementation led to reduced lipid peroxidation and also lowered viral load in the treated group compared with the untreated group.[241] The most commonly identified alterations in trace element and mineral levels in HIV infection involve zinc, selenium, and magnesium, with losses of selenium and zinc showing a relationship to clinical course.[185,230–233] Skurnick and colleagues found that use of supplements was associated with a better level of antioxidant micronutrients in HIV+ persons but that almost one-third of patients on supplements had reduced levels of at least one nutrient.[232] Vitamins A, C, E, and B_{12} and carotenoids are also frequently reduced.[242]

Trace elements such as zinc and selenium decline in HIV disease as lipid peroxidase levels increase, and this low status may persist at a later stage of disease, when polymorphonuclear leukocyte production of lipid peroxidases decreases. Look and colleagues found a strong correlation between the stage of clinical disease and reduced selenium such that selenium levels were positively correlated with CD4+ T-cell count and negatively correlated with TNF-α levels.[243] Furthermore, coinfection with hepatitis C virus was associated with further reduction in selenium levels. Other studies have shown that there is a correlation between very low selenium levels and morbidity.[230] The relationship between low selenium level and deficient immune response was also observed in children with HIV infection before the advent of highly active antiretroviral therapy.[184]

Vitamin A deficiency has been associated with maternal HIV transmission and as an etiologic factor in mortality from infections in general.[244–246] Assessment of vitamin A in children congenitally exposed to HIV has shown that higher proportions have levels less than 20 μg/dL, the lower limit of normal.[247,248] Semba and Tang have shown that vitamin A supplementation reduces morbidity and mortality in a wide range of bacterial and viral infections, including HIV infection.[242,249] These studies suggest that reduced levels of *trans*-retinol might compromise immune response in children congenitally exposed to HIV who are not infected. For example, these reduced levels may affect response to usual childhood immunizations or other environmental pathogens.

Host Defense against Endemic Infection

The interrelationship between parasitic infections and host nutritional status has been the object of speculation and scientific investigation for at least six decades.[250–252] The difficulty in unraveling these relationships is a consequence of the heterogeneity of human parasites, their varied life cycles, the pathology they evoke from their host, and the complexity of host immune responses to parasitic infection. The relationship among parasitic infection, malnutrition, and host immune response is also complex because parasitic infections (like all infections) not only contribute to malnutrition and reduced host immune response but are also affected by host nutrition. Intestinal parasites may irritate the intestinal tract and cause symptoms, including inflammation and loss of appetite. Intestinal protozoa that damage the intestinal tract may impair host nutrition directly as a result of inflammatory or non-inflammatory diarrhea, resulting in the loss of nutrients and micronutrients (eg, *Blastocystis hominis*, *Cryptosporidium* spp, *Entamoeba histolytica*, *Microsporidia* spp, *Giardia lamblia*). The acuteness of symptomatic infection (eg, amebiasis), diagnostic difficulties with some of these organisms (eg, *Cyclospora*, *Cryptosporidium*, *Microsporidia*), and the recognition only recently of the pathogenicity of some of these organisms (eg, *Cyclospora microsporidia*, *B. hominis*) may explain in part the emphasis of early nutrition studies on the importance of intestinal helminths as a cause of malnutrition in children.

The role of intestinal hookworms (*Necator americanus* and *Ancylostoma duodenale*) in the cause of anemia has been well documented.[38] Blood loss occurs from the worms feeding on the intestinal mucosa and is directly proportional to the intensity of infection. Even a modest infection of *N. americanus* can result in blood loss that exceeds physiologic daily requirements. Light infections of *A. duodenale* may cause severe anemia in an infant that is difficult to correct with iron supplementation alone.

The relationship of hookworms and other intestinal helminths (eg, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Enterobius vermicularis*) to other forms of nutritional impairment (eg, growth stunting, protein/caloric malnutrition, avitaminoses) has been more controversial and difficult to elucidate. Heavy infections with *Ascaris* may result in malabsorption, mild anemia, wasting, and poor growth. The worm metabolizes vitamin A, and heavy infections have been associated with vitamin A deficiency. Anemia and wasting are common in heavy infections with *Trichuris*, but light-to-moderate infections are not felt to result in significant blood loss. Strongyloidiasis causes abdominal pain and diarrhea, but hyperinfection with *S. stercoralis* has profound nutritional consequences resulting from severe diarrhea, malabsorption, and wasting.

Impairment of food absorption from sheer parasite bulk and heavy (quantitative) infection with intestinal helminths was postulated by Jelliffe.[251,252] In addition, Jelliffe and Jung also observed that heavy *Ascaris* worm burdens were frequently associated with signs of avitaminosis, including Bitot's spots, follicular keratitis, lusterless and scaly skin, and dry, light-colored hair.[253] They suggested

that the adult worm, especially the parturient female producing 200,000 eggs/day, competed directly with the host for essential nutrients. Others have proposed different adverse mechanisms, including absorption of nutrients through the worm cuticle, the elaboration of toxins, trauma to the intestinal mucosa, anorexia, and vomiting. Also of concern to early helminthologists were parasite factors that influence pathogenicity, morbidity, and mortality in the host: population density, mode and pattern of entry, virulence and adaptation to the human host, responses to intercurrent and associated infections, and responses to the "modified host."[254] Beaver emphasized the not universally accepted helminthologic principle that worms in small numbers are relatively well tolerated but that heavy and massive infections cause signs and symptoms that are characteristic of each specific infection, such as malabsorptive syndrome in ascariasis.[254] The quantitative assessment of disease-producing levels of infection and the quantitative impact of parasitic infection on protein, vitamins, and other nutrient elements have been the object of intense study during the past three decades. Large studies of schoolchildren in Kenya have demonstrated the adverse effects of ascariasis on child growth and development, as well as the beneficial effects of periodic deworming.[255–257]

More elusive is the interrelationship between parasite and host nutrition of tissue protozoa; tissue nematodes, filarial worms, and other helminths; flukes; and cestodes. An exception is schistosomiasis, which has long been known to have serious nutritional consequences. Both urinary (*Schistosoma haematobium*) and intestinal infections (*Schistosoma mansoni* and other species) cause significant blood loss. Intestinal infection results in severe pathologic lesions with accompanying malabsorption, protein loss, and anemia. Additional nutritional compromise results from the liver damage found in advanced schistosomiasis. As with hookworm, adverse nutritional consequences of schistosomiasis are related to the intensity of parasitic infection.

Malaria causes the most serious nutritional consequences of any major parasite.[38] It causes hypochromic, microcytic anemia, but this is not associated with iron deficiency, except in the case of hemoglobinuria that occurs with blackwater fever (*Plasmodium falciparum*). Anemia also results from rapid hemolysis and in cases of chronic malaria (*P. ovale*, *P. malariae, P. vivax*). Erythroid recovery from malaria requires increased amounts of folate. The malaria parasite infects the placenta of pregnant women, compromising blood flow to the fetus, and increases the risk of low birth weight among infants in developing countries. Additionally, malaria is associated with PCM in the pregnant or lactating woman and in young children, which may be caused by increased caloric requirements secondary to chronic, recurrent fever and the acute-phase cytokine response. Clinical illness also causes vomiting and anorexia, which produce adverse nutritional consequences in an already fragile child or pregnant woman.

During the past two decades, new developments in in vitro culture techniques for T lymphocytes have resulted in new understanding of cellular immune responses in parasitic infections.[258,259] A variety of immune mechanisms are elicited in helminthic infections (antibody-independent macrophages, antibody-dependent granulocyte killing), and central to this immune mechanism is a balance between Th1- and Th2-type responses, which is biased strongly toward the type 2 pathway.[260,261] The balance between the host immune response and parasitic strategies for survival is one that centers on host expulsion of the worms versus persistence of the worms and their products.[262] The results are critical for both the production of host pathology and survival of parasite progeny. The protective effect of IL-4-dependent expulsion of intestinal nematodes involves regulation of TNF and operates by mechanisms other than merely gross degradation of the parasite's environment through immune enteropathy.[263] There are essentially three major types of hypersensitivity responses to helminth infection accounting for most immunopathology: (1) DTH Type I, mediated by Th1 cytokines; (2) DTH Type II, which is mediated by the Th2 cytokines IL-4 and IL-5 and leads to eosinophilic granuloma formation; and (3) DTH Type III, which is associated with IL-4 and TGF-β and leads to fibrosis. In addition, there are down-regulatory effects associated with Th2-type cytokine expression.[264] This may be considered an evasive strategy that helminth parasites have developed against host-mediated cytokine response.[265–267]

Zinc deficiency impairs immune response to intestinal nematode infections at both the systemic and the intestinal level.[172] Conversely, infection itself can alter host nutritional status with respect to zinc. Diarrhea promotes zinc loss, and oral zinc has been used prophylactically and therapeutically to treat diarrhea. An indirect relationship also appears to occur between body zinc levels and infection with *G. lamblia*, although it is unknown whether low zinc levels predispose to giardiasis or whether the parasite depletes body zinc levels.[268] On balance, studies show that CD4+ T cells are critical for host protection and that IL-12 and IFN-γ inhibit protective immunity because Th2-type response is required for protection. In particular, IL-4 is required for host protection, can limit severity of infection, or can induce ancillary protective mechanisms. However, it is important to note that some cytokines that are stereotypically produced in response to gut nematode infections fail to enhance host protection against the eliciting parasite.[269] The nutritional status of children is affected by the symptoms of parasitic infections, for example, protein-losing enteropathy, and this also has a direct effect on the ongoing immune response toward parasitic infections, as shown by studies on the IgE response against *A. lumbricoides*.[270] Indeed, protein malnutrition may actually increase the survival of nematode parasites by decreasing gut-associated IL-4 (Th2) and increasing IFN-γ (Th1), leading to reduced intestinal and systemic Th2 effector responses.[271]

Further, proinflammatory cytokines initiated during acute-phase response to infection act to elicit cellular responses throughout the body, and nutrients are lost during any generalized febrile infections. IL-1, IL-6, TNF, and IFN-γ are particularly important in this response. Symptoms associated with the acute phase include fever, malaise, myalgia, arthralgia, anorexia, nausea, vomiting,

somnolence, weight loss, and loss of nitrogen and intracellular ions and minerals. Energy expenditure increases at the same time that the infected host experiences a decrease in intake, and diarrhea may result in decreased intestinal absorption of nutrients.[36]

Humoral immune response may play a more important role than cellular immune response for some parasites, such as *G. lamblia*. Furthermore, the evaluation of immune response to intestinal parasites is complex because polyparasitism is common, and the presence of other parasites in the stool may suppress both the type and number of other parasites present.[272] Age-related seropositivity of antibody to *G. lamblia* and other parasites may vary widely for children living in different areas and under different environmental conditions, possibly resulting from different levels of sanitation, water contamination, and person-to-person transmission.[273] A recent study of *G. lamblia* infection in infants and young children reported significant variations in the humoral immune response of children from different clinical settings. Children in a daycare setting with good hygiene habits and asymptomatic infections, children from a poor, farming community with *Giardia*-associated diarrheal episodes, and infants followed since birth in a community with universal *Giardia* infection by 2 years of age were compared.[274] Although the level of *G. lamblia*–specific IgM antibody results from exposure to the parasite, the development of sustained levels of specific IgA antibodies may require recurrent exposure to the parasite,[275] as commonly occurs in developing countries where infection is common and reinfection frequent.[276] Studies of children with chronic *Giardia* infection have suggested an impaired IgA response to *Giardia* heat shock antigen in affected children and an ineffective switch from an IgM to an IgG or IgA response.[277]

The immune response to protozoa such as *C. parvum* and *C. cayetanensis* has not been studied as extensively. The significance of these parasites in immunocompromised patients (eg, HIV-infected individuals with AIDS) supports an important role for T cell–mediated immunity. The role of specific antibodies is not yet clear. The persistence of protracted diarrhea owing to *C. parvum* infection in a group of HIV-infected individuals with lower CD4+ lymphocyte counts, despite high levels of both serum and secretory antibodies, suggests that specific secretory antibodies are not sufficient to control infection of the intestinal mucosa by this organism.[278]

In summary, susceptibility to parasitic infections is enhanced by malnutrition, and malnutrition can attenuate host response and promote parasitic survival. Most parasitic infections are subclinical and chronic in nature, and often only the most severely malnourished individuals (usually women and children) seek medical care, even though the majority of the population experiences undernutrition and growth stunting or growth retardation.

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CHAPTER 21

BRAIN DEVELOPMENT

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Nutritional deprivation is a major international concern. In some low-income countries, over 20% of newborns begin life with a birth weight below 2,500 g and up to 50% of the children under 5 years of age experience moderate and severe underweight.[1] Without adequate nutrients, children's expected rate of weight gain falls off, leading to wasting, followed by a decline in their rate of linear growth, leading to stunting. Thus, millions of children experience nutritional deficiencies that are severe enough to interfere with their early growth.

This chapter examines the relationship between nutritional deficiencies and brain development in children, primarily manifested as child development. It reviews the history of research linking nutrition and children's development, methods used to study child development, and the evidence linking nutrition and child development, with an emphasis on micronutrient deficiencies. Finally, recommendations are made to reduce the burden that children experience from nutritional deficiencies. A review of the potential role of dietary fatty acids and neurodevelopmental status is included in Chapter 5.1, "Macronutrient Requirements for Growth: Fat and Fatty Acids."

HISTORICAL CONSIDERATIONS

The association between nutritional deprivation and child development has been a topic of interest for over 40 years. Initially, investigators focused on protein-energy malnutrition (PEM), caused by a lack of calories. Undernourished children adapted to the lack of calories through a decline in their rate of growth. First, they experienced a decline in their relative weight for height, followed by a decline in their height for age. Thus, wasting served as a marker of acute nutritional deprivation, and stunting was a marker of chronic nutritional deprivation. During the acute phase of nutritional deprivation, children have been described as lethargic, apathetic, and inactive, with poor performance on measures of cognitive functioning.[2,3]

Most of the research has addressed the long-term consequences associated with early nutritional deprivation. Guided by findings from animal research that nutritional deprivation leads to structural changes in the developing brain,[4] investigators used functional assessments, such as intelligence quotient (IQ) or performance tests, to determine whether previously nutritionally deprived children recovered or experienced long-term consequences. Most investigators used case-control, retrospective designs to study children with a history of nutritional deprivation and compared their performance on tasks with the performance of adequately nourished children.

Changes in height over the past century illustrate that the influence of individual factors on children's development cannot be considered in the absence of environmental factors. Although individual differences in height are determined largely by heredity, environmental influences, such as access to healthy nutrition and medical care, have contributed to the increase in the average height of adults.

Nutritional deprivation often occurs in the context of poverty. Most investigators handled socioeconomic differences in study populations by recruiting comparison children from similar socioeconomic backgrounds, matched on variables such as maternal education. Little attention has been directed to individual differences or how children's response to nutritional rehabilitation may vary by environmental characteristics. Recent advances in nutrition, animal research, behavioral neuroscience, and child development have had major impacts on the investigation of nutritional deprivation and child development.

NUTRITION

Although PEM continues to be a prevalent problem, especially in low-income countries, recent evidence suggests that micronutrient deficiencies may have greater specificity in children's development. Micronutrients represent small quantities of essential vitamins and minerals that promote healthy growth and development. Because they are not produced by the body, they must be acquired either through the diet, fortification, or supplementation. The relationship between micronutrient deficiency and early cognitive development has captured recent attention because micronutrients are related to specific physiologic and neurologic processes.[5]

Micronutrient deficiencies are a critical concern among children throughout the world. Iodine, iron, and zinc have been linked to cognitive processes in infants and young children and are addressed in this review. Approximately 30% of the world's population live in iodine-deficient areas and 25% of the world's children under age 3 years have iron deficiency anemia, with higher rates in developing countries.[6] When iron deficiency without anemia is considered, rates are even higher.[7] Less is known about rates of zinc deficiency. Estimates from dietary intakes of children from developing countries suggest high rates of zinc deficiency among infants and toddlers,[8] and low zinc intake may be common among middle-class infants and toddlers in America.[9]

Animal Research

Animal models, primarily rats, have been widely used in research linking nutrition to cognitive functioning. Much of the neurologic development of rats occurs postnatally, enabling investigators to study the timing and chronicity of nutritional deprivation.[4] In the past, animal researchers often experienced difficulty disentangling the environmental and nutritional effects on young animals. Many of the techniques used to introduce nutritional deprivation (eg, increasing the number of infants for a mother to feed, decreasing access to the mother, feeding the mother a low-nutrient diet, ligating the mother's nipples) altered mother–pup interaction and the social environment, thus confounding the research. Through innovative designs, such as the introduction of artificial feeding, investigators were able to vary both nutritional intake and environmental stimulation.[10,11] Animals who experienced both nutritional and environmental deprivation tended to have worse performance than animals deprived in only one condition, suggesting that the environmental stimulation may have "buffered the worse effects of the undernutrition."[10] Levitsky and Barnes described the process whereby nutritional deficiencies are partially mediated through caregiving behavior as functional isolation.[12] Thus, in addition to the direct effects of nutritional deprivation, undernourished animals who are unable to elicit environmental stimulation may also be denied the environmental enrichment that promotes development.

The recognition that the link between nutritional deprivation and intellectual performance depended on non-nutritional factors and could be influenced by environmental stimulation had an important impact on research involving nutritionally deprived children. It illustrated the necessity of incorporating caregiving variables, such as the quality of parent–child interaction, into models of child development rather than merely controlling for socioeconomic differences.[13]

The timing of nutritional deprivation has been a particularly relevant question in animal research because early investigations were guided by the sensitive period hypothesis that developing organs deprived of essential nutrients would experience irreversible structural damage.[4] Although some changes induced by nutritional deprivation remain following rehabilitation, particularly related to myelin (the fatty substance that surrounds nerve cells and aids with transmission), neuronal mitochondria, and neurotransmitter metabolism,[10] many structural changes can be reversed with nutritional rehabilitation.[14] The cerebellum and hippocampus were thought to be particularly vulnerable to nutritional deprivation because substantial growth occurs postnatally. However, evidence has challenged this assumption.[10]

In a review of 165 animal studies, there were no consistent findings of long-term consequences to cognitive functioning.[15] Smart concluded that following rehabilitation, nutritionally deprived animals are compromised in their ability to run complex mazes, perform tasks requiring visual discrimination, and extinguish learned responses. Their cognitive flexibility is limited, thereby inhibiting their ability to shift to new cognitive tasks and giving them a "tendency to perseverate."[10] However, rehabilitated animals are not impaired in all tasks (eg, spatial learning, active avoidance, and left/right discrimination) and, in some cases, achieve better performance than adequately nourished animals, particularly when performance is tied to a food reward.

Rehabilitated animals with a history of nutritional deprivation appear to be at risk for changes in their emotionality, motivation, anxiety, and cognitive flexibility. These behaviors are evidenced by increased spilling, hyperreactivity to unfamiliar stimuli, increased aggression, and the like and may interfere with performance on cognitive tasks. Levitsky and Strupp explained that early malnutrition may alter neurochemical receptor systems and result in "a decreased ability of adrenergic receptors to exhibit down regulation," which may result in a "diminished ability to adapt to stressful situations."[14] A recent study among stunted school-aged children with an early history of undernutrition showed an altered stress response, as indicated by elevated cortisol levels, heart rates, and urinary epinephrine.[16] Although the findings from the early animal studies linking nutritional deprivation to brain development and cognitive performance have not been as clear as originally hoped, they have made important contributions to research with children by highlighting the importance of the contextual environment and the role of emotionality, motivation, anxiety, and cognitive flexibility.

Behavioral Neuroscience

Recent advances in behavioral neuroscience have shown the important role that experiences play on brain development, particularly synaptic formation.[17] Brain development begins prenatally and continues through school years. It begins with the formation of brain cells, followed by cell migration and differentiation, and the development of synapses to enable cells to communicate with one another. Finally, the supportive tissue (myelin) is formed to protect the nerve cells and facilitate communication.[18]

The process of forming and eliminating synapses occurs throughout the developmental period and is influenced by experiences.[18] Greenough and Klintsova argued for the distinction between two types of experiences: experience expectant and experience dependent.[19,20] Experience-expectant development refers to species-specific

development, such as sensory and motor systems. The maturational influences that guide development are operationalized by experiences that are expected, such as adequate nutrients. Nutrients, like other experiences, "influence the brain by causing chemical changes within cells that influence cell function and structure."[18]

In contrast, experience-dependent development occurs by experiences that are unique to the individual. They enable individuals to adapt to specific cultures and the demands of their environment. When individuals are denied these experiences (eg, through sensory deficits or lack of nutrients), they may not develop the synapses necessary for optimal functioning. The structural changes in synaptic formation appear to be dependent on neurochemical receptor systems that, in turn, are influenced by experiences as basic as caregiving.[18]

The timing of early developmental experiences has been a central issue in studying behavioral neuroscience. The critical or sensitive period hypothesis suggests that if an event, such as nutritional deprivation, occurs during a specified period of time, often during a period of rapid development, it will have specific effects on the organism.[4] Developmental scientists often prefer the term "sensitive" period rather than "critical" period because it implies less rigidity.[21] In addition, because components of the central nervous system develop along differing schedules, it is likely that the sensitive periods of the components vary. Although there are examples of sensitive periods, particularly in the animal research, there is limited evidence to support the notion of sensitive periods related to experiences in human development.[21]

Child Development

Child development refers to the orderly progression of skills that children acquire as they mature and adapt to their specific caregiving settings. Although there are universal aspects of child development, particularly early in life as children gain motor skills and learn to roll over, sit, stand, and walk, there are also individual differences in the acquisition of skills. In addition, there are culture-specific aspects of child development that depend on specific interactions that children have with their caregivers. For example, children learn to understand and speak the languages that they hear in their household.

The transactional system provides a useful framework for understanding the link between nutrition and early child development because it emphasizes the interplay that occurs between children and their environment, mediated through relations with their caregivers.[13,22,23] Thus, children's development is influenced by characteristics from the child (eg, nutritional status), from the caregiver (eg, maternal education), and from interactions between the child and caregiver (eg, reciprocity and clarity of communication during feeding). The process becomes clear when applied to problems associated with children's growth.

For example, a woman who is undernourished during her pregnancy and does not receive prenatal care is more likely to give birth to a child with low birth weight (LBW) (< 2,500 g). In comparison with full-term infants, infants born with LBW are smaller and often have weaker cries and sucking skills.[24] These characteristics make infants with LBW more difficult to feed, particularly for mothers who are undernourished themselves. A cycle emerges whereby the small and weak infant is difficult to feed, does not grow well, may be vulnerable to illnesses, and lags behind in developmental skills. Mothers often feel frustrated and/or frightened by their infants who are small and sickly and may limit their caregiving to holding rather than talking or encouraging exploration.[25] This process results in a negative cycle whereby infants do not elicit or receive the care and attention they need to promote optimal development.

Intervention can occur at multiple points within the transactional system. For example, intervention could be directed to the infant with LBW, perhaps through nutritional and developmental intervention that might be available through community nutrition programs or through early intervention programs. If the child's growth and development improve, the child will be more likely to elicit and receive age-appropriate care and interaction from the caregiver.

Intervention could also be directed toward the caregiver and the interaction between the caregiver and the child.[26] Children's cues are analyzed to ensure that the caregiver understands how the child expresses hunger or satiety, and caregivers learn how to read and respond to children's cues. There are several examples of successful randomized controlled trials that use components of the transactional system to promote the development of undernourished children.[27,28]

Although most of the attention has been directed to the impact of inadequate nutritional and caregiving practices on children's nutritional status, children may influence caregiver behavior through their nutritional status, as predicted by the transactional system. Children with PEM have been described as negative, wary, and lethargic.[29] It is not surprising that during home observations, mothers of malnourished infants were less sensitive and responsive than mothers of healthy infants[30] and tended to hold or carry them rather than play with them.[25] Caregivers who treat their infants as though they are ill or unable to participate in age-appropriate activities may be inadvertently denying them opportunities for developmental stimulation and enrichment.

In one of the only studies to observe caregiver–child interaction prior to the child's becoming malnourished, investigators in Mexico reported that infants of mothers who lacked sensitivity and affection were more likely to become malnourished compared with infants of more sensitive mothers.[31] In turn, after infants received nutritional supplements, their mothers were more engaged, both in caregiving and in enrichment activities, compared with mothers of nonsupplemented infants, suggesting that mothers respond to their infants' increased energy and activity.

Young children depend on interactions with their primary caretaker and are more active when their caregiver is present than absent.[32] As children grow physically and demonstrate more skills, their caregivers respond with expectations for increasingly complex behavior. For exam-

ple, caregivers are likely to have higher expectations for a 3-year-old child of average height who communicates in sentences compared with a 3-year-old child who is stunted and speaks in single words or brief phrases. In addition, children who are perceived by their caregivers as having easy or pleasant temperaments are more likely to elicit positive caregiving interactions, whereas caregivers tend to become less involved with children whom they perceive to be difficult.[33]

METHODOLOGY

Most research examining associations between early nutritional deprivation and subsequent intellectual skills has been retrospective and observational. The choice of an adequate control group has been challenging, and many studies have not accounted for differences in environmental or caregiving factors that could contribute to differences in findings. This section examines the choice of outcome and predictor variables and considers environmental and caregiving variables that may confound findings.

Childhood Measure of Intelligence

The primary outcome measures used in studies of recovery from nutritional deprivation have been generalized tests of intelligence administered during the school-age years, such as the Wechsler Intelligence Scale for Children-III (WISC-III). The WISC is a standardized assessment that yields an IQ that is stable over time and predicts both academic performance and occupational status.[34] Although many other factors contribute to academic performance and occupational success (eg, motivation), the IQ is a useful indicator of successful rehabilitation.

Infant Measures of Intelligence

Infant intelligence is very difficult to measure. Not only is it challenging to ensure that infants are not hungry, tired, or irritable when testing is scheduled, but infancy is marked by rapidly changing skills with discontinuities in early development. In addition, generalized infant tests require the integration of multiple cognitive and noncognitive processes.

General Tests of Intelligence Investigators have used either generalized tests of infant intelligence, such as the Bayley Scales of Infant Development (BSID), or specific information processing tests. The BSID is a well-standardized assessment that includes three scales: a Mental Scale that yields a Mental Developmental Index (MDI), a Motor Scale that yields a Psychomotor Developmental Index (PDI), and the Behavior Rating Scale, which yields a percentile score. The BSID was designed to determine if infants were able to complete age-normed tasks, not to predict future functioning.[35] It has excellent psychometric properties, with internal consistencies measured by coefficient alphas ranging from .84 to .88 and test–retest reliabilities at 12 months ranging from .77 to .90, depending on the scale. However, correlations from infant assessments administered prior to 18 to 24 months of age to later intellectual performance are notoriously low, lower than predictions from socioeconomic variables, such as maternal IQ or education.[36] In addition, correlations between scores from the Bayley Scales and specific information processing tests, such as visual habituation and attention to a novel stimulus, are low,[37] probably because the information processing tests are tapping specific areas and the BSID examines higher-order functioning, thereby incorporating motivation, attention, and multiple cognitive processes. Beyond age 2 years, once children gain the skills of symbol formation, predictability from early childhood assessments to subsequent intellectual performance increases dramatically.[36]

Specific Tests of Information Processing There has been a great deal of enthusiasm about specific information processing tests administered during infancy (eg, visual attention, learning, and memory) because they are predictive of school-age intellectual performance.[38] The predictability from rate of habituation (number of trials to reach habituation) and response to novelty is higher than the predictability from generalized tests of infant intelligence, particularly when infants are assessed between 2 and 7 months of age. It is not clear why the associations are strongest during this period. The early infant information processing tests may measure speed of processing and/or the ability to inhibit attention to irrelevant stimuli. The drop in predictability after 7 months of age may be related to competing systems, such as sociability.

Habituation is a measurement of visual learning that has been widely used. It is measured by an infant's response to a repeating series of stimuli.[39] As the infant forms an internal representation of the stimulus, the intensity of the response decreases, resulting in a learning curve. Examiners may score the rate of the decline, the number of trials necessary to reach criterion, the duration of looking time prior to response decline, the pattern of the decline, and the infant's ability to recover and respond to a novel stimulus.[39] The psychometric properties of habituation measures, as indicated by test–retest reliability, are only modest.

The paired-comparison test has been used to assess short- and long-term visual recognition memory.[39] It includes two phases: familiarization and test. During the familiarization phase, two identical stimuli are presented, and the infant has an opportunity to view them. During the test phase, a familiar stimulus is paired with a novel stimulus. The observer notes the proportion of time the infant gazes at each stimulus. Because infants are likely to spend more time gazing at the novel stimulus, a novelty score is calculated by dividing the amount of time the infant looked at the novel stimulus by the time the infant looked at both stimuli. As with the habituation test, the psychometric properties are only modest.[39]

The Fagan test is the most widely used test of visual recognition memory. It has been standardized and published and includes guidelines for training, administration, and scoring, with reference data.[40] However, only one indicator from the test has predictive validity: percentage of infant visual fixation to the novel stimulus averaged over all items.[40]

A number of other processing tests can be administered during infancy, including focused attention (concentration

devoted to processing information about an object),[41] cross-modal transfer (transfer of learning from one sensory modality to another),[42] and the A-not-B task (a Piagetian task that examines object permanence).[43] There has been only limited use of infant information procedures with infants who experienced nutritional deprivation. For example, Rose found that nutritionally deprived infants (5 to 12 months of age) from India had difficulty with two tasks related to cognitive processing: visual recognition memory and cross-modal transfer.[44] In addition, they had difficulty demonstrating age-related improvements. Most investigators recommend that tasks should be selected to assess specific processes and that multiple measures be used, beyond IQ, to gain a comprehensive understanding of how nutritional deprivation and recovery impact processing skills.[36,39]

Direct Measures of Brain Functioning During recent years, there has been much interest in brain-behavior relationships and increased attention to behavioral neuroscience. However, there are few methods to measure brain functioning in children. Two direct measures of brain functioning are positron emission tomography (PET) and functional magnetic resonance imaging (MRI).

PET scans are done to identify the location of neural activity but require the injection of a radioactive substance. As the substance is metabolized by the brain and the radioactivity decays, positrons are emitted and can be measured by the PET scan. Thus, investigators can localize synaptogenesis or other neuronal activity.

Because the PET scan requires the injection of a small amount of radioactive substance, the procedure is not without risk and therefore is primarily used with patients who have medical reasons for the scan. In addition, the test is expensive and the spatial and temporal resolutions are low, meaning that it is not possible to identify precise locations or to identify exactly when neural activity is occurring.

Functional MRI is an alternative technique used to identify the location of neural activity. Although it does not require the injection of radioactive substances, it requires the child to be still. When a specific area of the brain is activated, blood flow to that area increases, and oxygen is created. By monitoring changes in oxygen in consecutive "slices" of the brain, the MRI scanner can determine areas of greatest activation. The functional MRI procedure has been used with adults to study the location of neural activity, and developmental scientists are beginning to use it with children.

Environmental and Caregiving Factors Related to Nutritional Deprivation

Nutritional deficiencies often occur in a context of poverty among families who have few economic resources and limited education. Not only do many low-income families have restricted access to nutritionally healthy food, but mothers who are poorly educated are less likely to choose nutritionally appropriate foods for their children compared with better educated mothers.[45] Thus, poverty and factors associated with poverty, such as low maternal education, may have a direct effect on children's development.

Caregivers contribute to their child's development through their care practices, such as providing food and basic care required by young children.[46] In the past, much attention regarding care practices was directed toward defining the quality and quantity of food that children require. However, recent evidence has demonstrated that care practices play a role in children's development that extends beyond the provision of food. Care practices include the relationships that caregivers form with their children during feeding and other daily activities.[18,46] Healthful care practices include behavior that is responsive to children's needs and is characterized by warmth and affection.[46]

Although most investigators have recognized the importance of controlling for demographic variables, little attention has been given to the role of moderating or mediating variables. Moderating variables examine how recovery works under differing conditions. For example, are there differences in cognitive performance related to the timing of the nutritional deprivation? Mediating variables examine the process whereby nutritional deprivation influences cognitive functioning.

EVIDENCE LINKING NUTRITION AND DEVELOPMENT

Long-Term Consequences of Early Nutritional Deficiencies

Information on the long-term consequences of early nutritional deficiencies is available from several natural experiments, including nutritionally deprived children being adopted into middle-class families or nutritional deficiencies occurring among children from middle-class families caused by disasters or chronic illness. In addition, information is available from follow-up studies of children from low-income countries who experienced moderate to severe nutritional deprivation or children from middle-income countries who experienced mild nutritional deprivation. However, data on the long-term consequences of early nutritional deficiencies can be difficult to interpret because children who experience nutritional deficiencies are often raised in low-income families in which they also experience environmental deficiencies.

Natural Experiments

Orphans from Korea who varied in their nutritional status were adopted by middle-class American families and tested during their school-age years. The children who had been undernourished early in life achieved scores in the normal range but lower than those of better-nourished Korean adoptees.[47] Although these findings demonstrate the impact of an enriched environment on children's intellectual skills, they also suggest that early nutritional deficiencies may limit children's ability to benefit from their environment.

In 1944, there was a famine in Holland that affected the entire population, regardless of economic standing. When the youth were tested at 19 years of age as part of an army physical, there was no long-term evidence of intellectual deficiencies compared with scores from nonfamine years.[48] These findings suggest that environmental enrichment had

overcome any deficiencies associated with the early nutritional deficiencies.

Children with chronic diseases, such as cystic fibrosis, sometimes experience malnutrition because they cannot absorb nutrients. Several investigators demonstrated that among children from middle-income families, there were no differences in intellectual scores when children who experienced nutritional deficiencies secondary to chronic diseases were compared with children who had been hospitalized but were well nourished.[49,50] In contrast, among low-income children, those who experienced nutritional deficiencies secondary to chronic disease had lower scores than those who had been hospitalized but were well nourished. These studies illustrate the buffering effects of a nurturing environment on the intellectual performance of nutritionally deprived children.

Long-Term Consequences of Moderate to Severe Nutritional Deficiencies

Mounting evidence from Peru,[51] Jamaica,[2,52] the Phillipines,[53] Guatemala,[54] and Kenya[55] suggests that children who experienced nutritional deprivation severe enough to cause stunting early in life have cognitive deficits during school-age years that can interfere with successful academic performance. In a review, Grantham-McGregor reported that previously malnourished children had academic problems, lower cognitive skills, more soft neurologic signs, more attention problems, and more problems with peer relationships compared with adequately nourished control children.[56]

Long-Term Consequences of Mild Nutritional Deficiencies

Findings on the long-term consequences of children from middle-income countries diagnosed with failure to thrive (FTT) add to our information on nutritional deprivation and cognition. Although there are no agreed-on criteria for the diagnosis of FTT, the term is generally used to describe children under age 3 years who have experienced a deceleration in growth over time, such that their weight for age or weight for height is below the 5th or 3rd percentile.[57] Children with FTT are usually experiencing milder forms of deficiency than children identified with nutritional deficiencies in low-income countries. During infancy and toddlerhood, the cognitive scores of children with FTT are lower than scores of comparison children with adequate growth and often remain low through the preschool period.[58–60]

The pattern of cognitive development is less clear during school-age years and adolescence. Two follow-up studies of infants referred for FTT reported that the children continued to score lower on cognitive assessments than comparison groups at age 11 years and during adolescence.[61,62]

In contrast, evidence from other studies suggests that by school age, children with a history of FTT do not have lower cognitive skills than children without a history of FTT, when comparison groups are matched for socioeconomic variables.[63–66] However, there is some evidence that children with a history of FTT experience more academic problems than adequately nourished peers.[64]

The differences in findings may be partially explained by differences in sampling. The studies showing no long-term cognitive deficiencies employed community samples of children who had not been hospitalized,[63–66] whereas the studies suggesting that long-term cognition is affected included children with more severe FTT, either those hospitalized or those with chronic growth failure.[61,62] Hospitalization is more likely if FTT is severe and complicated by multiple social problems,[67] which may also undermine school-age cognitive development.

The relationship between nutritional status and cognitive functioning is often mediated by family, environmental, and cultural variables,[58,68,69] making the family an ideal context for prevention of the negative consequences of FTT. Intervention studies among children with FTT highlight the importance of environmental enrichment. We conducted a randomized trial in which all infants received services through an interdisciplinary growth and nutrition clinic, but experimental infants also received weekly home intervention targeted toward enhancing caregiver–child interactions.[58] After 1 year, infants who received the home intervention had a more child-centered home environment, better cognitive scores, and better expressive language scores compared with infants who did not receive the home intervention. Two years after the intervention ended, the effects were attenuated and moderated by the affective behavior of the caregivers. Infants who received the intervention had better motor scores only if their caregivers did not report symptoms of depression, anxiety, or hostility.[59] In a similar investigation, Ramey and colleagues reported that infants with FTT who received both nutritional supplements and response-contingent stimulation had better scores on a vocal conditioning task than infants who received only the nutritional supplement.[70]

Some caution is recommended in reading the existing literature on FTT because much of the information has been derived from hospitalized children in academic referral centers. Because most children with FTT are treated on an outpatient basis, studies that rely on hospitalized patients are likely to represent extreme and complex cases of FTT.[71] In addition, many studies of FTT include small samples, a lack of appropriately matched comparison groups, unstandardized assessments, evaluators who are aware of group assignment, inattention to differences in age or nutritional status, and cross-sectional rather than longitudinal research designs.[67,72]

Intervention Studies

As illustrated by the transactional system, optimal child development depends not only on food quality and availability but also on the care the family provides to the child, especially during the first few years of life.[18] Evaluations of psychosocial stimulation delivered to malnourished children provide evidence for the importance of the caregiving environment in promoting development. In Jamaica, Grantham-McGregor and colleagues demonstrated that stunted children who received either nutritional supplementation or psychosocial stimulation showed improved mental and motor development.[27] The effects of the inter-

ventions were additive: children who received both supplementation and stimulation achieved mental and motor scores that approximated those of the nonstunted comparison group. Long-term follow-up demonstrated that although the benefits of the early interventions were still present, they were rather modest, suggesting some decay over time.[73] These findings are extremely encouraging because they demonstrate that not only can children benefit from environmental enrichment, but their benefits extend over time. They also suggest that enrichment should extend over the developmental period.

Studies from Cali and Bogota, Columbia, also illustrate the importance of including both nutritional and psychological interventions.[74,75] In the Cali study, children who received both supplementation and stimulation had better psychological performance at age 9 years compared with control group children.[76] In the Bogota study, supplemented infants were more active than nonsupplemented infants, and 3 years after the study ended, when the children were 6 years of age, those who received both supplementation and stimulation were taller.[75]

In a long-term evaluation of a community-based supplementation program in Guatemala, Pollitt and colleagues found that children who were supplemented early in life had a faster reaction time in information processing tests and higher scores on tests of knowledge, numeracy, reading, and vocabulary during adolescence compared with children who did not receive the high-protein supplement.[77] Their analysis also demonstrated the importance of looking for moderator effects because in the villages that did not receive the supplement, they found the greatest benefits on academic performance among children from the poorest homes.[78]

Micronutrients

Micronutrient deficiencies are often evaluated by conducting randomized trials among populations thought to be micronutrient deficient (see Chapter 6). Although the use of randomized trials provides a robust evaluation of the link between micronutrient deficiencies and cognitive development, the research examining the effects of micronutrient deficiencies on children's development suffers from many of the same methodologic problems that have hindered research examining PEM. Micronutrient deficiencies often occur in the context of poverty and among families who are beset by multiple stressors that may interfere with the healthy development of their children. In addition, micronutrient deficiencies often co-occur, particularly if the micronutrients are derived from the same source. Thus, if children are deficient in multiple micronutrients, it can be difficult to interpret the effects of single-micronutrient supplementation trials.

Observational studies have compared children who are thought to have a micronutrient deficiency with those who do not. Although these studies can yield useful information about micronutrients and individual differences, they lack the rigor of randomized trials because there are often other factors separating the groups that may influence children's development, such as caregiving practices. Randomized trials can often clarify differences related to micronutrients, but they are expensive and must also control for confounding factors that may influence children's development, such as the quality of the caregiving environment. In addition, as the evidence demonstrating the detrimental effects of specific micronutrients on children's development is clarified (eg, iodine), it is unethical to identify micronutrient-deficient children and not offer treatment.

Iodine Deficiency Iodine deficiency is a major problem that affects children in areas where iodine is depleted from the soil, primarily mountainous regions, such as the Himalayas and the Andes, and flood plains.[79] A 1993 World Health Organization (WHO) report estimated that 1.6 billion people or 30% of the world's population live in iodine-deficient areas and are therefore at risk for iodine deficiency.[6]

Iodine is an essential component of at least two thyroid hormones that are necessary for skeletal growth and neurologic development.[79] When iodine is deficient, hypothyroidism occurs, resulting in increased production of thyroid-stimulating hormone, which stimulates production of thyroid hormones. The most common manifestation of iodine deficiency is goiter, which is an enlarged thyroid gland.[79]

When iodine deficiency occurs in utero, it leads to fetal hypothyroidism and irreversible neurologic and cognitive deficits, manifested as cretinism. Neurologic cretinism includes mental retardation, primitive reflexes, visual problems, facial deformities, stunted growth, and diplegia.[80] When iodine deficiency occurs postnatally, the child may experience thyroid failure that can lead to hypothyroidism. Observational studies that have compared children with and without a goiter have had mixed results; some have reported cognitive deficits among children with goiters and others have not. One explanation for the lack of clarity may be that differing levels of hypothyroidism can lead to a goiter.[79] In a meta-analysis of 18 observational studies that compared children based on whether they lived in an iodine-deficient area or not, children who lived in iodine-deficient areas had deficits in cognitive functioning.[81] In a well-controlled observational study in Bangladesh, investigators found that children who were mildly hypothyroid had deficits in spelling and reading compared with healthy controls.[82] Although evidence from these studies is compelling, families who live in iodine-deficient areas are often more impoverished than families in areas where iodine is adequate.

Several randomized trials have been conducted to examine the impact of iodine supplementation on the cognitive performance of children in iodine-deficient areas. However, the results have not been consistent. In a recent longitudinal follow-up of school-aged children, all of whom received iodine, those who received iodine in utero prior to the third trimester had better scores on a measure of psychomotor performance than children who received iodine later in pregnancy or at age 2 years.[83] There was a similar trend when measures of cognitive performance were considered; however, the differences did not reach significance. Thus, the effects of postnatal iodine defi-

ciency on children's cognitive performance are less clear than the effects of prenatal iodine deficiency. In addition, many of the studies have had methodologic problems that interfere with interpretation.

Iron Deficiency Iron deficiency is the most common nutritional deficiency in the world. UNICEF and WHO committees estimate that worldwide there are 2 billion individuals with anemia and up to 5 billion who are iron deficient.[7] The highest risk of iron deficiency occurs during times of rapid growth and nutritional demand, during infancy (ages 6 to 24 months), early childhood, adolescence, and pregnancy.

Iron is necessary for hemoglobin synthesis. Iron deficiency leads to reduced oxygen-carrying capacity and can impact immunity, growth, and development. Although iron status is often assessed by anemia (low blood hemoglobin concentration), only 50% of anemia is caused by iron deficiency.[84] Iron has multiple roles in neurotransmitter systems and may affect behavior through its effects on dopamine metabolism.[85] Dopamine clearance has strong effects on attention, perception, memory, motivation, and motor control.

A number of observational studies have found that children who experienced anemia early in life had low scores on tests of mental performance and were fearful, inattentive, and solemn, with low levels of initiation and exploration.[86–88] Many children continued to demonstrate lower academic performance during their school-age years, even when the anemia had been treated. For example, Hurtado and colleagues examined the records of children who enrolled in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) prior to age 5 years.[89] Those who were anemic were more likely to experience academic problems at 10 years of age compared with children who were not anemic on enrolment. Concurrent iron status is also related to academic performance, as demonstrated in a recent investigation using data from more than 5,000 6- to 16-year-old children from the Third National Health and Nutrition Examination Survey (NHANES III).[90] When standardized mathematics test scores were examined controlling for background variables, children with iron deficiency with and without anemia had lower scores than children with normal iron status. These findings suggest that iron deficiency, even without anemia, may place children at risk for cognitive delays.

The results of randomized trials of iron supplements have been inconsistent, regardless of the children's initial iron status.[91] Most short-term trials (< 15 days) among anemic infants have shown no differences in children's motor or mental performance.[92] Of the longer-term trials among anemic infants, only one showed positive effects of iron treatment on children's motor and mental development.[93] There have been at least seven prevention trials among infants at risk for iron deficiency. Four authors have reported that iron supplementation promotes cognitive development among children at risk for iron deficiency[94–97] and three have reported no effects.[98–100] These findings are difficult to interpret because methods varied, and some authors did not account for socioeconomic and caregiving differences among nutritionally deficient children.

Zinc Deficiency Zinc is a trace mineral that is involved with deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis and the metabolism of proteins, carbohydrates, and fat. Findings on the cognitive effects from the zinc supplementation studies also lack clarity.[101] Four published trials reported beneficial effects of zinc supplementation on children's activity, motor quality, or motor development[102–105]; one reported that zinc-supplemented infants were more cooperative[106]; three found no differences on mental development[102,105,107]; and one reported that supplemented children had slightly lower scores on mental development than comparison children.[107]

There have been at least three randomized trials of zinc supplementation measuring cognitive development among school-aged children. A trial in Canada found no differences when children were tested with subscales from the Detroit Test of Learning Abilities.[108] However, trials in China and Mexican-American children from Texas have found that zinc-supplemented children demonstrated superior neuropsychological performance, particularly reasoning, when compared with controls.[109,110] The evidence for improved neuropsychological performance among zinc-supplemented children is increasing, but more work is needed to replicate existing studies and clarify the effect on academic performance.

SUMMARY

Most of the research examining the impact of nutritional deficiencies on children's intellectual development has hypothesized a direct effect, possibly through changes in neuroanatomy or neurotransmission. However, most studies have relied on general measures of intellectual skills, and, as a result, little is known about specific processing changes related to nutritional deprivation.

It is also possible that behavior changes associated with nutritional deficiencies alter the caregiving that the child receives, thereby compromising the child's development even further. The result could be a child who experiences both the neurologic changes that have been associated with nutritional deficiency and limited environmental enrichment. Future research should consider how the caregiving system is related to child development and whether it mediates the effects of nutritional deficiencies.

The findings linking nutritional deficiencies, especially micronutrient deficiencies, and child development point to the importance of effective prevention programs that begin prenatally or early in life and extend through the periods of vulnerability, which may include adolescence. Yet there are many unanswered questions regarding nutritional deficiencies and child development that require further research, including the timing of the deficiency, the long-term consequences on academic achievement, the specific processes involved, and the impact of multiple nutrient deficiencies.

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CHAPTER 22

NUTRITION AND THE BEHAVIOR OF CHILDREN

Kathleen Gorman, PhD, Elizabeth Metallinos-Katsaras, PhD, RD

The association between nutrition and behavior is widely believed to be causal. Although there is strong evidence to suggest behavioral effects of some nutrient deficiencies (ie, iron deficiency anemia [IDA]), the evidence for other nutrient deficiencies is much weaker. However, popular opinion seems to rely heavily on anecdotal data, which suggest that behavioral problems and poor academic achievement are the result of poor nutrition. Given the implications of such beliefs and the fact that many social programs have grown out of the theory that nutrition is a critical factor in children's development, it is important to thoroughly examine the available evidence.

Establishing a causal link between nutrition and behavior is complicated by the fact that malnutrition, and much less specific nutritional deficiencies, rarely occurs in isolation. Even children who are mildly malnourished are likely to come from families or homes characterized by factors (eg, low levels of education and income) well known to pose risks to the optimal development of children (Figure 22-1). Although the role of the environment has long been recognized as an explanatory factor in the association between nutrition and development, only recently has the research attempted to build environmental variation into the designs and to explore the interactions between nutrition and environmental variables.

This chapter examines the evidence for the causal effects of nutrition on behavioral outcomes in children. In general, malnutrition refers to a condition that results from an "excess, imbalance, or deficit of nutrient availability in relation to tissue needs."[1] The literature on malnutrition comes primarily from low-income countries and provides evidence for the effects of nutrient restrictions on infant and child development. In addition, a growing body of literature has emerged on the effects of hunger and related nutritional insufficiencies among well-nourished populations. A third body of literature explores how specific nutrient deficiencies or the ingestion of particular nutrients (or non-nutrient additives) may pose potential harm (or benefit) to individual development. The section on the role of specific nutrients hypothesized to affect behavior includes sugar, multivitamins, and minerals, as well as brief attention to issues of food additives. The research on overnutrition and eating disorders is not reviewed here (see Chapters 51 and 54).

Behavior, as discussed in this chapter, refers to a variety of outcomes that have been studied in association with nutrition, including cognition, achievement, activity, and attention. The behavioral outcome examined varies depending on the type of nutritional input; for example, low energy intake during gestation and infancy is often believed to affect overall cognitive function, whereas short-term hunger and intakes of specific nutrients (eg, sugar) are more often thought to affect attention and activity levels.[2]

Given the limitations of experimental research on malnutrition in human subjects, much of what is known about the causal effects of malnutrition on behavior comes from the animal literature. Early research noted that inadequate intake of nutrients results in changes in brain structure and size, and it was hypothesized that malnutrition during fetal development and periods of rapid brain growth directly impairs brain development.[3] This impaired brain growth was presumed to result in brain damage and subsequent mental retardation.

Although it is well documented that malnutrition can affect brain development and structure, there is no clear consensus that such changes are permanent or that they necessarily result in functional consequences.[3,4] At the same time, advances in neuropsychobiology have identified more subtle alterations in function associated with nutritional deficiencies such as central nervous system (CNS) changes at the level of neuroanatomy and/or neurochemistry.[4] Furthermore, it has been hypothesized that many of the behavioral effects of malnutrition observed in animals (eg, increased emotionality) may be involved in the observed deficits in learning and cognition in humans as well.[5,6] The growing body of literature on the relationship between nutrition and brain development is reviewed in Chapter 21, "Brain Development."

PROTEIN-ENERGY MALNUTRITION AND BEHAVIOR

Recent estimates (2000) suggest that 150 million children (28%) under the age of 5 years suffer from malnutrition in the developing world (see Chapter 10).[7] Nutritional deficiencies are both less common and less severe in countries such as the United States. Nonetheless, data from the Pediatric Nutrition Surveillance System 1997 on low-income

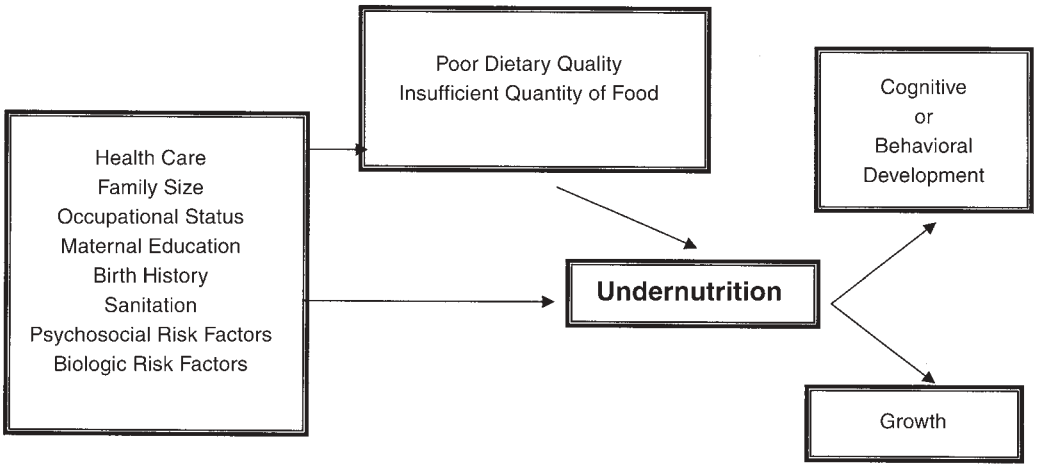

FIGURE 22-1 Model for malnutrition in environments with limited resources.

Description of Studies included in the Review: Malnutrition and Cognitive Development

children and families who participate in federally funded programs (eg, Special Supplemental Nutrition Program for Women, Infants, and Children [WIC], Head Start) show the prevalence of low height for age among children under 2 years of age to be twice as high as that expected within the general population and an overall prevalence of IDA of between 15 and 25% for this population.[8] Although the high prevalence of anemia and growth stunting within this sample may reflect, in part, the successful targeting efforts of at-risk populations (eg, WIC gives preferential enrolment to high–nutritional risk families), the evidence indicates that a large number of children in the United States are at elevated levels of health and nutritional risk. Although there remains little doubt that severe levels of malnutrition adversely affect the psychomotor and cognitive development in children as well as long-term school learning and achievement,[3,9] of relevance here is the research on mild-to-moderate malnutrition. Several large field studies were conducted in low-income countries during the 1960s and 1970s to test the hypothesis that improved nutrition at different developmental periods was associated with improved cognitive performance.[2] In each study, children at nutritional risk were supplemented and compared with children who remained unsupplemented. Overall, a summary of the results suggests small yet statistically significant findings on a variety of outcomes (eg, mental and motor development, preschool cognitive function) (Table 22-1).[2]

During the 1980s, better-designed studies and the use of improved statistical analyses strengthened the conclusions of a causal relation between nutrition and behavior.[2,5,10,11] In Jamaica, Grantham-McGregor and her colleagues randomly assigned previously malnourished children, as defined by low height for age, to one of four treatment groups: (1) food supplementation, (2) psychosocial stimulation, (3) supplementation and stimulation, and (4) control.[12] The results showed significant and independent effects of both nutrition and stimulation on the Developmental Quotient of the Griffiths Mental Development Scales compared with control subjects and an additive effect of the combined intervention. After 2 years of treatment, the combined intervention group scored significantly better than the other groups and similarly to a matched group of nonstunted children. The use of children with different nutritional histories and multiple treatment conditions in a randomized study highlights the significance of individual differences and potential interactive effects of interventions. However, follow-up of these children at 4 and 8 years post-treatment indicates few significant enduring effects of the nutritional intervention. In the first follow-up, the authors report benefits of psychosocial stimulation on cognitive performance and an interaction of the supplement with parental behavior. Children whose mothers had higher vocabulary scores showed increased effects of nutritional supplementation on cognitive performance.[13] By the time the children were about 12 years of age, only the effects of psychosocial stimulation remained.[14]

A follow-up of rural Guatemalan children who had been supplemented with either a high-calorie/high-protein supplement or a low-calorie supplement throughout the first several years of life found significantly better performance on various measures of psychoeducational tests (eg, reading, numeracy, vocabulary, and general knowledge) in adolescents who were exposed to the high-calorie/high-protein supplement.[15] More important, the effects of the supplementation varied by levels of socioeconomic status (SES) and by schooling history. That is, subjects from the poorest families seemed to benefit the most from the supplementation and performed similarly to those from higher SES homes. In addition, children with more exposure to school (beyond 3 years) showed greater benefits of the supplementation than those with fewer years of schooling. Taken together, the results of these studies provide evidence for the effects of nutritional supplementation on cognitive development. Further, the results illustrate the potential for long-term effects and the role that the environment (ie, characteristics of families, home, school) plays in mediating such a relationship.

TABLE 22-1 Description of Studies Included in This Review

			Nutrient Characteristics of Supplement					
	Age of Subjects at Initiation	*Supplementation Duration*	*Kcal*	*Protein*	*Micro-nutrient*	*Control**	*Educational Component*	*Outcomes*
Guatemala, 1969–1977	Gestation–7	Gestation and 7 yr	X	X	X	Q[†]	C, MV	Composite infant scale, preschool battery, school, psychoeducational test
Jamaica	2 mo–2 yr	2 yr	X	X		N	X	Griffiths
Cali, 1971–1974	4 yr+	3 yr	X	X	X	N	X[‡]	Preschool battery, WISC
Bogotá	Gestation–6 mo	Gestation and 3 yr	X	X	X	N	X	Griffiths, Einstein
Indonesia	6–20 mo	3 mo	X	X		Q	N	Bayley
Taiwan	Maternal only	Gestation and lactation	X	X	X	Q	C, MV	Bayley, 5-yr-old IQ
New York City	Maternal only	Gestation	X	X	X		MV	Bayley, object permanence, play, habit/deshabit
Mexico		Maternal and 3 mo+	5 yr	X	X	X	N	Mother-infant contract activity, maternal care and concern

Reproduced with permission from Gorman KS.[2]

*Supplement administered to control group: C = calorie; MV = multivitamin and mineral supplement; N = none.

[†]Consumption quantifiable.

[‡]Education not separate from nutritional intervention.

Bayley = Bayley Scales of Infant Development; Einstein = Einstein Measurement of Children's Cognitions; Griffiths = Griffiths Mental Development Scales; WISC = Wechsler Intelligence Scale for Children.

Finally, the results highlight the significance of both the timing and duration of the intervention, as well as the particular domains of cognition that may be linked to particular nutritional deficiencies.[15,16]

As a result, the focus of current research has been to attempt to elucidate the potential pathways that may account for the effects of malnutrition on behavior.[3,15–17] Most notable is the work on assessing the role of activity and motor development as a mediator in the relationship between nutrition and cognitive development.[5] In the Jamaican study of stunted children previously described, data were also collected on activity levels.[18] Baseline comparisons showed that stunted children were significantly less active than nonstunted children. However, there were no effects of supplementation on activity levels, and activity was not found to mediate the relationship between supplementation and cognition. In contrast, data from an experimental study in Pangalengan, Indonesia, provide some initial evidence on the complexity of developmental trajectories of malnourished children.[19] Building on hypotheses developed from his work in Guatemala, Pollitt and his colleagues explored the relationships among nutrition and growth, motor development, motor activity, parental behavior, affective behavior, and cognitive development.[15,16,20] In this study, two cohorts of infants (12 and 18 months) were each randomly assigned to one of three types of supplements over the course of 12 months: high energy + micronutrients, low energy + micronutrients, and low energy.[21] Data on a wide range of variables were collected periodically over the course of a year. In general, the results provide support for the benefits of a high-energy supplement on a number of outcomes. Infants receiving the high energy + micronutrient supplement showed earlier acquisition of motor milestones, higher motor development scores, and increased duration of activity compared with children receiving the low-energy supplement.[22,23] Furthermore, high energy–supplemented children showed earlier acquisition of object concept, increased vocalizations, and earlier emotional maturity (decreased fussing) than their peers.[24] The effects of the micronutrient supplement were less clear, except in the case of children with IDA.[25] This study represents the first empiric test of the complex model of relationships among malnutrition, growth, motor development, activity, and mental development (Figure 22-2).[26] Despite several of the limitations of this study (eg, small sample sizes and different patterns of results between the 12- and 18-month-old cohorts), the results provide an important addition to our increasing understanding of the mechanisms underlying the relationship between malnutrition and behavior.

BREAST MILK AND COGNITION

Although the benefits of breast-feeding on immune function, morbidity, growth, and infection are well established, the evidence for its effects on mental development, particularly among healthy, well-nourished infants, is less convincing.[27–31] The research on the effects of breast milk on cognitive function is complicated by two main factors: the fact that mothers who choose to breast-feed vary in a number of ways from those who do not and the researcher's inability to randomly assign mothers to treatment groups.[31–34] Mothers who choose to breast-feed and mothers who bottle-feed have been reported to differ in age, SES, education, and ego development, all factors also known to affect infant developmental outcomes.[32–35] Research controlling for these variables has resulted in a reduction in the magnitude of associations between breast-feeding and men-

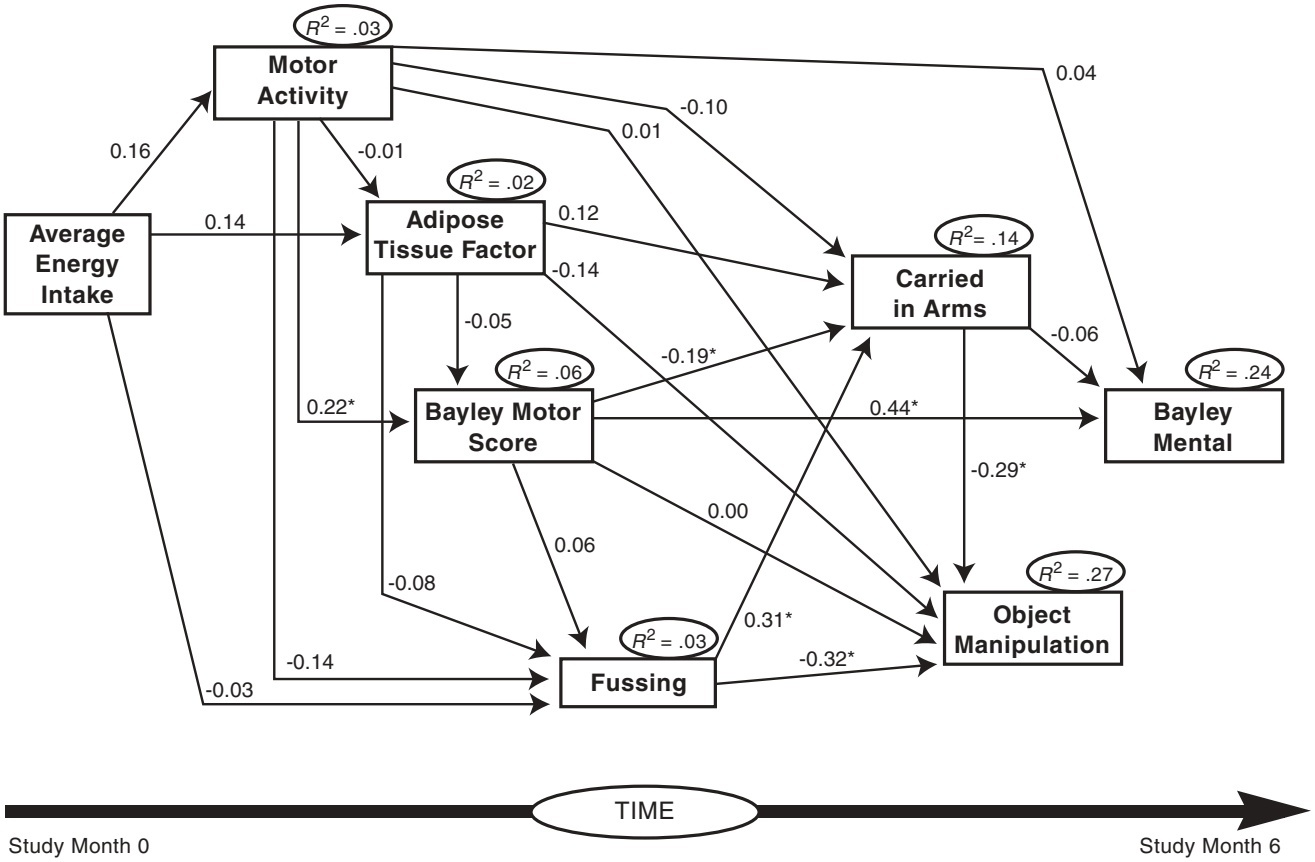

FIGURE 22-2 Path diagram of the adjusted model of the combined cohort that received the energy plus micronutrient and skimmed milk supplement (χ^2 NFI = 0.95; NNFI = 1.00; CFI = 1.00). Reproduced with permission from Pollitt E et al.[26]

tal development, suggesting that these variables account for a significant portion of variation often attributed to breast milk.[32,34–36] Furthermore, the association between breast-feeding and cognition has been reduced to zero when maternal IQ and parenting skills were also factored in.[30] Hence, studies that purport to establish a relationship between breast-feeding and cognition without controlling for these variables may not be valid.

In a series of studies in Great Britain, Lucas and colleagues attempted to control for many of these potentially confounding variables.[37–39] In their study of preterm, low birth weight infants (< 1,850 g), infants of non-breast-feeding mothers were randomly assigned to a standard full-term or a special preterm formula (designed to more closely mimic the properties of breast milk than standard formula), whereas infants whose mothers chose to provide breast milk were also randomly assigned to one of two supplemental formula groups for a period of 4 weeks. In this way, differences between breast milk and formula could be compared as well as differences in standard versus preterm formula. In an assessment of the infants at 18 months, comparisons between formula types demonstrated significant benefits of preterm compared with term formula on the Bayley Psychomotor Development Index (PDI).[37] Similarly, among infants receiving supplementary feeding in addition to breast milk, those who had received preterm formula scored higher on the social quotient from the Vineland Adaptive Behavior Scales than those receiving term formula. When subjects were combined, comparisons between term and preterm formula indicated the advantages of preterm formula on the PDI and the Vineland social maturity scale.

In a follow-up at age 7 years, comparisons were made between infants of mothers who chose to provide breast milk and those who did not on the Wechsler Intelligence Scale for Children (WISC) (revised for the United Kingdom).[38,39] According to the authors, similar percentages of infants in each group had received the different types of formulas. Initial findings show a 10-point advantage on each of the IQ scales (Verbal, Performance, and Full-Scale) for those in the breast milk group. In a subsequent analysis between formula groups,[39] the authors reported that males showed a benefit from the preterm formula compared with term formula relating to language development. There was an apparent dose-response to the preterm formula, suggesting that the more formula ingested, the greater the developmental gains.

The authors concluded that the combined results of this study, showing both the benefits of breast milk over formula and the benefits of preterm formula over standard formula, provide strong evidence that these benefits are attributable to the specific properties of breast milk.[40] These conclusions are further strengthened by the fact that all infants were fed by nasogastric tube, hence controlling for any potential behavioral differences associated with the act of breast-feeding. Additionally, the results of these studies have advanced a number of theories regarding specific properties of breast milk, most specifically, long-chain

polyunsaturated fatty acids (LC-PUFAs) and their association with brain development.[41–44]

Illustrative is a recent review on LC-PUFAs that reported that breast-fed infants have higher plasma levels of LC-PUFAs than formula-fed infants.[45] Studies that supplement formula with these LC-PUFAs, namely docosahexaenoic acid and arachidonic acid, in preterm infants, have shown some benefit of human milk or supplemented formula on visual function and visual acuity in comparison with unsupplemented formula. In contrast, studies of visual acuity in term infants have been inconsistent; some have shown the effects of supplemented formula, whereas others have not. The research on the effects of LC-PUCFAs on more general measures of cognitive and behavioral development in preterm or term infants is inconclusive.[45] Limitations owing to small sample sizes and the tests used have been noted as potentially responsible for the lack of agreement in the findings. In addition, the length of follow-up in most of these studies has been short, which makes it difficult to draw conclusions about the long-term benefits of the LC-PUFAs.

Nonetheless, it is important to note that even if subsequent analyses uphold these findings of a causal association between breast milk properties (eg, LC-PUFAs) and cognitive development among at-risk infants, the issue of generalizability must be addressed. There is little evidence to suggest that the effects observed in these studies, composed entirely of preterm, very low birth weight infants, would generalize to otherwise healthy full-term infants.

IRON DEFICIENCY ANEMIA AND OTHER MICRONUTRIENT DEFICIENCIES

Data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) showed that 9% of toddlers ages 1 to 2 years and 9 to 11% of adolescent girls and women of childbearing age were iron deficient based on laboratory tests of iron status (see Chapter 49).[46] Thus, risk for IDA continues to be high in the United States. The elevated risk among toddlers during a time considered sensitive for cognitive development has provided the impetus for the infancy period being the most common target for investigations of the behavioral effects of IDA. Much less has been done on preschool- and school-aged children.

It is well established that IDA infants score lower on the Bayley Mental Development Scale and Motor Development Scale in comparison with nonanemic infants.[47] It has also been found that children's achievement, among both preschool- and school-aged subjects, is poorer for formerly anemic children than nonanemic children.[47–49] The fact that IDA rarely exists in isolation but rather coexists with a host of social, health, and environmental risk factors has constrained the interpretation of such differences as being causal.

Randomized clinical trials provide the best evidence for a causal association, although the results have not always been consistent. In some, IDA infants treated with iron show significant gains in developmental scores compared with IDA infants receiving placebo.[50] More recent investigations have focused on the reversibility of effects of IDA, which has been reported by some but not all investigators.[49–51] Several possible reasons for the lack of significant improvement with iron supplementation have been proposed, although the research has not provided support for any reason in particular. Potential explanations include the possibility that IDA is not the causal factor or that IDA causes permanent and irreversible alterations in the developmental trajectory of the infant. In addition, in some cases, the IDA may not have been successfully treated, or in other cases, the correlates of more severe and chronic IDA (eg, poorer home stimulation, lower parental IQ, socioeconomic factors) may be the cause of lower performance among those with a history of IDA.[47]

In a clinical trial of iron supplementation in Indonesian infants (12 to 18 months), iron supplementation resulted in reversal of both IDA and developmental indicators.[50] At baseline, IDA infants scored significantly lower on both the Bayley Mental Development Index (MDI) and the PDI than either iron-replete or iron-deficient nonanemic infants. After supplementation, there were no significant differences among the three groups on either the MDI or the PDI. Conversely, the IDA placebo-treated infants continued to score significantly lower than all other groups on both the MDI and the PDI.

Several preventive trials among infants have been conducted. Of the four that were randomized trials, three demonstrated some benefit of iron treatment, whereas one did not.[47,52–54] Two of these studies demonstrated effects on developmental test scores and one on fixation times at 12 months of age.[47,52,53] The one study that did not show any benefit of the trial was limited by the fact that there was only a small subset at risk for deficiency, thus limiting the statistical power of the study.[47]

Finally, a recent quasiexperimental study on infants in Indonesia examined the effects on a variety of developmental outcomes, including several indicators of motor development, mental development, and observations of children's interactions.[25] This analysis was based on a subset of children originally included in a supplementation study. This subset had biochemical evidence of IDA. At baseline, there were significant differences in scores on the Bayley Motor Development Scale, as well as in a measure of motor activity between IDA and non-IDA children. Motor development, physical activity, and emotional regulation have been postulated to be intermediate processes affected by nutritional status as well as affecting cognitive outcomes.[19] The improvement in motor activity during the first 2 months and during the first 6-month observation period was significantly larger in the IDA nontreated children than in the non-IDA children. It should be noted, however, that this design is weaker than the randomized clinical trials.

In contrast to studies showing effects with iron supplementation, some studies suggest that differences between IDA and nonanemic controls persist even after iron supplementation. Generally, these studies had one feature in common: they did not include an IDA placebo group, hence weakening the study design.

A study in Costa Rica showed that IDA infants scored significantly lower on the MDI and PDI than iron-replete

infants and that, on average, these differences persisted even after 3 months of iron therapy.[55] Further analyses revealed that the effect of iron supplementation depended on the degree to which the anemia was reversed.[56] Specifically, infants whose IDA was completely reversed (n = 9) scored similarly to the iron-sufficient infants on the MDI and PDI, whereas infants whose deficiency was not completely corrected continued to score significantly lower than the iron-sufficient infants. It should be noted that significant treatment effects were the result of an observed decline in performance in the iron-sufficient children, which was not evident in those children successfully treated with iron.[56] Such a decline in the latter part of infancy has been reported elsewhere in disadvantaged populations.[56,57] It is possible that the successful iron treatment of these nine infants prevented a further decline in this group; however, without a comparable placebo group, this hypothesis could not be tested.[56] At a follow-up of subjects (age range 11 to 14 years, with excellent current hematology), children who had had severe chronic anemia during infancy (defined as those whose hemoglobin increased in response to treatment but in whom biochemical evidence of iron deficiency persisted) had significantly lower scores in writing, arithmetic, motor tests, and tests of specific cognitive processes (Table 22-2).[49] Among older children only, those who had been previously anemic had poorer selective attention. These differences persisted even after controlling for sex, mother's IQ, and an index of the home environment. As noted by the authors, these differences may be attributable to some factor that is associated with iron deficiency and not iron deficiency per se, or it may be attributable to effects of iron deficiency on the nervous system, which affect later behavior and development. Although the authors made a compelling argument for the latter, the other important aspect of this study to consider in interpreting the findings is that for this group of formerly iron-deficient infants, the iron deficiency was not fully corrected. It is not known what the long-term development of these children would have been had their iron deficiency been fully corrected.

An iron supplementation study examining the effects of IDA on CNS development indicated that infants with IDA at 6 months had longer central conduction time (proposed as an indicator of poorer CNS development) than a

TABLE 22-2 Overall Mental and Motor Functioning at 11 to 14 Years of Age*

Test	*Severe, Chronic Iron Deficiency in Infancy* (n = *48*)	*Good Iron Status in Infancy* (n = *114*)	*Significant Background Factors*
Wechsler Intelligence Scale for Children-Revised			
Verbal IQ			
Unadjusted‡	99.5 ± 2.1	105.5 ± 1.4	
Adjusted	101.8 ± 2.0	104.6 ± 1.4	Gender, mother's IQ, HOME
Performance IQ			
Unadjusted	97.7 ± 2.2	100.2 ± 1.4	
Adjusted	99.1 ± 2.1	99.7 ± 1.4	Gender, HOME
Full-Scale IQ			
Unadjusted†	98.4 ± 2.1	103.2 ± 1.3	
Adjusted	100.4 ± 1.9	102.3 ± 1.2	Gender, mother's IQ, HOME
Wide Range Achievements Test-Revised			
Arithmetic			
Unadjusted§	86.9 ± 2.2	96.5 ± 1.4	
Adjusted	88.8 ± 2.2	95.7 ± 1.4	HOME
Reading			
Unadjusted	120.1 ± 2.3	127.6 ± 1.5	
Adjusted†	121.6 ± 2.4	126.9 ± 1.5	
Directed Writing Task			
Unadjusted§	91.7 ± 1.9	99.2 ± 1.2	
Adjusted	93.2 ± 1.9	98.6 ± 1.2	
Bender Visual-Motor Gestalt Test			
Unadjusted	2.1 ± .3	2.2 ± .2	
Adjusted	2.0 ± .3	2.2 ± .2	HOME
Bruininks-Osteretsky Test of Motor Proficiency, Short Form			
Unadjusted‖	44.4 ± 1.8	47.4 ±.1.1	
Adjusted‡	42.4 ± 1.8	48.0 ± 1.1	Gender

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*Values are means with and without adjustment for background factors. Standard scores take age into account; age is included as a covariate for Bender raw scores. Adjusted means are derived from analysis of covariance, controlling for gender, HOME score, and mother's IQ. A cumulative HOME index summed the scores obtained in infancy, school age, and early adolescence, which were highly intercorrelated (r values > .70), and all related to test scores at 11 to 14 years. Mother's IQ was the covariate, rather than mother's education, because mother's IQ generally showed higher correlations with adolescent outcome; the regression coefficient of maternal education on mother's IQ was used to estimate IQ if the mother had not been tested (32 cases). Tests of statistical significance are based on analysis of variance or covariance.

HOME = Home Observation Measurement of the Environment Inventory.

†$p < .05$.

‡$p < .01$.

§$p < .001$.

‖Suggestive trend; $p < .10$.

nonanemic control group.[58] Even after iron supplementation, significant differences persisted at 12 and 18 months of age despite improvements in hematology in response to treatment. It should be noted that the IDA infants improved in their central conduction time but failed to reach the levels of the nonanemic controls. The authors postulated that these differences may be owing to the effects that IDA has on myelination and/or neurotransmitter function.[58] Again, there was no IDA placebo group included in this study.

Although fewer in number, some studies on preschool- and school-aged children show an effect of IDA on measures of intelligence and other cognitive processes (eg, discrimination learning tasks, visual recall).[40,59–64] Others have shown no effect of supplementation,[65] although this may have been owing to an improvement in iron status in the IDA placebo group attributable to deworming.[47] Generally, the studies on preschool- and school-aged children provide support for the notion that brain function is vulnerable to the effects of iron deficiency even after the brain growth spurt has been completed.

A recent comprehensive review of the literature summarized the proposed mechanisms linking IDA to cognitive changes. One of the proposed mechanisms includes changes in the structure and function of the CNS. This includes effects on brain myelination and on levels and function of neurotransmitters. Another mechanism that has been proposed is based on the observation that anemic children explore their environment less and induce less stimulating behaviors in their caretakers.[47] This functional isolation may account for observed delays in anemic children.

In summary, the evidence from numerous studies supports the contention that IDA has an adverse impact on cognitive development. The effects of iron supplementation have been observed on a wide range of outcomes from performance on global tests of intelligence to specific cognitive processes and CNS development. Still, the research has not consistently found that developmental outcomes improve with iron supplementation, and, frequently, children with a history of IDA continue to perform more poorly than their nonanemic peers. Further research is needed to disentangle the effects of long-term social and economic deprivation that occur alongside IDA to more definitively label this relationship as causal and to establish the independent contribution of IDA to cognitive development.

Iodine

In addition to the fairly conclusive evidence on IDA, it is well established that maternal iodine deficiency results in cretinism, deafness, and poor motor and cognitive outcomes for the fetus.[66–70] Iodine supplementation prior to pregnancy or during the first trimester results in improved developmental outcomes.[67] The effects of mild maternal iodine deficiency are less clear; however, recent research among well-nourished populations indicates that maternal hypothyroidism during pregnancy may affect later cognitive development of offspring.[71] The effects of iodine deficiency on later cognitive development for children who display signs of iodine deficiency are inconclusive.

Zinc

More recently, considerable attention has focused on the effects of zinc deficiency on behavior. The known effects of zinc deficiency on growth have led researchers to hypothesize that there are effects on cognitive and behavioral development as well. Zinc deficiency is characterized by lethargy, apathy, and slow movement, all behaviors that closely parallel those described in other malnourished groups. In laboratory animals (eg, rhesus monkeys), zinc-deprived animals had lower activity levels, longer response times, and impaired success at learning tasks compared with controls.[72,73] In one study in which the monkeys were moderately zinc deprived, significant effects on a test of attention (Continuous Performance Task [CPT]) were observed prior to effects on growth.[73] In recent zinc intervention studies conducted on infants or toddlers at nutritional risk (low birth weight or from low-income countries), effects have been noted on motor development scores, time spent in high movement activities, and infant responsiveness.[74–76] Unfortunately, in this latter study, assignment to zinc was not random, thereby limiting the internal validity of the design. Among school-aged nutritionally at-risk children, one intervention study reported a significant improvement in scores on several neuropsychological tests (ie, CPT, oddity learning, tapping, tracking),[77] whereas another found a significant effect of zinc on reasoning (ie, fewer trials were needed to learn simple concepts).[78] In the former study, it was unclear whether assignment to different intervention groups was random. Finally, another study of stunted school-aged boys found no effect of zinc supplementation either on attention or academic performance.[79]

In summary, there is limited evidence that zinc deficiency may affect development, but, at this point, no definitive statements can be made regarding the effect of zinc deficiency on child development. Many more randomized, controlled trials are needed in human populations. In addition to general indices of development and academic performance, it has been suggested that researchers examine how neuropsychological functioning (eg, activity in infancy or abstract reasoning or concept formation in school-aged children) may contribute to overall performance within a developmental context. These mediating factors are likely to vary by age group.

Despite our brief attention to other micronutrients, it is important to note that the number of nutrients with the potential to affect behavior is vast; our knowledge of the roles of specific nutrients is constantly being revised. For example, evidence from a correlational study has suggested that maternal vitamin B_6 status is associated with performance on neonatal assessments, maternal responsiveness, and infant development between 3 and 6 months.[80]

MULTIVITAMIN AND MINERAL SUPPLEMENTATION

Over the past 20 years, a number of researchers have proposed a causal association between multivitamin supplementation and performance on intelligence tests. The hypothesis driving much of this research is that a subset of

the population, despite the absence of any anthropometric, biochemical, or clinical signs of micronutrient deficiencies, may have compromised cognitive function owing to marginal micronutrient status, even though there is no physiologic basis for such an effect in a normally nourished population (see Chapters 6 and 58). A recent review argued that the first signs of a micronutrient deficiency may be psychological[81]; however, a causal association would need to have been demonstrated vis-à-vis repeated positive findings using internally valid study designs to support such a conclusion. Whereas some studies have shown support for a causal association between multivitamin/mineral supplementation and cognitive performance,[82–86] others have not.[84,87,88] Given the implications that such an association would have for public health policy, it is important to closely scrutinize the evidence.

To test whether specific nutrients are causally related to behavioral outcomes, a rigorous model requires: selecting samples that are deficient or replete in the nutrient in question (based on quantitative assessment of nutritional status), establishing an initial relationship between cognition and a deficiency in this nutrient, conducting a randomized, placebo-controlled trial of supplementation of the nutrient that is deficient in both the replete and deficient groups, examining the differential effect of the supplement based on initial nutritional status, and accounting for any effect of study participation.[89] Although this model has been used with relative success in the iron deficiency and cognition literature, it has not been used in other areas of nutrition and behavior research, most notably in the assessment of the relationship between multivitamin/mineral supplementation and cognitive performance.[84] It should be noted that one challenge to use of this rigorous model is that unlike iron status, which is accurately assessed using a combination of biochemical indicators, some micronutrients do not have such biochemical (blood or urine) indicators that reflect status accurately.[90] On the other hand, the first step in designing such a well-controlled experiment is to determine which nutrient is of interest and is most likely to be related to the outcome in question, in this case, cognitive performance of school-aged children.

The evidence for the positive effects of multivitamins/minerals comes from several studies in which healthy children have been mass supplemented. The length of supplementation has varied between 6 weeks and 12 months, and the levels of nutrients provided differed considerably within multivitamin/mineral supplement (as low as 10% of the Recommended Dietary Allowance [RDA] for iron in some supplements) and between studies (average levels ranged from 50 to 200% RDA). Although several early studies concluded that multivitamin/mineral supplementation significantly improved the nonverbal intelligence of preschoolers and school-aged children,[84,85,91] a critical examination of the research reveals methodologic shortcomings that call the validity of these conclusions into question. For example, studies failed to document convincing evidence of a nutritional deficiency,[82–85,91] to control for confounding factors or bias that may have influenced the results,[82,85,91] and to provide a rationale for the nutrient composition of the supplementation.[82–85] Further, in some cases, the "effects" are the result of a negative effect of the placebo rather than improved performance resulting from supplementation.[84,85]

In addition to nonverbal IQ, other studies have examined multivitamin effects on more specific cognitive processes. Two studies on university students reported statistically significant treatment effects on reaction time.[82,83] However, in one study, the effects were noted among females only and were limited by a potential selection bias (only 61.4% of the original sample included in the final analysis).[82] In the second study, the treatment effect of a multivitamin supplement on reaction time was attributed to thiamin despite the fact that blood transketolase activation values did not indicate a thiamin deficiency.[83]

The results of the largest and most controversial of the mass supplementation studies of children showed a net gain of 3.5 IQ points among 401 children provided with 100% RDA of most micronutrients (compared with placebo); there were no effects in the groups supplemented with either 50% or 200% RDA.[85,91] Current knowledge of nutritional biochemistry makes a theoretical explanation of such effects difficult. Furthermore, incomplete and incorrect presentation of data, errors in statistical analyses, the exclusion of 35% of the original sample owing to their refusal to give blood, and evidence for less than ideal testing conditions for some of the tests raise serious questions about the validity of the findings.[91–93]

Three studies were conducted that attempted to address some of the limitations of previous studies by matching on baseline cognitive measures and/or on anthropometric indicators of nutritional status and/or assessing blindness to treatment.[84,86,87] Two showed no effect of multivitamin/mineral supplementation on nonverbal intelligence,[84,87] whereas one demonstrated a significant effect.[86] In the latter study, school-aged children, 6 to 12 years of age ($n = 388$), completed a randomized, double-blind, placebo-controlled trial of a multivitamin/mineral tablet; only 245 subjects were included in the final analyses owing to an a priori decision to exclude data from 6 testers who did not meet specific criteria.[85] The duration of the intervention was 3 months, and randomization was stratified by preintervention nonverbal IQ and by classroom. The multivitamin/mineral tablet included between 50 and 67% of the RDA depending on the vitamin/mineral. Teachers distributed the tablets at the schools. There were no significant group differences in age, gender, race, grade, or primary language at baseline. At the post-test, both groups showed a mean IQ score gain with a statistically significant difference ($p < .038$) of 2.47, favoring the multivitamin/mineral group. Subsequent analysis revealed that this difference was primarily attributable to a subset of the children whose increase in IQ score was greater than 15 points. Over a third of those randomized to multivitamins (35%) exhibited such an increase compared with only 21% of those given placebo ($p < .01$, chi-square test). The authors contended that the significant increase among the multivitamin group was likely attributable to improved nutrition

among a subset of poorly nourished children despite a lack of any evidence to support this claim. The fact that 21% of the placebo group showed similarly large IQ improvements (> 15 points) raises questions about underlying reasons, which may be related either to study design or implementation; these reasons may in and of themselves be both independent of nutritional status and a cause of the increase in the multivitamin group.

A recent macroanalysis of 13 trials concluded that the improved performance on nonverbal IQ tests in favor of multivitamin groups over controls was not due to chance ($p < .0002$).[88] In fact, when all of the data were aggregated from these 13 studies, the author reported a net gain of 3.2 IQ points among those given the multivitamin/mineral. Despite statistical significance, a difference of this magnitude is of questionable applied significance. Among the studies that showed no effects of multivitamin supplementation, several limitations were noted, including concerns regarding the measure of IQ and a design that varied between placebo and vitamin-supplemented groups. In addition, the author concluded that the reason for the nonsignificant differences between multivitamin/mineral supplementation and improvement in IQ in some studies was because of a lower sample size limiting statistical power, even though three of the five studies listed as having nonsignificant findings had larger sample sizes than others in which significant effects were found.[88] Despite a strong argument in support of an effect of multivitamin supplementation on nonverbal IQ, the author concluded that the most plausible explanation for the observed benefits was attributable to the large response of a subset of presumably malnourished children.[88]

In summary, available research does not support the contention that supplementation with multivitamins/minerals improves intelligence test scores of the general pediatric population. One finding that was common to several of the studies is that a subset of those supplemented exhibited a large change in test scores. It may well be that a subset of children are deficient in a specific nutrient or nutrients and hence respond favorably to treatment. However, although the data supporting this hypothesis are intriguing, they are by no means conclusive. Another consideration is the fact that none of the essential nutrients can be individually implicated. Indiscriminate supplementation of most essential vitamins and minerals is neither a feasible nor an acceptable public health practice.

To respond to these concerns, future research will need to use better designs that allow for a true test of the hypothesis. At a minimum, such studies should include (1) samples of deficient and nondeficient children, (2) multiple measures to assess nutritional status, (3) double-blind, randomized, placebo-controlled trials for both types of children, (4) randomization by initial nutritional status, and (5) assessment of both nutritional and cognitive outcomes.

Megavitamin/Megamineral Therapy

A related area of research has provided limited support for megavitamin therapy for two clinical conditions: autism and hyperactivity. Megavitamin therapy refers to the consumption of vitamins in amounts of more than 10 times the RDA, whereas megamineral therapy describes the consumption of minerals above the recognized biologic requirements.[94] One consideration in both the evaluation of the research in this area and its application to clinical practice is the potential toxicity of specific micronutrients in such large quantities.[95] Fat-soluble vitamins, particularly vitamin A, have shown toxic effects in large amounts, and although most water-soluble vitamins have been considered relatively safe, pyridoxine (vitamin B_6), a vitamin used frequently in megavitamin therapy, has produced ataxia and a severe sensory neuropathy in some individuals.[96] The basic assumption underlying this research is that the metabolic requirements of certain groups of children may be greater for certain nutrients, although there is little biochemical evidence to support this contention.

The arguments supporting the use of megavitamins with clinical populations date back to a study on autistic children showing a therapeutic effect of megadoses of vitamin B_6 on their behavior.[97] One complication of this study was that subjects had already been receiving megadoses of vitamin B_6 and other vitamins and medications prior to the experimental intervention. Therefore, children were randomly assigned to either a placebo, which meant taking them off the vitamin B_6, or varying doses of vitamin B_6 (75 to 3,000 mg). Although children's physical symptoms were reported to be significantly worse when on the placebo, other factors (ie, drug withdrawal), which were not well controlled in the study, could have been responsible for this deterioration. Furthermore, not all subjects were clinically autistic.[98]

Two studies have reported positive effects of combined treatment with vitamin B_6 and magnesium on the behavior of autistic children.[99,100] In a double-blind, randomized, placebo-controlled clinical trial, the effects of vitamin B_6 alone ($n = 37$) and vitamin B_6 in combination with magnesium ($n = 21$) were tested.[46] The combined treatment (vitamin B_6/magnesium) had a significant effect on 8 of 17 behaviors evaluated, but there was no effect of vitamin B_6 alone on any of the behavioral measures. In particular, positive benefits of the combined treatment compared with placebo were noted on behaviors reflecting interest in other people, verbal and nonverbal communication, and responses to the environment. In contrast, two other smaller studies, one that used lower doses of pyridoxine and magnesium than those used in the past, found no effect of the treatment on the behavior of autistic children.[101,102] Unfortunately, the small number of subjects in each of these studies increases the likelihood that the statistical power was inadequate to detect an effect even if it did exist, although one of the studies did find an improvement simply associated with being in the study.[100] Calcium and folic acid are two additional nutrients for which effects have been proposed; however, the research has been sparse.[103]

In a review of three well-controlled studies examining the effect of megavitamin supplementation on behavior in children with attention-deficit/hyperactivity disorder (ADHD), two showed no effect, whereas one reported adverse effects of supplementation.[98] The authors noted

that all of these studies employed a between-subjects analysis, that is, the response of the control group (those ADHD children on the placebo) was compared with that of the treatment group (those ADHD children given megavitamins), which may not be sufficiently sensitive to detect the effects of the supplement.[98] A fourth study assessed the impact of a megavitamin supplement (250 mg niacinamide, 250 mg ascorbic acid, 50 mg pyridoxine, 100 mg calcium pantothenate) on 12 children with ADHD, using a crossover design so that children would be exposed to both the vitamin and the placebo.[104] Unfortunately, because of parental refusals and one dropout, only seven subjects were included in the final analysis. Parent and teacher ratings were recorded weekly, and a trained behavioral observer recorded the child's behavior in the classroom, using the Stony-Brook Observational Code, for 30 minutes per week (at the same time of day). Despite the small sample size, several significant effects emerged; however, the direction of effects was not consistent. Teachers' reports of conduct problems and parental reports of hyperactivity and learning problems significantly declined while subjects were on the placebo. At the same time, teachers' reports of both inattentive and passive behavior and mothers' reports of psychosomatic complaints significantly decreased during the megavitamin treatment. Furthermore, there were some reported side effects of the megavitamin preparation, such as nausea and vomiting. These inconsistent findings are particularly important because the sample consisted solely of children who had responded to an open trial of megavitamin therapy, which should have maximized the probability of finding effects.

In summary, it does not appear that megavitamin supplementation has a consistent positive impact on the behavior of autistic or hyperactive children. For children with autism, supplementation with vitamin B_6 alone does not consistently improve behavior. Some evidence suggests that vitamin B_6 in combination with magnesium may have a positive impact on some aspects of behavior in autistic children, but this has not been demonstrated consistently. Further research using a greater number of children is needed to replicate such findings before recommendations can be made. In addition, the available evidence does not support the contention that megavitamin supplementation of children with attention-deficit disorder (ADD) or hyperactivity improves behavior. Furthermore, the fact that adverse side effects of such megavitamin preparations have been documented points to prudence in the scope of clinical use of such regimens.[104]

HUNGER: FASTING AND COGNITION

Hunger is typically defined as the "uneasy or painful sensation caused by a recurrent or involuntary lack of food…"[105] A related term, food insecurity, refers to the inability to acquire adequate and safe foods in socially acceptable ways. All people who experience hunger, that is, people who skip meals or reduce their food intake owing to a lack of necessary resources, are considered food insecure; not all of those who are food insecure experience hunger. Estimates for the year 2000 indicate that in the United States, approximately 13 million children under 18 live in food-insecure households and that approximately 4.1% of all children experience hunger.[106] With approximately 1 of every 6 children in the United States living in poverty, it is clear that hunger poses a serious problem for large numbers of children.[107]

In general, there seems to be a public perception that a relationship exists between hunger and psychosocial and academic functioning.[108–110] The potential mechanism to account for such delays is hypothesized to result from either the effects of deficient dietary intake over time or the more immediate metabolic or hormonal short-term effects of reduced food intake on cognitive functions, including but not limited to memory and attentional processes.[111] Methodologically, the association is difficult to establish because children who are at risk for hunger are frequently exposed to a wide variety of other risk factors (eg, poverty). In general, two types of designs have been used to assess the effects of hunger on cognition. The first refers specifically to whether the condition of hunger affects cognitive function, and the data come from a number of experimental studies that have measured children's response to fasting (eg, eating or not eating breakfast). The second refers to whether provision of food to children at nutritional risk can affect school performance and comes from food assistance and feeding programs that target low-income children in an attempt to reduce hunger and thereby improve school performance. In both types of studies reviewed, breakfast is the treatment variable. Breakfast has been shown to be a key component of a good diet by providing an important portion of the day's calories.[112,113] Its absence is considered to have potential effects on learning and school performance. Various surveys of children's eating habits suggest that anywhere from 5 to 26% of school-aged children frequently skip breakfast.[114,115]

Experimental Studies

In a series of clinical trials of short-term hunger in adequately nourished school-aged children, Pollitt and colleagues assigned children in random order to both a fasting and a breakfast condition, with each child serving as his or her own control.[116,117] Children were provided with dinner and spent the night in a controlled setting. Behavioral testing was conducted the following morning after 15 hours of fasting. Initial results showed no effect of missing breakfast, but differences emerged when IQ was considered in relation to test performance. Although missing breakfast had no effect on children whose IQ was above the median, children whose IQ fell below the median exhibited an increase in errors on the matching familiar figures tasks (MFFTs) in the absence of breakfast compared with the breakfast condition.[116] In contrast, on a memory test, subjects who had not eaten breakfast performed significantly better than those who had. Following similar procedures, the results of the second study showed statistically significant differences on the total number of errors in the MFFTs favoring the breakfast condition.[117] As in the first study, one measure of learning recall favored the no-breakfast (NBR) condition. In both studies, changes in performance (increase in errors)

were paralleled by physiologic responses to the feeding condition (glucose levels fell in NBR). The apparent benefits in incidental learning of the NBR condition were attributed to inefficient cognitive strategies.[116]

Two studies have explored the duration of fasting on cognitive function. In one study, the effects of increased duration of fasting were compared in well-nourished children under both BR and NBR conditions.[118] Although errors in performance on similar tests increased throughout the day for all children, children made fewer errors in the BR than in the NBR condition. On tests of arithmetic, between-group differences increased over the course of the morning, with BR-condition subjects performing significantly better than the NBR condition by midmorning. In a separate study, performance on a wide range of tests was compared between students who ate breakfast at home and those who ate breakfast at school.[119] Differences favoring the school breakfast condition were interpreted to reflect the benefits of eating within 30 minutes of the testing situation compared with the approximately 90-minute lag between breakfast eaten at home and testing. The study did not control for the nutritional content of home breakfast or the motivational effect for those children given breakfast at school.

Studies using healthy adolescents yield mixed results. In one, adolescents randomly assigned to a breakfast or a control group (given a very-low-calorie meal) showed no effects of hunger on cognitive function, including short-term memory, vigilance, impulsivity, and mood,[120] but another study reported that fasting resulted in slower word recall but no differences on spatial memory tasks compared with the breakfast group.[121] In two similar studies, students were allowed to eat their habitual breakfast (breakfast or not) and then were given either glucose or a placebo.[121] The results indicate that among students who had not eaten breakfast, glucose improved their word recall performance, whereas it had no effects on those who typically ate breakfast. There were no effects of breakfast or glucose on abstract reasoning.

A number of studies have focused specifically on glucose and cognition. It has been argued that because the brain has a high requirement for glucose relative to other organs,[122] the provision or availability of glucose prior to cognitive tasks may be particularly critical. The results of these studies are mixed, and weakness in study design further complicates their interpretation. In two studies, it was unclear whether subjects had eaten breakfast,[123,124] and in another, the nutritional content of the breakfast was not controlled.[125] Interestingly, research using animal models finds a U-shaped relationship between blood glucose and memory; at both high and low doses of glucose, the ability to retain learned information is impaired.[126] Although this type of relationship could account for the mixed findings, it is unclear whether this relationship would be replicated in children. Finally, other studies have reported a relationship between glucose tolerance and cognitive performance.[127] Given what is known about individual differences in diet and glycemic effect, research on glucose studies of fasting and cognition must include consideration of previous diet.

Research on fasting and cognition among low-income populations at nutritional risk reports mixed results. In Peru, using the same laboratory design used with well-nourished children, school-aged boys were categorized based on nutritional risk and then randomly assigned to a fasting or a breakfast condition, with each child serving as his own control.[128,129] The results showed no effects of fasting on tests of intelligence or vocabulary. In contrast, boys classified as at nutritional risk (low weight for height, low height for age) performed worse on a Stimulus Discrimination Task and the Sternberg Memory Search under fasting conditions compared with the breakfast condition. The authors concluded that attentional processes may be particularly sensitive to metabolic changes induced by the fasting condition.[130] Given that glucose levels were similar between the nutritionally at-risk youth and those considered not to be at risk, the mechanisms for such effects were unclear.

In Jamaica, Simeon and Grantham-McGregor tested the effects of missing breakfast on cognitive function among children of different nutritional histories: stunted, previously malnourished, and nonstunted controls.[131] All children were tested under both a breakfast condition and a tea-only condition. The results showed that both stunted and previously malnourished groups of children performed similarly and that missing breakfast resulted in lower test performance on verbal fluency and coding in these subjects. In contrast, the nonstunted controls' mathematics performance and MFFT efficiency scores improved as a function of missing breakfast. In a separate study, using a crossover design, poorly nourished Jamaican children performed significantly better on tests of verbal fluency (but not visual search, digit span, or speed of processing) after eating breakfast compared with well-nourished children.[132]

Finally, a study of school-aged children in Chile compared the effects of breakfast or no breakfast on the cognitive performance of normal, wasted, and stunted children and found no significant differences on any of the cognitive tasks.[133] Although this study was less controlled than those previously reviewed (randomization was only partially successful), the authors argued that testing children in the schools rather than a clinical laboratory may be a more valid test of the hypothesis. The absence of findings is attributed in part to the fact that highly motivating tasks, such as those employed in their study, may have masked potential between-group differences.

In summary, the results of well-controlled studies appear to indicate that fasting has effects on short-term memory that do not necessarily generalize to other domains of cognitive function. In addition, these effects likely vary as a function of previous nutritional risk.[130–132] Notably, it is unclear whether the reported effects are of meaningful magnitude, whether they can be sustained over time, or whether they are uniformly adverse. At least four studies have reported some small improvement in performance on certain tasks among healthy children under fasting conditions. Finally, although the results of several studies indicate that children at higher nutritional risk may be more susceptible to the effects of hunger,[131] this finding has not been consistent.[133]

School-Based Programs

One of the underlying assumptions of the school-based programs is the notion that children who come to school hungry will have a more difficult time attending to the learning process (see Chapter 9.1).[111] With the introduction of federally funded nutrition assistance programs in the schools and, in particular, the school breakfast program, investigators have been able to use these interventions as an alternative model to assess the effects of breakfast on school performance and to evaluate the effectiveness of the investment.

Data from evaluations of school breakfast programs have provided support for their benefits.[134] In one study, data on achievement, absenteeism, and tardiness collected prior to the initiation of school breakfast programs were compared with similar data after the school breakfast program. Compared with nonparticipants, children participating regularly in the school breakfast program showed significantly higher performance on the Comprehensive Test of Basic Skills (CTBS) and lower rates of absenteeism and tardiness. Most notably, even after controlling for a large number of potentially confounding variables (eg, sex, ethnicity, family size, income, pretest CTBS scores), the school breakfast program continued to show independent effects on the outcomes. One limitation of this study is that participation was voluntary, and this introduced a potential self-selection bias that could not be taken into account in the analyses.

In a two-state, three-school evaluation of the breakfast program, researchers found initial differences in academic performance between students with high participation in the school breakfast program (ie, those who typically ate school breakfast) compared with those with lower participation rates on a wide range of assessments, including test scores, indicators of depression and anxiety, hyperactivity, and attendance.[109] After introducing Universal School Breakfast (making the program free for all students in the school), program participation rates increased 100%. The authors reported that after 4 months of this breakfast program, students who frequently ate school breakfast showed improved rates of attendance and punctuality, decreased rates of psychosocial symptoms, and improved academic functioning (mathematics grades) compared with those who ate breakfast infrequently. Although suggestive, multiple methodologic problems (nonrandom design, small sample sizes, loss of subjects, and no control for usual breakfast consumption) prohibit the ability to establish any causal relationship between breakfast and student behavior. It is likely that children who choose to eat breakfast are significantly different in a number of ways from those who do not eat breakfast

Several studies from low-income countries suggest that children's performance and attendance improve with the introduction of a breakfast program, although, based on the designs, these effects are likely the result of increased motivation rather than any specific nutritional effect.[129,135,136] A comprehensive review of 15 school feeding programs in developing countries examined the association of school feeding with school attendance, participation, and achievement, with inconclusive results.[137,138] The results of this review highlight the difficulties associated with the implementation and evaluation of school feeding programs. Shortcomings likely to account for low program impact include inadequate targeting, food substitution rather than supplementation, inadequate supplementation (not meeting nutritional needs), poor administration and inefficient program implementation, and lack of nutrition education.

In summary, despite the absence of strong support for a direct impact of school feeding programs on school performance, consideration of the issues noted above in both programming and evaluation is likely to lead to more robust findings.[139] It should not be surprising that program evaluations of school feeding programs have not yielded strong effects on learning given the limitations of study designs available in school-based research. Furthermore, although one would expect that children at highest risk might benefit the most from such programs, this hypothesis has not been adequately tested. Finally, research on the effectiveness of such programs requires a recognition of the complexity of such relationships. Specifically, more attention needs to be focused on the multitude of factors (eg, attendance, absenteeism, time in school, time on tasks, etc) that mediate the relationship between school breakfast and school achievement (Figure 22-3).[134,137,138]

SPECIAL TOPICS

Sucrose

There is no shortage of literature attesting to the strongly held belief by parents and teachers that sugar causes behavioral alterations in children, particularly hyperactivity. However, most of the evidence to support such an association is purely correlational. The best test of the effects of sugar on behavior come from double-blind challenge trials that have shown an adverse effect of sugar on measures of sustained attention, performance on learning tasks, and play behavior.[140] At the same time, others have reported no effect of sucrose on behavior,[140,141] whereas still others have reported effects in the opposite direction as those hypothesized, that is, a decrease in activity and an increase in drowsiness in children after sugar ingestion.[141–143] Several potential explanations have been offered for this lack of uniformity in the research findings, including differences in subjects (ie, various ages and clinical status), state characteristics (fasting, nonfasting), study design issues (dosage of sucrose, differences in research settings, amount of time elapsed between challenge and testing, the placebo used), and the behavioral measures used. Furthermore, some researchers have failed to account for total energy intake, which is a potential confounder because of the inherent differences in energy content of sucrose and noncaloric sweeteners.[140] In addition, some but not all researchers have reported that aspartate, the most commonly used placebo, may also cause behavioral changes.[141,143,144]

One of the underlying assumptions of such research is that children with specific behavior problems such as ADD and hyperactivity may be particularly sensitive to the effects of sugar. Despite this assumption, many studies have examined samples composed primarily of normally active (without ADD or hyperactivity) children, whereas

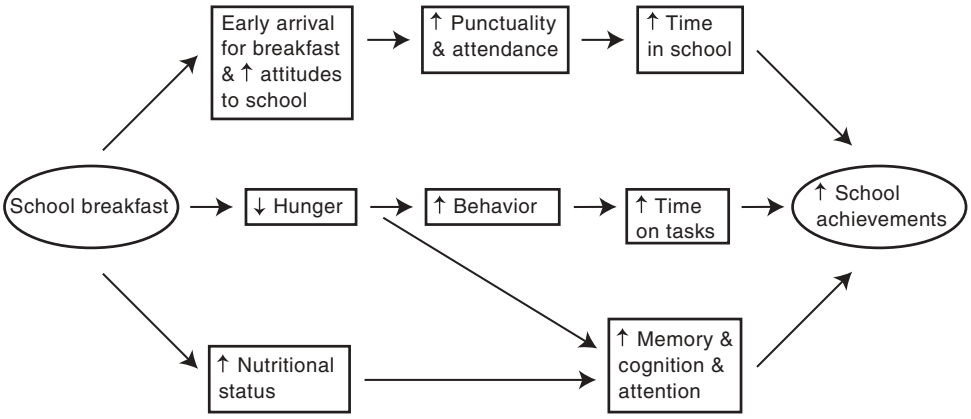

FIGURE 22-3 Possible mechanisms of the effect of school breakfast on school achievement. Reproduced with permission from Grantham-McGregor S, et al. Environmental effects on cognitive abilities. Mahwah (NJ): Lawrence Erlbaum Associates; 2001.

others have focused specifically on samples composed primarily of children diagnosed with ADD, with or without hyperactivity.

In six double-blind sucrose-challenge studies in normal children, two found no effects of sucrose on behavior,[140,144] two showed what might be considered positive effects,[141,143] and two others showed negative effects.[140,145]

Among the studies reporting adverse effects of sugar consumption, weaknesses in design may account for such findings. For example, in one study, after the high-sucrose challenge, girls (but not boys) made a greater number of errors on the paired associates task than when on the low-sucrose challenge; there were no differences between high sucrose and aspartate.[145] In addition, a global rating of children's behavior indicated that teachers perceived significantly greater activity in the high-sucrose versus low-sucrose challenge. There were no effects of the high-sucrose challenge on other cognitive measures, fidgeting, or the Abbreviated Conners' Teacher Rating Scale (used to diagnose hyperactivity). Of particular concern is that the significant differences were between high sucrose and low sucrose rather than the aspartate control, suggesting some mechanism other than sugar content (eg, perceived sweetness) as mediating the behavioral changes observed.

Studies that have examined the effects of sucrose on children diagnosed with ADD with or without hyperactivity have shown very little support of a causal association.[140,146,147] In a study of 7- to 10-year-old hyperactive boys, there was no effect of a sucrose challenge on performance on a sustained attention test (CPT), paired associate learning, matching familiar figures, fine or gross motor movements, or the draw-a-line slowly or draw-a-line fast tests.[140] Another study using hyperactive boys attending a day treatment program for hyperactive children reported no differences in behaviors during recreational periods, academic performance, or teacher ratings based on sucrose challenge.[140] In still another study that also used tests of attention among children with ADD, an oral 5-hour glucose tolerance test found no effect of glucose on the CPT, although, interestingly, the catecholamine response to the glucose was significantly lower in those with ADD than in the control group.[146] Finally, the results of a recent meta-analysis conclude that the available evidence does not support a relationship between sugar consumption and behavior or cognitive performance of children.[140] This conclusion is strengthened by the fact that only designs that met criteria of scientific rigor were included.

Despite all of the research to the contrary, there has been an obvious resistance of parents and teachers to fully accept such a conclusion. Some of this may stem from expectancy and common association (ie, high sugar consumption corresponding to events that may in and of themselves cause excitement in children). The results of one study illustrated the effect of parental expectancy on behavioral ratings.[148] Boys who were 5 to 7 years of age and who were reported to be sugar sensitive took part in a challenge study. Although all children received a placebo (aspartame), half of the mothers were told that their children were given a large dose of sugar and the other half were told that their children were given a placebo. Mothers who were told that their sons received sugar rated their children as significantly more hyperactive than those who were told that their children were given a placebo. Videotapes failed to corroborate their perceptions.[148]

In summary, research from well-controlled studies, including multiple outcomes and comparisons, does not support a consistent causal association between sucrose ingestion and children's behavior. These results are true for children diagnosed with ADD and/or hyperactivity and normally active children. Positive effects of elimination diets in treating ADD children may be attributable to the concurrent elimination of other substances such as caffeine or allergens and not the elimination of sucrose.[149] In addition, parental or teacher expectancy likely plays a role in reports of sugar sensitivity and in the perceived success of elimination diets. Whether a highly specific subgroup of children is sensitive to sucrose still is not supported by the bulk of the available research; however, this possibility cannot be definitely eliminated based on current research.

Food Additives

In addition to sugar, food additives have frequently been implicated as causes of children's behavioral problems, specifically hyperactivity. Although data from correlational

studies and open trials, in which normal diets are replaced with additive-free diets (the Feingold diet), have provided support for such an association, the evidence of a causal link is limited.[98] One of the major difficulties of such research is that neither the child nor the family is blinded to treatments involving changes in a child's diet. Furthermore, many other factors may also change with dietary manipulations, making it impossible to directly link food additives to behavioral change.

Two other types of studies offer a better test of the association between food additives and behavior: dietary studies and challenge studies. Dietary studies include two randomly assigned diets (one without additives and a placebo); in challenge studies, the subject is provided with either a food with additives or an additive capsule after being on a nonadditive diet for a specified period of time. Of 11 studies using these two techniques in children diagnosed with hyperactivity to test for the effect of a single or a class of substances (ie, artificial colors), only 3 found an effect of the challenge on the child's behavior.[150] In those studies, two showed effects on teachers' ratings of child behavior.[149]

More recently, studies have employed a standardized technique of double-blind, placebo-controlled food challenge to diagnose adverse food reactions.[151] This procedure includes an elimination diet and a subsequent reintroduction of the suspected food (or additive) and may also include allergy skin testing. Although a well-controlled design, this technique does not always allow the investigator to identify any one item or specific substance but rather to identify a food or a class of foods to which the individual may be sensitive.

Three studies using this technique provide limited support for either specific food sensitivities of some children with ADD and/or sensitivity to food additives,[152,153] although effects were often seen in only a subgroup of children.[150] In one study, differences in energy intake between diets may have affected the behavioral effects attributed to food additives.[150]

In summary, the available evidence does not support the notion that food additives adversely affect the behavior of hyperactive children. What does seem to be true, however, is that a small subset of hyperactive children may be particularly sensitive to some foods and/or food additives, and these children may benefit from a modified diet.

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CHAPTER 23

ENERGY AND SUBSTRATE REGULATION IN OBESITY

Susan B. Roberts, PhD, Daniel J. Hoffman, PhD

Overweight and obesity are widely considered to be the major public health problem in affluent countries[1,2] and are becoming increasingly common in some economically disadvantaged societies as well.[3,4] Previously considered a problem mainly occurring in adults, overweight and obesity are now prevalent in children, with an estimated 18 to 28% of US children and adolescents thought to be affected.[5]

DEFINITION OF OBESITY

The definition of obesity is deceptively simple: it is a state of excessive accumulation of body fat. However, the translation of this simple definition into working standards for excess body fat and body weight has been complicated for several reasons. First, because body fatness is a continuum, the cutoff point for the definition of obesity is necessarily arbitrary.[1] In addition, controversy remains over what constitutes the optimal range of body fat in infants and children because of the normal developmental changes in adipose tissue mass that need to be taken into account. Finally, the harmful effects of obesity result primarily from the excessive accumulation of fat, but there is no simple method for the direct measurement of this body compartment in individuals of any age. These concerns notwithstanding, the Centers for Disease Control and Prevention (CDC) recently published new body mass index (BMI; kg/m^2) percentiles for children aged up to 20 years (see Appendix), together with useable definitions for "risk of overweight" and "overweight."[6] These definitions recognize that BMI is a better indicator of relative weight than weight for height, even if they are not precisely aligned with body fatness in all population groups.[7]

The new charts provide an improved set of reference growth data that have been updated and smoothed using statistical techniques. However, as reviewed elsewhere,[8] it should be noted that the latest national survey data for children ages 6 years and over were not included in the data set used to calculate the BMI percentiles because of the marked increase in weight of children 6 and older in the latest survey (Third National Health and Nutrition Examination Survey [NHANES III]) compared with previous surveys. The inclusion of the latest survey data would have shifted the percentiles up and resulted in a relative underclassification of the prevalence of overweight. Because the 85th percentile of BMI is used to classify risk of overweight and the 95th percentile is used to classify overweight,[7] the data used effectively define overweight as a fixed percentage relative to population surveys prior to NHANES III. Thus, the BMI charts can be considered more as recommendations for the healthy range of BMI rather than as current population values because they are designed primarily to provide a reference for the diagnosis of overweight. They can also potentially be used to diagnose underweight (eg, at the 10th or 5th percentiles), but accepted definitions for underweight are needed.

One concern with using BMI to identify overweight children is the potential for misclassification.[8] The relationship between weight and height and body fat content can be weak,[9] and, especially in children younger than 5 years when the high BMI percentiles are very close together, factors such as enhanced muscular development, large head size, and a high torso-to-leg ratio could all falsely elevate the BMI of a child with a healthy amount of body fat into an overweight range. For example, differences in head circumference between a 3-year-old child on the 10th head circumference percentile and one on the 90th percentile translate into a body weight difference of approximately 0.75 kg (assuming that the head weighs 1.7 g/cm^3 and is a sphere). A 3-year-old child's BMI would therefore vary by approximately 0.85 units depending on whether head circumference was on the 10th or 90th percentile. This could mean the difference between the 75th and 85th to 90th percentile for BMI—in other words, the difference between no weight concern and a diagnosis of risk of overweight. The effect of the relative length of torso and legs can also be predicted using theoretical calculations. Assuming that the proportion of standing height attributed to torso varies from 0.35 to 0.38 and that for a given contribution to height, torso weight is twice that of legs or neck,[10] BMI would vary by approximately 0.4 units. These calculations highlight the potential for misclassification of individuals, especially those between the 85th and

95th percentiles. Until improved methods for determining body fatness are routinely available, some individual judgment is needed in applying standard BMI definitions for overweight in individual children.

At the same time that the 2000 CDC percentiles were published, Cole and colleagues reported internationally derived, age-specific BMI values for children equivalent to BMI definitions of overweight (BMI = 25 or more) and obesity (BMI = 30 or more) in adults.[11] The adult cutoff values of 25 and 30 were originally developed based on increased health risks[12]; the theoretical advantage of creating equivalent values for children is that they would provide absolute standards for fatness rather than standards relative to population fatness at any given period of survey.[13,14] It should be noted that it is not currently known whether equivalent percentiles in childhood confer similar risk to those found in adults, but because BMI tends to track from childhood through adult life, the approach seems a reasonable one.

As reviewed elsewhere,[8] Cole and colleagues obtained national survey data from six countries (Brazil, the United Kingdom, Hong Kong, the Netherlands, Singapore, and the United States).[11] For each country, the percentiles equivalent to BMI values of 25 and 30 at age 18 years were determined, and then BMI values at different childhood ages were obtained for the same percentiles. There was substantial agreement in childhood BMI values among the six countries; thus, mean values for different ages were computed to give age-specific BMI cutoffs equivalent to adult BMIs of 25 and 30 kg/m^2. Figure 23-1 shows a comparison of the CDC 85th and 95th percentiles with the overweight and obesity cutoff points for BMI provided by Cole and colleagues. For both boys and girls, the 2000 CDC definition of overweight (95th percentile) is markedly higher than the Cole and colleagues[11] definition of overweight,[11] except for the period between age 4 and 5 years. In other words, by the current US definition, many fewer children in the United States and worldwide are overweight. In fact, the 2000 CDC definition of risk of overweight (85th percentile) most closely approximates the Cole and colleagues definition of overweight, with the Cole and colleagues values tending to be slightly higher for ages 2 to 10 years and slightly lower for 17 years and older.[11] In addition, the CDC BMI definition of overweight is not similar to the Cole and colleagues definition of either overweight or obesity, but the CDC 97th BMI percentile is similar to the Cole and colleagues definition of obesity for the period between 7 and 14 years.[11]

These comparisons raise the important issue that greater agreement is needed among national and international agencies with regard to definitions of what age-specific BMI values constitute risk of overweight and obesity. In the meantime, the 2000 CDC percentiles for BMI might be most appropriate for assessing different degrees of overweight in US children, and the BMI cutoffs of Cole and colleagues could be used for international comparisons of obesity prevalence.[11]

RISKS OF OBESITY

The short-term risks of overweight in children and adolescents extend to reduced scholastic performance, psychological problems, and a number of significant health risks, including hyperlipidemia.[15] In addition, obese children are at increased risk of becoming overweight or obese adults compared with children of normal weight[16] and therefore are at long-term risk of the substantially increased morbidity and mortality, psychological problems, reduced economic achievement, and discrimination that are seen in obese adults.[17] In a summary of 17 studies investigating the long-term risks of childhood overweight for the development of adult obesity, Serdula and colleagues observed that 26 to 41% of overweight preschool children go on to become obese adults, with the risk of adult obesity increased to 2.0 to 2.6 times that of nonoverweight children.[18]

The risk of adult obesity in overweight children increases progressively with age. Data from Braddon and colleagues[19] on changes in the risk of adult obesity according to the age

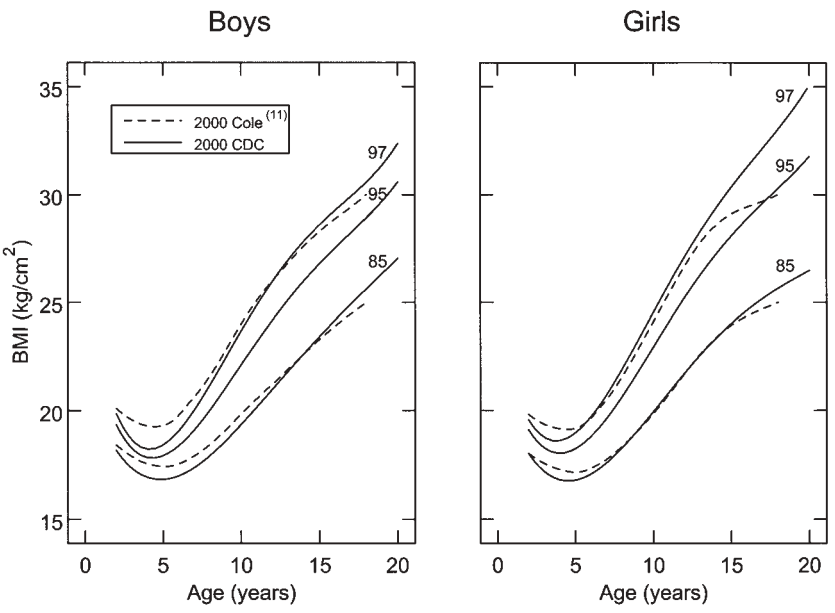

FIGURE 23-1 Comparison of Cole et al's[11] BMI definitions of overweight and obesity during childhood (*broken line*) with 2000 CDC 85th and 95th percentiles (defined as risk of overweight and overweight, respectively) and the CDC 97th percentile (*solid line*). Reproduced from Roberts SB and Dallal GE.[8]

of childhood manifestation are shown in Figure 23-2. In that study, which was conducted in a cohort of English children, the percentage of obese adults who were overweight at age 7 years was only 2.6% for men and 7.5% for women, whereas values increased to 13.9% for men and 25.5% for women who were overweight at age 14 years. In addition, these figures might substantially underestimate the true relationship between early fatness and later obesity because 28.6% of obese men and 36.5% of obese women were already obese or overweight by age 7, a substantially increased percentage relative to the group of children who were categorized as overweight, and again there was an increase in the number of obese adults who were overweight in childhood as age increased (Figure 23-2).

A further issue relevant to the risks of childhood overweight is that there is evidence to suggest that *severe* overweight developing early in life is particularly likely to lead to adult obesity. Whitaker and colleagues showed that childhood overweight was increasingly likely to predict adult obesity from age 3 years and older.[16] Similarly, Abraham and Nordsieck reported that 72.2% of severely overweight children (weighing more than 120% of the average for the population) became obese adults[20]; a similar result was found by others.[21] Although these data illustrate the substantial risk of childhood overweight leading to adult obesity, it is also important to note that many overweight children do not become obese adults. Data from Poskitt indicate that only one in nine overweight infants remain obese as adults in England,[22] whereas other studies similarly indicate that a minority of overweight children remain overweight.[19]

Recent studies have also raised the issue of whether, in addition to increasing the risk of adult obesity, obesity in childhood could also exert an independent influence on adult morbidity and mortality. In an analysis of longitudinal anthropometric data from the Third Harvard Growth Study (1922–1935), Must and colleagues observed that over a 55-year period, men who were overweight in adolescence had significantly increased all-cause mortality (relative risk 1.8) compared with men who were lean during adolescence.[23] This effect of adolescent weight, confirming a similar result found previously by Mossberg,[24] persisted even when weight at age 53 years was controlled. The implication of this finding is that the effects of adolescent weight on morbidity and mortality resulted from the adolescent obesity directly rather than from the effects of adolescent obesity on adult weight.[24] There was no association between adolescent weight and adult mor-

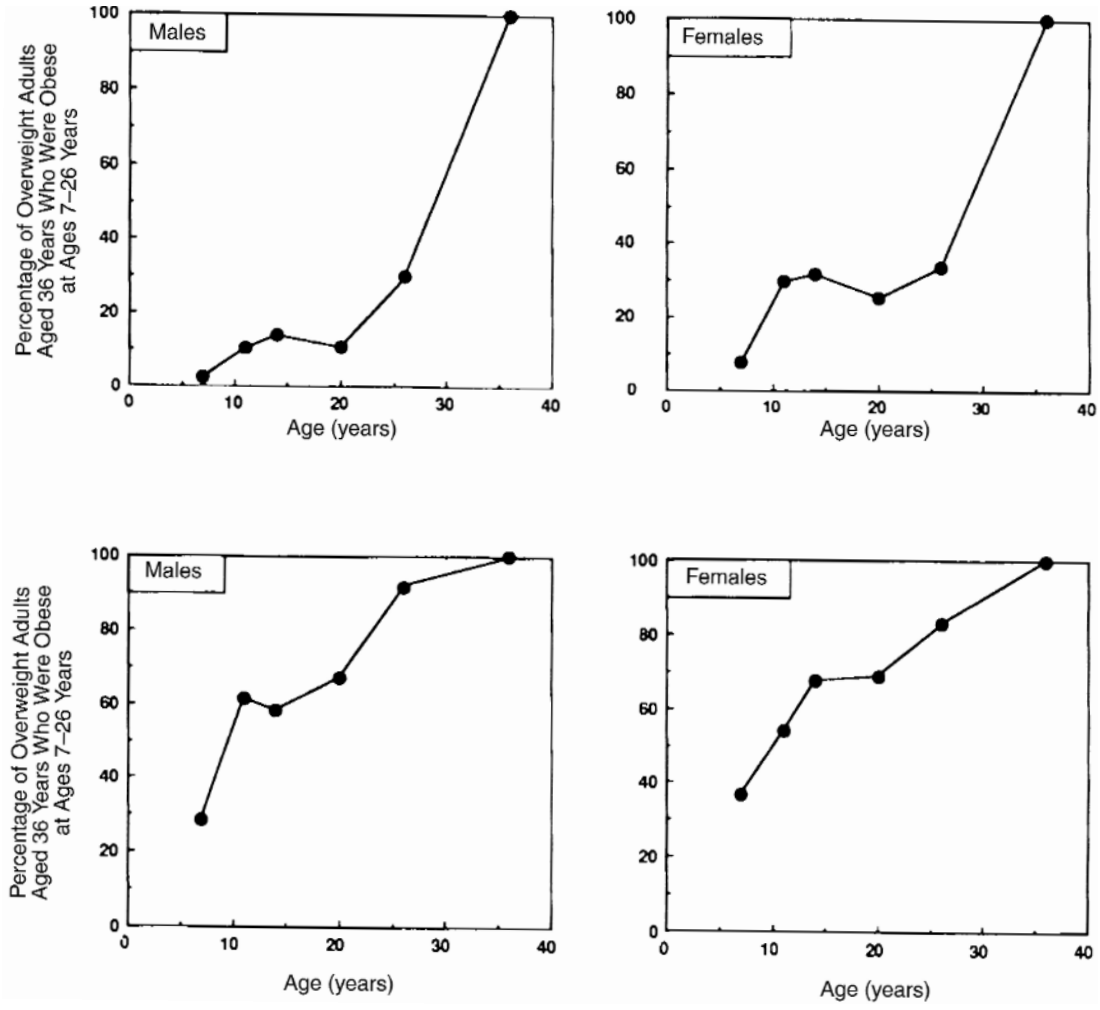

FIGURE 23-2 Percentage of obese men and women aged 36 years who were already obese (top) or either obese or overweight (bottom) by ages 7 to 26 years. Adapted from Braddon FEM et al.[19]

tality in females in the study of Must and colleagues,[23] and gender was not distinguished in the study by Mossberg.[24]

The mechanisms by which adolescent weight might exert an influence on adult morbidity independent of adult fatness in men and possibly in women are not known. However, reports of increased plaque deposition in the arterial walls of overweight children suggest that there could be long-term effects of early body weight on morphology or metabolism that are not easily reversible. Consistent with this suggestion is the fact that overweight girls have been shown to have a reduced age of menarche, a risk factor for developing breast cancer.[25–27] This effect appears to be primarily related to increased body size rather than to differences in dietary intake in the obese.[28–30] A study by Meyer and colleagues suggested that the lowered age of menarche in overweight girls might be associated with increased weight rather than with increased fat mass.[31]

It is important to note that not all studies of the relationship between childhood weight and adult morbidity have reported positive associations. The study of Barker and colleagues reported an opposite trend, with a negative association between weight at 1 year of age and vascular disease in adult life.[32] Further studies are needed to clarify this issue and in particular to determine whether the long-term effects of early obesity could be important at some ages during childhood but not at other ages.

GENETIC VERSUS ENVIRONMENTAL FACTORS IN THE DEVELOPMENT OF OBESITY

Studies in Animals

In animals, there is substantial evidence that obesity can be transmitted genetically.[33] Several genetically obese animal strains exist, such as the Zucker rat and the ob/ob mouse, which have substantially more adipose tissue than lean counterpart animals. The fat gain in genetically obese animals is caused by a variety of mechanisms, including hyperphagia and an increased efficiency of energy use. The increased energy efficiency can be attributed primarily to a reduced thermogenesis for body temperature regulation. It is likely that some degree of imbalance in the autonomic nervous system contributes to the defective thermogenesis, as indicated by reduced sympathetic nervous drive in response to mildly cold ambient temperatures and in response to overeating.[34] In addition, parabiotic studies, in which the circulatory systems of lean and genetically obese animals are joined, have indicated that unidentified circulating factors (or the ability to respond to them correctly) are also important in the development of obesity.[35]

Animal studies also demonstrate that obesity can result from environmental factors, most particularly the availability of high-fat or high-variety diets. Some—but not all—strains of laboratory rodents gain substantial weight and fat when offered cafeteria diets containing a variety of snack foods such as cookies, cheese, cakes, processed meats, nuts, and so forth. Similar results have also been produced by offering synthetic high-fat diets, as well as by providing sucrose solutions in addition to standard rat chow. It could be noteworthy that physical activity does not have as much of an influence on body fat content as does diet in these rodent species. The fact that only some strains of animals, and only some animals within a strain, are susceptible to this diet-induced obesity[36,37] strongly indicates that "environmentally induced" obesity occurs only in genetically susceptible individuals and should therefore really be viewed as a genotype–environment effect. In relation to this observation, it is important to note that the willingness to overconsume food is not entirely a result of absolute standards of taste in animals. Instead, in studies that have separated the process of eating from the process of digestion by the use of esophageal cannulae, it has been shown that unidentified postingestion factors play a dominant role in determining food preferences.[36]

Studies in Humans

Studies on the importance of genetic inheritance versus environmental factors in the development of overweight and obesity have been harder to conduct in humans. It is widely accepted that body fat mass and fat distribution are subject to significant familial transmission[38–43]; in other words, the body compositions of children to a large extent reflect those of their parents. There remains a great deal of uncertainty, however, over the relative importance of genetic inheritance and environmental transmission (transmission between generations through the sharing of common environmental circumstances) in determining body fat content. Reported values for genetic heritability range from negligible to 0.8, implying that genetic inheritance accounts for between 0 and 80% of the variability in body fat mass in the community, and rates of environmental transmission range almost as much.[39,41,43–55]

This uncertainty over the relative importance of genetic and environmental transmission probably relates in large part to the methods that have been used to measure body composition and to the populations that have been studied. Most previous studies have used simple anthropometric indicators of body fat mass (such as weight corrected for height or one or more skinfold thicknesses).[39,43–48,50–55] However, the relationship between anthropometric parameters and fat mass can be very weak.[9] In addition, muscle mass, bone size, and height appear to be strongly inherited.[43] This could help explain the genetic inheritance of indicators of apparent fatness based on weight and could indicate that weight measurements will tend to result in an overestimation of the genetic inheritance of fat mass.

Probably the best data available on the inheritance of body composition come from Bouchard and colleagues, who have been the only groups to use hydrostatic weighing (a gold standard method) for assessment of body composition.[49,56] Data from these investigations indicate that there are significant genetic and environmental components to the transmission of body density, with genetic inheritance accounting for 25% and environmental transmission for 30%. Thus, it appears that the family environment is at least as important as genetic inheritance in determining body fat mass.

Other lines of evidence from studies that effectively separate genetic inheritance from environmental factors confirm the importance of environmental factors in human overweight and obesity. For example, the body fat content of unrelated married couples becomes more similar over time.[40] In addition, the prevalence of obesity varies by the season of the year (it is highest in the fall and winter) and location within a country.[57] As further evidence, surveys show that the prevalence of childhood obesity has increased in the United States during the past two decades despite a relatively stable population pool.

METABOLIC PROGRAMMING IN THE DEVELOPMENT OF OBESITY

There is increasing awareness of the possibility that there might be critical periods during the life span when diet and other environmental factors exert a long-term influence on body fat content and the risk of adult obesity in humans,[58–61] a potential event that has been termed "metabolic programming." As emphasized by Lucas, the fact that this tremendously important issue has not yet been resolved reflects the relative lack of randomized dietary intervention trials with long-term follow-up in infants and children.[58,59] More studies of this type are needed despite the complex ethical issues involved.

Evidence consistent with the view that metabolic programming of adult body fatness might exist at different ages comes from several different sources, in particular indicating that either long-term energy insufficiency or long-term energy excess in childhood can lead to excess body fat content in adult life. In 1976, Ravelli and colleagues published the first study suggesting that nutrition of the mother during the intrauterine period might have a long-term influence on the risk of obesity.[62] Specifically, the investigators followed the incidence of obesity among men whose mothers lived in Holland during the Dutch "Hunger Winter," a time when the food supply was reduced in specific areas of the country at the end of the Second World War. A significant *increase* in the incidence of obesity at age 19 years was noted among the male offspring of mothers whose energy intake was reduced to famine levels (estimated at approximately 600 kcal/day) specifically during the first trimester of pregnancy, whereas a significant *decrease* in the risk of obesity was observed in women who had undergone energy deprivation during the third trimester. Although "metabolic programming" of intrauterine malnutrition can explain this result, it is also possible that other factors were important. For example, the mothers who were deprived of food might have been particularly concerned about feeding their infants substantial amounts of food after giving birth. In addition, the food provided by the Allied Forces after the famine was extremely high in fat, and the possibility cannot yet be ruled out that this might have had an important long-term effect.

Nevertheless, recent studies in animal models have also reported that malnutrition during the early part of pregnancy can be associated with increased body fat in adult life,[63,64] supporting the belief that long-term metabolic changes can be induced through diet. Although the mechanism for this effect is not known, Anguita and colleagues suggest that morphologic changes in the hypothalamus might be important.[64]

Similar to in utero energy insufficiency, childhood stunting (which is widely considered an indicator of chronic energy insufficiency during early childhood and typically occurs before age 5) has also been correlated with high BMI in several transitional countries, such as Brazil, China, and South Africa.[4,65–68] The risk for obesity and overweight for adults who were stunted as children and adolescents varies among countries but is consistently positive. The relative risk for obesity for an adult who was stunted in childhood is 1.7 in Brazil, 2.6 in South Africa, and 7.8 in Russia.[65] Mechanisms to explain these associations remain unclear; however, recent studies have offered possible metabolic as well as behavioral evidence that might explain part of this association.

In perhaps the first piece of evidence that early nutrition has long-term effects on metabolism that predispose a child to subsequent obesity, Hoffman and colleagues reported that nutritionally stunted children have a higher respiratory quotient and lower fat oxidation compared with healthy children from the same environment (Figure 23-3).[69] In the same series of experiments, stunted children also appeared to have impaired regulation of food intake compared with control children from the same environment,[70] resulting in greater energy consumption per kilogram of body weight when the stunted children were exposed to an abundant, ad libitum diet (Table 23-1). The results of this study need to be replicated but are consistent with the hypothesis that exposure to food insecurity early in life can disrupt normal perceptions of hunger and satiety. Taken together, these studies provide multiple lines of evidence consistent with

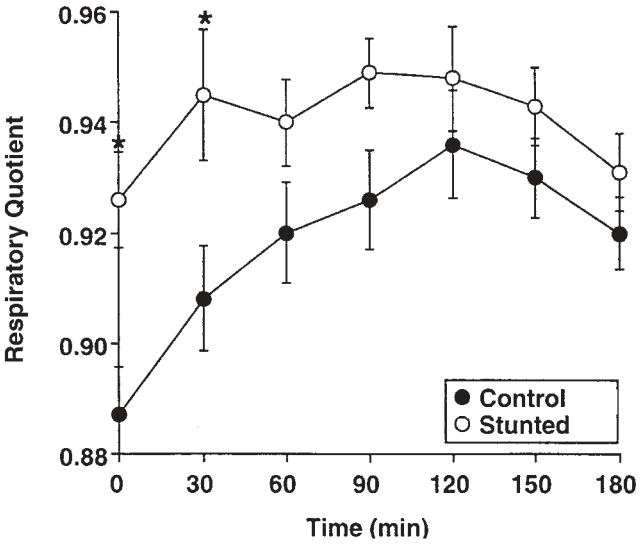

FIGURE 23-3 Fasting and postprandial respiratory quotient (RQ) in stunted and control children.[69] Values are means ± SEM. The stunted children had a significantly higher fasting RQ compared with control children (t = 0) and postprandially at t = 30 minutes ($p < .05$). The average postprandial RQ was not significantly different between the two groups ($p = .10$). Reproduced with permission from Hoffman DJ et al.[69]

the suggestion that undernutrition during early life can have long-term metabolic effects that can promote obesity later in life.

The first months after birth have received considerable attention as another potential time when metabolic programming, through the choice of diet (breast milk or formula) and the time of weaning, could have a long-term influence on body fatness. In particular, although several studies have suggested no effect of formula feeding on body fatness, the more recent studies have consistently indicated that breast-fed infants tend to become leaner adults.[71–79] The finding of a tendency for formula feeding to promote later body fatness in full-term babies is consistent with preliminary findings from randomized studies in preterm infants[80] and also with the well-known effect of early overfeeding in rodent models (resulting in a permanent increase in body weight and fat content).[81] Additionally, similar results have been demonstrated in nonhuman primates.[82]

Further studies are needed to determine whether metabolic or behavioral influences of formula versus breast-feeding are responsible for the differences observed. However, of potential relevance to this issue is the fact that Singhal and colleagues conducted a prospective study of preterm infants who were fed either a standard infant formula, banked breast milk, or an enriched preterm formula (5 g protein/L and 9 g fat/L greater than the standard formula) to examine long-term effects on circulating leptin.[80] Between the ages of 13 and 16 years, the children were measured for body fatness and leptin concentrations. It was found that the children who had received the preterm formula had a 30% higher ratio of leptin to fat mass compared with both of the other groups,[80] suggesting that the excess energy intake or altered nutrient composition of the preterm formula might have programmed higher circulating leptin during adolescence.

ENERGY AND SUBSTRATE REGULATION IN OBESITY

Energy Regulation

Average nonoverweight children consume more than 2 million kilojoules a year, but their body fat stores increase only modestly if growth is normal and energy expenditure approximates energy intake. A change of only 10%, either in intake or output, can lead to a 15-pound change in body fat in a single year, in addition to that deposited as a normal consequence of growth. The majority of children, who are of normal weight, do not exhibit such undesirable changes in body weight and fat, implying that normal energy regulation must be remarkably sensitive.

Until recently, our understanding of the underlying cause of this sensitive energy regulation was dominated by the guiding principle of energy balance:

Energy stored = Energy intake – Energy expenditure

Thus, it has been recognized that high levels of body fat (ie, energy) cannot have been accumulated without energy intake being unusually high or energy expenditure being unusually low, or a combination of these two options. Similar calculations to those given above can illustrate that the dysregulation of energy in obesity needs to be only very small for excess adipose tissue to accumulate. For example, a child who becomes 100 pounds overweight by the age of 15 years needs to have eaten less than an extra ≈ 100 MJ per day between the ages of 5 and 15 years. There has been considerable interest in defining whether energy intake or energy expenditure is the primary factor determining this energy dysregulation in obese individuals, as well as seeking to identify metabolic mechanisms that determine the separate regulation of these parameters. As described below, most of the investigations conducted in children have been cross-sectional in nature, that is, comparing measurements of energy intake and expenditure between lean and obese individuals or examining the relationship between these parameters in groups of individuals differing widely in body composition.

TABLE 23-1 Energy Intake and Ratio of Energy Intake to Resting Energy Expenditure

	Girls		*Boys*	
Variable	*Control* (n = *15*)	*Stunted* (n = *13*)	*Control* (n = *14*)	*Stunted* (n = *14*)
Energy kJ/kg body weight*	60 ± 15	74 ± 14	67 ± 18	81 ± 9
Energy intake (kcal/d)/ resting energy expenditure*	1.67 ± 0.4	1.89 ± 0.3	1.69 ± 0.4	1.93 ± 0.2

Adapted from Hoffman et al.[70]
± SD.
*$p < .05$ between groups.

Energy Intake

The energy intake of an individual is usually understood to be that energy available to the body after obligatory losses of energy in urine and stools. Although complex metabolic balance studies are needed to precisely determine this "metabolizable energy," it can also be predicted from the dietary intakes of protein, fat, carbohydrate, and alcohol using the standard conversion factors of 4.0, 9.0, 4.0, and 7.0 kcal/g, respectively, which take into account the obligatory losses.

The regulation of food intake clearly plays an important part in the sensitive energy regulation in children of normal weight. More than 70 years ago, Davis demonstrated that very young children of normal body weight are capable of choosing a balanced diet and maintaining normal growth without dietary intervention from adult caregivers.[83] This remained true over periods of several days or longer, although food choices at individual meals were frequently extremely erratic. Recently, Birch and colleagues[84] and Shea and colleagues[85] provided additional strong evidence in support of an important role for the regulation of food intake in the energy regulation of young children of normal body weight. These investigators showed that although there might be substantial meal-to-meal fluctuations in energy and nutrient intakes, prompt and appropri-

ate compensation occurs spontaneously so that the 24-hour energy intake remains relatively stable. A further report by Birch and colleagues also demonstrated that young children are able to compensate for the inclusion of low-calorie fat substitutes in a meal to maintain a constant energy intake.[86]

These studies clearly demonstrate that in children of normal body weight, energy regulation through the regulation of food intake occurs and plays an important role in the maintenance of a stable pattern of body composition change throughout childhood. However, a caveat to these studies is that the observed capacity for normal energy regulation may occur only when relatively healthy foods are offered, and the ability of young children to accurately regulate energy intake when offered many highly energy-dense foods of low nutritional value has not been systematically explored.

Individual studies of differences in reported energy intake between overweight and nonoverweight children have been conflicting, but taking all of the data together, reported energy intakes of overweight children are not significantly greater than those of nonoverweight children of the same age and are significantly less when expressed in relation to body weight.[29,85,87–105] However, it is known that overweight individuals, including adolescents,[106] underreport their energy intake to a greater degree than do individuals of normal weight, which indicates that the finding of normal food intake in overweight children might be owing to methodologic error.

In contrast to the studies of reported energy intake, studies from psychological investigations of eating behavior in overweight children suggest that already-overweight children consume more total energy than do nonoverweight subjects. Studies by several groups have suggested that overweight children and adolescents are faster eaters, chew less, prefer high-fat foods, and do not exhibit the normal pattern of decelerating eating toward the end of a meal, as seen in children of normal weight.[107–110] Furthermore, obese parents have been reported to give more encouragement to their children to eat than do parents of nonobese children and serve them larger portions of food.[111] These findings are also consistent with results from studies in adults.[112] In addition, overweight children may have an abnormal pattern of energy consumption within the day, with a reduced percentage of calories being consumed at breakfast.[113] As described below, studies of total energy expenditure (TEE) might be more reliable for estimating the energy intake of overweight children than studies of reported energy intake and confirm that already-overweight children consume more total energy than children of normal weight.

Energy Expenditure

The TEE of an individual, which is equal to the metabolizable energy intake when body energy stores remain constant, can be divided into compartments that relate to the different types of energy expenditure measurements that are made. Typically, three major compartments are defined. The resting energy expenditure is the energy expended at rest after an overnight fast and is the major compartment, comprising at least half of the TEE in a typical individual. The thermic effect of feeding is the increase in energy expenditure above baseline resulting from the consumption and processing of food and comprises 7 to 15% of TEE on average. This thermic effect of feeding has been further subdivided into facultative and obligatory components, where obligatory energy expenditure is the expenditure for necessary aspects of digestion and assimilation, whereas the facultative component has been proposed as a form of energy wasting that can perhaps serve to burn off surplus dietary energy. The final component of TEE is the energy expended for physical activity and arousal, which is generally the second-largest component of TEE and the most variable because to a large extent it is under voluntary control.

The role of energy expenditure in the regulation of energy balance remains controversial. Studies in both adults[114–117] and adolescents[118] have suggested that humans have a relatively limited capacity for dissipating surplus dietary energy by thermogenesis. In these studies, subjects have been overfed, and changes in energy expenditure and energy storage have been measured to assess the fate of the excess dietary energy. In all carefully controlled studies, the ability to dissipate excess energy, seen as an increase in TEE or components of energy expenditure, has represented a relatively minor component of the excess dietary intake.[114–117] Thus, the majority of the surplus energy was stored, primarily in the form of additional body fat. Studies of this kind highlight the importance of the regulation of food intake, rather than thermogenesis, in the short-term regulation of energy balance.

It is possible, however, that energy expenditure plays other critical roles in energy regulation that these studies do not address. In particular, it has been speculated that low energy expenditure in one or more of the components of expenditure could have an association with increased body fatness over the long term. This could be a result of the low energy expenditure promoting increased fatness or of an underlying mechanism promoting fat gain that precipitates low energy expenditure to provide the surplus energy needed for the weight gain. Studies of differences in components of energy expenditure between obese and nonobese children are discussed below. These cross-sectional studies do not define the causal role of energy expenditure in obesity but do serve to define the energy expenditure of children who are already obese in relation to normal values. Prospective studies that have investigated the role of energy expenditure in the weight gain in obesity are discussed below under "Roles of Energy Intake and Expenditure in the Development of Obesity."

Concerning resting energy expenditure, a summary of studies in otherwise healthy overweight and nonoverweight children reveals that the overweight individuals do not have reduced resting energy expenditure. In relation to age, the resting energy expenditure of overweight children appears to be within the normal range at 8 to 10 years and increases subsequently compared with values of normal children (Figure 23-4). Values for energy expenditure per unit of fat-free mass (the metabolically active component of the body

because fat mass is relatively metabolically inactive) are somewhat lower in overweight compared with nonoverweight children. However, this is an inappropriate method of expressing resting energy expenditure in individuals of different sizes because there is a wide variability in the energy expenditure of different tissues that comprise the lean mass. Tissues such as brain and heart have a very high energy expenditure and tissues such as muscle have a low energy expenditure. It appears that overweight and nonoverweight individuals have more similar amounts of tissues with high energy expenditure than they have tissues with low energy expenditure. Thus, it is more appropriate to examine the relationship between fat-free mass and resting energy expenditure than to compare resting energy expenditure per unit of fat-free mass between different groups.

As seen in Figure 23-5, neither the intercept nor the slope of the relationship differs between obese and nonobese individuals, demonstrating that there is no difference in the resting energy expenditure of overweight and nonoverweight children when the data are appropriately normalized for metabolically active tissue. This result, obtained by combining data from studies in which data from at least two groups of subjects were available, is compatible with results from regression analyses in a group of children with a wide range of body compositions,[119] as well as with results of numerous studies in adults.[120]

Several studies on the thermic effect of feeding demonstrate a normal energy expenditure in overweight compared with nonoverweight children and adolescents,[118,121,122] a result that contrasts with the numerous studies that indicate a reduced thermic effect of feeding in obese adults.[123,124] There is one report of a reduced thermic effect of feeding in obese children,[125] and the duration of obesity has been implicated as a possible explanation for differences in results among different studies.[121] This explanation could also help explain the fact that the thermic effect of feeding is reduced in obese adults.

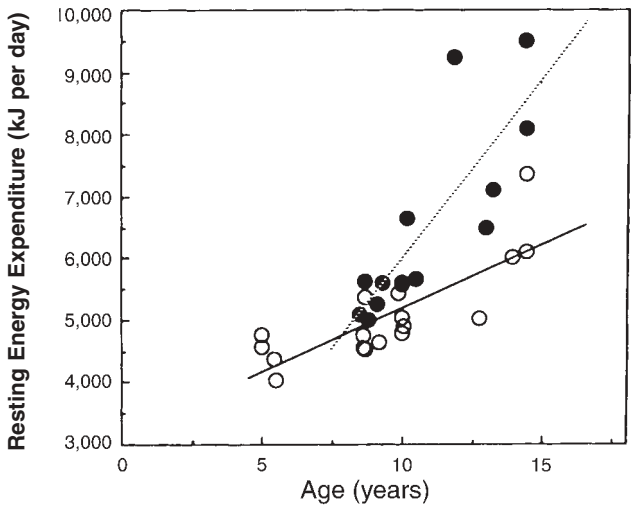

FIGURE 23-4 Relationship between resting energy expenditure (in kJ/d, where 1 kJ = 0.239 kcal) and age in nonoverweight (*solid line*) and overweight (*broken line*) boys and girls aged 5 to 15 years.[171] Data points are group means reported between 1989 and 1994.[92,103,122,132,137,141,144,172–178] There was a significant effect of obesity status on the relationship between resting energy expenditure and age ($p < .001$), and the relationship between resting energy expenditure and age was significant in both nonoverweight ($r^2 = .630$, $p < .000$) and overweight children ($r^2 = .682$, $p < .000$).

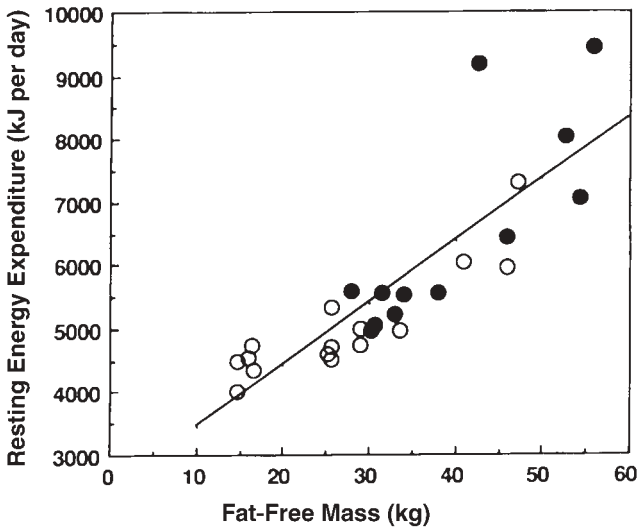

FIGURE 23-5 Relationship between resting energy expenditure and fat-free mass in nonoverweight and overweight boys and girls aged 5 to 15 years.[171] Data points are group means (in kJ/d, where 1 kJ = 0.239 kcal) reported between 1989 and 1993.[103,122,132,141,144,172–178] There was no significant effect of overweight status on resting energy expenditure in multiple regression analyses, including fat-free mass as an independent variable. The relationship between resting energy expenditure and fat-free mass is significant ($r^2 = .712$, $p < .000$).

Concerning physical activity, several studies have reported no difference in physical activity between lean and overweight children,[71,87,126,127] whereas other studies have reported low[128–131] or even high[132] levels of physical activity in overweight children relative to nonoverweight controls. Television viewing has also been investigated separately as a marker for low physical activity and for its relationship to body composition in children.[133] Although the mechanism by which television viewing might influence body fat mass is not known, a reduction in physical activity is strongly implicated as part of the mechanism because television viewing is a sedentary activity that might replace more strenuous ones, together with the possibility that dietary intake could be increased as well.[134,135] Studies in this area have not produced consistent results, with some studies reporting a negative association between the time spent watching television and body fatness[134] and other studies failing to substantiate this result.[127,136]

This controversy might reflect the fact that inactivity during television viewing can potentially be compensated for by strenuous activity at other times; more research is needed to elucidate the relationship between body fat mass and physical activity in children as well as in adults. A further unresolved aspect of the literature on television viewing is that there are reports of both a decrease[126] and normal[137] resting energy expenditure during television viewing in obese children compared with nonobese controls. On the basis of the studies described above, it cannot

be concluded that the obese child is necessarily inactive, or that inactivity is an important cause of obesity. However, this conclusion does not exclude an important role for physical activity in obese children, and further studies are needed to clarify this important issue.

Studies on TEE as determined using the doubly labeled water technique[138,139] have been conducted as a way to examine the combined effects of different components of energy expenditure in normal-weight and overweight children and also as a more accurate way to assess energy expenditure for physical activity (when combined with measurements of resting energy expenditure). Using this method, several studies in children and adults have indicated an inverse association between energy expenditure for physical activity and body fat mass when values for physical activity are normalized for body size by the use of the ratio of total to resting energy expenditure as a physical activity index.[106,140,141] The mechanism of this association is not known but is likely to include the fact that inactivity promotes insulin resistance and could enhance fat oxidation.[142] Although this ratio of total to resting energy expenditure is reduced with increasing body fat content, the TEE for physical activity is typically high. This is because resting energy expenditure and the energy costs of most activities increase with body size. These consistent findings contrast with the substantial controversy over the effects of obesity on physical activity when studies using reported estimates of physical activity are considered.

Doubly labeled water measurements of TEE have also been used to examine differences in energy intake and energy requirements between normal-weight and overweight children. The recent Dietary Reference Intakes for Macronutrients[143] summarized all available data on TEE in childhood to report that there is no substantial difference between normal-weight and overweight children in the relationship between TEE and body weight, height, and age, with equations suitable for all children based on summaries of all available doubly labeled water data:

$$\text{TEE (kcal/day)} = 89 \times \text{weight (kg)} - 100 \text{ (boys and girls 0–2 years)}$$

$$\text{TEE} = 88.5 - 61.9 \times \text{age (years)} + \text{PA} \times 26.7 \times \text{weight (kg)} + 903 \times \text{height (mm)} \text{ (boys 3–18 years)}$$

$$\text{TEE} = 135.3 - 30.8 \times \text{age (years)} + \text{PA} \times 10.0 \times \text{weight (kg)} + 934 \times \text{height (mm)} \text{ (girls 3–18 years)}$$

where PA is a physical activity coefficient used for children 3 years and older:

PA = 1.00 if physical activity level is sedentary
PA = 1.13 if physical activity level is low
PA = 1.27 if physical activity level is active
PA = 1.45 if physical activity level is very active

TEE does not equal energy intake in children because there is additional consumed energy used for growth that is deposited in the form of lean tissue and fat. However, except during the early months of life and during the peak of pubertal development, energy used for energy deposition is only 20 to 25 kcal/day[143]; thus, TEE closely reflects energy intake. The equations given above indicate that children who are overweight do indeed need more energy to maintain current body weight than do normal-weight children. For example, a child more than 3 years of age who is already overweight by 10 kg compared with normal-weight children will have increased TEE and hence energy intake of 100 to 267 kcal/day. Table 23-2 summarizes estimated energy requirements for children of reference weights, based on the above equations with an increment added for the energy deposition in normal growth.

A final issue to consider when comparing differences in energy expenditure between lean and overweight individuals is the energy expenditure response to overfeeding. As detailed above, an ability to burn off surplus dietary energy has been suggested as potentially important in the regulation of energy balance. However, in a study of overweight and nonoverweight adolescents, Bandini and colleagues found no difference between groups in the ability to dissipate excess energy intake.[144] This finding is consistent with the view, outlined above, that diet-induced thermogenesis plays only a small role in the regulation of energy balance.

Substrate Balance

As an extension of the energy balance principles detailed above, it has been suggested that body carbohydrate balance could play a critical role in overall energy regulation.[145] The basic principle behind this theory of energy regulation, which is in keeping with the earlier glucostatic theory of energy regulation, is that balance of the primary energy substrates, fat and carbohydrate, have to be considered separately.[145] Thus:

$$\text{Fat stored} = \text{Fat intake} - \text{Fat oxidation}$$

$$\text{Carbohydrate stored} = \text{Carbohydrate intake} - \text{Carbohydrate oxidation}$$

Because the energy in carbohydrate stores is very small in relation to that in fat stores, the carbohydrate stores have a high turnover rate and are liable to be depleted quickly and frequently. The essential requirement of key tissues for glucose suggests that signals should exist to efficiently monitor and correct body carbohydrate balance. An extension of this theory of nutrient regulation is that dietary macronutrient composition plays an important role in determining body fat content.[145] This is because the higher the dietary fat content, the more total food (and energy) needs to be consumed to maintain carbohydrate intake and therefore carbohydrate stores, and the fatter the individual will be because of increased energy intake.

Flatt has also suggested that the increase in body fat induced by a high-fat diet could be self-limiting because reduced insulin sensitivity and increased circulating free fatty acids tend to occur with increased body fat content, promoting increased fat oxidation and preservation of carbohydrate stores, resulting in a stabilization of hunger and

TABLE 23-2 Estimated Energy Requirements*

		Activity Level (kcals/day)			
Age	*Reference Weight (kg)*	*Sedentary*	*Low Active*	*Active*	*Very Active*
Boys					
1 mo	4.4	472	(No activity level specified before 3 yr)		
6 mo	7.9	645			
12 mo	10.3	844			
18 mo	11.7	961			
24 mo	12.7	1,050			
3 yr	14.3	1,162	1,324	1,485	1,683
6 yr	20.7	1,328	1,535	1,742	1,997
9 yr	28.6	1,530	1,787	2,043	2,359
12 yr	40.5	1,798	2,113	2,428	2,817
15 yr	56.3	2,223	2,618	3,013	3,499
18 yr	67.2	2,383	2,823	3,263	3,804
Girls					
1 mo	4.2	438	(No activity level specified before 3 yr)		
6 mo	7.2	593			
12 mo	9.5	768			
18 mo	11.0	899			
24 mo	12.1	997			
3 yr	13.9	1,080	1,243	1,395	1,649
6 yr	20.2	1,247	1,451	1,642	1,961
9 yr	29.0	1,415	1,660	1,890	2,273
12 yr	41.6	1,617	1,909	2,183	2,640
15 yr	52.0	1,731	2,057	2,363	2,870
18 yr	56.2	1,690	2,024	2,336	2,858

*Values are estimated average requirements from Dietary Reference Intakes.[143]

satiety signals from body carbohydrate stores and stability of food intake and body fat stores.[145] This model provides a potential explanation for body fat regulation that does not rely on the concept of a novel "signal" from fat stores that detects and corrects a body set point.

Support for the importance of nutrient balance in the overall regulation of energy balance can be derived from several sources, although there is currently little information available on infants and children. Flatt has demonstrated in mice the critically important idea that energy balance is indeed adjusted on a day-to-day basis to maintain stable body carbohydrate balance, through adaptive fluctuations in food intake.[145] Studies in humans have indicated that carbohydrate balance is more closely regulated than is fat balance.[146,147] Concerning the effect of dietary composition on energy intake and body composition, animal studies have repeatedly demonstrated that hyperphagia and obesity can be induced in many strains of normal-weight rodents by feeding a high-fat diet as described above.[36]

In humans, results from some,[148–151] although not all,[152–154] short-term intervention studies in adults indicate that energy intake increases with consumption of a high-fat diet. The fact that not all human studies have found an increase in energy intake with consumption of a high-fat diet does not invalidate the nutrient balance theory of energy regulation because a high-fat diet could induce positive energy balance by decreasing energy expenditure, rather than increasing energy intake as suggested by both animal and adult human studies.[155,156] Also consistent with the nutrient balance model are the data from cross-sectional studies that indicate that consumption of a high-fat diet is frequently associated with high body fat mass in adults.[157–161] Thus, as predicted by the nutrient balance model above, obese and overweight adults tend to consume a higher-fat diet than do nonobese subjects and, at least in the short term, might be hyperphagic.

Some,[131,132] but not all,[87] studies in children and adolescents support the view that high dietary fat intake is associated with obesity. It is possible that this controversy could be owing to the fact that the fiber content of the diet and its energy density might have significant effects on food intake. Although high-fat diets tend to be low in fiber and have a high energy density, this is not always so, and differences in these aspects of the diet (unreported in the studies described above) might have been important. An additional important consideration in relation to dietary intake is that on theoretical grounds, saturated fat can be expected to have more adverse effects on body fat mass than other fats do because of its influence on insulin sensitivity.[142] Consistent with this suggestion are the results of a recent study that observed increased intake of saturated fat as well as increased total fat intake in obese boys and girls compared with normal control subjects.[132] Also consistent with the nutrient balance theory of energy regulation is the fact that obese adults do tend to have reduced insulin sensitivity and increased circulating levels of free fatty acids (which could be interrelated, as predicted by the hypothesis of Randle and colleagues[162]). Furthermore, the increased circulating levels of free fatty acids promote fat oxidation in the fasting state and are associated with increased body fat,[163] and reduced-obese adults have reduced rates of fat oxidation.[164]

ROLES OF ENERGY INTAKE AND EXPENDITURE IN THE DEVELOPMENT OF OBESITY

As described above, the majority of published investigations into the causes of early overweight have been cross-sectional in nature, that is, they have related measurements of body fat mass to energy expenditure or other parameters measured at the same time. This approach provides important information on energy intake, energy expenditure, and substrate oxidation in individuals who are already obese but does not address the question of what happens during the development of the obese state. A finding, for example, of high energy intake in overweight children does not preclude the possibility that energy intake was normal or even low during the period of excess weight gain. Recent prospective studies have addressed the issue of causality in overweight by investigating whether energy expenditure is low in individuals with increased susceptibility to overweight (because of parental obesity). However, the results have been conflicting, with reports of both low energy expenditure[165–167] and normal energy expenditure[168–170] in the pre-overweight state. These conflicting reports emphasize the potential for both high energy intake and low energy expenditure to contribute to the overweight state. Additional research is currently under way by several groups to investigate this important issue, as well as to investigate the role of impaired fat oxidation in the development of overweight in children.

SUMMARY AND IMPLICATIONS FOR THE TREATMENT OF OBESITY

The excess fat mass that characterizes obesity is attributable to both genetic susceptibility and environmental factors and results from energy intake exceeding energy expenditure plus the energy requirement for normal growth over a prolonged period of time. However, this increment in energy intake over energy expenditure can be as little as 400 MJ/day or less if it persists over a period of years. The studies summarized in this chapter do not provide definitive evidence as to whether this differential between energy intake and energy expenditure is caused primarily by decreased energy expenditure or by increased energy intake. However, the weight of evidence currently indicates that both overeating and underexpending can be primary causes of overweight in childhood, and that once a child is overweight, energy intake is higher than that of normal-weight children. In addition, dietary fat, in particular saturated fat, can promote fat deposition through its influence on energy intake.

Further studies are needed in this area, in particular to delineate the usual roles of high energy intake and low energy expenditure as causal factors in excessive weight gain leading to overweight in childhood. Current prescriptions for the treatment of childhood overweight, taking into account the degree of caution that is appropriate for a disorder in which the treatment can itself have detrimental consequences, should be based on individualizing for each child a decrease in energy intake relative to energy expenditure by a combination of moderate dietary therapy and promotion of energy expenditure from physical activity (see Chapter 54, "Evaluation and Management of Obesity").

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CHAPTER 24

MATERNAL NUTRITION AND PREGNANCY OUTCOME

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Adverse pregnancy outcomes such as preterm delivery, intrauterine growth restriction, and low birth weight are increased two- to threefold among infants born to poor urban women from countries such as the United States.[1] Other factors affecting outcome include inadequate gestational weight gain, inadequate prenatal care, smoking, drinking alcohol, and substance abuse.[2,3] A history of spontaneous abortion or other poor outcome in a prior pregnancy plays a role by increasing risk in the current pregnancy.[3] Poor maternal intake of micronutrients, iron, folic acid, calcium, and zinc in particular also is associated with an increased risk of adverse events in the course and outcome of pregnancy.[2] However, apart from rare occurrences, inadequate intake of a single nutrient does not occur in isolation. Unlike in animal studies that involve experimentally induced deficiencies of single nutrients, the link between maternal nutritional status and the course and outcome in human pregnancy is less secure. Apart from its immediate effects, maternal nutrition during pregnancy also has important implications for risk of chronic disease development in later life (see Chapter 25, "Fetal Nutrition and Imprinting").

IRON AND ANEMIA

Iron is essential for the formation of hemoglobin, which transports oxygen, and for the synthesis of enzymes that use oxygen to provide cellular energy.[2] Iron deficiency is defined by three stages of increasing severity: depletion of iron stores (Stage 1), impaired hemoglobin production (Stage 2), and iron deficiency anemia (IDA) (Stage 3). Anemia is an abnormally low concentration of hemoglobin (or hematocrit). Specific cutpoints have been formulated for its diagnosis by age and sex and by trimester during pregnancy.[2]

The increase in anemia during pregnancy is partly an artifact of maternal plasma volume expansion, a normal physiologic response to pregnancy.[4] Although the maternal red blood cell mass also increases during gestation, its expansion and the expansion of the plasma volume occur at different times.[2,5] During the first and second trimesters, hemoglobin concentration declines, reaches a low point early in the third trimester, and rises thereafter. Consequently, depending on the stage of gestation when anemia is assessed, it can be difficult to separate truly anemic women from those whose anemia occurs as a result of hemodilution.

Supplementation with iron is recommended during pregnancy to meet the demands of both the mother and the rapidly growing fetus.[2] Table 24-1 shows the intakes that are currently recommended by the Institute of Medicine for iron and other nutrients during pregnancy (on-line at <http://www.nap.edu>). Anemia (low hemoglobin levels) and IDA sometimes also serve as indicators of overall maternal nutritional status during pregnancy. When overall dietary intake is inadequate, risk of anemia is increased.[6–8]

Maternal anemia and hemoglobin (or hematocrit) concentration are linked with an increased risk of poor pregnancy outcome. Evidence suggests that anemia and iron deficiencies are associated with an increased risk of low infant birth weight, preterm delivery, and perinatal mortality. The relationship between maternal hemoglobin and pregnancy outcome is U shaped, with "low" hemoglobin probably reflecting a mix of true and physiologic anemia and "high" hemoglobin reflecting hypovolemia—failure of the plasma volume to expand in association with maternal pathology—maternal hypertension, preeclampsia, or diabetes.[9,10] Poorly nourished animals have reduced maternal plasma volume expansion during pregnancy and low cardiac output, lower uteroplacental blood flow, and reduced

nutrient transmission to the fetus.[11] Thus, it is possible that hypovolemia has nutritional antecedents.

Maternal anemia, when diagnosed before midpregnancy, is associated with an increased risk of preterm birth, fetal growth restriction, and low birth weight. Murphy and colleagues studied 44,000 singleton pregnancies in women from Cardiff, Wales, who sought prenatal care by 24 weeks gestation.[9] The prevalence of anemia based on "low" hemoglobin before week 24 (hemoglobin < 104 g/L) among these women was 3.9%. Increased risk of preterm birth (before 37 weeks) was associated with low hemoglobin when women entered care before week 13 or after week 20. For those who entered between 20 and 24 weeks, risk also was increased when hemoglobin was high. Risk of low birth weight (< 2,500 g) was increased for women entering care before 20 weeks gestation. A high maternal hemoglobin concentration (> 145 g/L) was also associated with hypertension and pregnancy-induced hypertension (PIH), both of which could reflect inadequate expansion of the maternal plasma volume.

Garn and colleagues analyzed data from more than 50,000 consecutive pregnancies that were followed as part of the Collaborative Perinatal Project (CPP) using the lowest hematocrit anytime during pregnancy, thus confounding the effects of true and physiologic anemia.[12] Low (< 0.29) and high (> 0.39) hematocrit were associated with increased risk of fetal death, preterm delivery, and low birth weight. At the lowest hematocrit (< 0.25), risks of preterm delivery, low birth weight, and fetal death were increased approximately two- to threefold for the white women in the study. For black women, only the risk of fetal death was raised substantially. Overall, for both black and white gravidas, the risk of fetal death was increased appreciably when hematocrit levels were very high (> 0.41).

Steer and colleagues studied a multiethnic sample of women from the Northwest Thames region of London.[13] For all ethnic groups, there was an increased risk of preterm delivery and low infant birth weight when the hemoglobin level during pregnancy was either low (< 85 g/L) or high (> 115 g/L).

Meis and colleagues analyzed data from the Cardiff Birth Survey, a population-based survey of data on the pregnancies of more than 25,000 Welsh women.[14] Both low (< 104 g/L) and high (> 135 g/L) maternal hemoglobin at entry to care increased risk of preterm delivery. After controlling for other potential confounding variables, high hemoglobin remained a significant risk factor, whereas low hemoglobin did not. However, early-pregnancy bleeding, a factor that often gives rise to anemia and lowers hemoglobin concentration, was associated with nearly a twofold increase in risk of preterm birth.

Lieberman and colleagues examined the association of hematocrit at delivery with spontaneous preterm birth in a sample of approximately 8,000 Boston women.[15] Each 5-point drop in hematocrit was associated with an approximately twofold increase in the risk of preterm delivery. Maternal anemia and socioeconomic factors accounted for the twofold difference in preterm delivery for blacks compared with whites.[16]

Klebanoff and colleagues attempted to replicate the above results using prospective data from the CPP.[5] They regarded the strong association between maternal anemia and preterm delivery as a time-of-sampling artifact caused by the changes in hemoglobin and hematocrit over the course of pregnancy. That is, when sampled at the time of delivery a lower hematocrit and an increased risk of anemia characterize pregnancies that are delivered late in the second or early in the third trimester, whereas a higher hematocrit (and lower anemia risk) characterized those pregnancies that are delivered at later gestations. When data were examined prospective to delivery, anemia diagnosed at any time during the late second to early third trimester was associated with a modestly increased risk of preterm delivery, which diminished substantially after adjustment for maternal race, education, and age.[5] A subsequent prospective study gave a consistent result.[17]

Lu and colleagues examined the relationship of maternal hematocrit to pregnancy outcome in approximately 17,000 iron- and folate-supplemented Alabama women, delivered between 1983 and 1988.[18] Low hematocrit before midpregnancy was associated with a modestly increased risk of preterm delivery and fetal growth retardation. After

TABLE 24-1 Dietary Reference Intakes or Adequate Intake and Upper Limit of Intake during Pregnancy

	Dietary Reference or Adequate Intake	*Upper Limit of Intake*
Minerals		
Iron	27 mg*	45 mg
Zinc	12 mg,† 11 mg‡	34 mg†, 40 mg‡
Calcium	1,000 mg	2,500 mg
Phosphorus	700 mg	3,500 mg
Magnesium	350 mg	350 mg§
Iodine	220 µg	900 µg†, 1,100 µg‡
Selenium	60 µg	400 µg
Copper	1.0 mg	10.0 mg
Manganese	2.0 mg	9.0 mg†, 11.0 mg‡
Chromium	50 µg	Not set
Molybdenum	50 µg	2,000 µg
Vitamins		
Folate	600 µg‖	800 µg,†,# 1,000 µg‡,#
Thiamin	1.4 mg	Not set
Riboflavin	1.4 mg	Not set
Niacin	18 mg	30 mg,† 35 mg‡
Vitamin B_6	1.9 mg	80 mg,† 100 mg‡
Vitamin B_{12}	2.6 µg	Not set
Biotin	30 µg	Not set
Pantothenic acid	6 mg	Not set
Choline	450 mg	3,000 mg,† 3,500 mg‡
Vitamin A	700 µg	2,800 µg,† 3,000 µg‡
Vitamin C	85 mg	1,800 mg,† 2,000 mg‡
Vitamin D	5 µg	50 µg
Vitamin E	15 mg	800 mg,† 1,000 mg‡
Vitamin K	90 µg	Not set

*Often requires iron supplements.
†Pregnant women 14–18 years.
‡Pregnant women 19+ years.
§For magnesium supplements.
‖Includes 400 µg synthetic folic acid.
#Synthetic folic acid.
Adapted from Institute of Medicine. Dietary reference intakes. Washington (DC): National Academy Press; 1999, 2000, 2002.

midpregnancy, the relationship between maternal hematocrit and risk of preterm delivery became inverse, although the relationship was weak.

Higgins and colleagues reported findings from supplemented Montreal women that suggested some potential benefit for a low maternal hematocrit level late in pregnancy.[19] They found a weak effect of initial hemoglobin on infant birth weight but a strong, inverse relationship after 33 weeks gestation, when the highest infant birth weights were associated with the lowest third-trimester maternal hemoglobin levels (< 110 g/L). There was also a relationship between birth weight and the change in hemoglobin level between entry to care and the third trimester; women with the greatest decrements gave birth to the largest infants.

Zhou and colleagues described the relationship between maternal hemoglobin levels during the first trimester and poor pregnancy outcome in 829 Shanghai women.[20] In this population, other risk factors associated with poor pregnancy outcome (eg, smoking, alcohol use) were uncommon, and women enrolled for care early in the first trimester (6 to 8 weeks). The risk of preterm delivery was increased about twofold when hemoglobin was between 100 and 109 g/L, increased nearly threefold when hemoglobin was 90 to 99 g/L, and increased approximately fourfold for hemoglobin below 90 g/L.

Recently, Scanlon and colleagues used data from Pregnancy Nutritional Surveillance to examine the relationship between maternal anemia (severe or mild) and pregnancy outcome (preterm delivery or fetal growth restriction) in 173,031 low-income gravidas.[21] Because Z scores were used to define hemoglobin levels of interest, cutpoints varied with gestation but were always less than 110 g/L during trimesters 1 and 2. Whereas preterm delivery was increased for anemic women and women with low hemoglobin levels during the first or second trimesters, for women with moderate to severe anemia, risk was approximately doubled. For the others, risk of preterm delivery was increased between 10 and 40%. During the third trimester, the association reversed: anemia and low hemoglobin levels were each associated with a decreased risk of preterm birth and there was little association between high maternal hemoglobin levels and preterm delivery or fetal growth restriction. However, throughout trimesters 1 and 2, high hemoglobin was associated with a 30 to 80% increase in fetal growth restriction. The association of maternal anemia in early pregnancy to preterm delivery and other poor outcomes has been confirmed in recent studies from countries in the developing world, including Nepal and Egypt.[22,23]

In Camden, New Jersey, Scholl and colleagues combined anemia with low serum ferritin to index IDA.[6] Data from more than 800 women in the Camden Study were used to examine total anemia, IDA, and anemia from causes other than iron deficiency at entry to prenatal care as risk factors for preterm delivery. They found a better than twofold increased risk of preterm delivery and a threefold increase in low birth weight with IDA. When vaginal bleeding was present at or before entry to care, risk of preterm delivery was increased fivefold for IDA and twofold with anemia from other causes. However, later in pregnancy (after week 28), maternal IDA did not increase risk of preterm birth or low birth weight.[24] Consistent data were obtained from Papua, New Guinea, where severe anemia (hemoglobin < 80 g/L) that was attributable to iron deficiency and occurred early in pregnancy increased risk of low birth weight about sixfold among primiparous women.[25] Risk was not increased with IDA at delivery. Thus, it seems reasonable to presume that some, but not all, maternal anemia and IDA is attributable to the expansion of maternal plasma volume. At present, this state is poorly differentiated from anemia or IDA late in pregnancy but is easier to differentiate in the first or second trimesters.

Allen recently reviewed the mechanisms and changes that underlie the relationship between maternal anemia and pregnancy outcome.[26] The link between maternal anemia in the first and second trimesters and preterm delivery and other outcomes might involve alterations in the growth and development of the placenta. Severe maternal anemia is associated with increased placental weight and size as well as functional changes that permit the placenta to carry more oxygen.[27,28] Maternal iron stores affect the growth of the placenta even when the mother is not anemic. In one study of more than 500 British gravidas, placental volume measured by ultrasonography at 18 weeks gestation was inversely related to the maternal hemoglobin and ferritin levels 4 weeks earlier.[29] This relationship was recently confirmed by data from more than 1,600 gravidas.[30] Maternal ferritin levels at entry to care (mean, 12.9 weeks) correlated negatively with placental weight at term, controlling for factors also associated with placental size (maternal weight, height, parity, and smoking).

In a subsample (n = 17), serum ferritin correlated with capillary surface area of the placenta and the proportion of terminal villi that was capillary. These results suggest that maternal iron stores in the low-normal range are associated with increased placental size and with changes in the oxygen-carrying ability of the placenta. Interestingly, shorter gestation duration was associated with a higher ratio of placental weight to birth weight among deliveries in that study.[30]

During pregnancy, low intakes of two micronutrients, zinc and folate, have been associated with IDA at entry to care.[7,8] Recommendations for intake of these nutrients during pregnancy, along with information about the upper limit considered safe, are given in Table 24-1. Zinc is an element involved either directly as a metalloenzyme in the production of enzymes, which include deoxyribonucleic acid (DNA) and ribonucleic acid polymerase, or as a catalyst in the synthesis of other enzymes.[2] Folic acid functions as a coenzyme in the transfer of single-carbon atoms from donors such as serine and histidine to intermediates in the synthesis of amino acids, purines, and thymidylic acid.[2] Although many other nutrients in addition to these two would be limited in a marginal maternal diet, inadequate intake of either zinc, folate, or both potentially leads to impaired cell division and alterations in protein synthesis. Such alterations are most notable and have the greatest

potential to do harm during times of rapid tissue growth, such as pregnancy.

ZINC

Neggers and colleagues demonstrated a positive association between maternal serum zinc at 16 weeks gestation and birth weight in a large population of low-income Alabama women.[31] Serum zinc in the lowest quartile was associated with an eightfold increase in risk of low birth weight, suggesting a threshold effect for circulating zinc levels during pregnancy. Kirksey and colleagues examined the relationship of maternal zinc nutriture to birth weight and found that plasma zinc concentrations in the second trimester, along with pregnancy weight at 3 months gestation, formed the best predictor model of birth weight for these pregnancies, accounting for 39% of the variance.[32]

Scholl and colleagues examined dietary zinc intake in 818 Camden women and reported increased risks of complications and adverse pregnancy outcomes in association with low intakes of dietary zinc (6 mg/day or less).[7] These complications included decreased gestational weight gain and an increased risk of IDA at entry to care. Poor outcomes associated with low zinc intake included risk of low birth weight, preterm delivery, and very preterm delivery that were two to three times greater than in controls. In the presence of IDA, the risk of very preterm delivery was greater than fivefold higher. Others have also reported a positive relationship between low serum zinc and reduced birth weight or an increased risk of low infant birth weight.[33–35] However, the finding of inverse relationships between maternal zinc levels and birth weight could also suggest greater fetal uptake of maternal zinc by larger infants.[36–38]

Tamura and colleagues used data from more than 3,400 gravidas to examine the relationship between pregnancy outcome and zinc in the first to early third trimesters.[39] They found no relationship between maternal plasma zinc and risk of fetal growth restriction, preterm delivery, or selected pregnancy complications and no significant correlation with birth weight or gestation duration. However, women with plasma zinc below the median had been removed from the sample and enrolled in a clinical trial that demonstrated a positive effect of zinc on gestation duration and birth weight.[40] Thus, prescreening might have removed vulnerable women from the population at risk.

Because serum or plasma zinc represents less than 1% of the total body zinc pool, it might not be the most reliable indicator of zinc status. Meadows and colleagues were the first to demonstrate that both lower leukocyte zinc concentration in maternal serum and in cord blood were associated with impaired fetal growth.[41,42] No differences were noted between the mean leukocyte zinc concentrations of women delivering preterm appropriate for gestational age and normal-weight infants. Wells and colleagues also noted an association between maternal leukocyte zinc and lower birth weight.[43] Simmer and Thompson measured maternal concentrations of zinc in polymorphonuclear and mononuclear cells within 48 hours of delivery and found lower zinc levels associated with fetal growth retardation.[44] Adeniyi reported the opposite: maternal leukocyte zinc and placental zinc concentrations were lower in preeclamptic women with normal birth weight infants compared with women delivering lower birth weight infants.[45]

Inconsistencies in the relationship of zinc and pregnancy outcome could arise from the fact that there is no agreed upon indicator of zinc status; maternal serum or plasma zinc might not reliably assess zinc nutritional status. Clinical trials of zinc supplementation have focused on entire groups of low-income women in which the mean zinc intake is low. These trials have also yielded equivocal results, perhaps because of an approach that selects a population, as opposed to individuals, at risk.

Two trials have shown effects that were conditional on maternal weight, that is, a lower rate of preterm delivery in zinc-supplemented women who were not overweight.[40,46] Cherry and colleagues reported a response to supplementation status for pregnant adolescents at less than 25 weeks gestation.[46] Low serum zinc concentrations were more common in underweight and multiparous women. The frequency of preterm delivery was less in the zinc-treated normal-weight women compared with the placebo group. Zinc treatment of underweight multiparous women was associated with a gestational age increase of nearly 3 weeks. Zinc supplementation was also associated with a reduced need for assisted respiration in newborns of normal-weight women.

The trial conducted by Goldenberg and colleagues took a more targeted approach and recruited women with plasma zinc levels below the median and randomly assigned them to zinc or placebo.[40] The analysis was stratified after the fact by body mass index (BMI) above or below 26 kg/m^2. Zinc supplementation was associated with longer gestation duration—by approximately half a week (p = .06)—and increased birth weight, mainly because of longer duration of gestation. Women with BMIs of less than 26 benefited most from zinc treatment, experiencing a 248 g increase in infant birth weight and a 0.7 cm increase in infant head circumference. Consistent with prior results, effects were increased for women with lower pregravid BMIs. In addition, Kynast and Saling found that zinc treatment between 20 and 34 weeks gestation was associated with lower incidences of preterm labor, placental abruption, vaginal bleeding, fetal acidosis, and fetal growth retardation when zinc-supplemented gravidas were compared with control subjects.[47]

In contrast, two recent trials from the developing world (Peru and Bangladesh), where one might suppose that zinc deficiency would be prevalent, did not show this.[48,49] It is possible that if gravidas from the developing world have multiple nutritional deficiencies, these might reduce the bioavailability of zinc or otherwise limit fetal growth. Low plasma zinc, however, has a number of potential causes.[50] It is of interest that when Bangladeshi women were screened for low plasma zinc, less than 4% had levels at or below the median plasma zinc cutpoint used to enrol women from the United States in Goldenberg and colleagues' trial.[40,49] In addition to its effect on protein synthesis, zinc also has an antiseptic action.[50] In theory, a low

zinc intake could be associated with an increased risk of infection during pregnancy, leading to fragile fetal membranes (and premature rupture of membranes); conversely, a low plasma zinc level might be an acute-phase response to a stressor such as maternal infection.

FOLIC ACID

Folate is critically important for development and is a cofactor for many essential cellular reactions, including the transfer of single-carbon units; it is required for cell division because of its role in DNA synthesis.[51,52] Folate also is a substrate for a variety of reactions that affect metabolism of several amino acids, such as the transmethylation and transsulfuration pathways. A central feature of fetal development is widespread and sustained cell division. Because of its role in nucleic acid synthesis, the need for folate increases during times of rapid tissue growth. During pregnancy, folate-dependent processes include increase in the red cell mass, enlargement of the uterus, and growth of the placenta and fetus.

It is recommended that pregnant women consume 600 μg folic acid per day, which includes 400 μg of synthetic folic acid from supplements or fortified cereals, to reduce risk of neural tube defects (see Table 24-1). Recent data suggest that less than one-third of women in their reproductive years consume this amount.[53] Fortification of flour and cereal products in the United States with folic acid (since 1998) has been associated with a 19% decline in risk of liveborn infants with neural tube defects, along with changes in biomarkers of folate status, including increases in serum and red cell folate and a decline in homocysteine levels.[54,55]

Serum folate is a sensitive indicator of the folate available to replicating cells with high turnover rates, whereas red cell folate reflects folate status over preceding weeks. A metabolic effect of folate deficiency is an elevation of homocysteine.[56] Hyperhomocysteinemia can occur when dietary folate intake is low. In other cases, genetic factors and the interaction between genes and the environment increase the metabolic requirement for folate, increasing risk of spontaneous abortion and fetal growth restriction and decreasing gestation duration.[57]

More than three decades ago, Hibbard described an increased risk of placental abruption in gravidas with abnormal formiminoglutamic acid (FIGLU) excretion and attributed it to a defect in folate metabolism.[57] Hyperhomocysteinemia, a risk factor for cardiovascular disease, is now known to cause vascular damage.[56] About half of the pregnancies occurring in women with hereditary homocystinuria terminate in fetal demise.[52] High levels of homocysteine also might do injury in the course of pregnancy, increasing the risk of serious complications such as pregnancy-induced hypertension and placental abruption.[58] Both are risk factors for adverse outcome, increasing intrauterine growth restriction and with it the possibility of preterm delivery, in particular, preterm delivery that is medically indicated.

The role of folic acid in DNA synthesis and cell replication suggests its potential to have an important effect on birth weight, gestation duration, or both. An absolute deficiency of folate—from a diet inadequate to meet the needs of pregnancy—in theory interferes with growth of the conceptus. The influence of dietary and circulating folate on preterm delivery and low infant birth weight was studied in 832 women from Camden, one of the poorest cities in the continental United States.[8] Low intakes of folate from diet and supplements were associated with maternal characteristics reflecting poorer maternal nutritional status, including lower caloric intake, low rate of gestational weight gain, and a higher frequency of IDA at entry to prenatal care. After controlling for gestation at entry and the time in pregnancy when the samples were drawn, there was a significant relationship between dietary folate intake and serum folate at week 28. Low folate intake (< 240 ng/day) was associated with a greater than threefold increase in the risk of low infant birth weight and preterm delivery, after controlling for maternal age, parity, ethnicity, smoking, rate of gestational weight gain, and intake of energy and other nutrients (zinc, fiber, and vitamin B_{12}). Circulating folate at week 28 also was associated with risk; the adjusted odds for low birth weight increased by 1.5%, and preterm delivery increased by 1.6% per unit decrease in serum folate at week 28 after controlling for potentially confounding variables. Thus, lower concentrations of folate at week 28 were associated with a greater risk of preterm delivery and low birth weight.

Goldenberg and others presented data from a cohort of approximately 1,200 Alabama women with risk factors for intrauterine growth restriction.[59–62] Most analyses involved data from a subsample (n = 289) for whom circulating levels also were assayed. There was a significant and positive correlation within the subsample between maternal folate intake from diet and supplements and serum folate at weeks 18 and 30. Using data from the cohort as a whole, adjusting for gestation, smoking, ethnicity, infant sex, pregravid weight, and gestational weight gain, there was a significant increase in infant birth weight among infants of mothers whose folate intake was above the 90th percentile compared with those below the 10th percentile.[62] A psychosocial score, which encompassed measures of maternal depression, anxiety, mastery, stress, and social support, correlated positively with supplement use but did not confound the association between folate and infant birth weight.[60]

Likewise, studies by Frelut and colleagues showed a positive bivariate correlation between maternal red cell folate (at week 32) and infant birth weight in 21 infants (r = .48).[63] Ek found a positive relationship (bivariate) between maternal red cell folate and birth weight and birth length in 147 infants at delivery.[64] Whiteside and colleagues reported that shorter gestation duration (< 39 weeks) and reduced infant birth weight were associated with lower serum folate at week 26.[65] In two studies, Tchernia and colleagues found that shorter gestation correlated with lower serum folate and red cell folate.[66] Rondo and colleagues, after examining more than 700 mother-infant pairs comparing growth-restricted and normally grown infants, found a greater percentage of growth-restricted infants with abnormally low or high red cell

folate in cord blood but detected no difference in maternal red cell folate at delivery.[67]

In their case series, deVries and colleagues reported increased frequency of hyperhomocysteinemia (24% versus the 2 to 3% expected) among women with serious complications of pregnancy (placental abruption, fetal demise, or intrauterine growth retardation [IUGR]).[68] Growth-restricted infants averaged 1327 ± 498 g at birth, and most were delivered preterm. Likewise with placental abruption, mean birth weight was low (1,518 ± 981 g) and gestation was shortened (30.8 ± 5.7 weeks).

Further, preeclamptic gravidas from Rajkovic and colleagues' study had significantly higher plasma homocysteine levels and delivered at an average of 35 ± 4 weeks' gestation compared with 40 ± 1 weeks among controls.[69]

Malinow and colleagues assessed the influence of maternal homocysteine and serum folate at term (37 to 42 weeks) on infant birth weight and gestation duration in 35 healthy nulliparas.[70] They reported that higher maternal homocysteine was associated with significantly lower infant birth weight and shorter gestation, whereas higher maternal folate correlated with increased birth weight (univariate analyses). A concentration gradient was detected; homocysteine declined from maternal vein to umbilical vein to umbilical artery by approximately 1 μmol/L for each phase, suggesting uptake of maternal homocysteine by the fetus.

Burke and colleagues, however, failed to detect differences in fasting homocysteine among women giving birth to growth-restricted infants (n = 37) compared with controls (n = 35).[71] Inadequate statistical power, along with the use of a less-sensitive test (fasting versus postload homocysteine), posed limitations to this research.

Recently, maternal homocysteine levels measured in more then 5,800 women aged 40 to 42 were linked to past data on pregnancy outcome contained in Norwegian birth registries.[72] Higher maternal homocysteine correlated with older age at delivery, higher cholesterol levels, less multivitamin use, and lifestyle factors (cigarette smoking and high coffee consumption). Women with currently high homocysteine levels were more likely to have had a reproductive history that included preeclampsia, preterm delivery, low birth weight, or fetal growth restriction.

Unlike in observational studies, randomized trials of supplementation with folic acid have shown less uniform benefit. Fleming and colleagues enrolled 146 Australian women before midpregnancy (week 20) into a randomized trial with five arms:

1. Placebo
2. Folic acid (0.5 mg)
3. Iron sulfate (60 mg)
4. Iron in combination with low-dose folate (0.5 mg)
5. Iron combined with high-dose folate (5 mg)

A total of 89 women completed the study with sample sizes of 15 to 20 per group; there were no significant differences in placental weight, birth weight, or gestation duration among the groups.[73] Small sample size and associated statistical power would limit the ability to detect an effect of folate, if any.

Fletcher and colleagues conducted a randomized, controlled study comparing iron (200 mg ferrous sulfate) with iron with folate (5 mg). Supplements were administered to 643 London women at entry to care.[74] No significant differences in birth weight, gestation, or incidence of congenital defects were found.

Giles and colleagues performed a double-blind, randomized, controlled trial of 692 women in Melbourne, Australia, assigned to folate (5 mg/day) or placebo.[75] Four groups were stratified by gestation at entry from less than 10 weeks to greater than 30 weeks. Outcomes, examined in babies born alive and well, suggested small differences in birth weight and gestation among groups and in multiparas between the index and penultimate pregnancies. None, however, were statistically significant.

Baumslag and colleagues administered iron alone (200 mg) or in combination with folic acid (5 mg/day) or with folate and vitamin B_{12} (50 μg/day) to South African women who had been allocated to one of these three groups.[76] There was no effect of the folate among the white women who were studied, but among Bantu women, who subsisted primarily on maize porridge, the risk of bearing an infant of less than 1,870 g was reduced fourfold by folic acid supplementation.

Iyengar and Rajalakshmi allocated 500 poor Indian women alternately to either iron alone (60 mg as ferrous fumarate) or in combination with folate (500 μg/day). Of these, 239 delivered in hospital; 189 had data included in the analysis.[77] There was a significant difference between folate and iron supplementation, favoring folate in infant birth weight (+ 200 g) and placental weight (+ 61 g). Risk of low infant birth weight was nearly twice as high among iron-supplemented (34%) compared with folate-supplemented (18%) gravidas.

Rolschau and colleagues studied 40 Danish women, matched for age, parity, smoking, pregravid weight, and housing conditions and allocated them to iron (200 mg ferrous fumarate) plus multivitamins with and without folic acid (5 mg).[78] Among the folate-supplemented subjects, serum and red cell folate increased significantly, infant birth weight was greater by more than 400 g, and placental weight was higher by almost 50 g.

Blot and colleagues assigned 200 French women to iron (105 mg elemental iron) alone or in combination with folic acid (350 mg/day).[79] Of these, 109 were re-evaluated at delivery. Women treated with folate had higher serum and red cell folate at delivery. Gestation duration was increased among supplemented women (40.7 ± 1.2 versus 39.9 ± 1.2 weeks), as were birth weight (3,461 ± 430 g versus 3,303 ± 375 g) and placental weight (660 ± 130 g versus 604 ± 115 g). In this study, the main effect of folic acid was to extend gestation by nearly 1 week.

Finally, Czeizel and colleagues reported the effect of periconceptional supplementation (from more than 28 days before conception to second missed menstruation) with folate-containing multivitamins (0.8 mg folate) or trace minerals.[80–82] After the randomized periconceptional period, about 60% of each group was prescribed multivitamins with folic acid or folic acid alone

during pregnancy. Thus, only the effect of periconceptional folic acid supplementation on pregnancy outcome was addressed. In addition to increasing the number of recognized conceptions, supplementation with multivitamins containing folic acid increased the likelihood of multiple births, fetal demise, and female births. In the analysis that included both singleton and multiple births, there was a small but statistically significant excess of low birth weight infants among the folic acid–supplemented subjects compared with the trace mineral group. The increased risk of IUGR and preterm delivery among multiple pregnancies is well known. When the analysis was confined to singletons, however, the excess in low birth weight infants persisted in the folate group but was no longer statistically significant.

In summary, although observational studies of folate and pregnancy suggest a potential benefit of folate supplementation during pregnancy—a decrease in serious complications and an improvement in birth weight and gestation—randomized trials imply that routine folate supplementation might not benefit all pregnant women. Some who are at risk, either because of common genetic polymorphisms that alter folate metabolism or because of environmental factors associated with a diet low in folate, would seem to benefit the most.

MULTIVITAMIN AND MINERAL SUPPLEMENTS

In the United States, about one-quarter of women (26% of white women and 15.5% of black women) in their reproductive years regularly take vitamin or mineral supplements.[83] In one study, 16% of low-income gravidas in Massachusetts took vitamins before pregnancy.[84] In Camden, New Jersey, 17% of low-income minority gravidas reported using supplements before they became pregnant.[85] Preconceptional supplement use was more likely to occur in women with a history of spontaneous abortion or other poor pregnancy outcome.

Information on recommended dietary intakes for pregnant women in the United States are given in Table 24-1. However, information on the effects of prenatal multivitamin and mineral supplements on pregnancy outcome is limited. The women in Canada who used such supplements during pregnancy had a reduced risk of preterm delivery (twofold lower than controls) and very preterm delivery (fourfold reduction in risk with first trimester use; twofold reduction with second trimester use); low infant birth weight was also decreased.[85]

Fawzi and colleagues examined the effect of supplementing more than 1,000 human immunodeficiency virus–positive women from Tanzania with multivitamins, vitamin A, and placebo in a double-blind, placebo-controlled trial.[86] Multivitamin supplementation decreased the risk of very preterm delivery (an approximately twofold reduction) along with decreasing risk of low infant birth weight and fetal growth restriction. The multivitamin supplement had the bonus of increasing CD4, CD8, and CD3 counts in the women.

A third study examining multivitamin use from survey data (the 1988 National Maternal and Infant Health Survey) reported no effect of multivitamin use on pregnancy outcomes, including preterm delivery; multivitamin use also did not amend the effect of maternal smoking on the fetus.[87] However, these conclusions are limited by the fact that the survey questionnaire was geared toward regular multivitamin use (3 days/week or more) and did not differentiate women who used vitamins from those who did not.

An increasing number of individuals are using megadoses of vitamin or mineral supplements—5.5% in 1997, up from 2.4% in 1990.[88] The use of megadoses of nutritional supplements by pregnant women and their effect on the course and outcome of pregnancy have not been investigated. The upper limit of nutritional intake is the highest level considered safe for use. The recommendations of the Institute of Medicine for the upper limits of nutritional intake during pregnancy are given in Table 24-1.

HERBAL PRODUCTS

Herbal products are considered nutritional supplements. They are used during pregnancy primarily for relief of nausea and vomiting (eg, ginger, raspberry leaf, chamomile) and closer to term to ripen the cervix and to stimulate labor (eg, black cohosh, blue cohosh, raspberry leaf, castor oil, evening primrose oil).[89–92] Little is known of their safety and efficacy. There is also a serious bias in prevalence estimates. One cross-sectional survey of pregnant women from San Francisco reported a response rate of 24%, and surveys of nurse-midwives had responses of 34% and 68%.[89,91,92] The largest survey to date was done by telephone and, although not limited to pregnant women, had an estimated response of 60%.[88] Thus, use of herbal remedies by pregnant women could be much different (higher or lower) than the published literature currently suggests.

FISH OIL SUPPLEMENTS

Consumption of supplements that contain fish oil, as well as eating a diet rich in marine foods that contain omega-3 fatty acids, is also associated with longer gestation duration. The clinical trial conducted by the People's League of Health on 5,022 women in London in 1938 and 1939 suggested that supplementing a diet that was not markedly deficient with minerals, vitamins, and halibut oil extended gestation.[93] Fewer infants were born before the fortieth week of gestation to the supplemented women (20% among supplemented subjects versus 24% among the unsupplemented), although there was no difference in mean birth weight.

A trial of 533 Danish women who received fish oil, olive oil, or no supplement by 30 weeks gestation showed that women taking the fish oil supplement had longer average gestations (by 4 days) and bore infants with higher average weights (+107 g), which was mostly attributable to the change in gestation.[94] The effect of fish oil was strongest for women with low fish consumption at entry to care and amounted to an increase of 7.4 days gestation in this group.

There was little effect of the supplement on women with high fish consumption at entry (–1.6 days). Thus, the hypothesized effect of omega-3 fatty acids on gestation appears to have a threshold and to be specific to the initiation of idiopathic preterm labor.

Recently, a multicenter trial of high-risk women enrolled gravidas with a history of preterm delivery, fetal growth restriction, or preeclampsia. Some of the centers enrolled women with threatened preeclampsia or suspected fetal growth restriction. Women were randomized to either fish oil or olive oil. Fish oil reduced the recurrence risk of preterm delivery approximately twofold but did not alter the recurrence of the other poor pregnancy outcomes.[95] A recent prospective and observational study of seafood intake in early pregnancy bolstered this relationship: risk of preterm delivery was increased nearly fourfold among women with little or no intake of fish by 16 weeks gestation.[96]

Finally, ecologic studies have indicated that the consumption of large quantities of fish during pregnancy is associated with lower blood pressure and thus, in theory, with a lower incidence of pregnancy-induced hypertension. Consistent with this is the reduction in the incidence of preeclampsia in the People's League of Health Study.[93] However, because of the multiple supplementation regimen, it could not be attributed to the use of the fish oil per se. The recent multicenter trial of fish oil showed no effect on the recurrence risk of preeclampsia or on blood pressure.[95]

CALCIUM

The skeleton acts as the calcium reservoir of the body (99% is stored there), and when dietary calcium intake is low or poorly absorbed, calcium is withdrawn from bone to support serum calcium homeostasis.[2] During pregnancy, retention of an estimated 30 g of calcium, most of which is transferred during the third trimester, is needed to mineralize the fetal skeleton.[2] Although it is often assumed that pregnancy, like lactation, might be a setting for bone mass loss because of this requirement, this might be buffered by a 60 to 70% enhancement in intestinal calcium absorption during pregnancy.[97]

Although several studies have examined longitudinally the change in bone mass with pregnancy, only two have examined the influence of dietary calcium on bone mass as an independent variable.[98,99] Lamke and colleagues evaluated 14 mature pregnant women in the second trimester and postpartum and reported a significant decrease in trabecular bone and a small gain in cortical bone.[98] Christiansen and colleagues studied serial changes in radial bone mass in 13 Danish women during pregnancy and found no change.[99] These women were, however, ingesting an average of 650 mg/day in calcium supplements, apart from their diet. Sowers and colleagues found no change in femoral bone mineral density in 32 women, aged 20 to 40 years, with measurement prior to pregnancy and following delivery, compared with matched controls, but again the average calcium intake exceeded the Recommended Dietary Allowance (RDA) for both groups.[100] Drinkwater and Chestnut studied changes in bone mineral density (pregravid and 6 weeks post partum) in 6 women who experienced pregnancy and 25 controls; mean calcium intake was high (> 1,500 mg/day) in each group.[101] Despite this, pregnancy was associated with significant decrements in bone at the femoral neck and radial shaft; increased bone density was found for the tibia.

One reason for the limited number of subjects and studies during pregnancy is risk of radiation exposure, making ultrasonography desirable for measuring bone change during pregnancy. Several recent studies have measured change in either the os calcis or the phalanges, and all have reported significant decreases in ultrasonographic measures of bone density during pregnancy.[102–105] The largest of these, with a sample size of 250 gravidas, reported a quantitative ultrasonographic index 3.6% lower at 6 weeks postpartum than at entry.[102] Although the amount of bone lost was small, it is consistent with the fetal demand for calcium. In this study, there was no relationship between dietary calcium intake and bone loss. However, Aguado and colleagues detected an overall decrease in bone propagation (phalanges 2 to 5) as seen by ultrasonography during the second and third trimesters that was greater for gravidas with low dietary calcium intake (< 1,000 mg/day). Decreases in maternal bone propagation were paralleled by increases in markers of bone turnover.[103]

Calcium intake, particularly during growth, could be an important determinant of bone mineralization and thus bone density.[106] Higher calcium intakes during childhood and adolescence are associated with higher bone mass at maturity.[107] Maternal growth and pregnancy often coincide, and approximately half of all pregnant teenagers continue to grow while pregnant.[108] Recently, Sowers and colleagues reported that ultrasonographic bone measures of the os calcis during pregnancy showed that bone loss was greater for growing teenage gravidas (–5.5%) than for mature women (–1.9%).[102] In the case of pregnancy in a still-growing girl, calcium nutriture might be limited by maternal diet but simultaneously driven by the need to retain enough calcium to mineralize two skeletons.

Presumably, continued maternal growth could affect the risk of osteoporosis and osteoporotic fractures in later life, particularly if the maternal diet was deficient in calcium during childhood and adolescence. Sowers and colleagues, in a cross-sectional study of two Iowa communities, reported that women with a first pregnancy before age 19 had, at maturity, a bone mass (measured at the middistal forearm) that was –0.52 standard deviation units (SDU) below that of other women.[109] Calcium consumption was also related to bone density (– 0.68 SDU for lower intakes), and the joint effect for early pregnancy and lower calcium intake, assuming additivity, exceeded –1 SDU in bone mass. A longitudinal study from a third community carried out 5 years later also showed that bone mass was significantly reduced in those with a teenage birth.[110] A cross-sectional study by Fox and colleagues yielded similar results in perimenopausal women.[111]

Another approach has been to examine the cross-sectional relationship of parity to bone mineral density or risk of fracture. In general, cross-sectional studies of bone

mass and parity, usually confined to mature white women, have shown increased bone mass, decreased fracture risk, or no effect of parity on bone mass.[112] Lower bone mineral density has been reported in parous minority women compared with controls of the same ethnic group. Goldsmith and Johnston reported lower radial bone densities in 52 parous black women compared with black nulliparas. Among whites, parous women had a bone density 1% higher than nulliparous controls.[113] Carter and Haynes showed that lower bone density was present in adults with scoliosis.[114] Parous black women were more likely to have scoliosis than were nonparous blacks. However, parity does not measure the effects of pregnancy but the cumulative effect of the reproductive experience, along with antecedents and consequences. For example, a positive correlation between parity and bone density could reflect greater antecedent hormonal integrity and possibly increased body weight of women who bear children compared with women who are infertile. It is uncertain the extent to which small decrements in bone mass with parity among black women reflect an overrepresentation of women with adolescent childbearing.

Maternal calcium metabolism is altered during pregnancy, and these alterations could be involved in the etiology of preeclampsia. During pregnancy, maternal serum calcium levels fall and urinary calcium excretion rises, whereas serum ionized calcium remains unchanged. Preeclampsia and gestational hypertension are marked by aberrations involving calcium: affected women have hypocalciuria, low levels of ionized calcium, lower levels of 1,25-dihydroxyvitamin D, elevated levels of parathyroid hormone, and increased intracellular concentrations of calcium in erythrocytes, platelets, and lymphocytes.[115] Thus, preeclampsia might be a pathologic manifestation of a calcium-conserving mechanism. Calcium supplementation might reduce smooth muscle reactivity, including the reactivity of uterine and vascular smooth muscle by reducing parathyroid hormone and intracellular calcium levels.[116] On the other hand, disturbances in calcium metabolism could be a marker for preeclampsia, a response to an unknown and underlying metabolic perturbation.

Diets low in calcium, especially during pregnancy, have been associated with increased blood pressure levels through heightened smooth muscle reactivity (see Table 24-1 for recommended dietary intake of calcium and other nutrients during pregnancy). The pathogenesis of PIH may or may not involve calcium in the maternal diet. Belizan and Villar reported an inverse relationship between toxemia and dietary calcium from ecologic-level data.[117] More recently, gestational hypertension (but not preeclampsia) and maximum diastolic pressure were found to be weakly associated with low dietary calcium intakes.[118] Several smaller-scale clinical trials have confirmed that calcium supplementation is associated with decreased blood pressure during pregnancy, consistent with reports of an inverse association between calcium and systolic blood pressure in nonpregnant subjects.[119–120]

A meta-analysis of 14 randomized, controlled trials of calcium supplementation involving more than 2,400 pregnant women showed statistically significant reductions in systolic and diastolic blood pressure with the administration of calcium salts (375 to 2,000 mg/day elemental calcium).[121] Risk of preeclampsia was reduced more than twofold among women supplemented with calcium during these trials. Duration of treatment ranged from 10 to 22 weeks, with most studies starting the supplement during the second trimester. Although differences in the risk of preeclampsia were significant in the aggregate, only two of the nine studies showed statistically significant differences.

A large, randomized, double-blind, placebo-controlled trial of 5,489 low-risk nulliparous women showed no effect of calcium supplementation.[122] Pregnant women were enrolled at centers throughout the United States and prescreened for compliance with supplement use and for conditions associated with abnormal calcium metabolism or increased risk of preeclampsia. Women were supplemented with 2 g of elemental calcium (or placebo) beginning at 13 to 21 weeks gestation and continuing until they delivered. Calcium supplementation did not significantly reduce the risk of preeclampsia, gestational hypertension without preeclampsia (either mild or severe), or pregnancy-associated proteinuria without hypertension. Blood pressure was also unaffected. Between 20 and 40 weeks gestation, systolic pressure was lower by 0.3 mm Hg and diastolic pressure was 0.03 mm Hg higher among the calcium-supplemented subjects; these small differences were not statistically significant. Likewise, risk did not differ when data were examined according to hypothesized moderating variables: quintile of dietary calcium intake at baseline, maternal age, urinary calcium excretion, or gestation at entry to the study. These results suggest no effect of calcium supplementation on preeclampsia; however, participants' dietary intake of calcium was high, averaging about 1,100 mg/day.[122]

Recently, an Australian trial of calcium supplementation in gravidas ($N = 456$) with dietary calcium intakes (median, 1,100 to 1,200 g/day), maternal characteristics, and pregnancy outcomes very similar to those in the US trial reported a positive effect of supplementation.[116] Calcium supplementation (1.8 g/day from week 24) resulted in a greater than twofold reduction in the risk of preeclampsia. Although the proportion of women with pregnancy-induced hypertension (PIH), severe PIH, and severe preeclampsia was slightly less in the treatment group, differences from placebo were not statistically significant.

During pregnancy, an increased risk of PIH associated with lower calcium intake could result in an increased risk of preterm delivery because an indicated preterm delivery is one method of reducing the maternal–fetal morbidity and mortality associated with preeclampsia and eclampsia. Consequently, supplementation with calcium during pregnancy could have a side effect of reduced preterm birth risk. Preeclampsia involves the failure to adequately perfuse many organs, including the placenta, and is also associated with fetal growth restriction and low infant birth weight (< 2,500 g).

Two calcium supplementation trials among high-risk women showed promising results. In Ecuadorian women

with low calcium intake, gestation duration increased by 1.8 weeks ($p < .01$) for the calcium-supplemented subjects ($n = 22$).[123,124] Among teenagers from Baltimore, the calcium-supplemented group had a lower incidence of preterm delivery compared with the placebo group.[119] Further, life-table analysis demonstrated an overall shift to a higher gestational age with calcium. Another randomized, controlled trial of supplementation of 260 pregnant Ecuadorian teenagers (age 17.5 years and less) with 2,000 mg/day elemental calcium increased gestation duration from 38.7 weeks (0.3 weeks) for placebo to 39.6 weeks (0.4 weeks) with calcium supplement. Risk of PIH was reduced by 80% in this trial with calcium supplementation.[125] Baseline dietary calcium intake was low and amounted to less than 50% of the RDA for pregnancy. The more recent clinical trial from Australia also showed a reduction in the risk of preterm delivery from 10% (placebo) to 4.4% (calcium supplemented) as well as for low birth weight (7.4% versus 2.6%).[116] There were also reductions in admissions for threatened preterm labor ($p = .03$) and in preterm premature rupture of membranes ($p = .08$) for gravidas assigned to calcium.

A large calcium supplementation trial of more than 1,000 women from Argentina, however, showed a decrease in the incidence of PIH but no effect on preterm delivery.[120] The meta-analysis cited above also showed no effect of calcium intake on preterm delivery or fetal growth restriction.[121] Likewise, the US clinical trial performed by Levine and colleagues, discussed above, also found no effect of calcium supplementation on obstetric outcomes, including preterm delivery, and perinatal outcomes, including birth weight, low birth weight, or fetal growth restriction.[122] Thus, effects might be confined primarily to teenage gravidas or to gravidas with a very poor dietary intake of calcium.

DIET AND GESTATIONAL WEIGHT GAIN

The bulk of the research on gestational weight gain has focused on the relationship between total weight gain and birth weight. The body of evidence on this topic has been extensively reviewed by the Institute of Medicine and recently updated by Abrams and collegues.[2,126] Studies from developing countries and among different ethnic groups have been virtually unanimous in showing a positive relationship between weight gain and birth weight.[127,128] Maternal pregravid weight or BMI and weight gain appear to have independent and additive effects on birth weight. Correlations between weight gain and birth weight range between .20 and .30. The average magnitude of the effect on birth weight (in women with a normal weight for height) is, assuming a base birth weight of about 3,000 g, approximately 20 g of birth weight for every 1 kg of total gain; pregravid weight for height is a strong effect modifier on birth weight.[128] The relationship between gestational weight gain and preterm delivery appears more complex and more controversial. A current review concluded that most studies showed that a slow rate of gain, particularly in the second half of pregnancy, was associated with an increased risk of preterm birth.[129]

A poor or otherwise inadequate gestational gain could reflect an inadequate dietary intake. The first report of a positive relationship between diet and weight gain was made by Thomson, who found a correlation of .30 between caloric intake and weight gain in Scottish primigravidas eating "to appetite."[130] Among Camden gravidas, a significantly lower caloric intake was associated with an inadequate gestational gain.[131] This relationship was confirmed subsequently with three 24-hour dietary recalls taken during the course of pregnancy.[7] A diet that is low in energy is often one that is of poor quality with a low nutrient density. Thus, low intakes of the micronutrients iron, zinc, and folate are associated with inadequate gestational weight gain as well as with an increased risk of poor pregnancy outcomes.[6–8]

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CHAPTER 25

FETAL NUTRITION AND IMPRINTING

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The fetus exists in utero in a dynamic environment that attempts to protect the fetus from noxious insults, while, at the same time, providing adequate nutrition and oxygenation to ensure the delivery of a healthy baby at the end of pregnancy. The mechanism by which the fetal milieu is maintained is delineated in subsequent chapters. It has become increasingly evident, however, that insults impacting the fetus and its environment can have significant consequences, not only during the immediate postnatal period but also during adult life. This chapter attempts to summarize the evidence supporting the relationship between events in fetal life and long-term health, in humans as well as in animal models.

BARKER HYPOTHESIS

In the late 1980s, David Barker and colleagues began to uncover data that, considered in totality, have become known as the "fetal origins" or "Barker" hypothesis.[1] It proposes that alterations in fetal nutrition and/or endocrine status result in developmental adaptations that may permanently change an individual's body structure, physiology, and metabolism, thereby predisposing individuals to cardiovascular, metabolic, and endocrine disease in adult life. The hypothesis suggests that insults to the fetus, occurring at sensitive (critical) periods of development, may eventually manifest in chronic diseases of adulthood, including, among others, type 2 (non–insulin-dependent) diabetes mellitus (NIDDM), coronary artery disease (CAD), hypertension, and stroke (Table 25-1). The term "fetal programming" has been coined in relation to this effect. It has been further hypothesized that, during periods of rapid growth, fetal adaptations meant to counteract malnutrition in utero can negatively influence long-term health.[2] This "thrifty hypothesis" posits that adaptations undergone by the fetus in utero to become "thrifty," that is to say efficient in the use of scarce metabolic fuels, may, in fact, be counterproductive when the organism, after birth, is exposed to an environment in which resources (such as food) are plentiful.[2,3] Support for this hypothesis has been found in large population studies, such as those involving the Pima Indians of North America.[4,5] These groups have, over generations, become adept at survival under subsistence conditions. When suddenly introduced to an environment containing abundant food—the so-called "Western diet"—the incidence of diseases including NIDDM and CAD has become epidemic.

Early evidence for the relationship between conditions in utero and later health can be found in the work of Rose, who, in 1964, described high rates of stillbirth and infant mortality among siblings of adults with CAD.[6] Subsequently, Forsdahl, in 1977, showed that areas of Norway with the highest rates of CAD had had relatively high infant mortality rates 50 years previously.[7] Barker and Osmond, in 1986, demonstrated similar findings in a British population.[8] Much of the information provided subsequently by Dr. Barker and colleagues has been derived from extensive retrospective analyses of adult British men and women who, as infants, had birth measurements recorded. In one such cohort, from Hertfordshire, Great Britain, data on approximately 16,000 subjects born between 1911 and 1930 were available.[9–13] In this group, birth weight has been noted to be inversely proportional to subsequent mortality from CAD (Figure 25-1). This relationship held over a range of "normal" birth weights ranging from 5.5 to 9.5 pounds: over 9.5 pounds, death rates attributable to heart disease rose, presumably because of the inclusion of infants of diabetic mothers in this group.[13] These findings have subsequently been replicated in a variety of other populations.[14–16] Ultimate mortality rates in infants born small were higher in those men in whom poor growth had persisted at 1 year of age, as well as in women who were of above-average weight by 1 year of age.

The connection between small size at birth and subsequent mortality from CAD has subsequently been extended to include enhanced risk of stroke, hypertension, and NIDDM.[17] Martyn and colleagues have demonstrated that the eventual risk of stroke is associated with diminished

TABLE 25-1 Reported Associations with Small Size at Birth

Increased risk of
Type 2 diabetes mellitus
Hypertension
Death from coronary artery disease
Stroke
Hypercholesterolemia

birth weight and placental size in the setting of a relatively preserved head size.[18] An inverse relationship between size at birth and serum cholesterol values in adult life has also been reported.[10,19] Hypertension during adult life has been associated with birth size in many studies[10,20–22]; this relationship may be manifest during childhood.[23] The impact of birth weight on eventual blood pressure has been of variable degree; placental size has also been reported to directly correlate with systolic blood pressures.[20] Perhaps the most intriguing association noted thus far is that between low birth weight and NIDDM, first noted by Hales and coworkers in 1991.[12] This association has been confirmed in other populations in Great Britain,[10,24] as well as in other, although not all, regions worldwide.[25–30] The association between insulin resistance in later life and birth weight is strongest in infants born relatively "thin" (low ponderal index),[29] as well as in adults who are obese. In fact, the interaction between adult weight and the conditions described above has caused debate regarding the robustness of these findings.[31] Nonetheless, at present, the bulk of available evidence supports an association between fetal growth and later health. Timing of the insult also influences the body habitus of the baby at birth. Various epidemiologic studies have shown that if the insult occurs early in pregnancy, babies tend to be proportionate with regard to weight for length (thinness) and may be more prone to develop hypertension as adults.[14] Insults in the second or third trimester result in asymmetric babies who are thin (diminished weight for height); these babies are thought to be more likely to suffer long-term abnormalities of the glucose-insulin axis.[10] Infants with small abdominal circumferences are hypothesized to have suffered an insult during hepatic organogenesis; resultant long-term changes in hepatic function may result in abnormal cholesterol and fibrinogen levels.[19] Barker and others have also shown that lifestyle factors such as obesity are additive to the effect of intrauterine environment.[9] Less certain, perhaps, is the relationship between inadequate fetal nutrition and low birth weight. Genetic influences may play a significant role. In particular, Vaessen and colleagues have reported a polymorphism in the promoter region of insulin-like growth factor I, an important fetal growth factor. Those homozygous for deletion of this 192-basepair region have a significantly enhanced risk of low birth weight, NIDDM, and CAD.[32,33] This deletion may account for a significant proportion of the findings related above.

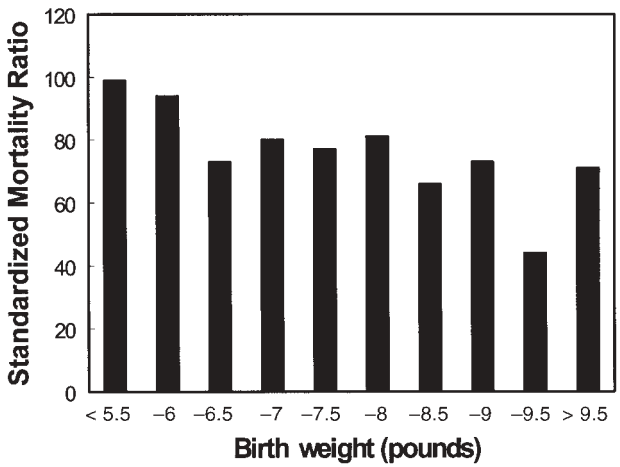

FIGURE 25-1 Standardized mortality ratio for men by birth weight in Hertfordshire study. Adapted from Osmond C et al.[13] Reproduced with permission from McClellan R, Novak D. Fetal nutrition: how we become what we are. J Pediatr Gastroenterol-Nutr 2001;33:233–44.

Convincing evidence for the association between intrauterine nutrition and later health can, however, be found through the study of infants exposed to malnutrition during times of famine. Under normal circumstances, fetal nutrition, perhaps as impacted by diminished uterine blood flow, as may be noted in preeclampsia, is difficult to estimate. During the extreme conditions found during famine, however, poor fetal nutrition is intuitive. The Dutch famine of 1944 to 1945 is an unfortunate but, given the excellent birth records kept in the country, instructive example of such a tragedy. Near the end of the Second World War, Allied Forces mounted a campaign into Nazi-occupied Holland, called Operation Market Garden. When the Dutch resistance called a general railway strike to support this campaign, German authorities retaliated by terminating food shipments into the region. This, combined with the severe winter of 1944 to 1945, resulted in severe famine. Food allowances dropped to levels approaching 300 to 600 calories per person per day during the height of the famine in December 1944 through April 1945. Infant weights fell in accordance with the caloric restriction. Infants born after exposure to famine in late gestation weighed an average of 3,133 g (n = 307), approximately 300 g less than infants conceived and born after the famine (average 3,413 g).[34] Infants born after exposure during midgestation weighed an average of 3,217 g (n = 297), whereas those children exposed only in early gestation weighed an average of 3,470 g (n = 217), more than control infants. It is unclear whether this increase in weight compared with that of the control group represents the end result of an early, biologic compensation to nutrient restriction gone awry when nutrients became abundantly available or is merely the result of available food and supranormal intakes during late gestation by the children's mothers. These children were again studied at approximately 50 years of age. Keeping in mind that clinically overt cardiac disease, as well as NIDDM, often does not present until after 50 years of age, those exposed to famine in mid- or late gestation had evidence of glucose intolerance, based on 2-hour plasma glucose values after glucose load. Elevations of serum insulin values were also noted in those exposed to famine during late gestation.[35] Those exposed in early gestation appeared to have an increased incidence of CAD, as well as a more "atherogenic" serum lipid profile.[34,36,37] Blood pressures were elevated compared with those of controls in a subgroup of individuals whose mothers had ingested a diet disproportionately deficient in protein.[38] These data generally support the "thrifty hypothesis," although further follow-up as the cohort ages will be necessary to appreciate the full impact of famine on their long-term health. It should also be pointed out that,

despite the extreme nature of the maternal dietary restriction during the famine, the impact on progeny was really quite minimal, demonstrating the extraordinary capacity of pregnant women to maintain fetal homeostasis. It is also noteworthy that the results of these studies are not universal; although methodologically limited, studies of infants born during and after the Leningrad famine of World War II have not demonstrated differences between adults exposed to famine in utero and those born later.[39]

There is evidence that insults in utero can be propagated beyond the first, directly impacted generation. Klebanoff and colleagues have shown that mothers born small for gestation are more likely to have children who themselves are small for gestation[40]; others have shown that mothers born either small (under 2,000 g) or large (over 4,000 g) suffer higher subsequent infant mortality rates than do controls.[41,42] This information must be interpreted in light of the fact that small mothers tend to have relatively small babies, suggesting a strong maternal genetic influence, independent of fetal nutrition.[43–45] This influence has been reproduced in an animal model.[46] There is some information suggesting that perinatal nutrition may influence growth beyond the first generation. Stewart and colleagues administered a low-protein (LP) diet to a colony of rats over 12 generations. LP diet–fed animals were approximately 67% of control size. When a regular (high-protein) diet was then introduced at weaning, weights did not "catch up" to control values for three generations. Of interest, however, when pregnant animals were switched to a regular diet during pregnancy, offspring rapidly caught up to and, indeed, surpassed control weights.[47] These data are strikingly similar to those reported in humans as a result of the Dutch famine and confirm the disparate impact of malnutrition in utero at different segments of pregnancy.

The role of neonatal nutrition on eventual health during adult life has also been examined. Serum cholesterol values appear to be influenced by breast-feeding: both Marmot and Fall and their colleagues have shown that exclusive breast-feeding can be associated with lower serum cholesterol values during later life.[48,49] These findings have been replicated by others.[50–52] Less consensus exists regarding the relationship between adult blood pressure and mode of feeding. Lucas and Morley, in a prospective study of low birth weight infants, documented lower arterial blood pressures in infants who had been exclusively breast-fed, at least until hospital discharge, compared with those given formula, at 13 to 16 years of age but not at 8 years of age.[53] Other studies have both supported and cast doubt on the benefits of breast-feeding with regard to eventual blood pressure.[54–57] Exclusive breast-feeding for a period of at least 2 months has also been shown to diminish the likelihood (compared with exclusive bottle feeding) of developing NIDDM in Pima Indians.[58] Although intriguing, this association has not been replicated in other populations.

The remainder of this chapter focuses on work done in animal models, thus beginning to explore the mechanisms by which in utero environment influences postnatal outcomes.

MECHANISMS UNDERLYING "PROGRAMMING": ANIMAL MODELS

Exploration of the mechanisms underlying the "programming" of physiology during fetal life has generally involved the use of animal models of growth retardation. Although many such models are available, the most widely used are those in which maternal diet is modified, thus causing malnutrition and subsequent growth retardation. This can be done either by limiting total caloric intake, similar to the situation seen during human famine, or by limiting a specific component of the maternal diet in a controlled way, for example, use of a diet low in protein. In this case, caloric intake may be held constant through an increase in the other components of the diet, that is, carbohydrates and fats. This method, although perhaps less "physiologic," allows insight into the mechanism by which changes observed may be produced. Still another method by which growth-retarded animals may be produced is limitation of uterine blood flow, mimicking preeclampsia in the human. This may be done in sheep through selective removal of placental subunits, or caruncles, whereas in the rodent, ligation of the uterine artery is most often performed, although the acute nature of this intervention, usually performed late in gestation, casts doubt on its applicability to the human situation. Other models, including that produced by heat stress[59] or by genetic manipulation, also exist.[60–64] We will focus primarily on work done in dietary and uterine artery ligation models, largely because the majority of published work has involved their use.

Perhaps the most attention has been paid to the relationship between in utero nutrition and subsequent hypertension in animal models. In a series of articles exploring this phenomenon, Langley-Evans and colleagues have demonstrated that the progeny of pregnant rats fed an LP diet throughout gestation develop systolic blood pressures that exceed those of controls.[65–70] These effects are noted at the time of weaning, last through approximately 5 months of life, and typically are in the range of 15 to 30 mm Hg. The changes noted are, to some degree, specific to the diet used. Specifically, LP diets varying in carbohydrate, fat, and amino acid content may not have similar effects, despite similar total protein contents.[71] Rats made small by maternal uterine artery ligation are not hypertensive, whereas sheep fetuses made small by placental embolization are.[72,73] Thus, the hypertension observed after administration of an LP diet to pregnant rats is not simply the result of small fetal size but rather seems related to a combination of variables, which have been elucidated only on a superficial level. More progress has been made toward determining the mechanisms of hypertension in this model. Specifically, in utero exposure to maternal glucocorticoids seems to be of key importance. The placenta normally contains an 11β-hydroxysteroid dehydrogenase activity that converts maternal glucocorticoids to inactive forms, thus protecting the fetus from their effects. Exposure of the mother to an LP diet is associated with an attenuation in the placental activity of this enzyme, as well as with increases in the activities of fetal and placental glucocorticoid inducible enzymes.

Treatment of pregnant rats with dexamethasone, which is not substantially inactivated by 11β-hydroxysteroid dehydrogenase, produces hypertension in offspring,[74,75] as does the administration of an inhibitor of 11β-hydroxysteroid dehydrogenase, carbenoxolone.[76,77] Administration of metapyrone, an inhibitor of corticosteroid synthesis, to pregnant rats fed an LP diet abolished elevated blood pressures in the offspring, unless the mothers were supplemented with exogenous glucocorticoid.[68] Postnatally, glucocorticoids are required for LP diet–associated hypertension to develop; adrenalectomy of hypertensive animals restores blood pressure to control levels.[67] Bertram and colleagues have shown that maternal LP diet administration is associated with enhanced expression of the glucocorticoid receptor in the offspring.[78] This alteration may account for some of the phenotypic differences noted. Langley-Evans and Jackson have also demonstrated alterations in the activity of the renin-angiotensin system in association with maternal LP diets. Activity of angiotensin-converting enzyme (ACE) is consistently increased in the offspring of LP diet–fed dams.[79,80] Captopril, an ACE inhibitor, and losartan, an inhibitor of the angiotensin II receptor, are both effective in reversing the hypertension brought about after in utero exposure to an LP diet, either temporarily, if given after weaning, or permanently, if given before weaning.[67,79,81,82] These results appear specific to drugs that have their effects on the renin-angiotensin system; Ca channel inhibitors were ineffective in this regard.[81]

Exposure to an LP diet in utero also appears to have long-term effects on renal morphology and function. Nephron numbers are diminished postnatally, and renal function, as determined by measurement of creatinine clearance, is diminished at 4 weeks of age. Older animals demonstrate increased urinary albumin excretion and blood urea nitrogen, suggesting that renal abnormalities persist past the immediate postnatal period.[83,84]

In summary, there is significant evidence that, in animal models, nutrition in utero has an impact on blood pressure postnatally, analogous to the situation documented above in humans. Although a variety of mechanisms by which this hypertension may occur have been suggested, the manner by which altered nutrition effects these changes remains elusive.

IN UTERO NUTRITION AND GLUCOSE INTOLERANCE

The impact, in animal models, of in utero nutrition on the pancreas and, more specifically, on pancreatic insulin secretion has been known for many years. Winick and Noble, in 1966, demonstrated that nutrition had an effect on cell number within the pancreas, and Swenne and colleagues showed that protein malnutrition in the weanling period was associated with glucose intolerance and impaired insulin secretion.[85,86] Snoeck and colleagues, in 1990, showed that B-cell proliferation and islet size were diminished in the pancreas of neonates exposed to an LP diet in utero, as was islet vascularization.[87] Dahri and colleagues, in 1991, continuing this work, demonstrated abnormalities in insulin secretion from these abnormal islets.[88] When animals were maintained on an LP diet into adulthood, glucose tolerance was impaired. Even when a normal diet was administered after birth, however, insulin secretion in response to a glucose load was abnormal in female rats tested at 70 days of age.[89] Others have shown that although glucose tolerance is roughly equivalent to that of controls at 3 months of age, impairment is clearly noted by 15 months of age, suggesting an ongoing or "programmed" response to in utero undernutrition.[90] Petrik and colleagues have subsequently shown that exposure to an LP diet through weaning is associated with increased pancreatic B-cell apoptosis, in association with diminished rates of proliferation and insulin-like growth factor II expression.[91] Studies of offspring at 3 months of age have shown that hepatic glucose output in response to glucagon is diminished compared with controls, whereas a paradoxical response, that is, an increase in hepatic glucose output, was noted in response to insulin, despite an increase in hepatic insulin receptors.[92] Hepatic glucokinase activity is decreased, whereas phosphoenolpyruvate carboxykinase (PEPCK) activity is increased,[93] contributing to an increase in hepatic gluconeogenesis noted in the offspring of protein-deprived mothers.[94] Peripheral adipocyte size was reduced compared with controls; adipocyte insulin receptor content was increased.[95] Insulin-induced suppression of lipolysis was diminished in the LP adipocytes.[96] Basal and insulin-stimulated glucose transport activities are enhanced in the LP group, and alterations in the insulin signaling pathway mediated by insulin receptor substrate 1–associated phosphatidylinositol 3-kinase have been documented.[96,97] In skeletal muscle, insulin receptor density and basal glucose uptake are enhanced compared with controls; however, stimulation with insulin has less impact on maximal transport, perhaps because the insulin-responsive glucose transporter 4 is already maximally translocated to the plasma membrane in the LP group.[98]

Offspring of mothers fed an LP diet through pregnancy and lactation may themselves have abnormal glucose tolerance during pregnancy.[99] Although this finding has not been universal,[100] abnormalities in fetal pancreatic insulin content, glucose turnover, and glucose use have been documented in the second- and even third-generation offspring, despite receipt of a normal diet throughout.[99,100] These data have been bolstered by those obtained in other complementary models. Provision of dexamethasone to pregnant rats produces growth retardation, with subsequent hyperglycemia and hyperinsulinemia in adult offspring, in association with increased PEPCK messenger ribonucleic acid and activity.[101] These findings, similar to those noted after LP diet exposure, suggest that some of the effects of LP diet on later glucose homeostasis may be mediated by maternal glucocorticoids. Others have used the uterine ligation model to examine long-term impacts on glucose homeostasis. Simmons and colleagues have demonstrated that animals born to mothers who underwent uterine artery ligation at day 19 of gestation develop fasting hyperglycemia by 10 weeks of age. Cell mass diminishes after 7 weeks of age, having been normal up until that point.[102] When these

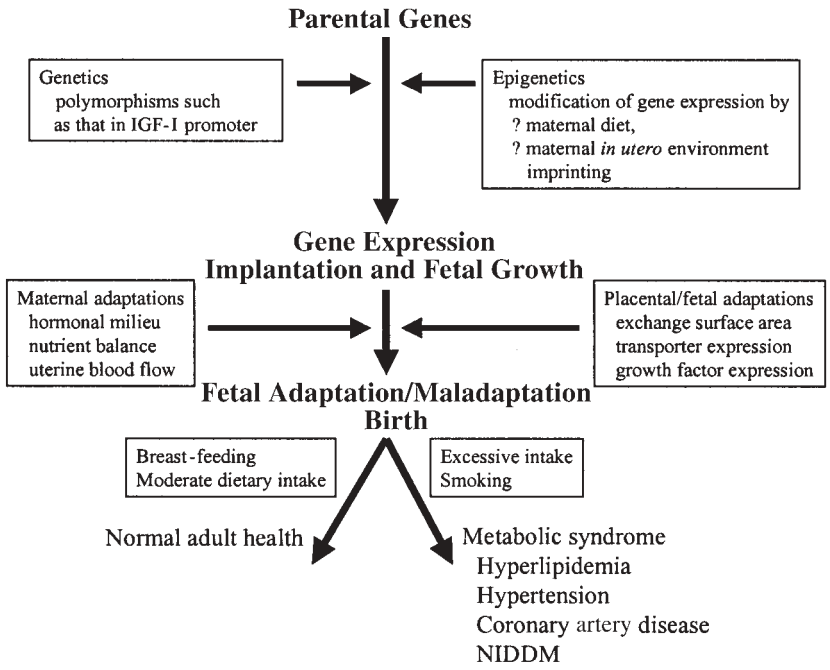

FIGURE 25-2 Proposed schema by which maternal, fetal, and environmental factors interact to produce adult disease. IGF = insulin-like growth factor; NIDDM = non–insulin-dependent diabetes mellitus. Adapted from Bertram CE, Hanson MA. Animal models and programming of the metabolic syndrome. Br Med Bull 2001;60:103–21.

animals become pregnant, their offspring develop glucose intolerance early in life and frank diabetes by 26 weeks of age.[103] Thus, there is significant evidence that nutrition in utero, in the animal as in the human, is capable of "programming" subsequent glucose homeostasis. The mechanisms underlying these phenomena, as delineated above, are beginning to be elucidated.

CONCLUSION

There is now clear evidence both from human epidemiologic studies and animal models that in utero conditions impact, in a significant way, postnatal health. Less certain is the manner by which these changes occur; a proposed algorithm is shown in Figure 25-2. As is depicted in other chapters, placental nutrient transfer is a complex process, the regulation of which, whether by genetic or environmental factors, remains poorly understood. As a result, the definition of and, if necessary, the augmentation of in utero nutrition continue to be a topic of intense investigation.

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CHAPTER 26

DEVELOPMENT OF THE FETUS: CARBOHYDRATE AND LIPID METABOLISM

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The rapid rates of metabolism and growth of the placenta and fetus require ready sources of carbon for energy production and deposition in energy stores (adipose tissue and glycogen) and for structural tissues (proteins). Maternal plasma glucose provides most of the carbon for placental and fetal energy requirements. As much as 20 to 30% of the amino acids taken up by the fetus can be oxidized, however, providing most of the additional carbon necessary to meet fetal requirements for oxidation. Glucose carbon also gets to the fetus as lactate that is produced in the placenta. Between 20 and 40% of glucose carbon also is deposited in growing body tissues; most of this goes to glycogen, some to protein, and some to adipose tissue. Lipid, on the other hand, appears to be directed primarily to growth as there is little capacity to oxidize long-chain fatty acids in fetal tissues. Lipids account for fetal growth through the provision of essential fatty acids supplied to developing structural membranes. Fatty acids also account for fetal growth through adipose tissue development and growth.[1–5]

Based on experimental data from late-gestation fetal sheep and estimated data from full-term human fetuses, it is possible to construct reasonable estimates for the rates of carbon supply to the fetus from glucose (including products of glucose metabolism in the placenta, such as lactate and fructose) and amino acids, as well as for fatty acids, and to compare these rates with requirements for energy production and storage. Such estimates are shown in Table 26-1.[5–7]

CARBOHYDRATES

Sources of Glucose for the Placenta and Fetus

Maternal Glucose Supply Maternal plasma glucose provides all of the glucose for the placenta and fetus, except under relatively uncommon conditions of prolonged maternal hypoglycemia or fetal hypoxia, when the fetus can produce its own glucose by glycogenolysis or gluconeogenesis. The placenta also can use its own glycogen for glycolysis, but insufficient glucose-6-phosphatase has been found in the placenta for its glycogen to be available for production into the fetal circulation.

Qualitative evidence demonstrating that maternal glucose is the sole source of glucose for the placenta and fetus under normal conditions comes from studies in which tracers of glucose that are infused into the mother have the same specific activity or enrichment (ratio of tracer glucose to unlabeled glucose) in blood sampled from the fetus, indicating no dilution of fetal glucose with glucose other than from the maternal circulation.[8,9] Quantitative evidence to support these observations has come from tracer studies in fetal sheep during fed, normoglycemic conditions.[9–11] In these studies, net uptake of glucose by the fetus from the placenta equals fetal glucose use, that is, there is no source of glucose for fetal glucose use other than what comes from the mother by way of the placenta.

Fetal Glucose Production Only after prolonged periods (several days) of decreased fetal glucose supply, producing sustained fetal hypoglycemia and hypoinsulinemia, does fetal glucose use exceed supply, demonstrating a new source of fetal glucose production.[12] A natural onset of fetal glucose production does tend to develop in late gestation.[13] Most species appear to have sufficient functional activities of hepatic gluconeogenic enzymes in late fetal life, except the rat, in which mitochondrial phosphoenol pyruvate carboxykinase (PEPCK) develops only after birth.[14] Thyroid hormone also is essential for glucogenesis, acting on both the hepatic glucogenic pathways and on the mechanisms activating glucogenesis. These thyroid effects include up-regulation of catecholamine secretion and effects and increased or maintained concentrations of enzymes necessary for glucose production, such as glu-

TABLE 26-1 Nutrient Substrate Balance in Late-Gestation Fetal Sheep and Humans

Carbon-Calorie Balance	*Carbon (g/kg/d)*	*Calories (kcal/kg/d)*
Requirement		
Accretion in carcass: nonfat (sheep)	3.2	32
Accretion in carcass: nonfat (human)	3.2	32
Accretion in carcass: fat (human)	3.5	33
Excretion as CO_2	4.4	0
Excretion as urea	0.2	2
Excretion as glutamate	0.3	2
Heat (measured as O_2 consumption)	0.0	50
Total without fat (sheep)	8.1	86
Total with fat (human)	11.6	119
Uptake		
Amino acids (sheep and human)	3.9	45
Glucose (sheep)	2.4	17
Glucose (human)	3.7	26
Lactate (sheep)	1.4	14
Lactate (human)	1.7	21
Fructose (sheep)	1.0	7
Acetate (sheep)	0.2	3
Fatty acids (human)	1.1–2.2	17–34
Total (sheep)	8.9	86
Total (human)	10.4–11.5	109–126

Adapted from Battaglia FC and Meschia G,[5] Hay WW,[6] and Sparks JW et al.[7]

cose-6-phosphatase, fructose diphosphatase, and alanine transaminase.[15]

In the case of selective hypoinsulinemia, produced, for example, by injection of streptozocin, a drug that destroys the pancreatic insulin-producing beta cells,[16] or by fetal pancreatectomy,[17] fetal glucose concentration actually increases. At the same time, the fetal glucose use rate remains near normal, despite a reduction of up to 70 to 80% in glucose supplied by the placenta. Infusion of glucose into these animals increases the glucose use rate but does not appear to decrease the rate of fetal glucose production. Only by reinfusion of insulin to normal or higher-than-normal levels can this glucose production by the fetus be diminished. Thus, fetal plasma insulin concentration appears to be a more important and more specific regulator of fetal glucose production than is fetal glucose supply or concentration.

Fetal glucose production also can come from glycogenolysis. The principal source of fetal hepatic glycogen is fetal plasma glucose. Circulating lactate[14] and certain amino acids, such as alanine,[18,19] serine,[20] and glutamine,[21] can label fetal glycogen. In vivo and in vitro studies with magnetic resonance spectroscopy using ^{13}C-labeled glucose indicate that only about 10% of glycogen (at least in fetal sheep) could come from nonglucose precursors, that is, by the indirect pathway of reverse glycolysis (DiGiacomo, Battaglia, Shapiro, et al, unpublished data). Glycogen accumulates progressively toward term in most organs.[22] Lung glycogen content decreases late in gestation, however, presumably as part of surfactant production, although this issue is controversial. Glycogenolysis in the fetus is rapidly activated by catecholamine infusion, glucagon injection, and hypoxia or ischemia[23]; all of the enzymes necessary for glycogenolysis are present early in gestation.[24]

Mechanisms of Placental Glucose Uptake and Transport

A principal action of fetal glucose production, regardless of cause or mechanism, is to divert uterine glucose supply to the placenta. As shown in Figure 26-1, an increase in fetal glucose concentration that is independent of the maternal glucose concentration can separately regulate the partition of uterine glucose uptake into glucose transfer to the fetus and uteroplacental glucose consumption. This observation demonstrates complex regulation of glucose uptake, metabolism, and transfer to the fetus by the placenta.

Maternal Glucose Concentration Glucose enters the placenta and fetus from the maternal circulation according to concentration-dependent mechanisms, making maternal plasma glucose concentration the principal regulator of placental and fetal glucose supply.[25] Maternal glucose concentration tends to decrease slightly during the second half of gestation[26] as a result of the balance of two opposing forces: (1) it tends to decrease because of the increasing consumption of glucose by the growing placenta and fetus and (2) it tends to increase from the development of maternal insulin resistance and glucose intolerance caused by certain hormones (perhaps, for example, placental lactogen, progesterone, prolactin, estrogen, and glucocorticoids)[27] and certain competitive substrates (eg, fatty acids).[28] In women who develop overt diabetes mellitus with insulin resistance and glucose intolerance during late gestation, the insulin resistance appears to be the primary defect. Studies by Catalano and colleagues,[29] Shao and colleagues,[30] and Barbour and colleagues[31] indicate that the mechanism for this insulin resistance involves alterations in the insulin signal transduction cascade independent of hormonal influence, as well as potentially significant effects of placental growth hormone.

Placental Glucose Transporters Glucose uptake and transport by the placenta are mediated by facilitative transporter proteins. Both GLUT 1 (all species) and GLUT 3 (human, rat, and sheep) isoforms have been identified at both the maternal-facing microvillous trophoblast membrane and the fetal-facing basal trophoblast membrane,[32] although quantitative distribution has varied among studies and species.

GLUT 4 also has been found in the human placenta, but there is no evidence that insulin signal transduction activates its translocation or increases glucose uptake. One recent study, however, showed increased glucose uptake in perfused human placentas from insulin-treated diabetic women; the mechanism for such an effect is not known.[33] In another study, JAr placental cells showed stimulation of mitogenesis via the MAPK signaling pathway but did not show insulin stimulation of PI3-kinase-dependent protein kinase B activation sufficient to stimulate glucose transport or glycogen synthesis, highlighting the placenta as a nonclassic target organ of insulin regulation of glucose metabolism.[34]

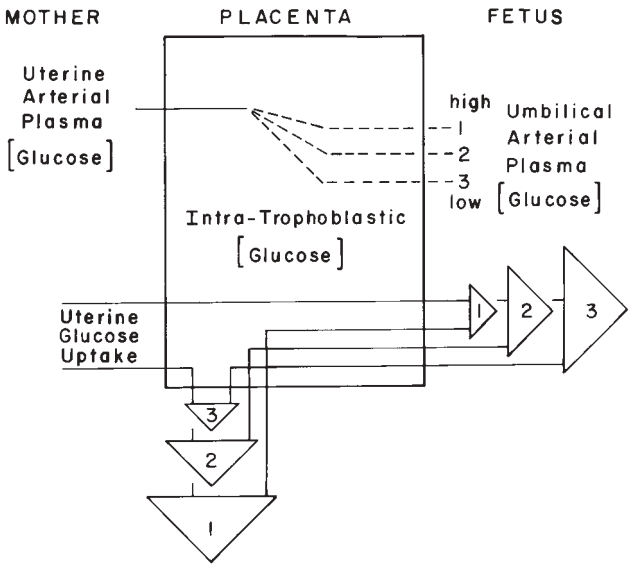

FIGURE 26-1 Schema of effects of fetal glucose concentration of placental glucose transfer to the fetus and uteroplacental glucose consumption, adapted from data in sheep. A decrease in fetal glucose concentration relative to maternal glucose concentration promotes maternal-to-fetal glucose transfer at the expense of uteroplacental glucose consumption. These findings demonstrate a reciprocal relationship between placental glucose transfer and uteroplacental glucose consumption that is determined by the fetal glucose concentration. Reproduced with permission from Hay WW.[2]

In the human placenta, GLUT 1 is the principal transporter at the maternal-facing microvillous membrane, whereas GLUT 3 occurs more on the fetal-facing basal membrane or localized in extravillous trophoblast and villous cytotrophoblast cells.[35] Hahn and colleagues found that hyperglycemia down-regulates the GLUT 1 glucose transport system in full-term placental trophoblast studied in vitro by down-regulating both GLUT 1 protein concentration and translocating membrane GLUT 1 protein to intracellular sites, where they would be less—or not at all—effective in mediating glucose.[36] In contrast, Illsely and others have suggested that hyperglycemia in diabetic pregnancies enhances fetal glucose-stimulated insulin and insulin-like growth factor (IGF)-I production, the latter acting to promote GLUT 1 at the fetal-facing basal trophoblast membrane, thereby maintaining an increased placental glucose transport capacity.[37–39] To date, however, there is no in vivo evidence for this mechanism, except for increased fetal-facing basal membrane GLUT 1 protein concentrations in placentas from diabetic pregnancies.

Hyperglycemia itself also can promote further hyperglycemia in pregnancy. For example, women with gestational diabetes mellitus release greater amounts of tumor necrosis factor α (TNF-α) from both the placenta and maternal adipose tissue in response to high glucose. TNF-α specifically interrupts the insulin signal transduction pathway leading to insulin resistance, glucose intolerance, and progression of hyperglycemia.[40,41] In other species, different patterns have been observed. For example, in sheep, chronic hyperglycemia was associated with reduced GLUT 1 and GLUT 3 concentrations and with increased glucose uptake by the uteroplacenta from the mother. There was no change in fetal glucose uptake, however.

In contrast, chronic hypoglycemia decreased placental GLUT 1 concentrations but did not appear to change placental GLUT 3 concentrations, although uterine, uteroplacental, and fetal glucose uptake rates were decreased.[42] Obviously, change in transporter expression can occur in response to changes in glycemia, particularly when the glycemic changes are chronic, but the impact of such changes in placental GLUT expression is not necessarily directly related to placental glucose transport to the fetus, which appears to exert independent control over its rate of glucose uptake.

Nutritional patterns during gestation also affect the expression of placental glucose transporters. In sheep, for example, early gestational nutrient restriction decreases placental size, but there is no change in placental weight-specific GLUT 1 transporter abundance. When such sheep were refed later in gestation, placental mass and GLUT 1 abundance both increased with sufficient feeding, but neither increased if the ewes were overfed.[43]

Nutrient restriction studies in the rat have shown no change in placental GLUT 1 expression but did show reduced GLUT 3 expression. However, there was no change in fetal glucose concentration.[44] An additional study compared rodent and ovine placental GLUT 1 responses to changes in glucose.[45] In rats, 6 days of sustained hyperglycemia caused no change in GLUT 1 protein levels, whereas 3 days of intrauterine growth retardation (IUGR) with fetal hypoglycemia and ischemic hypoxia decreased GLUT 1 levels by 50%. In pregnant sheep, maternal and fetal hyperglycemia caused an initial threefold increase in GLUT 1 with a persistent decline over the next 2 to 3 weeks, whereas maternal and fetal hypoglycemia led to a 30 to 50% decline in placental GLUT 1 levels. In a rat placental cell line, high glucose concentrations decreased GLUT 1 concentrations, which was counteracted in part by exposure to low oxygen concentrations.

Clearly, there is considerable need for more research into the regulation of placental glucose transporter expression and related placental glucose uptake, metabolism, and transport to the fetus because there are demonstrable differences among isoform specificity, time-dependency, and species.

The arrangement of glucose transporter proteins on both sides of the trophoblast allows bidirectional transport of glucose across both membranes, as well as across the whole placenta.[11] Thus, placental glucose transfer to the fetus is regulated by the combined effects of the concentrations of glucose in the maternal and fetal plasma and the kinetic function of the glucose transporter proteins at both the maternal- and fetal-facing trophoblast membranes.[46]

Transplacental Glucose Concentration Gradient Net transport of glucose from mother to fetus across the placenta requires a net maternal-fetal plasma glucose concentration gradient. In all species studied, including humans, the fetal plasma glucose concentration has been observed to be significantly lower than that measured in a simultaneously obtained blood sample from the mother.[47] In addition, a significant linear relationship has been observed

between the prevailing glucose concentration in the mother and that in the fetus.[11,48] This linear relationship between maternal and fetal glucose concentration covers the physiologic range of glycemia but experimentally has been seen during acute hyperglycemia induced by glucose infusion to the mother and during hypoglycemia induced by insulin infusion to the mother.[49]

Placental Glucose Consumption The transplacental glucose concentration gradient is produced by both placental and fetal glucose consumption. The contribution by the placenta is large because the placenta is a highly metabolically active organ; in pregnant sheep near term, for example, the placenta can consume almost twice as much glucose as does the fetus, even though the placental-to-fetal weight ratio is only about 1:10.[50] Thus, a large part of uterine glucose uptake is consumed by placental glucose metabolism, which contributes significantly to the physiologic hypoglycemia of the fetus and helps to establish the transplacental glucose concentration gradient; without placental glucose consumption, fetal arterial glucose concentration would more than double.[25] Glucose use in the placenta also contributes to glycogen formation via glycogenin.[35] There is no evidence, however, that this glycogen serves other than local purposes as the amount of glucose-6-phosphatase in the placenta appears insufficient to release enough glucose into the fetal circulation to account for any significant portion of fetal glucose use.[51]

Placental Glucose Transport Kinetics The relationship between the rate of placental glucose transfer to the fetus and the maternal-fetal plasma glucose concentration gradient is complex. Placental and fetal glucose consumption rates vary independently of each other. Furthermore, in vivo studies in sheep have shown that the glucose transporter proteins at both maternal and fetal placental membranes demonstrate saturation kinetics (Figure 26-2).[52–54] In these studies, glucose clamp experiments produced steady-state net fluxes of glucose into and across the placenta and into the fetus at different concentrations of glucose in the maternal and fetal circulations. Uptake and net consumption of glucose by the uteroplacenta demonstrated saturation kinetics with a V_{max} of about 0.23 mmol/min. K_m (maternal arterial glucose concentration at $V_{max}/2$) and K_s (maternal arterial glucose concentration at which V_{max} is reached) were 2.8 mmol/L and 8.0 mmol/L, respectively—not significantly different from the same parameters for uterine glucose uptake. Similar results have been measured in a variety of in vitro perfusion experiments in human placentas, although V_{max} in the human placentas studied in vitro is several-fold higher than under normoglycemic conditions.

Summary of Placental Glucose Uptake, Consumption, and Transport

Figure 26-3 summarizes the regulation and quantitative aspects of placental glucose uptake and transport. First, uterine, placental, and fetal glucose uptake are directly related to maternal glucose concentration (Figure 26-3A).[54] Second, fetal glucose uptake is separately regulated by fetal glucose concentration, by which a relatively lower glucose concentration in the fetus establishes a larger maternal-fetal glucose concentration gradient and thus increased transfer of glucose to the fetus (Figure 26-3B).[54] In contrast, at any

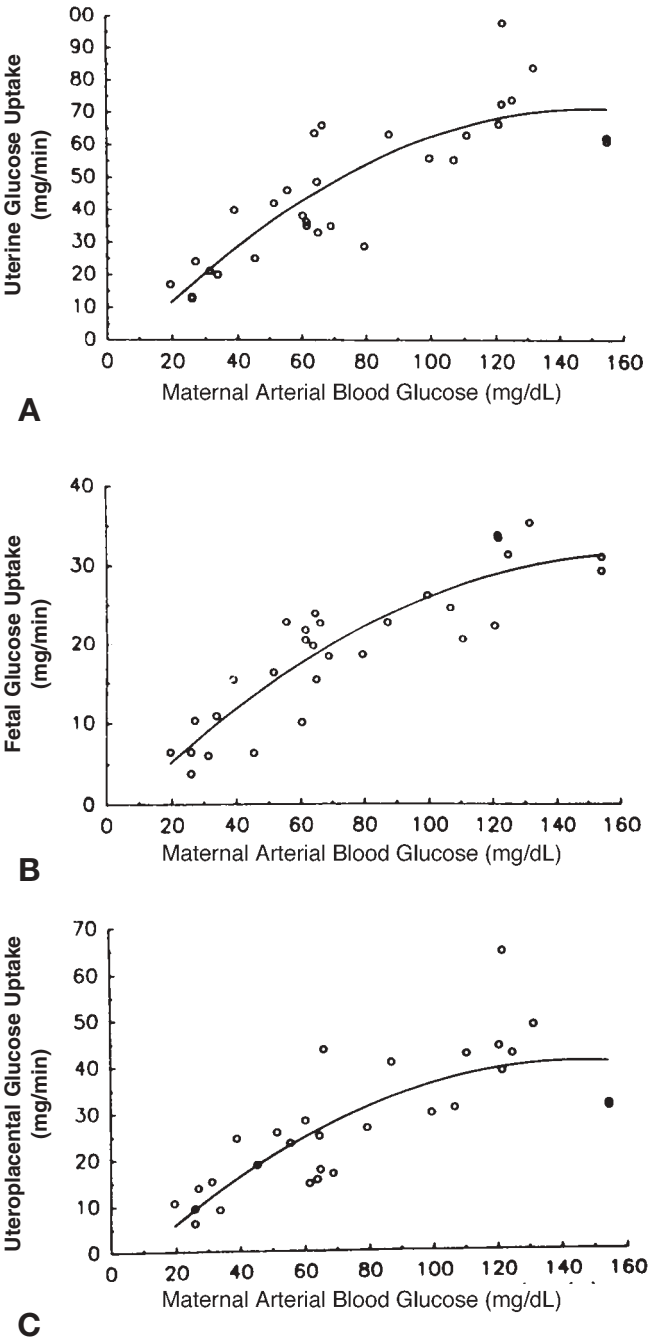

FIGURE 26-2 Relationship between maternal glucose concentration and the net uptake of glucose by the uterus, fetus, and uteroplacenta. Glucose was infused into pregnant sheep after an overnight fast to produce a large variety of maternal arterial blood glucose concentrations. Net glucose uptake rates by the uterus (*A*), fetus (*B*), and uteroplacenta (*C*) were quantified by the Fick principle. All three relationships show saturation kinetics with an approximate K_m value (a measure of the sensitivity of the transport processes to maternal glucose concentration) in the physiologic range of maternal glucose concentration (about 50 to 60 mg/dL [2.8 to 3.3 mM]). These results show that maternal glucose concentration determines the entry of glucose into the uterus, uteroplacenta, and fetus. Reproduced with permission from Hay WW and Wilkening RB.[54]

maternal glucose concentration, placental glucose consumption is directly related to fetal arterial plasma glucose concentration (Figure 26-3C).[46] In fact, the fetal side of the placenta has a capacity to take up glucose eightfold greater than that of the maternal side, so that changes in fetal glucose concentrations have a strong influence on placental glucose flux and metabolism.

Fetal Glucose Use

Kinetics of Glucose Use Placental glucose transfer to the fetus also is attributable to the saturation of the capacity for glucose use in the fetus. This capacity itself is variable as increased fetal glucose supply from the placenta and increased fetal plasma glucose concentration act to increase fetal insulin secretion. In turn, increased fetal insulin concentration augments fetal glucose use and plasma clearance, effectively limiting the increase in fetal glucose concentration as maternal glucose concentration and maternal-to-fetal glucose transfer increase.[16]

Effects of Plasma Glucose and Insulin on Glucose Metabolism The rate of fetal glucose metabolism (total use as well as the rate of fetal glucose oxidation) depends directly on the simultaneous interaction of fetal plasma glucose and insulin concentrations (Table 26-2). An example in near-term fetal sheep depicting the effect of glucose and insulin concentrations simultaneously on fetal glucose use, measured as the rate of glucose oxidation to CO_2, is shown in Figure 26-4.[55] Although both glucose and insulin act independently (ie, additively) to increase glucose use and oxidation in the fetus according to saturation kinetics, the relative proportion of glucose oxidized during short-term (3- to 4-hour) studies (about 55% in fetal sheep) does not change significantly over the entire range of glucose used.

Thus, the principal metabolic effect of insulin in the fetus is to increase the permeability of insulin-sensitive cells to glucose, enhancing glucose uptake and use in general, and oxidation of glucose in proportion to uptake and use, rather than differentially affecting intracellular pathways of glucose metabolism. This is true on balance for the whole fetus; individual tissues and metabolic pathways can vary significantly in their responsiveness to insulin. Such a permissive role for insulin in fetal sheep is different from that in adult humans, in whom higher rates of glucose use are partitioned more into glucose storage (fat and glycogen) than into oxidation. The same could be true in the human fetus, which, like the human adult, has the capacity to synthesize fat to a greater extent than does the leaner fetal sheep. In fetal sheep, the disposition of nonoxidized glucose-carbon is less certain. Recent studies, however, have demonstrated significant contributions of glucose-carbon to the formation of glycogen in the liver, heart, and lung, and a significant contribution to the carbon contained in amino acids and synthesized proteins (DiGiacomo, Carter, Battaglia, and Hay, unpublished data, 1990).

Glucose Transporters and Glucose Uptake and Metabolism Glucose is transported into cells in the fetus, just as in the newborn and adult, by a family of structurally related membrane-spanning glycoprotein transporters.[56–59] GLUT 1 is the predominant fetal glucose transporter isoform.[60–62] It is found in abundance in most fetal tissues.[60,62,63] In contrast, tissue-specific isoforms, such as the neuronal GLUT 3 in brain,[64] GLUT 2 in hepatocytes and pancreatic beta cells,[65] and GLUT 4 in insulin-responsive tissues such as skeletal muscle, heart, and adipose tissue,[66] are expressed in smaller amounts in fetal tissues than is GLUT 1.[64–66] Stud-

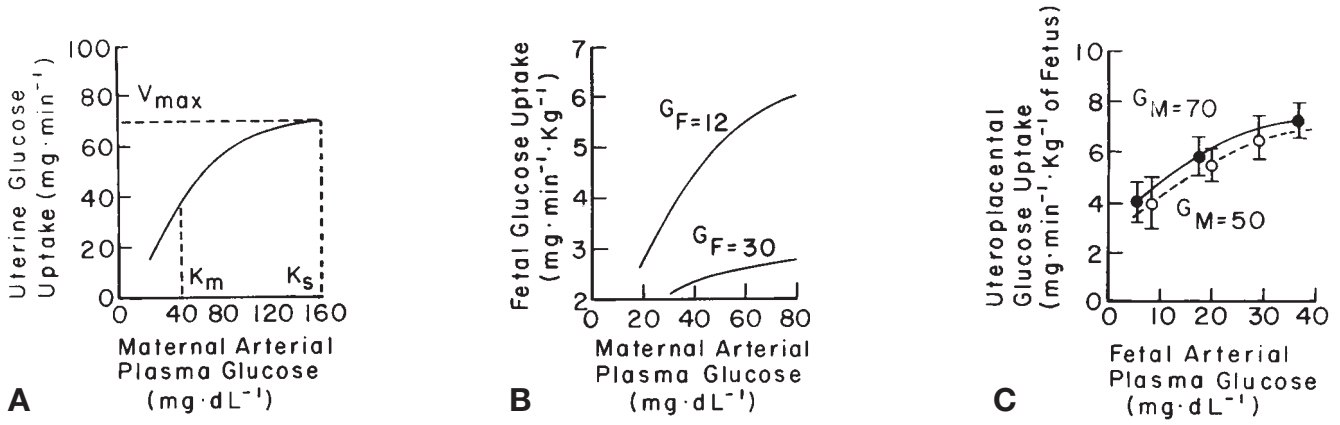

FIGURE 26-3 *A*, Net rate of glucose transfer into the uterus from the maternal plasma versus maternal plasma glucose concentration. V_{max} is the maximum rate at which glucose can enter the uterus; K_m is half of V_{max} and a measure of the sensitivity of uterine glucose uptake to maternal glucose concentration; K_s is the maternal glucose concentration at which V_{max} is reached. *B*, Net rate of glucose transfer into the fetus from uteroplacenta versus maternal plasma glucose concentration; a lower fetal glucose concentration relative to any maternal glucose concentration produces a greater maternal-fetal glucose concentration gradient and a higher rate of placental-to-fetal glucose transfer (upper curve versus lower curve). *C*, Net rate of uteroplacental glucose consumption versus fetal plasma glucose concentration; at any maternal glucose concentration (data for maternal glucose concentrations of 50 and 70 mg/dL are shown), uteroplacental glucose consumption is directly related to fetal glucose concentration. These data show that maternal glucose concentration determines the rate of glucose entry into the uterus (and thus the fetus and placenta), but the rate of uteroplacental glucose consumption is regulated by fetal glucose concentration. Adapted from Hay WW et al[46] and Hay WW and Meznarich HK.[54]

TABLE 26-2 What Glucose and Insulin Do in the Fetus

Glucose
Enters fetus from placenta according to transplacental, maternal-fetal plasma glucose concentration gradient
Enters fetal tissues (via glucose transporters) according to saturation-limited (Michaelis-Menten) kinetics, independent of and additive to that of insulin (in sheep)
Promotes its own oxidative and nonoxidative metabolism to equal extents in fetal sheep; perhaps more to nonoxidative fat deposition in humans
Increases fetal oxidation and oxygen consumption
Inhibits protein breakdown
Contributes most of the substrate for fetal glycogen formation
Increases insulin production and secretion
Maintains fetal growth
Insulin
Increases glucose uptake into insulin-sensitive (via GLUT 4 transporters) tissues according to saturation-limited (Michaelis-Menten) kinetics, independent of and additive to that of glucose (in sheep); perhaps more into adipose tissue in humans
Increases plasma glucose clearance
Produces hypoglycemia
Increases transplacental maternal-fetal glucose concentration gradient and thereby increases the transfer of glucose across placenta and into fetal plasma
Inhibits glucose production
Inhibits protein breakdown (most likely through increased glucose use)

ies in the fetal sheep have demonstrated time-dependent universal suppression of fetal peripheral tissue GLUT 1 and GLUT 4 concentrations by chronic hyperglycemia.[63] These observations in sheep mimic results obtained in the rat fetus exposed to a diabetic maternal environment.[67] Because the results varied in the rat depending on the timing and duration of exposure to hyperglycemia,[67,68] there obviously are independent effects of glucose and insulin on fetal glucose transporters, particularly GLUT 1.

Both acute and chronic changes in fetal glucose and insulin concentrations have been studied in fetal sheep to address the interrelationships among absolute changes in glucose and insulin concentrations, duration of change in glucose and insulin concentrations, expression of glucose transporter concentrations, and glucose use rates in the fetus. In chronic studies lasting 2 to 4 weeks in late gestation, sustained hyperglycemia was associated with a progressive decrease to normal or subnormal insulin concentrations.[69] Under these conditions, there was a transient increase in brain GLUT 1 but not in GLUT 3 concentrations and a progressive decline in liver and adipose tissue GLUT 1 and myocardial and skeletal muscle GLUT 1 and GLUT 4.[67]

Further studies showed that the chronic hyperglycemia and reduction in GLUT 4 correlated with the development of insulin resistance.[70] Chronic hypoglycemia (produced

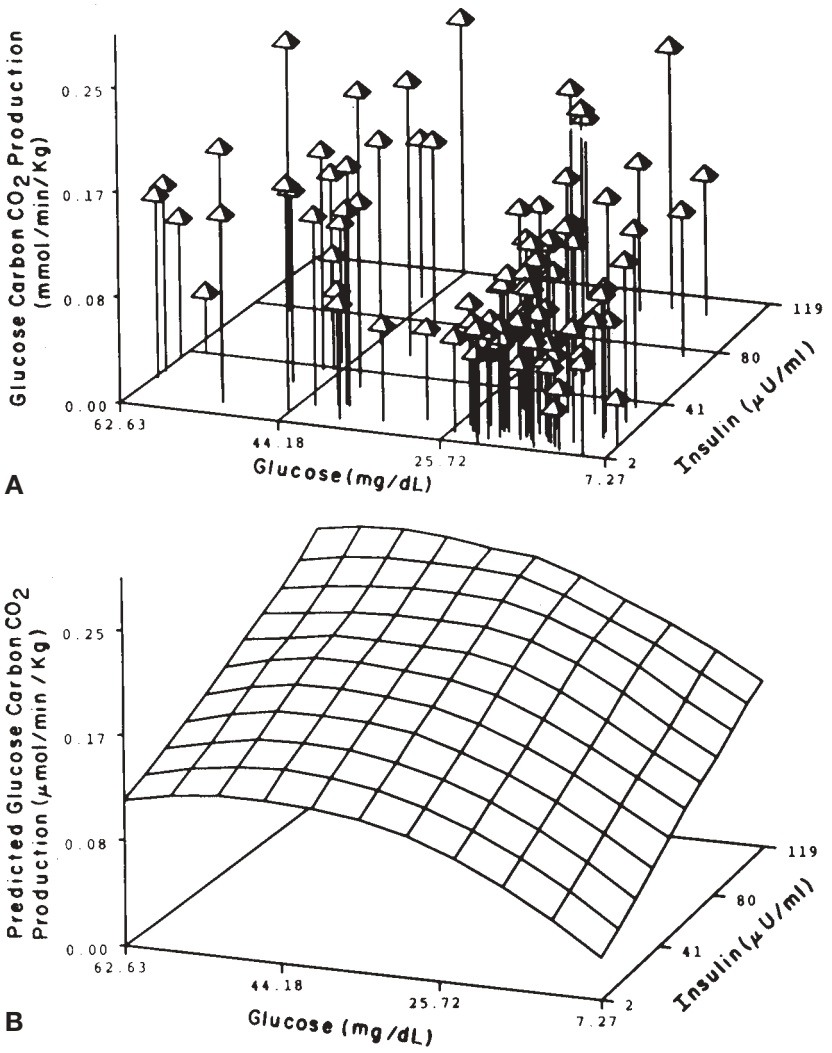

FIGURE 26-4 Data from fetal sheep showing the additive effects of plasma glucose and insulin concentrations on fetal glucose oxidation rate measured as CO_2 production rate. *A*, Three-dimensional plot of individual values of the rate of glucose oxidation to CO_2 at different concentrations of glucose and insulin. *B*, Predicted values of the rate of fetal glucose oxidation to CO_2 displayed as a three-dimensional glucose × insulin surface from the values in *A*. Reproduced with permission from Hay WW et al.[55]

by maternal insulin infusion) produced a decline in brain GLUT 3, an increase in brain GLUT 1, and a subsequent decline in liver GLUT 1 but no significant change in insulin-sensitive myocardium, skeletal muscle, or adipose tissue GLUT 1 or GLUT 4 concentrations.[67] These time-dependent and tissue- and isoform-specific changes in response to altered circulating glucose or insulin concentrations, or both, showed that cellular adaptations in GLUT 1 and GLUT 3 are geared toward protecting the fetus from perturbations in substrate availability, and the adaptations in GLUT 4 are geared toward development of insulin resistance.

In acute studies, expressions of GLUT 1, GLUT 3, and GLUT 4 were studied in response to 1, 2.5, and 24 hours of selective hyperglycemia or hyperinsulinemia.[71] Hyperglycemia initially increased the fetal glucose use rate associated with an increase in GLUT 1 and GLUT 3 isoforms, which mediate basal glucose use, but made no change in GLUT 4, which mediates insulin action. Fetal glucose use rates returned to normal values by the end of 24 hours. These results contrast with the tissue-specific effects of selective hyperinsulinemia, which produced a sustained increase in fetal glucose use rate associated with a sustained increase in hepatic GLUT 1 and a myocardial-specific emergence of mild insulin resistance associated with a down-regulation of GLUT 4. In skeletal muscle specifically, there was a lack of sustained temporal association between the increases in transporter proteins and glucose use rates.[72] This observation indicates that subcellular localization and activity of transporters or tissues other than skeletal muscle contribute to net fetal glucose use rate.

These observations support an immediate but transient cellular adaptation of augmented glucose uptake associated with a transient increase in GLUT 1 concentration in response to an acute hyperglycemic perturbation in the intrauterine milieu. In contrast, alterations in the hormonal milieu (specifically of insulin) did not demonstrate any acute effects on the mechanisms underlying insulin-induced cellular glucose transport, except for a sustained increase in hepatic GLUT 1 concentrations and an increase in skeletal muscle GLUT 4 concentrations. Whether chronic hyperinsulinemia in the presence of hyperglycemia or euglycemia leads to adaptations of fetal ovine glucose transporter proteins aimed at enhancing or limiting intracellular substrate delivery remains unknown, as do the mechanisms, such as GLUT gene transcription or translation and post-translational protein stability, that underlie both acute and chronic adaptation to changes in circulating glucose and insulin concentrations.

Basal Insulin Concentration The basal concentration of insulin in the fetus probably has a role in fetal glucose use, but direct evidence for this is not as convincing as the effect of hyperinsulinemia. For example, an acute decrease of fetal plasma insulin concentration with somatostatin infusion does not appear to affect fetal glucose concentration or glucose use.[39,73] In contrast, a chronic decrease of fetal plasma insulin concentration, either by pancreatectomy or streptozocin injection into the fetus, reduces fetal growth[17,74] and decreases umbilical glucose uptake in relation to fetal hyperglycemia. The hyperglycemia results from decreased peripheral tissue insulin sensitivity and glucose use and from the release of insulin's normal inhibition of hepatic glucose.

Interaction between Glucose and Alternative Carbon Substrates for Oxidative Metabolism With markedly reduced rates of glucose supply to the fetus, fetal glucose use rate decreases proportionally.[46,54] Under such short-term conditions, fetal oxygen consumption remains near normal,[55] indicating active reciprocal oxidation of other substrates, at least over the short term, such as glucose released from glycogen, lactate, amino acids, fatty acids, and keto acids. Over longer periods (more than 3 weeks) of reduced glucose supply, fetal oxygen consumption tends to decrease by 25 to 30%. Because the rate of fetal growth decreases at the same time and to the same extent as the decrease in oxygen consumption, the reduction in fetal oxygen consumption probably represents the oxidative requirements of the decreased protein synthetic activity.[74]

Glucose Use Rates Quantitative aspects of fetal glucose use have been studied in several large animal models. In most studies, fetal glucose use is about 5 mg/min/kg fetal weight near term, down from values nearly twice as high in midgestation,[75] when fetal growth and metabolic rate are as much as twice as great as they are closer to term. In humans, based on the increase in total maternal glucose production in late gestation, fetoplacental glucose use is estimated to be about 5 to 6 mg/min/kg fetal weight.[8] This rate is similar to that measured in normal full-term infants.[76] Table 26-3 presents estimated rates of glucose use in several fetal organs and the remaining carcass of fetal sheep in late gestation. The fraction of glucose oxidized versus that entering tissue accretion pathways in these organs has not been determined, and the factors that regulate glucose uptake in specific organs remain poorly studied. Most organs appear dependent on plasma glucose concentration for their specific rate of glucose uptake, and certain organs,

TABLE 26-3 Fetal Metabolic Rates That Account for Glucose Use*

	Glucose Use Rate (mg/min/kg fetus)	*Percent of Total*
Whole fetus (sheep, measured)	5.0	100
Whole fetus (human, estimated)	6.0–8.0	100
Brain (sheep, measured)	0.8	16
Brain (human, estimated)	4.0	50–67
Heart (sheep, measured)	0.65	13
Lungs (sheep, estimated)	0.1	2
Liver (sheep, measured)	0.1	2
Red blood cells (human, estimated)	0.1	2
Gut (sheep, estimated)		
Carcass/skeletal muscle (estimated, sheep)	3.25	65
Total of organs accounted for		
Sheep	5.0	100
Human	8.2	103–137

*Based on data in fetal sheep and estimates for human fetuses for brain.

such as skeletal muscle and probably the heart and liver, are insulin sensitive (at least in sheep studied in vivo).

Gestational Development of Placental Glucose Transport and Fetal Glucose Use The fetus grows severalfold in size over the second half of gestation and so does its absolute rate of glucose use. Placental glucose transfer to the fetus, therefore, must increase to meet the increasing metabolic requirements for glucose of the larger, growing fetus. The increase in placental glucose transport occurs for two reasons: (1) the transplacental glucose concentration gradient increases as the fetal glucose concentration decreases relative to maternal glucose concentration (Figure 26-5A), and (2) the placental transport capacity itself increases (Figure 26-5B).[75]

Placental glucose transport capacity develops primarily by an increase in the total amount,[77] rather than the affinity, of glucose transporters.[75] The number of glucose transporter proteins can increase via an increase in the trophoblast membrane surface area, an increase in the concentration of transporters per unit of membrane area, or both. Although there is some evidence from in vitro studies that glucose concentration can regulate placental glucose transporter expression, either directly or through IGF-I action,[78] GLUT 1 messenger ribonucleic acid (mRNA) can vary independently of GLUT 1 protein. For example, GLUT 1 protein decreases over gestation in rats, but it parallels GLUT 1 protein in sheep. There is no evidence, however, that such changes affect the actual rate or the capacity (maximal rate) of placental glucose transport. In fact, in vitro perfusion studies in human placentas and in vivo studies in humans and sheep indicate that placental glucose transport capacity is much greater than actual transport rates, indicating that small changes in placental glucose transporter content might have little or no effect on the rate of placental glucose transport.[53,54] By late gestation, however, glucose transport capacity by the placenta has a dominant role in the regulation of glucose transport to the fetus (Figure 26-5C).

Fetal glucose concentration can decrease relative to maternal glucose concentration over the second half of gestation for several reasons. First, fetal cellularity increases over this period, as does the fraction of body weight that consists of insulin-sensitive tissues (eg, skeletal muscle and adipose tissue).[79] Second, fetal insulin concentration increases, developmentally and in response to glucose and other secretagogues.[80] Third, insulin-sensitive GLUT 4 transporters on fetal skeletal muscle and adipose tissue cell membranes also increase over gestation, at least as a result of the increase in the relative body content of these insulin-sensitive tissues. The result is an increase in the effectiveness of insulin to promote fetal glucose use and glucose clearance, thereby reducing the relative fetal plasma glucose concentration. On balance, however, by late gestation, the increasing gradient of glucose concentration across the placenta contributes only limited control over placental transport of glucose to the fetus. The combination of these developmental processes and how they interact to promote net glucose transfer to the fetus by the placenta are summarized in Figure 26-6.[46]

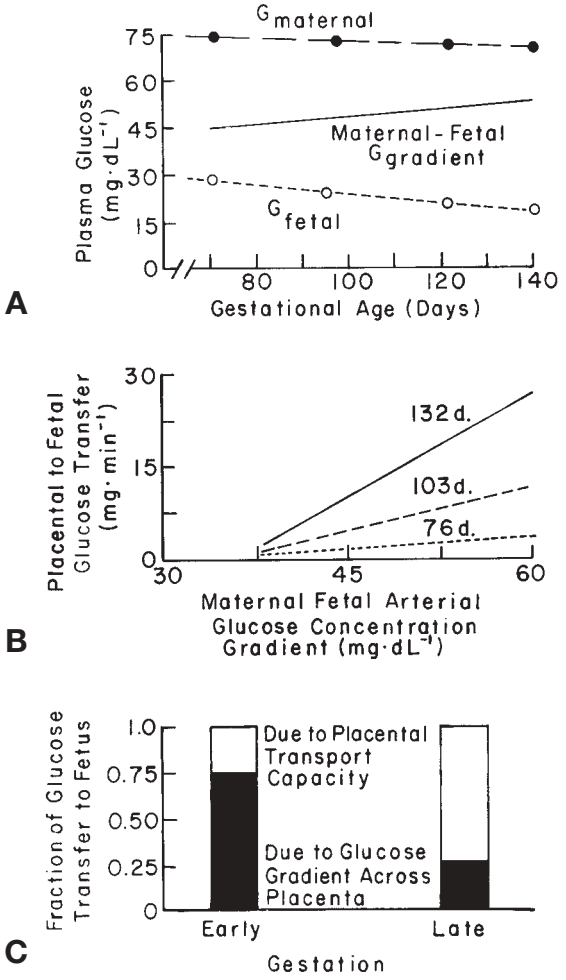

FIGURE 26-5 *A*, Plasma glucose concentration tends to decrease in fetal sheep (-○-) over the second half of gestation relative to maternal plasma glucose concentration (-●-). This increases the maternal-fetal plasma glucose concentration gradient or the driving force for transplacental glucose transfer (—). *B*, Placental-to-fetal glucose transfer (PGT) increases about eightfold over this same period. This increase in transport largely reflects transport capacity, shown by the increasing slope of PGT as gestational age increases. *C*, At midgestation, most of PGT is attributable to the maternal-fetal glucose concentration gradient, whereas by term, the placental transport capacity for glucose accounts for most of PGT. Adapted from Molina RD et al.[75]

Fetal Insulin Secretion

Many studies have addressed the onset and development of insulin secretion from the fetal pancreas. The fetal pancreas develops in the late first to early second trimester of pregnancy, producing measurable insulin concentrations by midgestation. As noted above, there is a gradual increase in basal insulin concentration and glucose- and arginine-induced insulin secretion toward term.[80] In the rat, very little insulin is secreted in the fetus,[81,82] whereas in the human fetus, which normally does not secrete much insulin,[49,83] sustained hyperglycemia in pregnant diabetics,[84] particularly when the hyperglycemia is pulsatile, produces considerable insulin.

Fetal sheep are somewhere in between, showing downregulation of glucose-induced and basal insulin secretion in the presence of chronic, sustained, marked hyper-

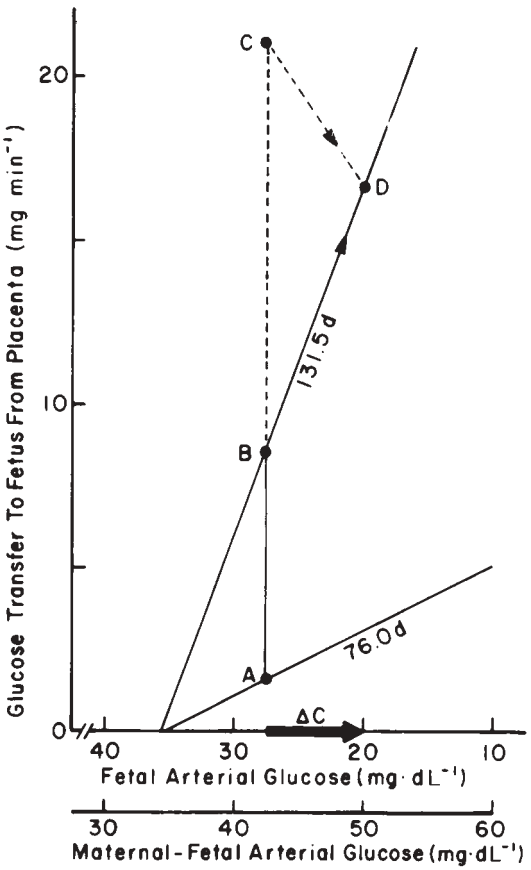

FIGURE 26-6 Graphic illustration of interrelationships among developmental changes in placental glucose transport capacity, fetal glucose demand, and fetal glucose concentration from mid- to late gestation in sheep. Placental glucose transfer capacity increases over gestation, shown by the increased slope of the 131.5-day gestational age line versus the slope of the midgestation, 76-day line, supplying more glucose to the fetus (A to B). Fetal growth demands more glucose, however, represented by point C. Additional glucose is provided by the simultaneous decrease in fetal glucose concentration relative to that of the mother, which increases the transplacental glucose concentration gradient (x-axis segment ΔC). Although fetal hypoglycemia increases fetal glucose uptake, it also tends to decrease disposal of glucose into fetal tissues from fetal plasma. These opposing forces combine to produce the actual glucose supply to the fetus at point D. Reproduced with permission from Hay WW et al.[46]

glycemia, as seen in rats,[68] but increased insulin secretion with pulsatile hyperglycemia, as seen in humans.[85] Hypoglycemia decreases basal and glucose-induced insulin secretion,[86] perhaps a fundamental aspect of how intrauterine growth retardation (IUGR) with fetal hypoglycemia decreases fetal pancreatic development and insulin secretion capacity. Clearly, fetal insulin secretion responds variably to changes in glucose concentration that are dependent on the absolute change in glucose concentration, its magnitude, and its pattern.

Alternate Carbohydrates Produced in the Placenta

The fetal glucose/oxygen metabolic quotient is less than 1.0,[5] which means that glucose does not (in fact, could not) account for all of the carbon necessary for the rate of fetal oxidation. Furthermore, tracer studies in fetal sheep have shown that the fraction of fetal glucose use that does produce CO_2 is only about 0.5 to 0.6.[38] Thus, there remains a need for carbon substrates other than glucose to meet the oxidative requirements imposed by the fetal respiratory rate (VO_2 or net rate of oxygen consumption), even if all of the glucose consumed by the fetus was oxidized. To meet at least part of the need for other carbon substrates, the placenta plays an important role by metabolizing glucose to lactate (in most or all species) and fructose (in ruminants).

Lactate and fructose are produced directly in relation to placental glucose supply.[87,88] Based on preliminary observations, approximately 50 to 70% of uteroplacental glucose consumption goes to lactate (at low and high values, respectively, of maternal and fetal glucose concentrations and the rate of placental glucose consumption), and 3 to 5% goes to fructose under the same conditions. Lactate produced in the placenta enters both maternal and fetal circulations at about equal rates under normal conditions,[87] whereas fructose produced in the placenta enters only the fetal circulation.[88] At normal rates of lactate and fructose uptake by the fetus and their oxidation fractions in fetal tissues measured in late-gestation sheep,[89] these two substrates could supply carbon sufficient to account for another 20 to 30% of the carbon requirements for fetal oxygen consumption above that provided by glucose. Amino acids and perhaps fatty acids and keto acids are the only other substrates available to make up the balance.

Adaptations to Changes in Glucose Supply

Hypoglycemia Short-term maternal hypoglycemia has been studied in late-gestation sheep.[90] As shown in Figure 26-7,[90] several days of fasting-induced hypoglycemia produce proportional reductions in glucose uptake by maternal nonuterine tissues, the fetus, and the uteroplacenta. Similar changes in glucose use by these tissues have been found with acute, insulin-induced hypoglycemia of several hours duration.[54] At the same time, however, the uteroplacental oxygen consumption rate does not change. Thus, even with hypoglycemic conditions, other substrates must substitute for glucose to maintain oxidative metabolism. Recent studies demonstrate that as glucose use by the placenta is decreased, so is uteroplacental production of lactate and fructose.[87,88] There is little or no change in placental use of free fatty acids, keto acids, or amino acids. Thus, uteroplacental oxygen consumption can be maintained by a balance in which a decreased supply of glucose to the fetus also results in decreased production of exported products of glucose metabolism, allowing glucose carbon to be used preferentially for oxidative metabolism.

This pattern is maintained with much longer periods of hypoglycemia, but two other adaptations develop under chronic conditions as well. First, fetal glucose production develops.[74] This increases the fetal glucose concentration relative to that of the mother and shifts the balance of glucose uptake by the uterus more to placental glucose consumption and less from glucose transfer to the fetus (see Figure 26-1). Fetal glucose production thus

serves two purposes: (1) the maintenance of fetal glucose metabolism and (2) the diversion of diminished glucose supply to the uterus into placental metabolism.[12] Fetal glucose production, therefore, maintains the glucose metabolic requirements of the fetus and placenta without further drain on the diminished availability of glucose in the mother; this could represent a simple "survival" adaptation (Table 26-4).

The second adaptation to chronic hypoglycemia in late gestation is a reduction in placental and fetal growth rates, resulting in lower fetal and placental weights.[74] Because placental glucose transfer capacity does not change at the same time, placental weight reduction, or failure to maintain weight, does not appear to include a reduction in placental membrane surface area or glucose transporter number or affinity. The advantage of a smaller placenta is not clear, but because the overall carbon balance in the placenta is maintained, it provides additional evidence that with chronic hypoglycemia and decreased placental glucose supply, placental glucose carbon is shunted to oxidative metabolism, that is, it is not shunted to nonoxidative processes such as the production of placental tissue and the production of normally exported products of placental glucose metabolism, such as lactate and fructose. It is interesting to speculate that all of these activities take place to substitute reduced rates of fetal and placental growth for reduced substrate supply, maintaining normal fetal and placental tissue-specific rates of metabolism and preserving their function and viability without further demands on maternal metabolism.

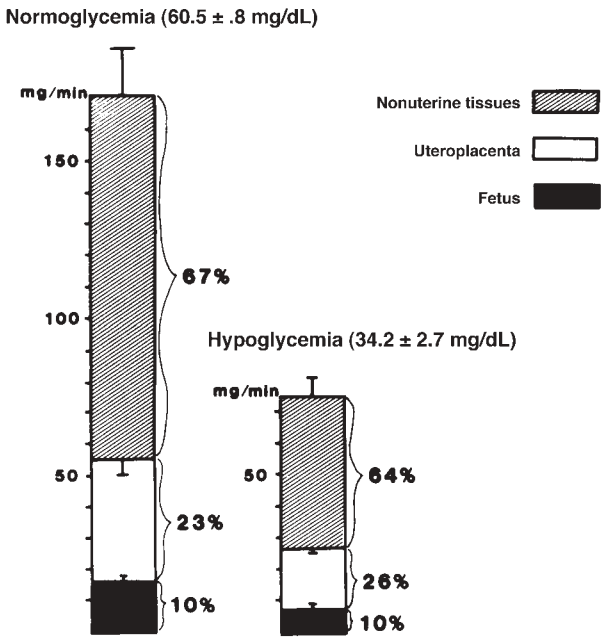

FIGURE 26-7 Fractional partition of maternal glucose production to nonuterine maternal tissues, uteroplacenta, and fetus in normoglycemic sheep (first column) and hypoglycemic sheep (second column), showing that in the short term there is no change in the relative proportions of glucose used by these three sets of tissues. Thus, fetal and placental glucose needs are dependent on the supply of glucose from the maternal plasma glucose pool; with maternal glucose deficiency, either the fetus must use its own sources of glucose (glycogenolysis or gluconeogenesis) or rely on other substrates, such as amino acids, for carbon balance. Reproduced with permission from Hay WW et al.[90]

TABLE 26-4 Fetal Responses to Decreased Glucose Supply and Hypoglycemia

Acute
Decreased glucose uptake
Decreased insulin production and secretion
Hypoinsulinemia
Decreased glucose use
Increase in rate of placental glucose transfer to fetus because fetal hypoglycemia tends to increase maternal-fetal glucose concentration gradient
Decreased placental lactate production
Decreased fetal lactate uptake and use
Substitution of other substrates to main oxidative metabolism
Chronic
Initial increase in fetal glucose production, then return toward normal condition of little or no fetal glucose production
Initial increase in amino acid oxidation, then return to normal rates
Decreased insulin sensitivity
Increased ratio of fetal to maternal glucose concentration
Increased ratio of placental glucose consumption to placental glucose transfer

Intrauterine Growth Retardation IUGR is a unique example of how fetal glucose metabolism and its regulatory mechanisms adapt to glucose deficiency and hypoglycemia to maintain normal fetal glucose metabolism. Regardless of the model (Table 26-5), when the fetus is deprived of glucose by placental insufficiency or maternal hypoglycemia, the fetal weight-specific glucose use rate is not very much different from the normal rate.[91]

This indicates that part of the mechanism to enhance glucose uptake by the fetus from the placenta is the production of further hypoglycemia, thereby increasing the maternal-fetal glucose concentration gradient. To do this, there must be an increase in the fetal tissue capacity for glucose uptake, use, or both. This could come about by increased concentrations, activity, or plasma membrane localization of glucose transporters; by increased insulin signal transduction and thereby increased effectiveness at promoting GLUT 4 (and perhaps GLUT 1) translocation to the cell membrane; or by mechanisms of insulin metabolism into oxidative and/or nonoxidative pathways. In both fetal sheep and fetal rats with IUGR, GLUT 1 and GLUT 4 concentrations in myocardium, adipose tissue, and skeletal muscle do not decrease with sustained hypoglycemia,[63,65,66] perhaps a positive adaptation to maintain glucose use despite hypoglycemia. It has not been determined if this maintenance of glucose transporter concentration is sufficient by itself to maintain glucose use at normal rates. More studies are necessary to sort out this fascinating and complex adaptation to glucose deficiency among the many tissues in the fetus.

Hyperglycemia Acute maternal hyperglycemia produces an increase in uteroplacental glucose uptake with saturation kinetics that parallel those of the fetus (Table 26-6). At the same time, uteroplacental oxygen consump-

TABLE 26-5 Fetal Weights, Glucose Concentrations, and Glucose Uptake Rates in Ovine Models of Intrauterine Growth Retardation

	Adolescent		*Heat-Stress*		*Caruncletomy*		*Hypoglycemia*	
	Control	*Study*	*Control*	*Study*	*Control*	*Study*	*Control*	*Study*
Fetal weight (g)	4,478	3,144**	3,112	1,645**	2,671	1,675**	3,500	2,700**
Fetal glucose (μmol/mL)	1.00	0.79****	1.17	0.74***	0.73	0.43***	1.14	0.67*
Fetal glucose uptake (μmol/min/kg)	34.9	30.0****	31.8	29.6	33.0	31.0	26.7	22.5*

Adapted from Wallace JM et al.[91]
Data are means. *P* values determined by unpaired Student's *t*-test comparing control with study animals within each model.
*$p < .05$; **$p < .01$; ***$p < .001$; ****$p < .06$.

tion rate does not change[54]; thus, increasing amounts of glucose consumed by the placenta are shunted into nonoxidative pathways. These include increased rates of lactate and fructose production, as well as increased use of glucose carbon for placental tissue, particularly glycogen.

With chronic hyperglycemia in the mother, produced by glucose infusion or experimental diabetes, similar patterns of glucose metabolism in the placenta have been observed. Fetal adaptations produce other changes as well. For example, in experimental animals, chronic fetal hyperglycemia in response to chronic maternal hyperglycemia eventually appears to down-regulate fetal pancreatic insulin secretion.[92] This involves the basal rate of insulin secretion and also appears to later involve the secretion of insulin in response to acute hyperglycemia.[93] As a result of the relative decrease in circulating insulin concentrations in the presence of hyperglycemia, fetal hyperglycemia is exaggerated, shifting the increased rate of uterine glucose uptake more into uteroplacental glucose consumption. Oxidative metabolism, measured as the uteroplacental rate of oxygen consumption, still does not change. Thus, uteroplacental glucose metabolism increasingly enters nonoxidative pathways.

The particular metabolic pathways of glucose carbon under these conditions have not been explored. Placental size is not dramatically increased, suggesting that export of placental glucose carbon into lactate and fructose and perhaps other products accounts for the balance of glucose carbon not used for oxidative metabolism. Of course, glucose carbon could substitute for the oxidation of carbon normally provided by other substrates, including keto acids and fatty acids, but principally the amino acids. Normally, the glucose oxidation fraction in the placenta of sheep in late gestation, corrected for lactate carbon and fructose carbon export, is still only about 50%. Thus, half of placental oxidative metabolism must be supplied by other substrates.

Some amino acids, such as leucine and serine, can be oxidized within the placenta directly as they are taken up from the maternal plasma and concentrated within the trophoblast cytosol. In contrast, glutamate is produced in the fetal liver from glutamine and then taken up by the placenta, where as much as 70 to 80% is oxidized.[94] It is certainly possible, therefore, that under hyperglycemic conditions, excess glucose carbon could substitute for carbon that is derived from amino acids, keto acids, and fatty acids under normoglycemic conditions. Thus, there are clear interrelationships among a variety of carbon substrates that can act as sources of carbon for placental oxidative metabolism, and placental glucose supply appears to regulate these interrelationships.

Summary of Placental and Fetal Glucose Metabolism

Acute and chronic adaptations to extreme changes in glucose supply to the placenta involve active and complex adjustments in the patterns of placental metabolism and growth. The one constant is placental oxidative metabolism, which, on a weight-specific basis, appears to be maintained in spite of major shifts in the relative supplies of substrate carbon and the rate of placental growth.

LIPIDS

Considerably less is known about placental lipid uptake, metabolism, and transfer to the fetus than is known for glucose, principally because most experimental animal models, especially sheep, demonstrate little capacity for lipid uptake, metabolism, and transport by the placenta. Also, lipid transport by the human placenta has not been

TABLE 26-6 Fetal Responses to Increased Glucose Supply and Hyperglycemia

Acute: Mild to Moderate
Increased glucose uptake
Increased insulin production and secretion
Hyperinsulinemia
Increased glucose use
Increased fetal oxygen consumption
Mild arterial hypoxemia
Respiratory acidosis
Increased placental lactate production
Increased fetal lactate uptake and use
Acute: Severe
Arterial hypoxemia
Hypoinsulinemia
Increased erythropoietin
Increased fetal oxygen consumption
Metabolic acidosis
Decreased placental perfusion
Fetal demise
Chronic
Decreased insulin secretion and/or synthesis
Decreased peripheral insulin sensitivity
Increased ratio of placental glucose consumption to placental glucose transfer

studied in vivo, and there is large variation in the data obtained from human placental tissue studied in vitro. Even so, the human placenta appears to have considerable capacity for lipid transfer. Transporters for specific fatty acids are primarily involved. More complex pathways include lipoprotein dissociation by placental lipoprotein lipase activity (although the exact cellular source of lipoprotein lipase in the placenta remains in question), triglyceride uptake and metabolism (including metabolic pathways of oxidation, chain lengthening, synthesis, and interconversion pathways), and release into the fetal plasma as free fatty acids or lipoproteins.[95]

Placental Lipid Uptake, Metabolism, and Transfer to the Fetus

Importance of Placental Lipid Metabolism to Fetal Lipid Supply The amount and type of fatty acids or complex lipids transported by the placenta vary among species; it is greatest in the hemochorial placenta of the human, guinea pig, and rabbit and least in the epitheliochorial placenta of the ruminant and the endotheliochorial placenta of the carnivores. Furthermore, it is interesting that fetal fat content at term varies among species reasonably directly with the lipid transport capacity of the placenta.[96] There are many lipid substances in the plasma that are transported across the placenta; they are essential for placental and fetal development even if they do not contribute to nutritional or energy metabolism. Also, brown fat is common to all fetuses; it is essential for postnatal thermogenesis even if the neonate is not "fat" with white adipose tissue. Furthermore, many lipid substances entering the fetus are qualitatively different from those taken up by the uterus and uteroplacenta, implying active placental metabolism of individual lipid substances. Placental lipid metabolism, therefore, is qualitatively and, in some cases, quantitatively important for fetal development and growth, even if the fetus does not get very fat.

Uptake, Synthesis, Metabolism, and Hydrolysis of Fatty Acids A schema of lipid uptake, metabolism, and transport in the human placenta is shown in Figure 26-8.[4,95] After entering the placenta, fatty acids can be used for triglyceride synthesis, cholesterol esterification, membrane biosynthesis, direct transfer to the fetus, or oxidation. The most important factor that regulates the flux of lipids into the placenta and into the various pathways of transport and metabolism is the concentration of maternal plasma lipids, including free fatty acids and triglycerides. For example, placental triglyceride content increases in women who are fasting, who deliver preterm infants, or who have diabetes mellitus—all conditions in which maternal plasma free fatty acid concentrations are increased.

Placental tissue from different species has been shown to express lipoprotein lipase activity as well as phospholipase A_2.[97–104] Maternal plasma triglycerides are hydrolyzed by these enzymes, and the fatty acids that are released are then taken up by the placenta. In the trophoblast cells, the fatty acids are then re-esterified and further hydrolyzed, facilitating their diffusion into fetal circulation. Cultured placental trophoblast cells have shown that esterified intracellular lipids provide a reservoir of fatty acids that can be released into the medium.[105]

All fatty acids cross lipid bilayers, such as those in the syncytiotrophoblast, by simple diffusion. Partition studies in pure phospholipid bilayers indicate that this diffusion is rapid, on the order of 20 to 30 milliseconds.[106] In addition, fatty acid transport across membranes is facilitated by fatty acid binding proteins (FABPs), which aid in intracellular channeling of fatty acids.[107–111] The main membrane-associated FABPs are the plasma membrane fatty acid binding protein (FABPpm) and the fatty acid transfer proteins (FAT/CD36 and FATP).[107] These transfer proteins have been found on both the maternal-facing microvillous and fetal-facing basal membranes of the placental trophoblast, whereas a placenta-specific protein, p-FABPpm, has been found exclusively on the microvillous membrane.[112] p-FABPpm has a unique amino acid composition that enhances the binding affinity and capacity of this protein for arachidonic acid and docosahexaenoic acid (DHA) compared with linoleic and oleic acids.[113–115] The syncytiotrophoblast also contains cytoplasmic binding proteins, which appear to act by removing fatty acids from the inner membrane and channeling them to their respective metabolic fates.[107,109,116]

Fatty acid transport into the fetal circulation is largely determined by the transplacental gradient of nonesterified fatty acids (NEFAs) relative to available circulating binding protein concentrations and the activity and availability of their binding sites. The concentration of NEFAs in the maternal plasma at term is about three times that in the fetal circulation, but the concentration of albumin, the primary carrier protein for NEFAs, is actually 10 to 20% higher in fetal than maternal circulation.[117] Thus, the ratio of plasma NEFAs to albumin on the fetal side of the placenta is about 25% of that on the maternal side at term.[118] The higher concentration of NEFAs relative to available binding sites on albumin, α-fetoprotein, and other lipoproteins in the maternal compared to the fetal plasma is reflected in the concentration of unbound NEFAs, which is greater in maternal (12 nM) than fetal (9 nM) circulation.[119] Human cordocentesis data from 18 to 36 weeks gestation indicate an exponential decrease in the concentration of NEFAs in the fetal circulation over this period,[120] presumably because of increasing use of fatty acids in the fetus for rapidly growing structures such as the brain and adipose tissue.

Although most fatty acids appear to be transported by diffusion and direct carrier-mediated mechanisms, some studies suggest that chain-altering metabolism in intratrophoblast peroxisomes could lead to a greater transfer of medium-chain fatty acids into the fetal circulation.[121] This might be advantageous to fetal lipid metabolism, which appears to be limited in its capacity for oxidation of long-chain fats, an apparent result of low cytosolic or mitochondrial carnitine concentrations or both.[122] Fatty acids also can be esterified to di- and triglycerides and to phospholipids. These can be stored transiently or for the long

term or hydrolyzed by phospholipases and acylglycerol lipases to release fatty acids into the fetal circulation.

Additional evidence for the hypothesis that transient placental esterification of fatty acids occurs during transport of fatty acids by the placenta comes from measurements of the activities of enzymes required for the isolation of glycerol-3-phosphate.[123] Such enzymes are located in the endoplasmic reticulum and have been identified in placental trophoblast cells. Although enzyme-specific activity and total enzyme content do not necessarily reflect metabolic flux, the presence of these enzymes indicates that fatty acid esterification followed by hydrolysis is a reasonable hypothetical pathway for placental lipid metabolism and transport.

Fatty Acid Synthesis Fatty acids also are synthesized in the placenta. Significant fatty acid synthesis has been measured in placental tissue and cultured trophoblast cells from human,[124] sheep,[125] and pig placentas.[126] Primarily long-chain fatty acids (oleic, palmitic, and palmitoleic acids) are formed.[105] Radiolabeled palmitate can be incorporated rapidly into triglycerides in human placental slices, and studies of human trophoblast cells in culture have shown that incubation with albumin-bound ^{14}C-oleate produces ^{14}C-labeled cellular triglycerides. Similar observations have been made in 21-day pregnant rats studied in vivo, showing incorporation of ^{14}C-palmitate into placental triglycerides and phospholipids.[127]

Lipoprotein Synthesis There is conflicting evidence regarding the synthesis of lipoproteins by placental tissue and their use for transport of fatty acids to the fetal circulation. By day 21 of gestation in the rat, the placenta appears to synthesize apoprotein B, which is normally an integral part of the major plasma lipoprotein carriers of triglycerides.[127] Such observations have not been made in the human placenta, which might secrete lipoproteins only during the early part of gestation, if at all.[128] Small amounts of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) have been identified in human amniotic fluid, but their source has not been determined.[105]

Cholesterol Metabolism and Transfer Low-density lipoprotein cholesterol is taken up by endocytosis into trophoblast cells and degraded by lysozymes.[129] LDL cholesterol appears to be the major precursor for placental production of progesterone and estrogen. High-density lipoprotein (HDL) cholesterol also contributes to placental progesterone production in cultured human trophoblast cells. Some of this cholesterol is transferred directly to the fetus, although the role of this transport is uncertain, given the large capacity and rate of cholesterol synthesis in the fetal liver.[130]

Nonessential Fetal Lipid Supply The bulk of placental lipid transport is dependent on maternal plasma fatty acid and lipid concentrations and maternal-fetal plasma fatty acid concentration gradients. In humans, concentrations of free fatty acids are higher in maternal blood than in fetal blood, and their concentrations are highly correlated. Under normal circumstances, the fetal-maternal ratio of free fatty acids is less than 0.5.[131] In humans, fetal patterns of essential fatty acids and structural lipids correlate directly with the fatty acid/lipid composition of the maternal plasma (and, indirectly, the maternal diet).[52] This direct correlation could be unique to humans because of the high lipid transport capacity of the human placenta. Sheep, for example, transport very little total lipid across the placenta, except for some long-chain essential fatty acids, and horses produce a lipid profile in fetal plasma that is qualitatively and quantitatively different from that in maternal plasma; this is perhaps the product of placental metabolism or different rates of transfer for different chain lengths of fatty acids.[132]

In fetal plasma, the fatty acids are bound to albumin and α-fetoprotein and transported to the liver, where they are synthesized into triglycerides and released into the fetal circulation. Because maternal triglyceride concentration determines the activity of placental lipoprotein lipase and

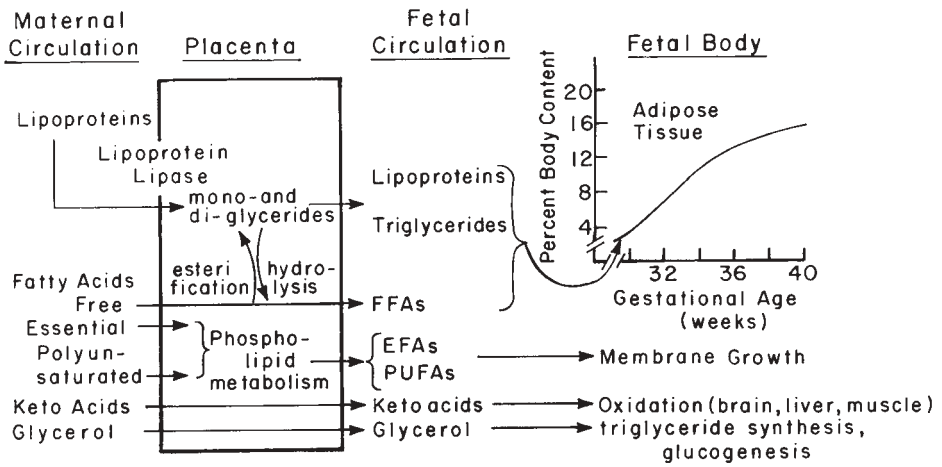

FIGURE 26-8 Schematic of placental-fetal interrelationships in humans for various aspects of placental lipid metabolism, fetal lipid uptake and metabolism, and fetal lipogenesis into adipose tissue. Adapted from Hay WW[4] and Coleman RA.[95]

fatty acid transport across the placenta is concentration dependent, there is a direct relationship between maternal and fetal plasma triglyceride concentrations, even though there is no direct uptake and transfer of intact triglycerides by the placenta.

The impact on the fetus of maternal plasma free fatty acid and lipid concentrations also is reflected in fetal lipid content and adipose tissue development. Fatter human fetuses develop in women who have higher plasma concentrations of fatty acids and other lipids. Experimentally, diabetic rats (induced by streptozocin) have increased free fatty acids, and their fetuses have carcass and hepatic lipid contents that are increased twofold above normal.[133] Similarly, rabbits fed oil-rich diets show increased neonatal adipose stores.[134]

In humans, umbilical venous–arterial fatty acid concentration differences in cord blood samples show that the net flux of free fatty acids into the fetus from the maternal circulation can account for the fetal requirement of fatty acids during the end stages of pregnancy.[135] In contrast, the perfused human placenta can transfer fatty acids at a rate that can account for only about 20% of what is required for the accumulation of fetal adipose tissue deposited during the third trimester.[72] Other estimates, based on fetal lipid accumulation as well as on in vitro transfer experiments, estimate that as much as 50% of fetal fatty acid requirements is transferred across the human placenta.[95] Similar estimates have been made in rats using the incorporation of ^3H from ^3H_2O into fatty acids, indicating that fatty acids are derived about equally from the mother and from fetal fatty acid synthesis.[137] Estimates in the rabbit[138] and the monkey[139] indicate that in these species, placental fatty acid transfer across the placenta could account for all fetal fat deposition in late gestation. Overall, therefore, it appears that there is a general relationship between the permeability of the placenta to lipids, especially fatty acids, and the adiposity of the fetus at term, with human fetuses developing the most fat (15 to 18% of body weight at term),[140] guinea pigs second at about 12%, and rabbits third at about 7% (Figure 26-9).

Availability of Essential Fatty Acids to the Fetus

Essential Fatty Acid Metabolism and Transfer by the Placenta The supply of essential fatty acids and long-chain polyunsaturated fatty acids (LCPUFAs) is critical and central to the synthesis of structural lipids and, hence, to normal development of the fetus. Linoleic acid (18:2 omega-6) and α-linolenic acid (18:3 omega-3) are the only fatty acids known to be essential for complete nutrition and must be supplied in the diet. All of the omega-6 and omega-3 fatty acid structures acquired by the fetus must, therefore, come from the mother via the placenta, either in the form of these two essential fatty acids or their LCPUFA derivatives, of which arachidonic acid (20:4 omega-6) and docosahexaenoic acid (22:6 omega-3) are metabolically the most important.[141]

Essential fatty acids are readily transferred to the fetal plasma in all species studied so far. Cultured trophoblast cells incubated with ^{14}C-acetate do not label arachidonic acid, however, and delta-5 and delta-6 desaturase activities in human placental microsomes are absent, at least early in gestation,[142,143] consistent with the absence of measurable conversion of γ-linolenic acid to arachidonic acid.[144] This emphasizes the requirement for direct transfer of the essential LCPUFAs to the fetus from the maternal plasma. In fact, higher concentrations of these essential fatty acids are found in the fetus than in the mother.[145–148] These results suggest that fetal arachidonic acid is either transferred directly from the mother or has a higher binding capacity in the fetal plasma but do not exclude the possibility that some might be synthesized from linoleic acid in the fetal liver.

Although formation of arachidonic acid and DHA from essential fatty acid precursors has been shown in term and preterm infants,[149–155] the degree to which the fetus is capable of fatty acid desaturation and elongation is not clear. Fetal baboons can synthesize both DHA and arachidonic acid from their precursors, α-linolenic acid and linoleic acid, respectively.[156,157] A low enzymatic activity of delta-5 desaturation has been proposed as one factor limiting arachidonic acid synthesis,[158] and although high delta-5 and delta-6 desaturase activities in the liver of one 18-week and two 22-week fetuses,[141] which were close to those found in adult liver,[159] have been reported, human fetal liver desaturase-elongase chain reactions have not been clearly demonstrated in physiologic conditions

Maternal Diet and Essential Fatty Acid Supply In general, reduced maternal essential fatty acid nutrition has been correlated with reduced neonatal growth and head circumference in humans.[160] Significant linear correlations between the mother and fetus or newborn have been found for both LCPUFAs and essential fatty acids in healthy women eating normal, unsupplemented diets.[161–163] Parallel increases in plasma DHA in the mothers and newborns also have been found after fish oil supplementation during pregnancy.[164,165] These observations show the importance of maternal dietary fatty acids to regulate the availability of

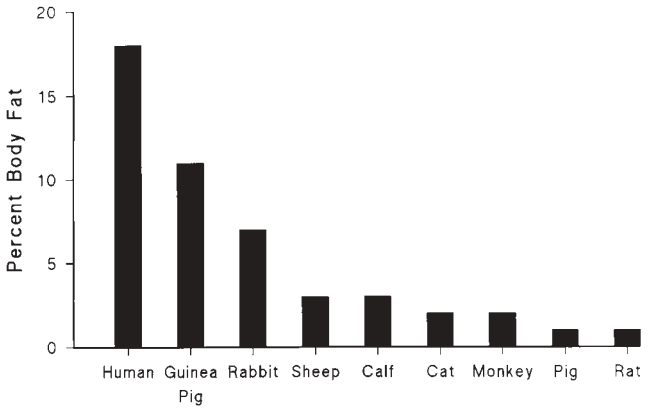

FIGURE 26-9 Fetal fat content at term as a percentage of fetal body weight among species. Adapted from Hay WW,[2] Hay WW,[4] Battaglia FC and Meschia G,[5] Sparks JW et al,[7] and Widdowson EM.[96]

LCPUFAs to the fetus and newborn. In fact, because the developing fetus depends primarily on the maternal supply of essential fatty acids, maternal dietary supplementation with LCPUFA-rich oils during the last trimester of pregnancy to increase levels in neonates has been advised.[164,165]

The competitive desaturation of the omega-3 and omega-6 series by delta-6 and delta-5 desaturases, however, is of major significance because of their controlling role in the desaturating and elongating pathways of the parent essential fatty acids.[166] Thus, excessive dietary intake of linolenic acid from vegetable oils, particularly safflower, sunflower, and corn oil, can inhibit delta-6 desaturase and decrease the formation of DHA from α-linolenic acid. Similarly, arachidonic acid formation is lower when excessive linolenic acid is provided, as seen in enterally or parenterally fed infants receiving corn or safflower oil as the predominant source of fatty acids.[167–170] Further, the inhibitory effect of eicosapentaenoic acid on delta-5 desaturase activity has been considered to be responsible for the lower plasma arachidonic acid found when fish oil, high in eicosapentaenoic acid and DHA, is consumed.[166] Also, excessive fish oil intake can inhibit intake of linolenic acid from vegetable oils, particularly safflower, sunflower, and corn oil; fish oils inhibit delta-6 desaturase activity and decrease arachidonic acid levels.[171,172] The consumption of fish oils modifies membrane phospholipid composition, increasing eicosapentaenoic acid and DHA concentrations at the expense of arachidonic acid content. Adverse effects of low arachidonic acid concentration in serum and red blood cell phospholipids on growth during infancy have been reported.[173–175]

Arachidonic acid status in preterm infants also has been correlated with birth weight.[173,176,177] Foods containing lipid peroxides are potentially toxic, and the higher the content of LCPUFAs in the diet, the more likely that peroxidation will occur.[178–180] Thus, excess intake of PUFAs could reduce antioxidant capacity,[181] enhancing susceptibility to oxidative damage,[182] a condition that has been shown to be responsible for fetal damage during pregnancy in rats.[183–185]

Dietary olive oil appears to protect the LCPUFA series better than fish oil does.[186] Olive oil also does not affect arachidonic acid concentrations[187–189] and is much more resistant to lipid peroxidation.[180,190,191] The effect on the fatty acid profile and vitamin E concentration in a diet supplemented with 10% fish oil versus the same amount of olive oil during pregnancy has been studied in rats. A decrease in both arachidonic acid and α-tocopherol concentrations, as well as delayed postnatal development, was found in the offspring of rats fed the fish oil–rich diet.[192] The study was extended to determine whether dietary supplementation with either vitamin E or γ-linolenic acid as a precursor of arachidonic acid could ameliorate these changes. Arachidonic acid concentrations and postnatal development indices, but not α-tocopherol concentrations, were improved when the fish-oil diet was supplemented with γ-linolenic acid.

In contrast, postnatal development indices were not improved when the fish oil–rich diet was supplemented with sufficient exogenous vitamin E to normalize α-tocopherol levels.[192] Thus, although feeding a fish oil–rich diet during pregnancy and lactation decreased both α-tocopherol and arachidonic acid concentrations, the latter deficiency rather than the former seemed to be responsible for delayed postnatal development of rat pups. In this same study, another group of pregnant and lactating rats fed the fish oil–rich diet received a supplement with arachidonic acid instead of γ-linolenic acid, and although both treatments restored brain phospholipid content and arachidonic acid content in the pups, improvements in growth rate and neurodevelopment indices were more efficient in the γ-linolenic acid group. The only difference between the two groups was the absence of linoleic acid in brain phospholipids when rats were supplemented with arachidonic acid, whereas it was present at a normal level in those supplemented with γ-linolenic acid.[192] These findings agree with previous findings in humans fed diets rich in arachidonic acid; the proportion of linolenic acid in plasma phospholipids decreased,[193] likely a consequence of replacing linolenic acid with arachidonic acid in tissues.[194]

These observations in humans and experimental animals emphasize the exquisite sensitivity of endogenous LCPUFA metabolism to changes in maternal dietary fatty acid composition during perinatal development and the quite remarkable consequences to fetal and neonatal development. Because the benefits and risks of modifying maternal fat intake in pregnancy and lactation are not yet completely established and the safety of high intakes of LCPUFAs during pregnancy is still unclear,[195–197] further studies are required before recommendations to increase LCPUFA intake in pregnancy can be made.

Placental Uptake, Metabolism, and Transfer of Essential Fatty Acids Maternal plasma essential fatty acids are the fetus's principal source of LCPUFAs.[117,143,147] Cellular uptake of free fatty acids occurs by facilitated transmembrane transport involving a FABPpm.[198–202] The preference for human placental transfer from the maternal to the fetal circulation has been reported to be DHA to α-linolenic to linoleic > oleic > arachidonic acid.[203] Arachidonic acid, however, has the highest accumulation of all of these fatty acids in the placenta.[203] Arachidonic acid uptake by placental syncytiotrophoblast membranes is highly dependent on adenosine triphosphate and sodium,[204] implying an active transport mechanism for this fatty acid. Selective LCPUFA placental transfer also is attributable to trophoblast cellular metabolism; for example, a certain proportion of arachidonic acid is converted to prostaglandins in the placenta.[143] Also, a selective incorporation of certain fatty acids into phospholipids has been found in the ovine placenta,[205] and selective placental trophoblast fatty acid oxidation[206] and lipid synthesis have been reported.[105,207,208]

Fetal Accumulation of Essential Fatty Acids Requirements for omega-6 and omega-3 fatty acids in the human fetus during the last trimester of fetal development and through the early weeks of life have been estimated to be 400 mg/kg/day and 50 mg/kg/day, respectively.[209,210] In tissues such as the brain, where lipids constitute about 50%

dry weight, almost half the total lipid content is composed of LCPUFAs.[211] Both arachidonic acid and DHA are readily incorporated into the structural lipids of the developing brain,[212] where, besides their role in maintaining membrane fluidity, permeability, and conformation, they play an important functional role. For example, once released from phospholipids by the action of phospholipase A_2, arachidonic acid is the main precursor for eicosanoids, prostaglandins, and leukotrienes[213] and is essential for fetal and neonatal growth[214]; DHA has a key role in the development of visual function.[145,215,216]

Although the relative rates of desaturation by rat liver and brain differ between adult and 10-day-old animals,[217] the degree to which the human fetus is capable of desaturation and elongation is not clear. It is normally believed that the supply of essential fatty acids and LCPUFAs is critical and central to the synthesis of structural lipids and hence to normal fetal development.[146,149,218]

Fetal Lipid Metabolism

Physiologic changes that develop in the fetus in late gestation and increase nutrient use, such as the increase in plasma insulin concentration, act to enhance net maternal-to-fetal fatty acid and lipid transport by increasing fatty acid use in the fetus (largely to develop adipose tissue, it appears). Increased use of fatty acids by fetal tissues lowers fetal plasma fatty acid concentrations relative to those in the maternal plasma and increases the maternal-to-fetal fatty acid concentration gradients. For example, human maternal venous blood concentrations of fatty acids are directly related to umbilical artery free fatty acid concentrations, and umbilical vein–artery differences in concentration of free fatty acids.[140]

Similar observations have been made in the rabbit[138] and the guinea pig,[219] including evidence in the latter that experimentally lowering the fetal fatty acid concentration relative to that in the maternal plasma independently increases fatty acid transfer across the placenta (using an in situ perfusion model). Even at the same concentrations, furthermore, naturally occurring or experimentally increased fetal plasma concentrations of albumin directly increase the transfer of fatty acids across the placenta; this observation is based on data from both in vitro perfused human placentas[220] and in situ perfused guinea pig placentas.[219] The effect of albumin seems to be one of simply providing increased esterification capacity in the fetal plasma to bind free fatty acids transferred directly across the placenta.

When the processes of fatty acid transfer to the fetus by the placenta and fatty acid incorporation into fetal tissues actually begin during gestation and whether or not they occur with simultaneous development of placental fatty acid transporters and placental lipid metabolic capacity remain to be determined, although human fetal fat accretion develops primarily in the third trimester.[7] During late gestation, maternal lipid metabolism changes to a catabolic state,[221] as shown by increased adipose tissue lipolysis and reduced uptake of circulating triglycerides.[222] The reduced uptake is the result of decreased adipose tissue lipoprotein lipase activity.[223]

There also is an overproduction of triglycerides by the liver and enhanced absorption of dietary lipids. Together, these changes in maternal lipid metabolism produce increasing concentrations of nearly all types of circulating plasma lipids as late gestation proceeds, including free fatty acids, glycerol, and triglyceride-rich VLDL and chylomicron particles. When the pregnant mother is well fed, plasma concentrations of keto acids (β-hydroxybutyrate and acetoacetate) are not increased, although during fasting, when concentrations of these substrates do increase, they also can contribute significantly to the supply of nutrient substrates to the uteroplacenta and fetus.

Fetal Leptin

Leptin mediates a multitude of biologic actions in the adult, including regulation of weight by controlling hypothalamic mechanisms involved in food intake[224] and regulation of insulin secretion,[225,226] insulin action to promote peripheral glucose use,[227,228] and metabolic rate.[229,230] Emerging evidence supports roles for leptin in the fetus as well, including enhancement of growth.[231] Umbilical cord leptin concentrations correlate with birth weight,[232,233] being higher in macrosomic infants of diabetic mothers[232] and lower in infants with IUGR,[233] indicating that the fetal metabolic and hormonal milieu independent of fetal fat content could regulate leptin synthesis and circulating concentrations. In fetal sheep, fetal white adipose tissue leptin mRNA amounts increase with fetal development and gestational age and with basal insulin concentrations.[234] Glucose infusions producing hyperglycemia and hyperinsulinemia and insulin infusions producing hyperinsulinemia alone also increased circulating leptin concentrations, showing that insulin itself can affect fetal leptin production, which thus could mediate at least some of insulin's influence on fetal growth.

Summary of Placental and Fetal Lipid Metabolism

The transport of fatty acids and other lipid substances across the placenta and the deposition of lipids in adipose tissue are late-gestation phenomena and are highly species-specific. The human hemochorial placenta transfers the most lipids and produces the fattest of all land mammals at birth. Essential fatty acid transport, however, occurs in all species and begins early in gestation, allowing membrane lipids, particularly those of neurons, to develop throughout gestation. At preterm birth, however, the human newborn is in a precarious balance with respect to lipid metabolism. Failure to provide sufficient nonprotein energy will lead to increased rates of lipolysis and fatty acid oxidation. This might or might not result in breakdown of membrane lipids for oxidation, but certainly it produces a metabolic situation in which essential fatty acids will be oxidized along with other fatty acids to produce necessary energy in preference to membrane deposition. This could lead to deleterious alteration in the amount and structure of critical membrane development in the brain, potentially leading to abnormal neurologic function and long-term outcome.[235]

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CHAPTER 27

AMINO ACID NUTRITION IN UTERO: PLACENTAL FUNCTION AND METABOLISM

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This chapter reviews placental function and metabolism as it relates to the issue of fetal amino acid nutrition. The review includes information available in human pregnancy, although, of necessity, most of the in vivo information has been collected in various animal species, and this, too, is reviewed. In all mammalian species, the 20 amino acids of the genetic code are required for net protein accretion. The rate of protein accretion, which varies among mammals, is based primarily on fetal growth rate. The nutritional supply of amino acids for growth is defined as the net umbilical uptake of amino acids, representing the net transfer from the placenta to the fetus, including backflux from the fetus to the placenta of essential and nonessential amino acids. In the ovine fetus, where these data are available, the quantity taken up by the fetus clearly exceeds requirements for growth[1–4] and is associated with a high rate of fetal amino acid oxidation. This review aims to detail aspects of fetal amino acid requirements, placental transport, and metabolism of amino acids and to highlight factors influencing these processes, such as fetal growth restriction (FGR). In addition, umbilical uptake, interorgan cycling, and fetal and placental amino acid use, including specifically fetal hepatic and hindlimb amino acid metabolism, are discussed. In conclusion, this chapter deals with the neonatal implications of fetal amino acid metabolism.

PLACENTAL DELIVERY OF FETAL AMINO ACID REQUIREMENTS

The primary source of nitrogen for the growing mammalian fetus is the circulating maternal free amino acid pool. In considering the primary role of the placenta in the delivery of amino acids to the fetus, it is important to consider the multiplicity of factors that may affect these overall delivery rates. Figure 27-1 presents in diagrammatic form the potential fate of an amino acid that has been transported across the plasma membrane of the microvillous maternal surface into the trophoblast cytosol, prior to its entry into the fetal circulation through the basal membrane. Pathway 1 represents the direct transplacental flux of an amino acid from the maternal circulation across the plasma membranes on the maternal and fetal surfaces of the trophoblast and into the fetal circulation. Pathway 2 represents the delivery of an amino acid that has entered the intracellular pool via protein turnover within the trophoblast. Pathway 3 represents the backflux from the fetal circulation into the trophoblast of the same amino acid, and pathway 4 refers to the transformation of the amino acid to a metabolite, which can then enter the fetal circulation. The latter example would be the transamination of leucine to ketoisocaproic acid, which can then be delivered to the fetus. The algebraic sum of these fluxes represents the net umbilical uptake, which is the nutritionally important measurement because it represents the net supply of the amino acid delivered to the fetus. The relative importance of each of the pathways in determining the umbilical uptake differs among amino acids. Examples of amino acids that are used extensively within the placenta (such as glutamate) or are synthesized at a relatively high rate within the placenta (such as glycine) are described in the following sections. There is already ample evidence to show that for different amino acids, one or another of these pathways may predominate.

It is becoming apparent that the fetus not only accrues nitrogen in the new tissues formed during growth but also extensively metabolizes its nitrogen source by synthesizing, oxidizing, and transaminating amino acids.[5] The current estimate of ovine fetal uptake of nitrogen is approximately 0.9 g/kg/day, which is approximately equal to the estimated fetal nitrogen requirement.[4] Therefore, the quantity of amino acids transported is sufficient to meet the current estimation of fetal nitrogen requirements. This estimation includes the fate of amino acids metabolized and excreted as ammonia or urea from the fetoplacental unit.[3,6–8] Other potential sources of nitrogen, such as intact proteins or peptides, which may be important in embryogenesis, do not appear to be required to meet fetal nitrogen needs.

Estimations of fetal protein synthetic rates have been performed in fetal sheep using a variety of methodolo-

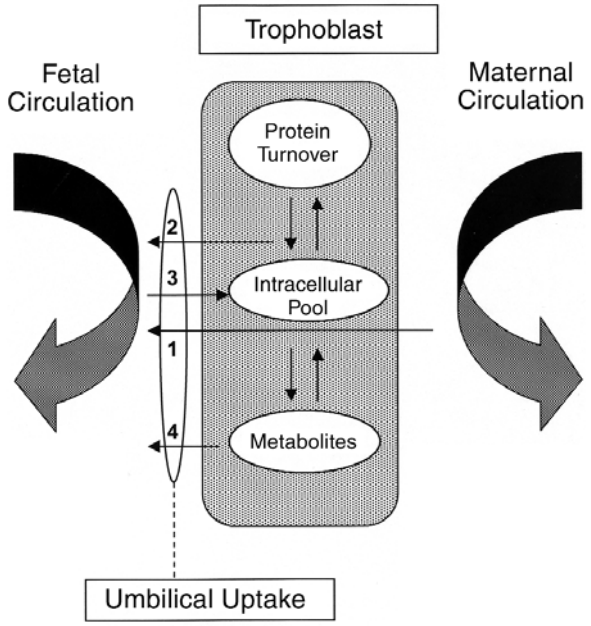

FIGURE 27-1 A diagrammatic representation of potential pathways for the delivery of an amino acid into the fetal circulation. See text for full description of pathways.

gies.[9–14] Leucine was used as a tracer amino acid in chronically catheterized fetal sheep to assess protein synthetic rates at different gestational ages.[9,14] These studies demonstrated that the absolute fractional protein synthetic rate (K_s) decreased from midgestation to term and that this decrease was greater than that seen in the fractional protein accretion rate. Figure 27-2 demonstrates the inverse relationship noted between the fetal K_s and fetal age. Therefore, protein breakdown, defined as the difference between protein accretion and synthesis, also appears to decrease in late gestation. The higher protein synthetic rate of the midgestation fetus is proportional to the higher metabolic rate at that stage of gestation. Absolute fractional protein synthetic rate declines at a rate similar to fetal O_2 consumption (VO_2), giving a relatively constant ratio of K_s/VO_2.[9] Thus, protein synthesis per millimole of oxygen consumed is quite constant from midgestation until term.[9] Fetal metabolic studies have advanced our conceptual framework of the key factors that alter metabolic rate per kilogram of body weight during development.[9,10,15–18] Because many metabolic variables, such as protein synthetic rate, lactate use rate, and urea production rate, bear a relationship to metabolic rate, studies of the ontogenetic changes in fetal metabolic rate have helped to clarify the developmental changes in metabolic measurements such as protein synthetic rate.[15,17,19]

PLACENTAL AMINO ACID TRANSPORT

In recent years, both in vivo and in vitro studies have brought out the complexity of the placenta as an organ for amino acid transport and metabolism.[2,4,20–35] It is important to emphasize that unlike an organ such as the liver, the placenta must function as an organ of transport, delivering amino acids from the maternal circulation into the fetal circulation. The complexity of the organ stems not only from the different cell types required to effect such net transport but also from the capacity of the placenta to metabolize or synthesize various amino acids. The human placenta has at least two cell types that are critically important in determining its overall transport characteristics: the trophoblast and the endothelium. In other species, additional cell layers may be present; for example, in the epitheliochorial placenta of sheep and goats, there is an endometrial cell layer as well.

The concentration of most amino acids, including some of the essentials, is higher in fetal than in maternal plasma,[2,4,36] consistent with a process of active transport of amino acids across the placenta. An increased fetomaternal ratio of plasma amino acid concentrations has been documented for humans,[37,38] primates,[39] rats,[40] guinea pigs,[41–43] sheep,[1,2,4,22] and cows.[44] Although the fetomaternal concentration ratio is greater than 1.0 for most amino acids measured, there are quantitative differences among species. For example, the fetomaternal ratio in human whole blood for the cationic amino acids lysine and histidine is consistently greater than 1.0, whereas in the sheep, the ratio is less than 1.0.

This concept of active transport has been corroborated by a variety of experiments. Studies of placental tissue cultured in vitro with nonmetabolizable amino acid analogues, for example, α-aminoisobutyrate (AIB), as well as other amino acids, have shown the concentration of those substances intracellularly to be a level several times greater than extracellular maternal concentration.[45–51] Placental tissues have also been found to have extremely high levels

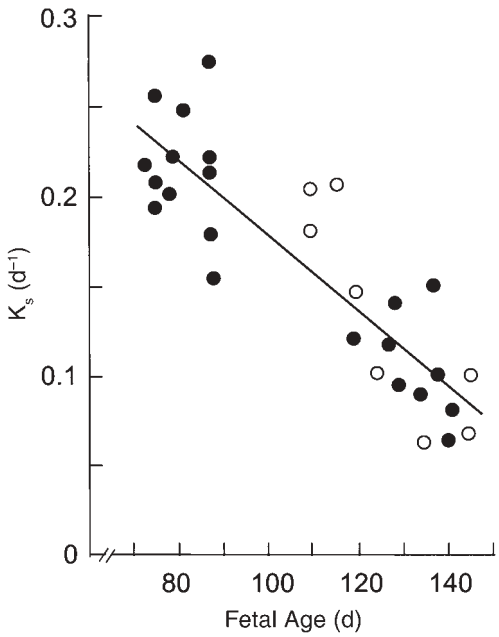

FIGURE 27-2 In chronically catheterized fetal sheep, the protein synthetic rate (K_s) was noted to decrease with fetal age. Protein synthetic rates were determined using [1-^{13}C]-leucine (*dots*) and [U-^{14}C]-lysine (*open circles*). Regression line (r = –.87) was drawn according to the equation: y = 0.39 – 0.02Ix. Adapted from Kennaugh JM et al.[9]

of the amino acids taurine, glutamate, and aspartate, as well as moderately high levels of alanine, glycine, serine, glutamine, and threonine,[38] when compared with maternal or fetal concentrations. It should be emphasized that measurements of placental tissue amino acid concentrations have not been corrected for extracellular fluid content of the tissue. Therefore, the intracellular tissue concentrations are likely to be considerably higher than the values in the literature.

The uptake of amino acids occurs through active transport, and mammalian transport systems have been characterized over the years by such general properties as ion dependence, kinetics, substrate specificity, and regulation of activity, and this has allowed the description of multiple transport systems for neutral, anionic, and cationic amino acids.[52,53] Studies in human and rat trophoblasts have yielded much information concerning the location and functioning of amino acid systems; however, care must be taken in the interpretation of data from different species. Figure 27-3 represents a summary of amino acid transport systems described for the maternal and basal membranes of the trophoblast. Each system is distinct but exhibits some overlapping substrate specificity.

System A is a sodium-dependent, unidirectional transporter with a characteristic affinity for *N*-methylated substances, and system A activity has been demonstrated in both microvillous and basal membranes.[54–56] Its activity is increased as an adaptation to cellular depletion of amino acid substrates, similar to that described for system X_{AG}^-.[57,58] System ASC has been described for neutral amino acid transport, specifically alanine, serine, and cysteine, as well as for some anionic amino acids.[54,55,59,60] It is a sodium-dependent obligate exchanger localized at the basal membrane, although studies using BeWo cells suggest that system ASC transporters may be present on the microvillous membranes as well, but after differentiation and syncytial formation, such activity is lost.[61] A sodium-independent group of transporters (Asc) has also now been reported to exist in placental tissue.[62,63] In addition, the broad-scope sodium-dependent transporter B^o is responsible for neutral amino acid transport, including branched-chain amino acids (BCAAs), and has been localized to the microvillous and basal membranes.[64–67] The β-amino acid taurine uses the system β transport system. Studies have demonstrated that this β transport system is a sodium-dependent transporter, found on both membranes,[68–73] although with a greatly reduced basal membrane activity compared with the microvillous membrane.[71]

System L (or l) transporters are sodium independent and have been localized to both trophoblast membranes.[54,74,75] They play a major role in the transport of essential amino acids, having a high affinity for leucine and

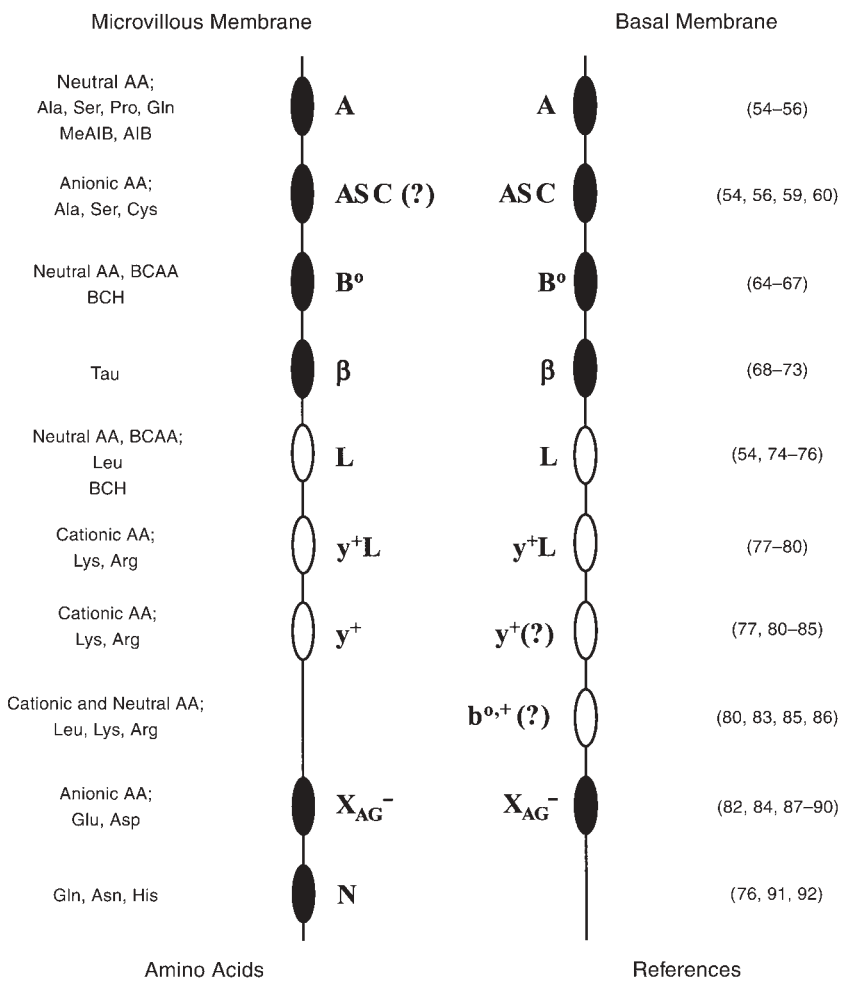

FIGURE 27-3 Schematic representation of the sodium-dependent (*closed ovals*) and sodium-independent (*open ovals*) amino acid transport systems for both the microvillous (maternal) and basal (fetal) membranes of the trophoblast. Amino acid substrates are listed on the left and references on the right. AA = amino acid; AIB = α-aminoisobutyric acid; BCAA = branched-chain amino acid; BCH = 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid; MeAIB = methylaminoisobutyric acid.

other BCAAs.[76] The cationic amino acid transport system y^+L is considered a low-capacity, high-affinity system that exchanges cationic amino acids for neutral amino acids, and its activity is localized to both the microvillous membrane and the basal membrane.[77–80] A proposed hypothesis is that this transporter system in the basal membrane is the major supply route of cationic amino acids to the fetus through the uptake of neutral amino acids from fetal circulation, in exchange for cationic amino acids from the placenta.[80] The sodium-independent low-affinity, high-capacity y^+ transport system is a high-capacity system that transports cationic amino acids such as arginine, lysine, and ornithine in a sodium-independent manner. It is considered to be the major cationic transport system in placental tissues[80–82] and is localized to the microvillous membrane[77,80,83,84] and possibly to the basal membranes.[85] A role for the related $b^{o,+}$ system in placental tissues has been reported[83,85,86]; however, further vesicle studies suggest that there is no functional evidence for this system in either term microvillous or basal membrane.[80]

The placenta takes up the anionic amino acids glutamate and aspartate from the maternal and fetal circulations but does not actively transfer these amino acids from mother to fetus. Recent studies using isolated human and rat placental membrane vesicles have revealed the presence of a high-affinity transport system for aspartate and glutamate via the sodium-dependent X_{AG}^- system within both the microvillous and the basal plasma membranes.[82,84,87–90] This system may mediate the concentrative uptake of anionic amino acids from the maternal and fetal circulations into the placenta. System N transports neutral amino acids but differs from systems A and ASC in that it displays a preference for amino acids containing nitrogen-bearing side chains, transporting only glutamine, asparagine, and histidine.[76,91,92]

PLACENTAL AMINO ACID TRANSPORTER PROTEINS

Historically, placental amino acid transport has been described in terms of transport systems based on competitive inhibition studies, although it is now becoming possible to move to a more precise description of the protein chemistry of the transporter system. The ability to clone, sequence, and study the expression of transporters has led to an explosion of data concerning the molecular basis of amino acid transport systems and their potential in vivo function.[93–95] It is now clear that some placental transporters exist as a monomeric protein, whereas other transport systems exist as a heterodimeric complex.[94,96,97] Those monomeric transport systems induce amino acid uptake in a similar manner to the amino acid uptake associated with permeases described in microorganisms,[98–101] although the regulation of placental membrane acquisition of monomeric systems has not yet been studied. Heterodimeric systems involve the grouping together of two proteins to facilitate amino acid transport. In placental tissues, monomeric transport systems are believed to include y^+[102] and most likely the X_{AG}^- system, whereas heterodimeric transport systems include system L, y^+L,[103] and the Asc system.[63,104] Those systems that operate in a heterodimeric manner are generally made up of a common heavy chain, specifically one of the type II membrane glycoproteins, 4F2hc (comparable to the CD98 surface antigen CD98hc),[105–107] the neutral and basic amino acid transport (NBAT; equivalent to rBAT or D2[108–111]) protein, or as yet undefined proteins,[62] which associate with one of a variety of light-chain transport proteins, providing a range of amino acid transport systems.[97,103,104,106,112] There is also evidence that these heavy chains may interact with themselves and each other to form homodimers and/or heterodimers before interacting with a specific light chain to induce activity.[80] A summary of the traditional transport systems and their heavy- and light-chain associations that have been reported in placental tissues and membranes is presented in Table 27-1.

The 4F2hc messenger ribonucleic acid (mRNA) is ubiquitously expressed,[113] although whereas 4F2hc is expressed in placental tissues throughout pregnancy, NBAT expression appears only in first- and early second-trimester placentae and is not in term tissues.[80,114,115] During human and rat pregnancy, whole-tissue studies have demonstrated 4F2hc predominantly in the microvillous membrane, with the content increasing as gestation advances.[80,107,115] However, 4F2hc has not been detected in the human basal membrane,[80,107] despite reports of 4F2hc mRNA in rat basal membrane preparations[115] and evidence that 4F2hc plays a role in basal membrane amino acid transport in other tissues, including the intestine and kidney.[111]

The glycosylated 4F2hc protein is composed of a single transmembrane region with a large C-terminal extracellular domain.[106,116,117] Because mammalian substrate transporters appear to have multiple transmembrane helices, it is unlikely that the 4F2hc protein is capable of inducing amino acid transport alone.[118] It is postulated that 4F2hc is, in fact, the modulator of heterodimeric transport systems and acts as a "guidance molecule," translocating the nonglycosylated light chains to the plasma membrane, after which disulfide linkage between 4F2hc and the light chain occurs.[97,119–121] This movement is independent of the formation of the disulfide bonds, which suggests a noncovalent steric association.[121] Functional transport may then occur as both heavy- and light-chain expression and interaction are required for transporter function.[97,114,122] The expression of the heavy chain and not that of the light chains is best correlated with placental amino acid transport system activity.[102,106]

Neutral Amino Acid Transporter Light-Chain Proteins

The subcellular location of the light-chain proteins and their interaction with 4F2hc protein is not well defined. Presently, the model of interaction involves an intracellular pool of light chains that are available for incorporation with the membrane-bound heavy chain.[102,106] Several specific light chains and their amino acid transport systems have been identified. Currently, three subtypes of the amino acid system A have been cloned: amino acid transporter (AT) A-1, ATA-2, and ATA-3. The ATA-1 (or GlnT[123,124]) system has

TABLE 27-1 Placental Transport Systems and Associated Light Side Chains

Transporter System	*Amino Acid Transporter Type*	*System Interaction*	*Heavy Chain Protein*	*Light Chain Protein*	*Reference*
A	Neutral Sodium dependent	Unknown		ATA1 ATA2	123 125
ASC	Neutral Sodium dependent	Unknown		ASCT1	129
B^o	Neutral Sodium dependent	Unknown (?)	rBAT(?)	ATB^o	65, 131
β	Neutral Sodium dependent	Unknown		TAUT	135
Asc	Neutral Sodium independent	Heterodimeric Unknown	4F2hc	Asc1 Asc2	62, 63
L	Neutral Sodium independent	Heterodimeric	4F2hc	LAT1 LAT2	107, 137, 139 104, 138, 140
y^+L	Cationic Sodium independent	Heterodimeric	4F2hc	y^+LAT1 y^+LAT2	103, 112
y^+	Cationic Sodium independent	Monomeric		CAT1, CAT2B, and CAT4	80–82
X_{AG}^-	Anionic	Unknown (?)		EAAT1, EAAT2, and EAAT3	89, 90, 144

Refer to text for light-chain protein expanded abbreviations.

a limited tissue expression, being expressed predominantly in the human placenta and heart, and is responsible for the transport of small short-chain neutral amino acids, such as alanine, serine, methionine, asparagine, and glutamine.[123] The functional characteristics of ATA-2 are similar to those of ATA-1, although found in a wider range of tissues, including the placenta.[123,125] ATA-3 appears to have a unique tissue distribution predominantly in hepatic and skeletal muscle tissues.[126,127]

The ASCT-1 (SATT),[118,128,129] a component of the ASC transport system, has been localized to human placenta tissue, although its expression is very low.[129] Another component of the ASC system, ASCT-2, has also been cloned,[130] although this complementary deoxyriboncleic acid (cDNA) is currently thought to code protein for the related transport family, the B^o system.[65,66] The B^o system is a sodium-dependent neutral amino acid transport system for which the related gene, *hATB°*, is proposed to represent the B^o system in the human placental choriocarcinoma cell line, JAR, and isolated human placental Poly(A)$^+$ mRNA.[65,131] The B title represents this system's broad substrate preference, and the capital status indicates its sodium dependence. The superscript ^{o} defines it as accepting zwitterionic or neutral amino acids, which distinguishes it from the $B^{o,+}$ system, which also accepts cationic amino acids.[65,132] These systems are differentiated from the $b^{o,+}$ system, which also transports neutral and cationic amino acids, but in a sodium-independent manner. This latter system has been reported in basal membrane preparations,[85] although, recently, this localization has been questioned, with its activity attributed instead to the y^+L system.[80] The sodium-independent transport of small neutral amino acids is carried out by the Asc system, composed of the proteins Asc1 and Asc2, both of which have been identified in placental mRNA.[62,63] Asc1 forms a heterodimeric complex with 4F2hc,[63] whereas Asc2 appears to interact with a presently unknown heavy chain.[62] System N activity was first found in the liver but has also been localized to the human placenta.[91] Recently, complementary DNAs (cDNAs) encoding two subtypes of system N, SN1 and SN2, have been described,[133,134] although expression of these subtypes in placental tissues has not yet been reported. The β transporter for taurine has displayed activity in placenta preparations,[68–73] and presently, this activity is associated with an mRNA encoding TAUT in human placental Poly(A)$^+$ mRNA.[135]

Light chain proteins also associate with 4F2hc to form the functional L transport system,[114,122] catalyzing the uptake of neutral amino acids in a sodium-independent manner. Two light-chain proteins have been reported to determine L system activity, system L-amino acid transporter (LAT) 1 and 2. The 4F2hc/LAT1 transport activity displays a narrow specificity toward neutral amino acids, uninfluenced by pH, whereas 4F2hc/LAT2 activity has a broad specificity and is stimulated by decreasing pH.[136] Both LAT1 and LAT2 have been reported in placental samples.[102,104,107,113,122,137–139] Immunologic and functional studies suggest that, at term, the light chain, LAT1 is located predominantly in the microvillous membrane and the syncytiotrophoblast layer of the villi.[107,139] Furthermore, the L transport system phenotype associated with that of the placental microvillous membrane is found to occur when the LAT1 and not the LAT2 catalytic subunit is coexpressed with the 4F2hc.[140] In a similar manner, human LAT2 mRNA has been identified in the choriocarcinoma BeWo cell line and placental villous tissues,[104,140] although it is localized to the basal membrane and not the microvillous membrane, as is the case for LAT1.[122,140,141] These studies suggest that the localization of system activity may be further defined through specific light-chain location.

Cationic Transport System Light-Chain Proteins

Transport of cationic amino acids is believed to occur through the y^+L and y^+ systems. Placental y^+L system activity is determined by which light chain, system y^+L-amino acid transporter-1 (y^+LAT1) or y^+LAT2, forms a heterodimer with the membrane-bound 4F2hc. Human placental preparations contain y^+LAT1 mRNA,[103,112] and when this mRNA is coexpressed with 4F2hc in *Xenopus laevis* oocytes, amino acid uptake characteristics similar to that of system y^+L are displayed.[112] Presently, it is unclear if system y^+LAT light-chain proteins display a tissue distribution pattern similar to that displayed by the LAT proteins. The related system y^+ activity depends only on the expression of monomeric proteins (or *CAT* gene products),[142] which, unlike systems L and y^+L, require expression of both a common heavy chain and a related light chain.[102,112,136] Currently, there are three known mRNAs that encode for proteins related to this cationic amino acid transport system in placental tissues, namely, the cationic amino acid transporters (CATs) 1 CAT 2B, and 4.[80,81] Recently, kinetic and substrate inhibition studies and reverse-transcriptase polymerase chain reaction studies localizing CAT4 mRNA in human placental tissue suggest that y^+ activity is limited to the microvillous membrane and not the basal membrane.[80]

Anionic Transport System Light-Chain Proteins

Five cDNAs encoding proteins capable of mediating high-affinity sodium-coupled transport have been reported, and three of these have been cloned from both rat and human placenta.[45,66,89] These placental proteins, excitatory amino acid transport (EAAT) 1 (GLAST1), 2 (GLT1), and 3 (EAAC1), are known to mediate placental sodium-dependent D-aspartate–inhibitable anionic amino acid transport or system X_{AG}– activity.[90] EAAT1 and EAAT3 have been detected in human placental tissue,[143,144] whereas these two and EAAT2 have been detected in rat placenta tissues.[89,145] The regulation of these proteins appears to be under the control of growth hormone and insulin-like growth factor family members,[145] and up-regulation of the system has been demonstrated through cell density and nutrient deprivation studies in muscle and placental cell lines.[57,89] These latter studies demonstrated that EAAT1 and EAAT3 play a key role in the basal anionic amino acid transfer, whereas EAAT2 may be involved in conditions of amino acid depletion.[89]

Alterations in Amino Acid Transporter Proteins and Disease

The importance of the heavy- and light-chain proteins in placental amino acid transport and metabolism is highlighted by studies showing that alterations in 4F2hc and/or y^+LAT1 expression may be responsible for lysinuric protein intolerance,[112,146] cystinuria,[147] alterations in maternal-to-placenta essential amino acid supply,[120,139] and maternal immune response failure during implantation.[148–150] The identification of individual transporter proteins in the trophoblast will be expanded considerably as sequence data for specific transporters permit rapid identification of other members of the same family of transporters. Thus, the information provided in Table 27-1 and Figure 27-3 should be regarded as an interim report in a rapidly changing field.

AMINO ACID TRANSPORT SYSTEMS AND FGR

In clinical studies, the concentration of amino acids has been observed to be lower in the fetal and maternal plasma of pregnancies that were complicated by FGR,[151–153] suggesting alterations in amino acid delivery. This depression in amino acid concentrations is true regardless of whether fetal concentrations were determined at the time of delivery or many weeks prior to delivery. Recently, these same investigators demonstrated that lower amino acid concentrations were found in FGR pregnancies even if the fetus had normal fetal heart rate and velocimetry measurements, suggesting that this may antedate other clinical pathologic findings.[151–154] Studies in human FGR demonstrate that system A may be impaired.[155] An in vitro study using microvillous membrane vesicles from the placentae of appropriate for gestational age (AGA) and small for gestational age (SGA) babies demonstrated markedly lower activity (by 63%) of the A system transporters in the SGA compared with the AGA membrane vesicles,[156] suggesting a positive association between fetal growth and system A activity. In human FGR, the transport of taurine from maternal to fetal circulation is reduced, thereby affecting fetal taurine concentrations.[71] In addition, studies inducing FGR through maternal protein deprivation in rats have demonstrated a down-regulation of placental amino acid transport, specifically system A, and also systems X_{AG}^- and y^+.[84,157] Inhibition of system A transport in rat pregnancies has also been associated with decreases in fetal weight, demonstrating a role for system A transport in maintaining normal fetal growth.[158] With regard to system X_{AG}^- transport, the basal membrane activity of EAAT1 is reduced in an FGR rat model, which could impact placental glutamate uptake from the fetal circulation.[84]

The microvillous membrane system y^+ and y^+L activity is not altered in human FGR,[79,159] although basal membrane transport of lysine is reduced as represented by reduced mediated lysine uptake and a reduced maximum velocity for the y^+L system.[79] Reductions in the uptake of leucine in both microvillous and basal membrane preparations of FGR placentae highlight possible alterations in the L transport system.[79] These changes in basal membrane transport properties could be an important adaptive response by the trophoblast, limiting the backflux of amino acids from the fetal circulation to the placenta. In vivo studies of ovine FGR placental transport have indeed shown a reduced backflux of leucine and threonine from the fetal circulation to the placenta, suggesting that changes in basal membrane function may have occurred.[160,161] At steady state, the fetomaternal enrichment ratio of leucine in normal human pregnancies is approximately 0.8, a much higher ratio than the 0.4 ratio in sheep.[160,162] However, in both species, this ratio is significantly lower in FGR pregnancies. In the ovine FGR model, the reduction in fetomaternal ratio was attributable to a significant reduction in transplacental leucine flux,[160]

which is probably also the mechanism in human FGR pregnancies. Furthermore, the magnitude of the leucine ratio reduction correlates with a clinical classification of FGR severity based on a completely different set of clinical data, namely, fetal arterial velocimetry and fetal heart rate data.[154] In addition, recent clinical studies have shown that the leucine and phenylalanine (fetomaternal) enrichment ratio is significantly lower in human FGR compared with normal pregnancies.[79,162,163]

OTHER FACTORS REGULATING PLACENTAL AMINO ACID TRANSPORT

As pregnancy advances, the increasing nutrient demands of the developing conceptus must be met through an appropriate increase in placental nutrient transport. This enhanced performance is facilitated through alterations in placental perfusion and changes in membrane exchange surface area. Recent studies in human pregnancies have shown that umbilical blood flow increases during gestation in a pattern similar to fetal growth rate. The relationship between blood flow and body size is quite good, although not perfect. As shown in Figure 27-4, when blood flow is expressed per kilogram fetal weight, it falls slightly throughout gestation. This pattern of decline is similar to the changes in fetal heart rate in human pregnancies, which decreases as gestation advances. Heart rate is closely linked to metabolic rate. Thus, the changes in blood flow and in fetal metabolic rate appear to be reasonably well linked in human pregnancies. The decrease in umbilical blood flow per kilogram fetal weight in human pregnancies does not present a problem in terms of supplying amino acids to the fetus as it grows. This is not the case as changes in blood flow are compensated for by an increase in placental surface area and presumably an increase in the number of membrane-bound transporters available for delivery of amino acids. Between the sixteenth week of pregnancy and term, human fetal weight increases approximately 20-fold, whereas the peripheral villous surface area increases only ninefold.[164–167] More importantly, the multiplication factor of nine actually decreases in late gestation.[167] It should be emphasized, however, that there are only a few careful ontogenetic studies of how total surface area, including microvillous surface, changes over gestation.[167,168] The increases in total surface area of the placenta alone cannot account for the exponential fetal growth occurring over this time period. These data suggest that fetal growth is supported not by changes in villous surface area alone; rather, the total transport capacity of the trophoblast is likely to be determined by total villous surface area, placental permeability, and the concentration of specific amino acid carrier proteins on cell membrane surfaces, as well as the affinity characteristics of these proteins and the circulating amino acid concentrations at both the maternal and fetal surfaces.

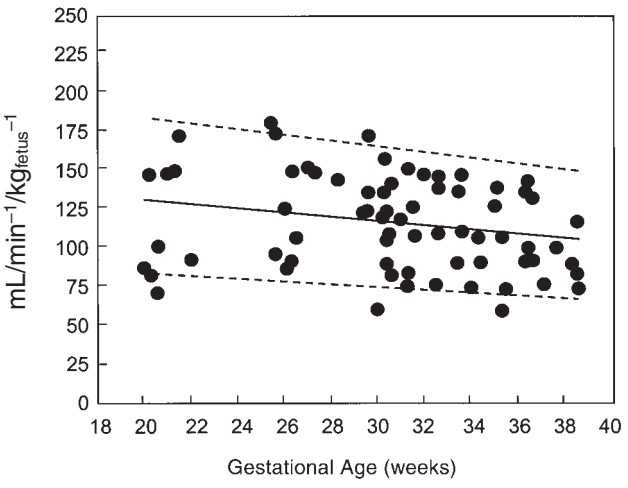

FIGURE 27-4 Umbilical vein blood flow per kilogram of fetal weight plotted against gestational age for human pregnancies. Slight linear decrease observed was not significant. (y = –1.3636x + 155.9964). Both 5th and 95th percentiles are shown (*dashed lines*). Adapted from Barbera A et al.[234]

The observations of differences in amino acid transport activity in the FGR placenta highlight the important point that the activity of transport systems must be considered in conjunction with other contributors to amino acid flux. In studies comparing normal and FGR placentae, there are reported reductions in total villous surface area,[168,169] suggesting that morphometric changes contribute to the overall reduction in placental amino acid transport capacity. Placental permeability is also suggested to play a role in amino acid transport, although in FGR vesicle studies, the composition and permeability of placental plasma membrane are not altered.[170] However, this is most likely not the case in vivo. Thus, at the present time, it appears that both reductions in surface area for exchange and reductions in specific transporter number and activities contribute to the reduction in amino acid transport in FGR pregnancies.

Accompanying the maturational changes in trophoblast surface area, amino acid transport systems are reported to have differing expression and transport parameters through gestation.[56,80,83,107,171,172] For example, in term placenta, L-arginine transport in microvillous membrane preparation is through both y^+ and y^+L systems, whereas in the basal membrane, transport may be restricted to the y^+L system.[80] Furthermore, the functional properties of transport systems may also change as gestation advances. For example, first-trimester microvillous membrane has increased transport activity compared with term placental vesicles,[172] and 4F2hc protein levels differ between early/midpregnancy and term placenta.[80,107] Early in gestation, the K_m of the microvillous high-affinity system y^+L is significantly less than in term preparations.[80] Such studies highlight the complex interactions that occur between developing microvillous membrane and basal membrane, within the trophoblast and between the two circulations, to facilitate an increase in nutrient delivery to the growing fetus as gestation advances.

Another factor to consider is the fact that placental tissue contains a number of hormone receptors (ie, for insulin, gonadotropins, growth factors, somatomedins, β-adrenergics, cholinergics, opiates). How hormones interact with the regulation of amino acid transport is incom-

pletely understood at present. There is some evidence, however, that insulin infusion may enhance placental amino acid uptake, concentration, and transport to the fetus.[173,174] Karl and colleagues found that AIB uptake by cultured trophoblast cells was enhanced by insulin as well as by dexamethasone, glucagon, and 8-Br cyclic adenosine monosphosphate.[173] They postulated that because trophoblasts are known to produce insulin-like growth factor (IGF)-I, insulin may initially enhance AIB uptake via IGF-I. Insulin receptor concentrations were found to be markedly reduced in placentas from SGA infants, and AIB uptake was decreased in the cultures of these trophoblast cells.[156,173,175,176]

MULTIPLE ROLES OF AMINO ACIDS

Since the first description of amino acids as important neuroexcitatory or neuroinhibitory compounds in the brain, it has become increasingly clear that amino acids serve important functions beyond that of components of proteins and/or as metabolic fuels for tissues. Even in the latter role, their importance had been underestimated by studies that examined the contribution of amino acids to total CO_2 production in the whole organism. It took some time to appreciate the fact that oxidation may be organ specific. Thus, glutamate/glutamine oxidation by the small bowel may represent a relatively minor contribution to total CO_2 production in humans but may be crucial to meeting energy requirements of the gastrointestinal tract. The oxidation of glutamate appears to be important not only in the small bowel but in the heart and in the placenta as well. Similarly, amino acids whose intracellular concentrations may change rapidly can play an important role as idiogenic osmoles in regulating water balance across tissues.[177] The interorgan shuttling and interconversion of amino acids may also play an important role for purposes not directly related to providing carbon and nitrogen for growth or as metabolic fuels.[93] Traditionally, we have come to appreciate the role of alanine and glutamine in shuttling carbon from skeletal muscle to the liver, where it is used for glucose production. Recent studies have brought out the importance of glutamate cycling between the fetal liver and placenta.[178–180] Normally, in fetal life, there is no significant rate of gluconeogenesis in the fetal liver. This is useful to the fetus because it permits the fetus to meet its glucose requirements by obtaining glucose from the maternal glucose pool via transplacental transport, but the large amount of carbon coming to the fetal liver would require oxidation if no alternative carbon was released from the liver instead of glucose. In fetal life, glutamate serves this important function. The fetal liver releases a large amount of glutamate into the circulation, which reduces the fetal hepatic oxygen requirement for the metabolism of glutamate. The glutamate is taken up almost in a first-pass clearance by the placenta, where it is used as a mitochondrial fuel.[181] In this sense, the placenta assists the liver by reducing its oxygen requirement significantly. Such interorgan transport and interconversion of nutrients may serve other functions as well. The placental oxidation of glutamate provides a source of reduced nicotinamide-adenine dinucleotide phosphate, which can be used in steroidogenesis.[181–183] These additional roles of interorgan shuttling between the fetal liver and placenta are also evident in serine and glycine metabolism.[184–186] Serine is another amino acid that is released from the fetal liver and is taken up from the fetal circulation into the placenta, where it is used for glycine production. This pathway provides a supply of methylene tetrahydrofolate within the placenta, as is discussed later in this chapter. More recently, attention has focused on the role of the interconversion of arginine and citrulline in providing substrate for nitric oxide synthase leading to nitric oxide production, a potent vasodilator.[187] Other functions of nitric oxide as a signaling compound are being described.[159] Its role in regulating insulin release from beta cells is under investigation and may provide a link between amino acid metabolism and endocrine regulation of carbohydrate metabolism. The work in fetal metabolism has only served to further strengthen the concept that amino acids play multiple roles in the body and that their metabolism and use tend to be organ specific.

PLACENTAL AMINO ACID METABOLISM

The amino acid requirements of the placenta for energy and for protein accretion during its growth are not well known. The placenta contains enzymes related to carbohydrate and amino acid metabolism that give it the capacity to oxidize a number of amino acids as well as perform glycolysis, glycogenolysis, and glycogen, protein, and fatty acid synthesis.[188,189] Four amino acids (alanine, glutamine, threonine, and serine) that are found in high concentrations in placental tissues and are known gluconeogenic precursors are transported by the three transport systems, A, L, and ASC.[5] This could be a protective mechanism to ensure adequate fetal supply of these important amino acids. Preincubation of placental tissue for several hours in amino acid–free medium leads to an increased concentrating capacity of the placental tissues for AIB.[25,190] This increased concentrating capacity can be blocked by inhibitors of protein synthesis, indicating that the placental vesicles respond to hypoaminoacidemia by up-regulation of the A system transporters. Far less is known about the placental vascular endothelium. Although still in debate, it may share at least one characteristic with that of the cerebral circulation, namely, the absence of system A transporter.[191] The metabolism of amino acids within the placenta during transport has not been well studied.

So far, amino acid oxidation by human placental mitochondria has been demonstrated for alanine, aspartate, glutamate, and glycine.[183] Given the data on the large uptake of glutamate by the placenta from the fetal circulation, it is likely that glutamate is the predominant amino acid functioning as a metabolic fuel for the placenta.[179] Placental metabolic requirements are very large. In vivo estimates of its oxygen consumption are approximately equal to those for the brain, and oxidation of amino acids is a major metabolic function of the brain and placenta.[192] In vivo, there is a significant production and excretion of ammonia into

both uterine and umbilical circulations by the ovine placenta.[6,7] The absolute rate of uteroplacental ammonia production, approximately 25 μmol/minute in the ovine pregnancy at midgestation (73 to 97 days, term 147 ± 3 days), is approximately equal to that of the term placenta. Because in vitro data indicate that there is minimal urea cycle activity within the placenta,[193] this suggests that ammonia and not urea is the end product of amino acid deamination within the placenta. Some of the ammonia produced by the placenta is consumed by the fetal liver, and in fetal sheep near term, the uptake by the fetal liver is approximately 1.5 to 1.8 times that taken up by the umbilical circulation from the placenta.[6,7,193] This indicates that fetal tissues, as well as the placenta, produce ammonia, and uptake of ammonia by the fetal liver undoubtedly contributes to its high rate of urea production.

In part, the ammonia production by the placenta is derived from the transamination of BCAAs.[194] The activity of the branched-chain aminotransferases is high in the placenta, and because the activity of α-keto decarboxylases is low, it is clear that the α-keto acids derived from the BCAA are not oxidized further. These α-keto acids represent part of a group of compounds that are produced in the placenta and are delivered into both uterine and umbilical circulations. These compounds include ammonia, lactate, and one of the polyols, sorbitol (Figure 27-5). The placental production of glutamate as a consequence of transamination of α-ketoglutarate from BCAA[93] and the placental uptake of fetal plasma glutamate at 4.8 μmol/min/kg fetus represent the two major influxes of glutamate into the ovine placenta. Although the ovine placenta contains the enzyme glutamine synthetase, only a small fraction of glutamate that is taken up by the placenta from fetal circulation is returned to the fetus as glutamine.[181,195] It is the oxidation of glutamate that appears to be the predominant pathway of placental glutamate disposal.

It is likely that placental ammonia production is not confined to the epitheliochorial placenta of the sheep. It has been described for the perfused human placenta, and a net efflux of ammonia from the pregnant uterus into the maternal circulation has also been found in rabbits, guinea pigs, and sheep.[19,194,196–198] It is intriguing to speculate on the possible biologic significance of mammalian fetuses growing and developing in an environment of an elevated ammonia concentration. Ammonia can affect hepatic metabolism and may play a role in glial development and in the development of other tissues rich in glutamine synthetase. Ammonia is now one of a number of compounds that have been shown to be produced in the ovine trophoblast and delivered into both fetal and maternal circulation. The enzymes involved in these pathways have been found in the human trophoblast, although, in most instances, studies that document the production of these metabolites in human trophoblast in vivo are lacking.

UMBILICAL UPTAKE OF AMINO ACIDS

Measurements of unidirectional flux are currently available only for the ovine species and not for other mammalian species. A number of studies involving examination of the umbilical uptake of amino acids in chronic, unstressed sheep models have revealed that most amino acids (particularly the neutral amino acids) are delivered into the fetal circulation in amounts that exceed their net rates of accretion.[2,4,16,199,200] The most complete data on the uterine and umbilical uptakes of amino acids are presented in Figure 27-6.[200]

Several studies of the umbilical uptake of amino acids under normal conditions have shown that there is no measurable uptake of aspartate and, in fact, a significant net uptake from the fetal circulation into the placenta of serine and glutamate. Thus, for these three amino acids, it is clear that fetal requirements must be met by production within fetal tissues. Stegink and colleagues infused labeled tracer isotopes of glutamate and aspartate into both fetal and maternal circulations of rhesus monkeys and found essentially no transfer of the compounds across the placenta.[201,202] Schneider and colleagues, using an in vitro perfused human placenta preparation, found significant uptake of glutamate from the fluid perfusing the fetal side of the placenta rather than a net transfer of glutamate from the maternal to the fetal side.[203] Not surprisingly, because amino acid requirements and protein synthetic rates are linked to fetal metabolic rates, the umbilical uptake or dietary supply of amino acids per kilogram of fetal body weight is much

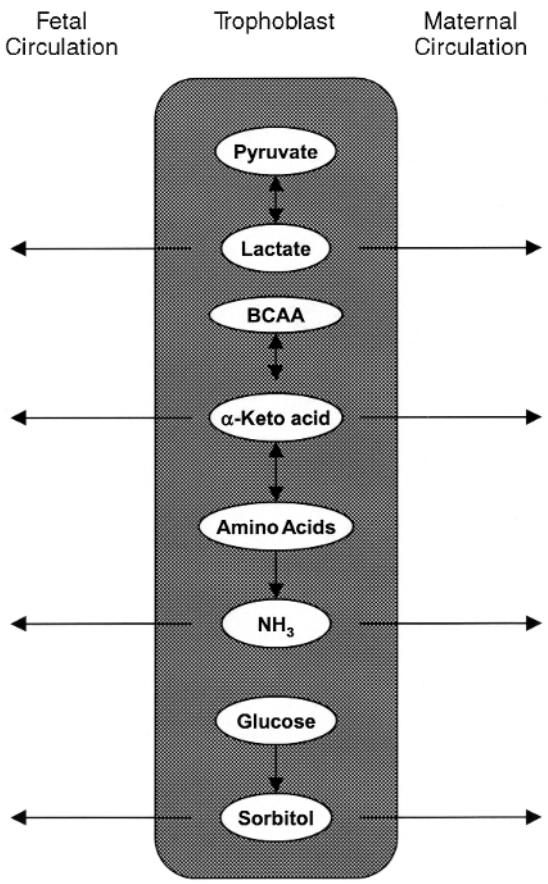

FIGURE 27-5 A schematic representation of some of the metabolites produced in the placenta, which are then delivered into both the maternal and fetal circulations. BCAA = branched-chain amino acid.

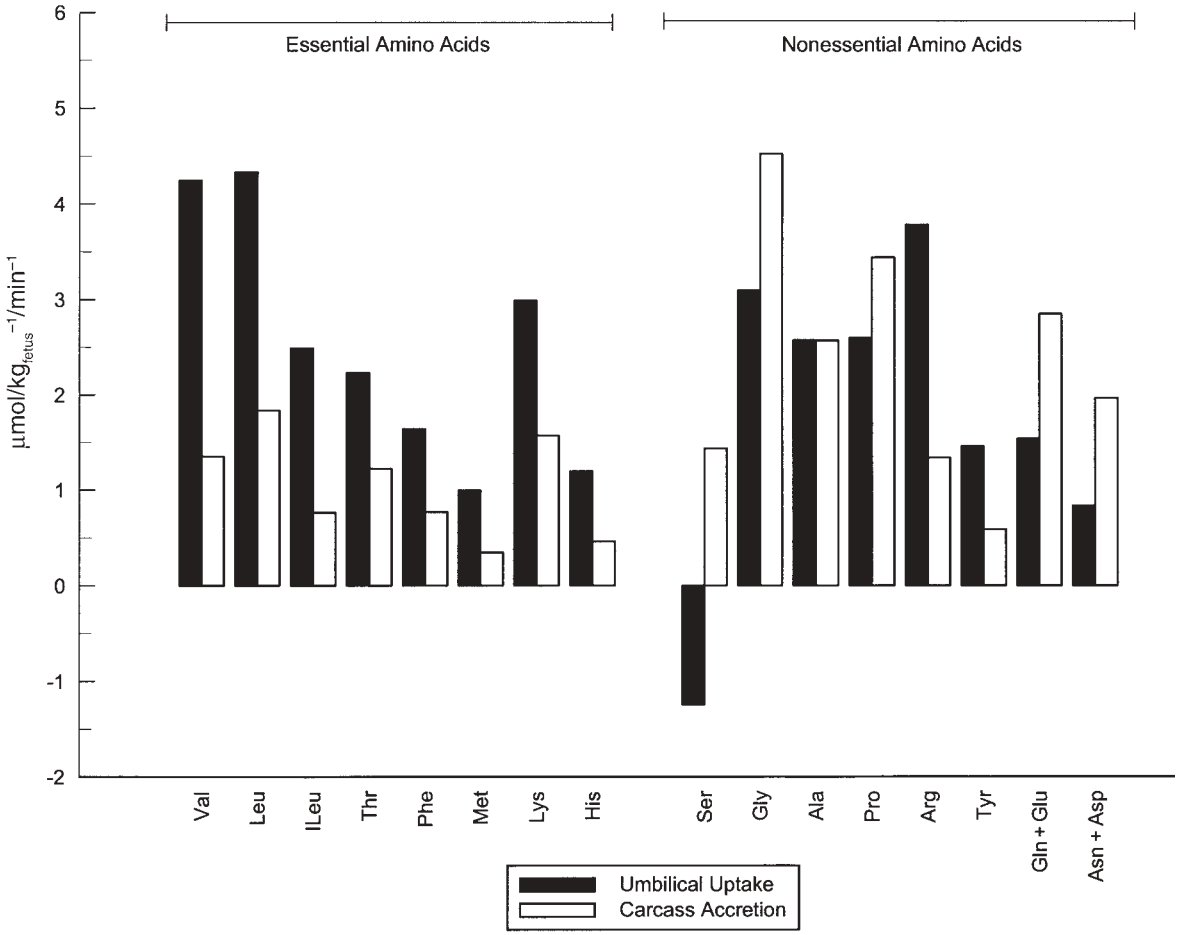

FIGURE 27-6 Comparison between mean umbilical uptakes and estimated normal fetal accretions of amino acids. For pairs of amino acids (glutamine + glutamate and asparagine + aspartate), individual accretion rates are not known. Adapted from Chung M et al.[200]

higher in early gestation compared with term.[16] A key question in fetal nutrition is how maternal concentrations of amino acids are related to the umbilical uptake. This question is important because it would help define the extent to which changes in maternal amino acid concentrations could impact the fetal delivery of amino acids. The question has been studied in both ovine pregnancies and human pregnancies by infusions of amino acids into the maternal circulation with measurements of their umbilical uptake. The relationship between maternal concentration and umbilical uptake is a complex one. In ovine studies, the flux from the maternal circulation to the fetal circulation is most rapid for five amino acids, and for those five, differences in their fluxes are directly attributable to differences in their normal maternal plasma concentrations,[204] as shown in Figure 27-7. In human pregnancies, it is possible for most amino acids to increase the fetal delivery by increasing the maternal concentration.[198] This has been shown for both normal pregnancies and pregnancies complicated by fetal growth restriction.[163] However, for some amino acids, this has not been possible when an infusion of many amino acids is given to the mother presumably owing to competitive inhibition by other amino acids in the infusate.

It is clear that the umbilical uptake of amino acids cannot be considered solely a reflection of the amino acid supply derived from the maternal plasma pool via transplacental transport but also may include a contribution derived from production within the placenta or release from placental protein breakdown. It is important to understand which amino acids are provided to the fetus primarily through placental production versus placental transport because differing forms of placental pathology may adversely affect the mode of delivery of those amino acids to the fetus.

FETAL AND PLACENTAL OXIDATION

The use of multiple-tracer methodology in animal models has allowed further elucidation of amino acid metabolism within the placenta and the fetus. Fetal and placental metabolism of the essential amino acids leucine and threonine have been studied in some detail.[160,161,205] For leucine, Loy and colleagues were the first to demonstrate that even for an essential amino acid, there may be extensive catabolism both within the fetus and within the placenta.[205] They found that 20 to 25% of the (1-^{14}C) leucine infused into the fetus could be accounted for as $^{14}CO_2$ produced by the fetus. Unlike glutamate, there was no measurable oxidation of leucine within the uteroplacental tissues. This indicated an extensive use of leucine as a fetal but not a placental fuel. The extensive fetal catabolism of leucine can be better

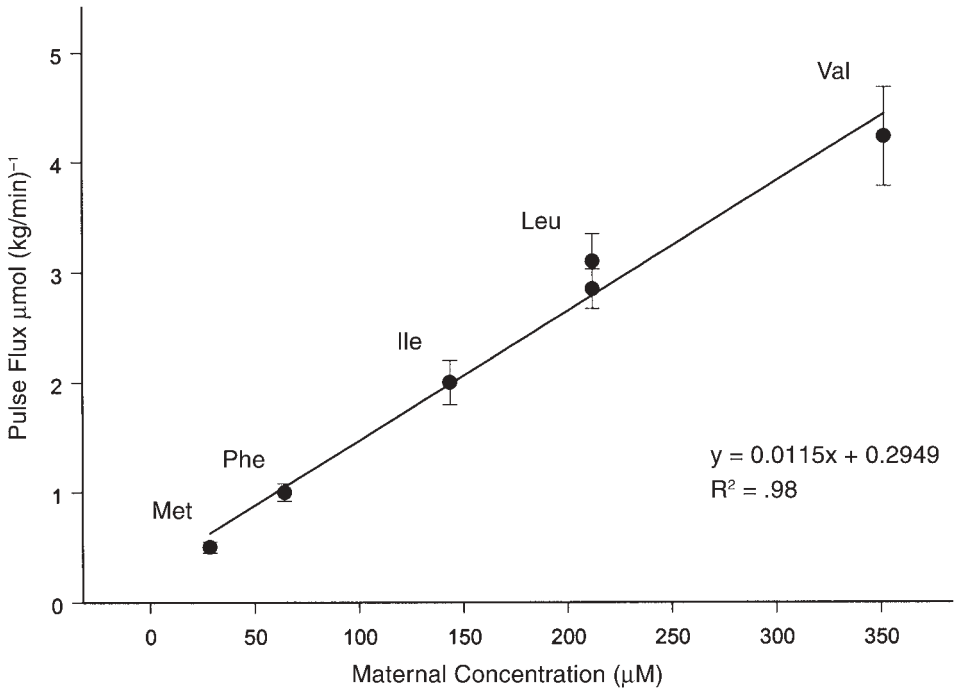

FIGURE 27-7 Pulse flux calculated over the first 10 minutes after the bolus versus maternal plasma arterial concentration for the five essential amino acids that have high and similar pulse flux clearances. The two leucine data represent two separate studies. Adapted from Paolini CL et al.[204]

appreciated by a comparison of its supply to the fetus via the placenta and its rate of oxidation and of accretion in tissue protein. The total umbilical uptake of leucine is approximately 4.9 µmol/minute/kg, and net accretion of leucine in tissue proteins accounts for only 2.0 µmol/minute/kg in late gestation. On the other hand, the rate of leucine oxidation is 2.8 µmol/minute/kg or 57% of its uptake. Thus far, the fetal and placental metabolism of other essential amino acids has not been studied in such detail.

The oxidation rates in the fetus and/or placenta have been measured for leucine, lysine, threonine, alanine, glycine, serine, and glutamate,[160,161,181,204,206,207] and it is apparent that fetal oxidation of amino acids is not confined to the nonessential amino acids. In fact, it is an important safety feature for fetal nutrition that amino acids are provided in amounts that exceed their rates of accretion.[4,5] This mandates a fairly high oxidation rate for most amino acids, including the essential amino acids. It is not surprising, therefore, that there is a relatively high rate of urea production by the fetus. This has been directly measured in the ovine fetus and estimated for the human fetus.[8,208]

In FGR, the oxidation of amino acids is decreased, sparing the amino acids for protein synthesis. The principal amino acid used as a metabolic fuel by the ovine placenta appears to be glutamate.[181] There are no data in other species, but an uptake of glutamate from the fetal plasma into the placenta has been shown for human pregnancies. This observation supports the idea that it probably plays a similar role for the human placenta.

FETAL HEPATIC CIRCULATION AND AMINO ACID METABOLISM

Probably no area of fetal physiology and metabolism has progressed more rapidly since the last edition of this book than fetal hepatic physiology. The advances are both in studies relating to the perfusion of the fetal liver and in studies of fetal hepatic metabolism of amino acids.

Fetal Hepatic Circulation

The umbilical vein carries the most oxygenated and nutrient-rich blood of the fetus, and a large fraction of this blood perfuses the fetal liver. Thus, the fetal liver, in contrast to the postnatal liver, is a site of preferred oxygenation. It is a vitally important defense for the fetus during periods of chronic or acute hypoxia because it continues to take up lactate from the fetal circulation and release pyruvate. The pyruvate can then be metabolized by other fetal tissues. For human pregnancies, the percentage of umbilical blood flow shunted away from the fetal liver through the ductus venosus has now been measured.[209,210] The shunt gradually decreases from 40 to 15% over a gestational age range from 20 weeks to term. In some FGR pregnancies, this shunt is significantly increased.[209,211] Because other studies have shown a reduction in umbilical blood flow per kilogram fetal weight in FGR pregnancies,[212] this, in itself, reduces perfusion of the fetal liver. However, if the reduction in umbilical flow is coupled with an increased ductus venosus shunt, the decrease in hepatic perfusion can be profound. These changes in the fetal circulation must be kept in mind in terms of its potential importance on fetal hepatic metabolism.

Hepatic Amino Acid Metabolism

Fetal hepatic uptake of amino acids has been studied in late-gestation fetal lambs, and fetal hepatic uptake and the umbilical uptake of amino acids have been compared. A large hepatic uptake of all of the essential and most of the nonessential amino acids by both lobes of the fetal

liver has been reported.[4] During normal fetal development, there is no appreciable rate of fetal gluconeogenesis. This is understandable because fetal hepatic glucose production would be self-defeating for the fetus. It would increase plasma glucose concentration, which would reduce the transplacental glucose gradient leading to a reduced umbilical glucose uptake from the mother. The absence of fetal gluconeogenesis is not accompanied by a reduced amino acid uptake in the fetal circulation from the placenta,[178] as shown in Figure 27-8. There is a large uptake of amino acids, including all of the gluconeogenic amino acids, as well as a large fetal uptake of lactate.[178] In fetal life, the carbon is released primarily as glutamate and pyruvate, with a smaller contribution coming from the hepatic release of serine, ornithine, and aspartate. This is in contrast to what occurs in postnatal life, where the carbon from these amino acids is released from the liver solely as glucose.

The hepatic uptake of lactate and release of pyruvate are of special interest because of the importance of these compounds during fetal hypoxia. As mentioned earlier, the fetal liver is a site of preferred oxygenation because it is perfused with oxygen-rich umbilical venous blood. This is quite different from hepatic perfusion in postnatal life. The uptake of lactate and release of pyruvate continue under conditions of fetal hypoxia providing pyruvate, which can be metabolized by nonhepatic tissues even under hypoxic conditions.[213]

The interorgan shuttling of the two amino acid pairs, glutamate and glutamine and serine and glycine, plays an important role in this overall carbon balance for the fetus. The release of glutamate, serine, and pyruvate effectively replaces the glucose carbon release characteristic of the liver in postnatal life. This is clearly brought out in Figure 27-8, which shows what happens when gluconeogenesis is triggered in the fetal liver by the infusion of glucagon.[178] With the advent of net glucose released from the liver, the efflux of glutamate, serine, and pyruvate is markedly reduced, and the overall carbon balance is maintained. The exchange of glutamate and glutamine between the fetal liver and placenta does not represent a cycling of carbon between the two organs. Glutamate is largely oxidized in the placenta and in the fetus. The exchange of glutamate and glutamine changes quite markedly during parturition and during glucocorticoid or glucagon administration to the fetus.[179,180] Under these conditions, there is a decrease of fetal hepatic glutamate release, which results in a decrease of placental glutamate uptake. What role these metabolic changes in the fetal liver play in parturition is not yet established. Studies have shown that FGR is also associated with changes in fetal and placental glutamate metabolism. Fetal plasma glutamate concentrations are significantly lower in ovine FGR pregnancies compared with normal pregnancies.[214]

Glycine and serine are another metabolically related pair of amino acids that demonstrate a similar pattern of release and uptake across the ovine fetal liver and placenta.[4,184,186] The fetal glycine oxidation rate is high, and glycine is almost totally oxidized within the fetal liver. Fetal hepatic glycine oxidation and serine production from glycine are linked in the fetal liver by the enzyme systems glycine oxidase and serine hydroxymethyltransferase.[186,206,215] The combined action of these enzymes is the production of one mole of CO_2 and one mole of serine for every two moles of glycine consumed.[184,85] This is also true in adult tis-

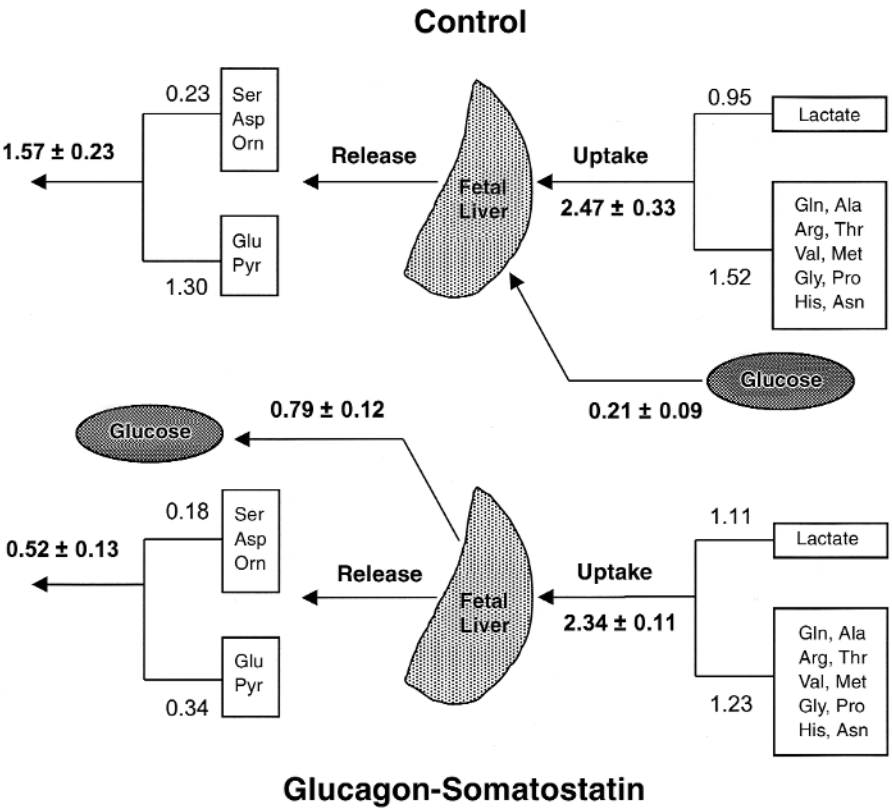

Figure 27-8 Fetal hepatic uptake and output of glucose carbon and glucogenic substrate carbon under normal physiologic conditions (Control) and during a fetal glucagon somatostatin infusion. Each number represents a substrate carbon to oxygen uptake ratio. Adapted from Teng C, et al.[178]

sues,[216,217] although adult liver is not normally a site of net serine release.[218]

Infusion of tracer serine into the fetus has demonstrated a rapid bidirectional transport of serine between the fetal blood and placenta, as well as placental conversion of fetal plasma serine to glycine.[185] In contrast to glycine oxidation, the bulk of fetal plasma serine oxidation occurs in extrahepatic tissues. Moores and colleagues infused labeled serine into the maternal circulation of pregnant sheep and found that, despite high maternal enrichments of serine, there was no fetal plasma enrichment evident.[206] However, the infusion of maternal tracer serine did lead to the appearance of labeled glycine in the fetal circulation. Thus, placental glycine production uses serine derived from both the maternal and fetal circulations. This brings out the complexity of pathways by which an amino acid such as glycine is delivered to the fetus from the placenta. The pathway for glycine production from serine is thought to be via serine hydroxymethyltransferase (SHMT) because ovine placental tissue is known to have moderately high activity for the mitochondrial isoform of this enzyme.[186] A by-product of placental glycine production via SHMT is methylenetetrahydrofolate, which could be involved in a variety of methylation reactions within the placenta.[186,206] These examples of placental-fetal interorgan shuttling of amino acids, particularly between the fetal liver and placenta, are now recognized to be an important and unique aspect of fetal metabolism.

FETAL HINDLIMB METABOLISM OF AMINO ACIDS

Several laboratories have studied the amino acid uptake by the fetal ovine hindlimb as being representative of the fetal carcass/extrahepatic tissues. Its metabolism has been evaluated under normal, maternal fasting and fetal euglycemic hyperinsulinemic states.[219,220] Under normal physiologic conditions, the hindlimb of a growing fetus shows a net uptake of both essential and nonessential amino acids from the fetal circulation.[220] This is in contrast to adult hindlimb studies that show a large output of alanine and glutamine.[221] It is theorized that the high amino acid uptake by the fetal hindlimb could be explained by the relatively high nitrogen accretion rate of the fetus.[220] There is a net uptake across the hindlimb of two amino acids that are not supplied by the placenta: glutamate and serine. It is estimated that the net fetal hepatic output could account for the combined uptake of glutamate by the placenta and the hindlimb.[220] Given the large uptake of alanine by the fetal liver, it is interesting that the fetal hindlimb shows no net release of alanine.

Theoretically, these amino acids could not be taken up by the fetal liver and be used for glucose production during a state of reduced umbilical glucose uptake (ie, maternal fasting).[222] Liechty and colleagues reported a relatively high activity for keto acid carboxylase activity in fetal skeletal muscle.[223] In pregnant sheep, after fasting, there is an approximate fivefold increase in the use of glutamine and a twofold increase in the use of the BCAAs by the uteroplacental tissues, suggesting a possible interorgan cycle between hindlimb and placenta, with the hindlimb supplying glutamine during the maternal fasted state.[224] Under euglycemic, hyperinsulinemic conditions, fetal lambs were noted to have significantly decreased arterial concentrations of most amino acids; a significantly increased limb uptake of alanine, asparagine, glycine, isoleucine, methionine, and tyrosine; and a decreased uptake of aspartate, but with no significant change in net total nitrogen uptake.[220] These studies show that the stimulation of alanine uptake by insulin is opposite to the effect of maternal fasting, suggesting that insulin or IGFs may play a role in regulating an alanine exchange between fetal circulation and nonvisceral fetal tissues.[220]

NEONATAL IMPLICATIONS OF FETAL AMINO ACID SUPPLY AND METABOLISM

One may ask what studies of amino acid nutrition and metabolism during fetal life can contribute to our approach to optimal nutrition for very premature infants in a neonatal intensive care unit. First, it is important to recognize that normal fetal development and postnatal development are vastly different biologic states. Not only are there profound endocrine changes triggered by delivery and its associated separation from the placenta, but the interorgan cycling of amino acids between the fetal organs and placenta is abruptly terminated. However, certain principles of amino acid metabolism during early development still apply. To summarize, during fetal development, amino acids are taken up in amounts that exceed their requirements for growth. This leads to a high rate of amino acid oxidation and a relatively high rate of urea production. A second general characteristic is the absence of gluconeogenesis, which leads to a hepatic production and release of serine and glutamate. It is important to emphasize that the requirements of amino acids change quite markedly with increasing gestational age and also on whether there has been normal or abnormal fetal growth. In the normal term newborn, the rate of net protein accretion in utero is quite low, with fat accretion dominating growth. In FGR fetuses, there are changes in plasma amino acid concentrations reflecting the reduced placental supply. There may also be vascular changes that lead to hepatic injury.

The delivery of optimal nutrition to the small premature infant is a critical factor to its overall care. Very premature infants have been delivered before they have gone through the phase of in utero development associated with rapid accretion of fat depots and glycogen stores. Preterm infants are born at gestational ages associated with rapid accretion of protein in utero. This has led to a neonatal nutritional approach that emphasizes the early provision of amino acids to very preterm babies. It should be emphasized, however, that this makes an assumption of good liver perfusion and the absence of any prenatal liver injury. Neither of these conditions necessarily applies to an individual newborn in the immediate neonatal period. The best guideline for assessing the nutritional status of the low birth weight infant is not clear. However, one approach

would include achieving a postnatal growth that approximates the in utero growth rate of a normal fetus.[225] By this guideline, the intrauterine accretion rate of amino acids becomes a reference point defining the minimal requirements in the neonatal period. As delineated in the previous discussion, the mammalian fetus uses the circulating maternal free amino acid pool as its primary nitrogen source for growth with certain conspicuous exceptions. Because amino acid oxidation is linked to hepatic gluconeogenesis in postnatal life and because gluconeogenesis is a requirement for postnatal adaptation, one would expect amino acid oxidation to be sustained during postnatal development, significantly increasing amino acid requirements. For the premature infant, the primary sources of nitrogen are obtained from a parenteral nutrition composition, human breast milk, or premature infant formulas. Current nutritional management for preterm and FGR infants aims at early provision of amino acids.

Recommendations for the quantity of protein delivery include 3.6 to 3.8 g/kg/day gross protein intake for the stable growing infant at < 27 weeks gestation and < 1,000 g and 3.0 to 3.6 g/kg/day for the 1,000 to 1,750 g infant at 28 to 34 weeks gestation. Although the exact quantity is debated (ie, European versus American guidelines), it is generally accepted that the stable growing low birth weight infant requires, on average, a parenteral amino acid intake of 3.0 g/kg/day to ensure accretion of nitrogen at the intrauterine rate of approximately 300 mg/kg/day. This amino acid intake, plus an energy intake of 80 to 100 kcal/kg/day, results in a weight gain that approximates the intrauterine rate of 15 g/kg/day.[226] However, the studies of the fetal circulation in FGR pregnancies make it clear that the general recommendations should be used with caution in newborns of any weight or gestational age when there is evidence of circulatory compromise in utero. A high carbohydrate and relatively low nitrogen intake is prudent. Certainly, if a high nitrogen intake is given to such infants, there should be an assessment of ammonia and urea levels as well as measurement of amino acid concentrations to ensure that the nitrogen load is not compromising the infant. This caution reflects the fact that there are still no ideal approaches to assess both the quality and the quantity of amino acids provided as protein in milk feedings to low birth weight infants. Breast milk provides a large array of compounds not included in formula feedings. Some of these compounds, such as glycoproteins and peptides, contain amino acids. However, owing to the instability of glutamine, it is currently omitted from parenteral nutrition solutions and infant formulas. Glutamine has recently been found to be an important metabolic fuel for lymphocytes[227,228] and intestinal epithelial cells[229] and is supplied to the fetus in large amounts throughout gestation.

It has already been demonstrated that formula-fed, very low birth weight infants whose weight gain was comparable to that of a normal fetus retained the same amount of protein (approximately 1.9 g/kg/day) but accumulated fat at approximately three times the rate of the fetus. This indicates that the body composition of the premature infant will differ from that of the comparable placentally nourished fetus.[230] How this will impact on long-term growth and neurodevelopment is unclear and a matter of much debate.[231–233]

As the complex interplay among fetus, placenta, and maternal dietary supply of amino acids becomes increasingly clear, it is hoped that this information can be used to understand more completely the remarkable process of fetal growth and maturation. This, in turn, will then be invaluable information in the further modification and design of feeding regimens for premature infants to optimize growth and long-term neurodevelopment.

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CHAPTER 28

THE LOW BIRTH WEIGHT INFANT

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In the neonatal period, low birth weight (LBW) infants have greater nutritional needs to achieve optimal growth than at any time in their life. Many LBW infants either are born at the beginning of the third trimester of pregnancy or are products of pregnancies complicated by diminished uterine blood flow. These circumstances result in decreased nutrient deposition in the fetus. Thus, many LBW infants are growth restricted at birth.[1] In addition, their medical condition postnatally may contribute to increased nutrient needs. Impediments to growth include the stress of common pathophysiologic events (hypotension, hypoxia, acidosis, infection, surgical intervention) and their therapies (corticosteroids), as well as physiologic immaturity (decreased gastrointestinal motility and enzyme immaturity).[1] There also is a fear that aggressive feeding may produce pathology (feeding intolerance, necrotizing enterocolitis) and that some nutritional regimens may produce toxic effects on organ development. Lastly, intense support is needed to correct growth restrictions at birth and to continue appropriate weight gain, which is nearly double that of a term infant.[2,3] Thus, the LBW infant requires specialized nutritional support to meet these great demands for growth.

Special considerations regarding nutrient needs of LBW infants begin at birth. Because of limited body stores, increased expenditure, severity of illness, and/or immaturity, LBW infants may be given parenteral glucose solutions immediately from birth. Enteral feedings often are precluded because of the multiplicity of medical problems. Thus, immediately after birth, total parenteral nutrition (TPN) is initiated, consisting of intravenous glucose, amino acids, electrolytes, vitamins, and lipid. Subsequently, minimal enteral nutrition is added to provide small, trophic quantities of milk. As the infant matures physiologically and the medical condition stabilizes, TPN is slowly replaced with enteral nutrition. This chapter describes the nutritional needs and goals for LBW infants. Both parenteral and enteral nutritional needs are addressed (Table 28-1).

GOALS FOR NUTRIENT INTAKES

The nutritional reference standard for the term newborn is the exclusively breast-fed infant. A similar standard is not available for LBW infants. Instead, the reference standard for the LBW infant is the estimated intrauterine nutrient accretion rate at corresponding stages during the last trimester of pregnancy. We use the data on the nutrient composition of the fetus derived from chemical analyses of fetal cadavers to determine the net deposition or retention of particular nutrients during the last trimester of pregnancy.[4,5] From analyses of smoothed curves, these data have been computed on a daily basis per kilogram body weight (Table 28-2). Although the original data were derived from fetal carcass analyses, the data for several minerals have been corroborated by noninvasive neutron activation techniques.[6]

TABLE 28-1 Comparison of Suggested Parenteral and Enteral Fluid, Energy, and Nutrient Intakes for Low Birth Weight Infants

Component, Units	*Parenteral Intake Unit/kg/d*	*Enteral Intake Unit/kg/d*
Water, mL	150	135–190 (160–220)*
Energy, kcal	80–100	110–130 (130–150)
Protein, g	3.0–3.5	3.4–4.2 (3.8–4.4)
Fat, g	1.0–4.0	5.0–7.0 (6.0–8.0)
Carbohydrate, g	16	7.0–17.0 (9.0–20.0)
Vitamin A, IU	500	700–1,500
Vitamin D, IU	160	400 IU/d
Vitamin E, IU	2.8	6–12 IU/d
Vitamin K,† µg	80	8–10
Thiamin (vitamin B_1), µg	350	180–240
Riboflavin (vitamin B_2), µg	150	250–360
Pyridoxine (vitamin B_6), µg	180	150–210
Vitamin B_{12}, µg	0.3	0.3
Niacin, mg	6.8	3.6–4.8
Folic acid, µg	56	25–50
Sodium, mEq	2.0–4.0	3.0–7.0
Potassium, mEq	2.0–3.0	2.0–3.0
Chloride, mEq	2.0–3.0	3.0–7.0
Calcium, mg	80–120	100–220
Phosphorus, mg	60–90	60–140
Magnesium, mg	9–10	8–15
Zinc, µg	350–450	1,000–3,000
Copper, µg	65	120–150
Iron, mg	—	2.0–4.0
Chromium, µg	0.4	0.1–2.25
Manganese, µg	10	0.7–7.5
Selenium, µg	2.0	1.3–4.5

Adapted from references 68 and 202 to 206.

*Values in parentheses refer to the extremely low birth weight infant.

†Vitamin K, 0.5–1.0 mg given at birth.

The following conversion factors are used: Ca, 40 mg = 1 mmol = 2 mEq; P, 31 mg = 1 mmol; Mg, 24 mg = 1 mmol = 2 mEq; Na, 23 mg = 1 mmol = 1 mEq; K, 39 mg = 1 mmol = 1 mEq; Cl, 35 mg = 1 mmol = 1 mEq; vitamin A, 1 µg retinol = 3.33 IU vitamin A = 6 µg betacarotene = 1.83 µg retinyl palmitate = 1 retinol equivalent; vitamin E, 1 mg α-tocopherol = 1 IU vitamin E; vitamin D, 1 µg vitamin D (cholecalciferol) = 40 IU vitamin D (cholecalciferol); niacin, 1 mg niacin = 1 niacin equivalent = 60 mg tryptophan.

TABLE 28-2 Estimated Intrauterine Nutrient Accretion Rates

*Nutrient**	*Unit/kg/d*
Calcium (mg)	105
Copper (μg)	50
Magnesium (mg)	2.7
Nitrogen (mg)	325
Phosphorus (mg)	70
Potassium (mEq)	0.7
Sodium (mEq)	1.2
Zinc (μg)	240

Adapted from Widdowson EM[4] and Ziegler EE et al.[5]
*Values averaged from last trimester, adjusted for body weight.

TABLE 28-4 Partition of Energy Needs for Growing Low Birth Weight Infants

Component	*kcal/kg/d*
Resting energy expenditure	50
Intermittent activity (+30% above resting)	15
Occasional cold stress (thermoregulation)	10
Thermic effect of feeding (synthesis)	8
Fecal loss (10% of intake)	12
Growth allowance (energy storage)	25
Totals	120

Adapted from Sinclair JC.[8]

The intrauterine accretion data provide a reference for nutrient deposition. To determine the advisable intake needed for a particular nutrient, we use the factorial approach.[7] This method includes a summation of the quantity of the nutrient deposited and an estimate of nutrient losses (Table 28-3). For infants receiving TPN, the advisable intake includes estimates of nutrient deposition, cutaneous and urinary losses, and an additional allowance to account for variability. For enteral nutrition, the factorial approach is amended to account also for the bioavailability of the particular nutrient. For example, the average calcium absorption from preterm formulas is approximately 50%. To provide a best estimate for calcium intake, we use the following factorial approach (see Table 28-3).

ENERGY

Based on a series of observations, the daily energy need for the growing LBW infant has been summarized (Table 28-4).[8] The values are not absolute. The range in resting energy expenditure has been reported from 49 to 60 kcal/kg/day at 8 to 63 days postnatal age.[9] When nourished parenterally, the LBW infant has less fecal energy loss, generally fewer episodes of cold stress, and somewhat lesser activity so that the actual energy needs for growth are lowered to approximately 80 to 100 kcal/kg/day. In circumstances of chronic disease, such as bronchopulmonary dysplasia, the resting energy expenditure rises significantly.[10,11] Total energy needs in LBW infants with bronchopulmonary dysplasia (BPD) are increased because of greater energy expenditure, activity, and possibly fecal energy losses. It is not surprising to find that these infants require 150 kcal/kg/day to achieve weight gain.

The distribution of nonprotein calories, the quantity of calories derived from fat and from carbohydrate, should be considered. A balanced distribution between calories derived from glucose and fat is appropriate to avoid potential effects on respiratory metabolism, especially in infants who are ill and receiving TPN. A distribution of calories favoring glucose (therefore low fat), or a surplus of glucose calories such that glucose is converted to fat, will increase the production of carbon dioxide, increase the partial pressure of carbon dioxide, increase alveolar minute ventilation, raise the respiratory quotient, and may increase the oxygen consumption.[12,13] In addition, a balanced distribution of glucose-lipid calories favors protein accretion, whereas glucose-only solutions are associated with protein oxidation.[14] Daily monitoring of the intakes for all energy sources in TPN is essential to ensure a relatively balanced distribution of calories derived from glucose and fat. One example of the computation of calorie distribution is provided in Table 28-5.

PARENTERAL NUTRITION

AMINO ACIDS

The essential amino acids include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. For the LBW infant, several investigators also consider histidine, tyrosine, cysteine, taurine, arginine, glycine, and glutamine to be conditionally essential amino acids.[15] The content of specific amino acids also varies among the representative preparations. For example, tyrosine and cysteine are not present in all preparations, principally because of difficulties in solubility.[15–17] Taurine and glutamic acid are not present in all solutions.[15,18] Because of the high proportion of essential and conditionally essen-

TABLE 28-3 Computation of Net Enteral and/or Parenteral Nutrient Need Based on the Factorial Approach Using Data from Rates of Fetal Nutrient Accretion

Net fetal Ca deposition = 105 mg/kg/d
Postnatal urinary losses = 5 mg/kg/d
Postnatal cutaneous losses = 2 mg/kg/d
Subtotal (parenteral need) = 112 mg/kg/d
Assume net absorption (%) = 50%
Total (enteral need) = 224 mg/kg/d

Adapted from Ziegler EE et al[5] and Schanler RJ et al.[25,190]

TABLE 28-5 Distribution of Energy Sources in One Example of a Parenteral Nutrition Solution for Low Birth Weight Infants

	Unit/kg/d	*kcal/kg/d*	*% kcal*
Glucose (12.5%)	16.3 g	55.3	(51%)
Protein (2.4%)	3.1 g	12.5	(12%)
Fat (20%)	4.0 g	40.0	(37%)
Total fluid	150 mL	—	
Total calories	—	108	(100%)

Adapted from Nutrition and Gastroenterology Clinical Review Committee[102] and Schanler RJ.[207]

tial amino acids, commensurate with the initiation of TPN in the first days after birth, a previously elevated blood urea nitrogen may decline more rapidly.[19] Although several amino acid solutions are available for parenteral nutrition, the percentage of essential/total amino acids is variable (Table 28-6): 53% (TrophAmine, Braun, Bethlehem, PA), 48% (FreAmine III, Braun, Bethlehem, PA), 48% (Aminosyn PF, Abbott Park, IL), 44% (Novamine, Fresenius, Lexington, MA), and 40% (Travasol, Clintec, New Providence, NJ).

It is known that there is a direct relationship between the quantity of nitrogen (amino acids) provided in TPN and nitrogen balance or retention.[20,21] It is also known that specific amino acids may affect nitrogen balance, a fact that has been useful in determining the essentiality of particular amino acids. Malloy and colleagues observed that the addition of cysteine hydrochloride to TPN increased plasma free and total cyst(e)ine and urinary cyst(e)ine concentrations.[22] Zlotkin and colleagues, however, were unable to demonstrate a significant effect of increasing cysteine intake on nitrogen balance or weight gain.[23] Cysteine also serves as a precursor of glutathione. In vitro studies suggest that, even in LBW infants, cysteine is an ideal substrate for glutathione production.[24] Thus, cysteine hydrochloride is added to TPN solutions, not only to meet cysteine needs and to enhance glutathione synthesis but also because it lowers the pH of the solution, which, in turn, enhances the solubility of the calcium and phosphorus salts.[25,26]

Glutathione is the major intracellular antioxidant, and its primary function is to protect the cell against free radical damage (eg, from peroxides). The liver synthesizes glutathione from cysteine, glutamine, and glycine. Not only is cysteine considered rate limiting for glutathione synthesis, but a lack of glutamine also may affect the rate of glutathione production.[27] Glutamine is abundant in muscle and plasma. It has a role in intestinal cell growth, a particularly important concern in parenterally nourished infants when the gastrointestinal tract is not being used. Plasma glutathione concentrations increase when glutamine is added to TPN solutions.[27] In extremely LBW infants, one study reported a shorter time to full feedings, fewer days of TPN, and less need for prolonged mechanical ventilation with the addition of glutamine to TPN.[28] A large, multicenter randomized trial, however, failed to identify a benefit of parenteral glutamine supplementation with respect to growth, protein synthesis, or host defense.[29] Routine parenteral nutrition solutions do not contain significant quantities of glutamine. Current formulations of the amino acid are not stable for prolonged periods in TPN mixtures, necessitating daily preparation.

Nitrogen retention can be augmented either by providing the best mixture of essential/nonessential amino acids, increasing the nitrogen intake, or within a narrow range by increasing the energy intake (from approximately 50 to 80 kcal/kg/d).[20] The positive relationship between energy intake and nitrogen balance for any given nitrogen intake is linear within the usual intakes of nitrogen and energy. Nitrogen balance (retention) increases markedly as energy intake is increased from 50 to 90 kcal/kg/day at the same nitrogen intake.[20,30] Understanding these principles is important when intakes of nitrogen are limited or when energy intakes are not maximized.

The use of TrophAmine and FreAmine III has been evaluated in LBW infants of 32 weeks gestation.[31] The group receiving TrophAmine had significantly greater gain in body weight and net nitrogen balance than the group receiving FreAmine III. It appears that the plasma amino acid pattern is directly related to the composition of the parenteral amino acid solution.[32] Because it was developed to ensure optimal levels, plasma amino acid patterns in

TABLE 28-6 Amino Acid Composition of Selected Parenteral Mixtures (Adjusted to 1%, 1 g Amino Acid/dL)

Component	*Aminosyn-PF (Abbott)*	*FreAmine III (Braun)*	*Novamine (Fresenius)*	*Travasol (Clintec)*	*TrophAmine (Braun)*
Essential amino acids	(48%)*	(48%)	(44%)	(40%)	(53%)
Isoleucine	76†	69	50	60	82
Leucine	120	91	69	73	140
Lysine	68	73	79	58	82
Methionine	18	53	50	40	34
Phenylalanine	43	56	69	56	48
Threonine	51	40	50	42	42
Tryptophan	18	15	17	18	20
Valine	67	66	64	58	78
Nonessential	(52%)	(52%)	(56%)	(60%)	(47%)
Alanine	70	71	145	207	54
Arginine	123	95	98	115	120
Histidine	31	28	60	48	48
Proline	81	112	60	68	68
Serine	50	59	39	50	38
Tyrosine	4	—	2.6	4	2
Glycine	39	140	69	103	36
Cysteine	—	< 2.0	—	—	< 1.6
Aspartic acid	53	—	29	—	32
Glutamic acid	82	—	50	—	50
Taurine	7	—	—	—	2.5

*Percentage of total amino acids listed; †mg/g amino acid.
Adapted from AHFS Drug Information 99.[208]

LBW infants receiving TrophAmine appear to be more "balanced" than plasma amino acid patterns of other formulations.[15,31,33,34] Thus, the importance of selecting the optimal mixture cannot be underestimated.

Serial balance studies were conducted for 3 weeks in a longitudinal study of TPN (using TrophAmine 2.2% at 130 mL/kg/day [2.9 g/kg/day] and Intralipid 20% at 20 mL/kg/day [4.0 g/kg/day]) in LBW infants.[25] Significant positive relationships were observed between nitrogen retention and intake. Based on those relationships, Table 28-7 depicts the amino acid concentration and intake needed to meet the intrauterine accretion rate for nitrogen. These and other investigations suggest that an amino acid intake of approximately 3 to 3.5 g/kg/day is appropriate for LBW infants receiving TPN.[15,25]

The use of a combined glucose and amino acid source for TPN may be initiated soon after birth.[19,35] The provision of this combination of nutritional support reverses the negative nitrogen balance attributed to a constant urinary nitrogen loss,[19,25,35,36] increases the serum concentration of essential amino acids,[19,37] and increases the rate of protein synthesis.[35,38] Doses of 1 to 3 g/kg/day have been used immediately after birth (Table 28-8).

Intravenous Lipid Emulsions

Essential fatty acids, linoleic acid ($C_{18:2\ \omega\text{-}6}$) and linolenic acid ($C_{18:3\ \omega\text{-}3}$), cannot be synthesized and thus need to be provided to the LBW infant. Without provision of these fatty acids, essential fatty acid deficiency, characterized by dermatitis, thrombocytopenia, infection, and failure to thrive, may manifest in the first week after birth. Classically, essential fatty acid deficiency is assessed by measuring the plasma triene-to-tetraene ratio. As a deficient intake results in decreased arachidonic acid (tetraene, $C_{20:4\ \omega\text{-}6}$) relative to a normal triene ($C_{20:3\ \omega\text{-}9}$) ratio, an abnormal state is characterized by a triene-to-tetraene ratio > 0.2 to 0.4. Small amounts of essential fatty acid (~ 4% of total calories or 0.5 g/kg/day) are required to prevent essential fatty acid deficiency.

Intravenous lipid emulsions containing soybean oil (or safflower oil) with glycerin and egg yolk phospholipids as emulsifiers added to the parenteral nutrition regimen in the first few days will prevent essential fatty acid deficiency,[39,40] provide needed energy for tissue healing and growth, and equalize the distribution of nonprotein calories (see Tables 28-1 and 28-9). Intravenous lipid emulsion has been used in sick LBW infants beginning on the day of birth without short-term adverse effects.[41] Intravenous lipid reportedly protects the lung from oxygen toxicity by increasing the content of polyunsaturated fatty acids in the lung.[42] This finding may be especially important in ventilator-dependent LBW infants.

The concentration of the lipid emulsion (10% versus 20%) affects the infant's tolerance of the lipid preparation. Despite similar or even greater doses of lipid, there is better tolerance of the 20% intravenous lipid solution. LBW infants receiving the 20% solution at the same or even greater lipid intakes had lower serum concentrations of triglycerides, cholesterol, and phospholipids than similar infants receiving the 10% solution.[43,44] Given the same dose of lipid, the greater volume required for the 10% solution contributes more phospholipid, cholesterol, and liposomes, which accumulate to form lipoprotein X. Lipoprotein X particles compete with lipoprotein lipase to reduce the clearing of triglycerides.[15,43,44] Thus, regardless of the dose of lipid or the age of the infant, LBW infants should receive the 20% solution.

The method of lipid infusion also affects triglyceride clearance. Intermittent infusion may produce higher serum triglyceride concentrations than continuous infusion (over a 24-hour interval) of the same dose.[45] The use of intermittent infusions and lipid-free intervals does not appear to be justified in routine circumstances.[46,47] Indeed, deleterious effects on pulmonary function have been demonstrated in adults who received large bolus doses of intravenous lipid, resulting in markedly elevated (> 300 mg/dL) plasma triglyceride concentrations.[48] For any given dose of lipid, triglyceride concentrations in LBW infants are more elevated at 1 week postnatal age than 2 to 3 weeks postnatal age.[49] Most authorities suggest using plasma triglyceride concentrations to monitor lipid tolerance. A plasma triglyceride concentration > 150 mg/dL usually is avoided. Plasma free fatty acid concentrations provide a more direct measure of lipid tolerance. Because of the complexity of the assay, however, this method is not performed routinely.

TABLE 28-7 Suggested Intakes of Parenteral Nutrients Available for Low Birth Weight Infants

Component	*Unit/kg/d*	*Unit/L*	*Molar Unit/kg/d*	*Molar Unit/L*
Amino acids*	3.0 g	24 g	—	—
Calcium	120 mg	920 mg	3.0 mmol	23 mmol
Copper	64 µg	500 µg	1.0 µmol	8 µmol
Magnesium	9.6 mg	72 mg	0.4 mmol	3 mmol
Phosphorus	87 mg	650 mg	2.8 mmol	21 mmol
Potassium	100 mg	800 mg	2.6 mmol	20 mmol
Sodium†	175 mg	1,300 mg	7.5 mmol	58 mmol
Zinc	350 µg	2,700 µg	5.4 µmol	42 µmol

Adapted from Schanler RJ et al.[25]
*Assumes TrophAmine as source.
†Derived from actual sodium intake from all sources, including medications.

TABLE 28-8 Early, Immediate Parenteral Nutrition for Low Birth Weight Infants

Component	*Quantity*	*Approximate Intake (Unit/kg/d)*
Amino acids	2.4 g/100 mL	2.4 g
Glucose	5–10 g/100 mL	5–10 g
Calcium gluconate	500–650 mg/100 mL	500–650 mg
MVI-Pediatric	2 mL/kg/d	2 mL
Heparin	1 U/mL	100 U
Lipid (by separate infusion)	5 mL/kg/d	1 g

Adapted from Nutrition and Gastroenterology Clinical Review Committee.[102]
Contains no electrolytes, phosphorus, magnesium, trace elements, or cysteine. Monitor glucose to determine whether to increase glucose infusion rate and electrolytes, phosphorus, and magnesium to determine when these are to be added. When phosphorus is added, ensure that cysteine has been added so that the solubility of minerals is optimized.

There have been some concerns regarding the worsening of pulmonary function and the potential for oxidant toxicity as a result of the use of intravenous lipid.[50–52] In vitro studies suggest that the formation of hydroperoxides in the lipid emulsion may be deleterious to lung function.[53] Clinical studies, however, do not indicate an increased risk from the administration of intravenous lipid emulsions.[54] Indeed, the concern actually may focus on the lack of appropriate antioxidants to protect the infant.[55] The use of intravenous lipid emulsion, even when administered within 12 hours of birth, was not associated with either an increase in oxygen requirement or the development of chronic respiratory disease in infants who were extremely LBW.[52] It appears that the benefits of intravenous lipid outweigh the potential risk.

Intravenous Carnitine

Carnitine is one of several conditionally essential nutrients that may be included in TPN solutions for neonates. Carnitine, present in all milks fed to infants but not included in usual TPN mixtures, has a role in fatty acid transport into the mitochondria, fatty acid oxidation, and ketogenesis. Supplementation of TPN with L-carnitine (8 to 10 mg/kg/day) results in greater plasma total and acylcarnitine concentrations in premature infants compared with control infants receiving TPN without carnitine.[56,57] Study infants who were supplemented with carnitine also appeared to have greater fatty acid oxidation as evidenced by increased ketone production.[57] Supplementation with high doses of carnitine (48 mg/kg/day), however, results in a slower weight gain and an anomalous increase in protein oxidation.[52] Thus, parenteral carnitine intakes range in doses of 10 to 20 mg/kg/day and are used until any milk is provided.

Minerals: Calcium, Phosphorus, and Magnesium

The LBW infant is prone to several clinical conditions that cause or result in abnormalities in mineral metabolism, for example, hypocalcemia, hyperphosphatemia, and hypermagnesemia. These conditions may affect how parenteral nutrition is provided. In the fetus, calcium (Ca) is transported actively from the mother, under the influence of parathyroid hormone–releasing peptide (PTHrP). Most transplacental transfer of Ca occurs in the last trimester. Postnatally, serum Ca declines, and the LBW infant may not have compensatory mechanisms to increase serum Ca. Parathyroid hormone response to hypocalcemia appears to be blunted, and some investigators report elevated calcitonin levels in LBW infants. Thus, Ca must be provided in the early postnatal period to prevent and to treat hypocalcemia. Because there is a transient period of oliguria and renal insufficiency, postnatal serum phosphorus (P) values may rise in some LBW infants. Yet, with renal maturation, serum P concentrations decline. Therefore, P must be provided in parenteral nutrition solutions. Ca and P must be provided together for optimal bone deposition; without P, bone Ca deposition is blunted, and hypercalcemia and hypophosphatemia will be manifest. Hypermagnesemia in LBW infants is not an uncommon finding following maternal magnesium therapy. However, once serum magnesium (Mg) concentrations normalize, parenteral Mg should be provided.

TABLE 28-9 Intravenous Lipid Emulsions for Low Birth Weight Infants

	Intralipid (Clintec)	*Liposyn II (Abbott)*	*Liposyn III (Abbott)*
Concentrations (%)	10, 20	10, 20	10, 20
Oil source	Soybean 100%	Soybean 50% Safflower 50%	Soybean 100%
Fatty acids (%)			
Linoleic	50	66	55
Linolenic	9	4	8
Palmitic	10	9	11
Oleic	26	18	22
Stearic	3.5	3.4	4
Egg yolk (%) phospholipids	1.2	1.2	1.2
Glycerin (%)	2.25	2.5	2.5
Energy density (kcal/mL)	1.1, 2.0	1.1, 2.0	1.1, 2.0
Osmolarity (mosm/L)	260, 260	276, 258	284, 292

Adapted from AHFS Drug Information 99.[209]

Inadequate intakes of Ca and P result in the spectrum of bone undermineralization, osteopenia of prematurity, rickets, and fractures in LBW infants.[58,59] Osteopenia may potentiate chronic lung disease because undermineralization affects chest wall stability. An increasingly more compliant chest wall leads to atelectatic changes in the lung.[60] P deficiency has been associated with diaphragmatic paralysis and respiratory failure in adults.[61] Ca and P deficiency also result in hypercalciuria and, in combination with the use of diuretics, may result in nephrocalcinosis.[62,63]

Although the direct relationship between intake and net retention aids in determining optimal intakes of these minerals, intakes are limited by the solubility of Ca and P in solution. Careful attention to pH, amino acid concentration and source, and temperature must be given to provide a recommendation for the appropriate quantity of Ca and P in TPN.[64,65] To optimize solubility further, during preparation of TPN, the P is added first and the calcium is added as the last step.

Proportional increases in Ca and P, up to 76 and 45 mg/kg/day, respectively, are retained by the infant.[65] Prestridge and colleagues demonstrated increased net retention, without increased urinary losses, when Ca intakes were increased from 60 to 80 mg/kg/day and P intakes were increased from 55 to 80 mg/kg/day, respectively.[66] The effects of the greater Ca and P intakes also were manifest by increased bone mineral content during and well beyond the 3-week TPN study interval.[66]

Daily intakes of Ca and P can be increased if each is delivered separately.[67] However, alternate-day infusion methods result in hypercalciuria and hypercalcemia when P is omitted and hyperphosphaturia and hyperphosphatemia when Ca is omitted. The two minerals, therefore, must be delivered together for deposition into bone. Indeed, abnormal serum Ca and P concentrations are observed when one of the two minerals is omitted in the

TPN solution. If P is omitted from TPN, the resulting biochemical pattern is observed: hypophosphatemia, hypophosphaturia, hypercalcemia, and hypercalciuria.

The optimal ratio of Ca to P in TPN for LBW infants is generally Ca:P ≥ 1:1 (molar).[59,68] Ratios of Ca:P < 1:1 result in elevated urinary P and serum P concentrations, suggestive of inadequate P use because of inadequate Ca intake.[66] However, it appears that the absolute quantity of Ca and P is more important than the ratio. If the quantity is limited, the ratio will affect net retention as much as an increase in the intake of the two minerals. Table 28-7 depicts the intake required to achieve the intrauterine accretion rate for Ca, P, and Mg. However, as mentioned earlier, solubility issues prevent the achievement of these intakes with current formulations. A plan for Ca and P concentrations in TPN is found in Table 28-10. Note that recommendations for Ca and P depend on the quantity of amino acids in the solution.

Early, immediate provision of parenteral nutrition solutions is provided to LBW infants. In addition to glucose, amino acids, and lipid, Ca is added to prevent/treat hypocalcemia. Generally, doses of elemental Ca of 25 to 75 mg/kg/day are used.[69] P may not be needed in the first 1 or 2 days, until the serum P normalizes (see Table 28-8).

The parenteral intakes of Mg needed to meet intrauterine accretion rates were derived in a longitudinal study evaluating serial Mg balance studies using TrophAmine 2.2% (130 mL/kg/day) and Intralipid 20% (20 mL/kg/day).[25,66] As elevated serum Mg concentrations and net retention were observed with intakes of 12 mg/kg/day, the linear relationship between intake and net retention suggested that a lower parenteral Mg intake was appropriate (see Table 28-7). That intake derived for Mg is easily attainable (see Table 28-10).

Electrolytes

Serum sodium (Na) is a useful indicator of hydration in LBW infants. Sodium needs in the early days postnatally may be determined by the serum Na. The usual parenteral needs for Na and potassium (K) are determined in each clinical circumstance, with a range of intakes recommended (see Table 28-1). Serial balance studies were conducted for 3 weeks in a study of TPN (using TrophAmine 2.2% at 130 mL/kg/day and Intralipid 20% at 20 mL/kg/day) in LBW infants.[25] It was also noted that the majority of the Na intake was derived from common medications received by the LBW infant. Significant relationships were determined between specific nutrient intake and net retention for Na and K. Thus, a derived intake for these electrolytes takes into account all potential sources for Na and K (see Table 28-7).

A relative degree of acidosis, manifest by a low serum bicarbonate concentration and a borderline low serum pH, also may occur with TPN. The LBW infant has decreased renal reabsorption of bicarbonate. Moreover, the use of amino acid solutions with low pH (generally 5.5 to 6.5) and the use of cysteine hydrochloride further reduce the pH.[15] The addition of acetate to the solution, as either the Na or K salt, has been reported to correct the acidosis. The small quantity of acetate, 1 to 2 mEq/kg/day, has not been observed to affect the solubility of the minerals in TPN solutions containing TrophAmine and cysteine hydrochloride.[26]

Trace Elements

Suggested parenteral intakes of copper (Cu) and zinc (Zn) for LBW infants have been evaluated from serial balance studies (using TrophAmine 2.2% at 130 mL/kg/day and Intralipid 20% at 20 mL/kg/day) conducted during the first 3 weeks postnatally.[18] Net retention and urinary excretion did not increase over the 3 weeks of study, suggesting that the elements were used by the infant during the early period of postnatal life.[25] As intakes were correlated with net retention, the estimated intake needed to meet the intrauterine accretion rate was determined (see Table 28-7). Estimated parenteral intakes of Zn have been reported, which are in a similar range of 350 to 450 g/kg/day.[68,70] A greater dose may be indicated in LBW infants with ongoing intestinal losses of Zn. Estimated parenteral intakes of Cu were similar to those reported by Zlotkin and Buchanan and slightly greater than those reported by Greene and colleagues.[68,70] Differences in recommendations may arise owing to the various sources of amino acids used and medical conditions of the infants studied.

An estimate of Zn status can be obtained from serum Zn concentrations that range between 70 and 120 μg/dL in adults. Severe Zn deficiency generally is associated with plasma zinc concentrations below 20 to 30 μg/dL.[68] Copper status is more difficult to define with serum indices.[71] Plasma Cu and ceruloplasmin concentrations increase with postmenstrual age.[68] At 30 weeks, plasma Cu concentrations are 35 μg/dL and at 40 weeks are between 50 and 60 μg/dL. Cu needs are increased in cases of excess biliary losses and in patients with jejunostomies. It is important to recognize that impaired biliary secretion, however, will lead to a build-up of Cu. Therefore, it is advised that Cu intakes be reduced in patients with impaired biliary excretion, such as that which occurs in cholestatic syndromes.[68]

Selenium (Se) is a component of glutathione peroxidase, and its absence from long-term TPN solutions results in a deficiency of the element.[72–74] Approximately 75% of an absorbed dose is excreted by the kidney, so Se intake should be reduced in patients with impaired renal function. The recommended intake of 2 mg/kg/day is derived from the Se intake of the term breast-fed infant.[68]

Recommendations for manganese (Mn) intakes are not clearly defined.[68] The ratio of Mn to Zn in the available trace

TABLE 28-10 Calcium, Phosphorus, and Magnesium in Total Parenteral Nutrition

	Term Usual	*Premature Short Term*	*All Long Term*	*All Special*
Calcium	1.2 (48)*	1.5 (60)	1.75 (70)	2.0 (80)
Phosphorus	1.2 (37)	1.5 (47)	1.75 (54)	2.0 (62)
Magnesium	0.21 (5)	0.25 (6)	0.25 (6)	0.25 (6)

Adapted from Lacey JM et al,[28] Greene HL et al,[68] and Schanler RJ and Rifka M.[157]
*mmol (mg)/dL.
Short term assumes total parenteral nutrition (TPN) with ≥ 2.4% amino acids + cysteine; long term assumes TPN with > 2.5% amino acids + cysteine; special assumes TPN with > 3% amino acids + cysteine.

element solution used for LBW infants provides a greater intake of Mn than presumed to be needed. Mn excretion is diminished markedly in cholestatic syndromes. The use of Mn in cholestatic disease should be avoided.

Chromium (Cr) needs may be associated with insulin activity at the receptor level.[68] Cr deficiency, therefore, may result in impaired glucose tolerance. High doses of Cr may accumulate in the body.[75] A recommended intake of approximately 0.3 μg/kg/day appears to be appropriate.

Vitamin A

Vitamin A has diverse functions, being essential for vision, growth, reproduction, cell differentiation, and immunocompetency.[76] Retinol is the dietary component present as retinyl esters (palmitate, stearate) in animal sources, and betacarotene is the vitamin A precursor of plant origin. The amount of vitamin A in the diet is quantitated as retinol equivalents (REs): 1 RE equals 1 μg all-*trans* retinol or 3.33 IU vitamin A; 6 μg betacarotene equals 1 μg retinol.

Carotene and retinyl esters are converted to retinol in the proximal small intestine. Retinol is absorbed into intestinal cells, esterified, and incorporated into chylomicrons that are transported via the lymphatics to the circulation and eventually taken up by the liver. In the liver, the vitamin is esterified and stored as retinyl palmitate.[76] Retinol is mobilized from the liver to the circulation bound with retinol-binding protein and transthyretin. More than one-third (37%) of LBW infants were found to have hepatic vitamin stores < 20 μg/g, signifying deficiency, whereas more than three-fourths (76%) had stores of < 40 μg/g.[77] Vitamin A also is stored in the lung and may be involved in growth and differentiation of the lung.[77] Therefore, LBW infants may be vitamin A deprived and their lungs susceptible to the effects of this deficiency.[77]

Photodegradation of retinol occurs when milk or an intravenous solution is exposed to light during continuous infusions, so increased light exposure should be avoided.[78,79] In addition, between 30% and 75% of the original retinol is lost by adsorption to the tubing before it reaches the infant. Greater plasma retinol concentrations occur when the vitamin is mixed with intravenous lipid emulsion or with the use of retinyl esters.[80,81]

Plasma vitamin A concentrations in LBW infants receiving TPN are low. When receiving 455 μg/day, there is no change in plasma vitamin concentrations over baseline.

Infants developing BPD reportedly have lower plasma vitamin A concentrations at 4, 14, 21, and 28 days of age compared with infants not developing BPD.[82] Randomized controlled trials of vitamin A supplementation in LBW infants susceptible to BPD have been reported.[83] In a randomized comparison of vitamin A intakes from all sources over the first month, an intake of 510 μg/kg/day was associated with less plasma vitamin A deficiency and less BPD than control infants receiving 130 μg/kg/day. Vitamin A–supplemented infants also had less airway infection and retinopathy of prematurity than control infants.[77]

Not all randomized studies observe a significant effect of vitamin A supplementation on BPD outcomes.[84] However, a recent meta-analysis suggests that supplementation with vitamin A is associated with a modest reduction in oxygen requirement at 36 weeks postmenstrual age (summary RR 0.85 [0.73, 0.98]) and a trend toward a reduction in retinopathy of prematurity.[83] Despite high vitamin A intakes in a recent large multicenter study, 24% of the supplemented group had plasma concentrations < 20 μg/dL. The authors concluded that because of the modest decrease in chronic lung disease, the safety, lack of toxicity, and low cost, further investigations using higher doses of the vitamin were warranted.[85]

Guidelines should be adopted and parenteral preparations reformulated to provide intakes that approximate 500 μg/kg/d for vitamin A, initiated within the first 12 hours after birth.[68]

Vitamin E

Vitamin E functions in humans as a biologic antioxidant: a free radical scavenger that inhibits the naturally occurring peroxidation of polyunsaturated fatty acids, components of the lipid layer of cell membranes.[86]

Daily parenteral administration of 2.1 mg is associated with normal plasma vitamin E concentrations by 48 hours.[87] Mixing the vitamin E dose with intravenous lipid increases plasma vitamin E concentrations. Early use of TPN-containing multivitamins is effective in raising plasma vitamin E concentrations to physiologic ranges within the first 24 hours.[88] Current TPN regimens recommend vitamin E intakes of 2.8 mg/kg/day (40% of a vial of MVI-Pediatric, Astra Pharmaceuticals) for infants below 2.5 kg and 7 mg/day (1 vial of MVI-Pediatric) for infants greater than 2.5 kg.[68]

Data from randomized trials in LBW infants suggest that there may be a relationship between pharmacologic doses of vitamin E and the entities of retinopathy of prematurity, BPD, and intraventricular hemorrhage. The incidence of severe retinopathy of prematurity (stage 3+plus) was 2.4% with vitamin E supplementation and 5.3% in the control group, a modest effect despite pharmacologic doses of the vitamin.[89–92] Despite initial studies demonstrating a modest effect on the reduction of BPD, pharmacologic vitamin E supplementation has not been demonstrated to reduce the severity of the disease.[93–95] If given within 12 hours of birth, vitamin E administration is associated with a reduction in the incidence and severity of intraventricular hemorrhage.[96,97] Studies demonstrating an effect of intramuscular vitamin E on intraventricular hemorrhage have suggested a target plasma concentration > 1.0 mg/dL by 24 hours and > 2 mg/dL at 3 days.[98] Those plasma vitamin E concentrations can be achieved with TPN-containing multivitamins if initiated soon after birth. Guidelines should be adopted and TPN preparations reformulated to provide intakes that approximate 3 mg/kg/day for vitamin E, which should be initiated soon after birth.

Water-Soluble Vitamins

Current formulations generally provide more water-soluble vitamins than are needed by LBW infants. Plasma ascorbate (vitamin C) and vitamin B_2 (riboflavin) concen-

trations reportedly were elevated in LBW infants receiving TPN.[80,99,100] The elevated riboflavin concentrations appear paradoxical in view of the known degradation of the vitamin under infusion and nursery lighting conditions. Thus, significantly lower doses of some of the water-soluble vitamins are indicated (Table 28-11). When used in a dose of 2 mL/kg/day (40% of the vial MVI-Pediatric), no deficiencies of thiamin or riboflavin were detected, and plasma concentrations of folate and vitamin B_{12} indicated sufficient status.[101]

Summary of Parenteral Nutrient Needs

Parenteral nutrient needs consider the needs for growth and greater energy expenditure and potential for nutrient losses as a result of illness. LBW infants receiving TPN should have biochemical monitoring to avoid excesses or deficiencies of particular nutrients (Table 28-12). Complications related to TPN therapy are recognized (Table 28-13). Early, immediate use of parenteral nutrition is important to prevent deficiencies in LBW infants. A general protocol has been devised (see Tables 28-8 and 28–14).[102]

GASTROINTESTINAL PRIMING

The lack of enteral nutrients poses several problems for the development of the intestinal tract. In several animal species, the absence of enteral nutrients is associated with diminished intestinal size and weight, atrophy of intestinal mucosa, delayed maturation of intestinal enzymes, and increases in permeability and bacterial translocation. A lack of enteral nutrients also affects intestinal motility, perfusion, and hormonal responses. The hormonal response to feeding premature infants has been evaluated by measuring the plasma concentrations of a variety of gastrointestinal hormones in response to milk feeding during the first week after birth.[103] Significant hormonal surges are noted after milk feeding, but no response is observed in absence of feeding. The responses to feeding are observed both in healthy premature infants and those with respiratory distress. Hormonal responses to small quantities of milk (24 mL) are noted for gastrin, gastric inhibitory polypeptide (GIP), and enteroglucagon, but the motilin response is not observed until the cumulative milk intake is 700 mL.[103]

The above observations prompted prospective randomized clinical studies of small volumes of milk as early minimal enteral nutrition, or gastrointestinal priming, in premature infants. When studied in the first or second week after birth, infants given "early" priming milk feeding had a better feeding tolerance when feedings were advanced, required a shorter duration of parenteral nutrition, and had a lower incidence of conjugated hyperbilirubinemia compared with similar infants given only parenteral nutrition during the same interval (Table 28-15).[104,105] Probably because of better tolerance to feeding, premature infants receiving the trophic feedings had cumulatively greater milk intakes, which was associated with lower serum alkaline phosphatase activity.[104] The lower alkaline phos-

TABLE 28-12 Nutritional Assessment for Low Birth Weight Infants Receiving Total Parenteral Nutrition

Fluid intake (mL/kg/d)	Daily
Nutrient intake (U/kg/d)	Daily
Energy intake (kcal)	
Protein intake (g)	
Specific nutrient (U)	
Anthropometry	
Body weight (g)	Same time each day
Length (cm)	Weekly
Head circumference (cm)	Weekly
Energy	
Urine glucose	Every void, then serially daily to weekly
Serum triglycerides	After dose changes or stress, then weekly
Protein	
Blood urea nitrogen (BUN)	After amino acid dose changes, then weekly
Albumin	Weekly to every other week
Prealbumin (transthyretin)	If low BUN/albumin
Minerals	
Ca, P, Mg	Ionized Ca daily for 1–3 d, then total Ca weekly Serum P daily until normal, then weekly Serum Mg daily until normal, then weekly
Alkaline phosphatase	Weekly
Na, K, Cl, CO_2	Daily, then weekly
Other laboratories	
Conjugated bilirubin, ALT	After 2 wk, start every other week
Other assessments	
Renal ultrasonography	2 mo

Adapted from Schanler RJ.[207]
ALT = alanine transaminase.

TABLE 28-11 Suggested Intakes of Vitamins for Low Birth Weight Infants Receiving Total Parenteral Nutrition

Vitamin	*Current Suggestion* (U/kg/d)*	*Best Estimate for New Formulation (U/kg/d)*	*Maximum not to Exceed Term Infant (U/d)*
Fat-soluble vitamins			
A (μg)†	280	500	700
E (mg)‡	2.8	2.8	7
K (μg)	80	80	200
D (μg)§	4	4	10
Water-soluble vitamins			
C, ascorbic acid (mg)	32	25	80
B_1, thiamin (mg)	0.48	0.35	1.2
B_2, riboflavin (mg)	0.56	0.15	1.4
B_6, pyridoxine (mg)	0.40	0.18	1.0
Niacin (mg)	6.8	6.8	17
Pantothenate (mg)	2	2	5
Biotin (μg)	8	6	20
Folate (μg)	56	56	140
Vitamin B_{12} (μg)	0.40	0.30	1.0

Adapted from Lacey JM et al[28] and Schanler RJ.[207]
*Practical approach using 40% of a vial of MVI-Pediatric (Astra Pharmaceutical Products, Westborough, MA) per kg body weight or 2 mL/kg/d.[68]
†1 μg retinol = 3.33 IU vitamin A = 6 μg betacarotene = 1.83 μg retinyl palmitate = 1 retinol equivalent.
‡1 mg "α-tocopherol = 1 IU vitamin E.
§1 μg vitamin D (cholecalciferol) = 40 IU vitamin D (cholecalciferol).

TABLE 28-13 Complications of Parenteral Nutrition

Mechanical
Infiltration
Skin slough
Air embolism
Infection
Liver dysfunction
Renal stones
Bone disease

Adapted from Schanler RJ.[207]

phatase activity, primarily of bone origin, was observed for 14 weeks, well beyond the initial intervention in the first week. Significant stimulation of gastrointestinal hormones, such as gastrin and GIP, also was reported following the early feeding of small quantities of milk.[106] Intestinal motility patterns matured more rapidly in premature infants receiving early enteral feeding.[107] Subsequent investigations demonstrated that trophic feeding was associated with greater absorption of Ca and P, greater lactase activity, and a reduced intestinal permeability.[108–110] The meta-analysis of several studies of gastrointestinal priming indicated that its use was associated with a shorter time to regain birth weight, fewer days when feeding was withheld, and a shorter duration of hospitalization but no increase in the incidence of necrotizing enterocolitis.

Noteworthy in the studies of minimal enteral nutrition is that the subject population consisted of premature infants selected because they had the greatest risk of feeding intolerance and necrotizing enterocolitis. For example, feedings were administered during mechanical ventilation and while umbilical arterial and venous catheters were in place.[104,105,111] The infants also had the usual morbidities of patent ductus arteriosus, intraventricular hemorrhage, and systemic hypotension. These data suggest that by the end of the first week after birth, in the absence of major cardiovascular instability (severe acidosis, hypotension, hypoxemia), the intestinal tract of the premature infant can be primed with small volumes of milk. In general, for infants who are ill, the small volumes of 10 to 20 mL/kg/d continue for approximately 4 to 7 days before there is any consideration of advancing the milk volume.[108] The decision for advancement of feedings, however, is made after clinical feeding tolerance is proven and clinical stability is achieved.

ENTERAL NUTRITION

PROTEIN

Milk Composition In the first few weeks after birth, the protein content of milk from mothers who deliver premature infants (preterm milk) is greater than term milk, the milk obtained from women delivering term infants.[112] The protein content in both milks declines, such that beyond 2 weeks, it levels off to what we call mature milk (Table 28-16). The quality of protein (eg, the proportion of whey and casein) in human milk is particularly suitable for the premature infant. Human milk contains 70% whey and 30% casein, whereas bovine milk contains 18% whey and 82% casein. A whey- and/or casein-dominant commercial formula, therefore, refers to these proportions of bovine milk. The whey fraction of milk consists of soluble proteins that are digested more easily. Human milk and then whey-dominant bovine milk, in that order, promote more rapid gastric emptying than casein-dominant milk.[113] Ele-

TABLE 28-14 Suggested Preparation of Total Parenteral Nutrition Solution for Low Birth Weight Infants

Component	*Concentration/Additive*	*Target Intake*
Glucose	12.5%	(Glucose = 16 g/kg/d)
Amino acids*	2.4%	(Amino acids = 3.1 g/kg/d)
Cysteine HCl	30 mg/g amino acids	
NaCl	2.6 mmol = 2.6 mEq	(Na = 3.4 mmol/kg/d)
KCl	0–0.2 mmol (mEq)	(Total K = 3.1–3.8 mmol/kg/d)
K_2PO_4-$KHPO_4$†	1.5–2.0 mmol P	(P = 2.0–2.6 mmol/kg/d)
Ca gluconate‡	1.5–2.0 mmol Ca	(Ca = 2.0–2.6 mmol/kg/d)
$MgSO_4$	0.25 mmol = 0.5 mEq	(Mg = 0.3 mmol/kg/d)
MVI-Pediatric§	40% of vial (2 mL/kg/d)	
MTE-5‖	0.1 mL/kg/d	(Zn, Cu, Mn, Cr, Se)
$ZnSO_4$	200 μg/kg/d	(Total Zn = 300 μg/kg/d) (Cu = 40 μg/kg/d) (Mn = 10 μg/kg/d) (Cr = 0.4 μg/kg/d) (Se = 2 μg/kg/d)
Heparin	1 U/mL	
Intralipid 20%#	5–20 mL/kg/d	
Total fluid	150 mL/kg/d	

Adapted from Schanler RJ.[207]

*TrophAmine (McGaw).

†Monobasic-dibasic phosphate contains 1.4 mmol K/mmol P or 1.3 mmol Na/mmol P, depending on the preparation used. Use the higher P concentration for total parenteral nutrition (TPN) duration > 2 weeks.

‡Use the higher concentration for TPN duration > 2 weeks. Add last in the preparation of TPN.

§Astra Pharmaceutical Products (Westborough, MA).

‖Lyphomed (Deerfield, IL).

#Begin lipid at 1 g/kg/d and increase stepwise to 4 g/kg/d.

TABLE 28-15 Advantages of Gastrointestinal Priming

Shortens time to regain birth weight
Improves feeding tolerance
Reduces duration of parenteral nutrition
Enhances enzyme maturation
Reduces intestinal permeability
Improves gastrointestinal motility
Matures hormone responses
Improves mineral absorption, mineralization
Lowers incidence of cholestasis
Reduces duration of phototherapy
Earlier use of mother's milk
Mothers begin milk expression earlier
Infants receive more mother's milk
Psychological advantage for mothers
Safety

vated concentrations of potentially toxic amino acids (phenylalanine, methionine, and tyrosine) are reported in premature infants fed formulas with high casein contents.[114,115] Hepatic enzyme immaturity may explain the higher plasma amino acid concentrations. Because we infer that elevations of particular amino acids may be toxic to brain development, there may be a concern when feeding premature infants a casein-dominant milk, especially at a high protein intake.

The composition of the whey fractions of human and bovine milks differs significantly. The major human whey protein is α-lactalbumin, a nutritional protein for the infant and a component of mammary gland lactose synthesis. Lactoferrin, lysozyme, and secretory immunoglobulin A (IgA) are specific human whey proteins that are particularly resistant to hydrolysis and, as such, line the gastrointestinal tract to play a primary role in host defense.[116] These proteins, therefore, may be suitable for the premature infant who is exposed to multiple pathogens in the nursery environment. The three host defense proteins are present only in trace quantities in bovine milk. The major whey protein in bovine milk is α-lactoglobulin, the protein often blamed for bovine milk protein allergy and colic.[117]

The major amino acid for the fetus and in human milk is glutamine, which is not found in commercial formula because of problems with stability of the free amino acid. Glutamine, however, is an important amino acid for cell growth, specifically intestinal epithelial growth, has a role in immune function, and is a precursor in glutathione synthesis. When commercial formula was supplemented with glutamine under experimental conditions, premature infants had better feeding tolerance and a significantly lower incidence of sepsis than infants fed unsupplemented formula.[118] Further research efforts are under way to define how to supply this amino acid if human milk is not fed.

Protein Needs The quantity and quality of protein needed for premature infants have been investigated.[119] Formulas providing protein intakes of 2.25 and 4.50 g/kg/day as either whey- or casein-dominant preparations and pasteurized human milk with a protein intake of approximately 1.6 g/kg/day were compared. Although absolute growth rates reportedly were similar during the in-hospital study, hospital duration was longer for the infants fed human milk, suggesting a slower rate of weight gain than infants fed formula.[114,115] Those infants receiving protein intakes of 4.5 g/kg/day, as well as infants given casein-dominant milk, had more abnormalities in plasma amino acids and protein indices of nutritional status (elevated blood concentrations of urea nitrogen and ammonia, acidosis, lethargy, and fever), suggesting excessive protein intake.[120] Although generally considered excessive protein intake, 4.5 g/kg/day were provided with relatively low energy (115 kcal/kg/day) and mineral intakes. Some investigators comment that energy and mineral intakes may have limited the ability to use the protein and that such intakes may be appropriate if the total diet is adjusted.

The appropriate protein intake for premature infants has been defined further from evaluations of weight gain, nitrogen retention, and serum biochemical indicators of protein nutritional status.[121,122] Protein intakes of 2.2 and 2.8 g/kg/day resulted in lower serum indices, weight gain, and nitrogen retention, and intakes of 3.8 g/kg/day appeared somewhat excessive. Therefore, protein intakes of approximately 3.5 g/kg/day at 120 kcal/kg/day seem appropriate for the otherwise normal premature infant.[121]

An alternate way to compute the protein needs of the premature infant is to use the factorial approach to add the needs for tissue deposition, derived from intrauterine accretion rates of 1.8 to 2.2 g/kg/day, to the postnatal losses of protein from the skin (approximately 0.2 g/kg/day) and the urine (1.0 g/kg/day). As approximately 85% of the protein is absorbed, the calculated enteral protein intake is 3.5 to 4.0 g/kg/day. A range of protein intakes is found if all

TABLE 28-16 Nutrient Composition of Human Milk and Selected Fortified Human Milk

	Human Milk (1 wk)	*Mature Human Milk (1 mo)*	*Mature Human Milk + Human Milk Fortifier*
Volume, mL	100	100	100
Energy, kcal	67	70	84
Protein, g	2.4	1.8	2.8–2.9
Whey/casein (%)	70/30	70/30	70/30
Fat, g	3.8	4.0	4.4–4.7
MCT (%)	2	2	10–15
Carbohydrate, g	6.1	7.0	7.2–8.8
Lactose (%)	100	100	80–85
Calcium, mg	25	22	112–139
Phosphorus, mg	14	14	64–81
Magnesium, mg	3.1	2.5	3.5–9.5
Sodium, mEq (mmol)	2.2	1.3	1.8–2.0
Potassium, mEq (mmol)	1.8	1.5	2.2–3.1
Chloride, mEq (mmol)	2.6	1.7	2.1–2.8
Zinc, μg	500	320	1,030–1,320
Copper, μg	80	60	104–230
Vitamin A, IU	560	400	1,020–1,350
Vitamin D, IU	4	4	124–154
Vitamin E, mg	1.0	0.3	3.5–4.9

Adapted from references 147, 172, 210, and 211.
Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, IN) and Similac Human Milk Fortifier (Ross Laboratories, Columbus, OH). Prepared according to manufacturers' directions: 4 packets + 100 mL mature milk.
MCT = medium-chain triglycerides.

TABLE 28-17 Nutrient Composition of Fortified Human Milk, Premie Formula, Enriched Formula, and Term Formula as Directed for Standard Formulation

	FHM	*Premie*	*Enriched*	*Term*
Volume, mL	100	100	100	100
Energy, kcal	84	81	73	67
Protein, g	2.8–2.9	2.2–2.4	1.9–2.1	1.4
Whey/casein (%)	70/30	60/40	50/50	60/40
Protein calories (%)	12	11–12	10–11	8
Fat, g	4.4–4.7	4.0–4.4	4.0–4.4	3.6
MCT (%)	10–15	40–50	20–25	2
Fat calories (%)	47–50	44–49	48–49	48
Carbohydrate, g	7.2–8.8	8.5–9.0	7.7–8.0	7.3
Lactose (%)	80–85	40–50	40–50	100
CHO calories (%)	39–42	42–44	42–43	43
Calcium, mg	112–139	130–145	78–90	53
Phosphorus, mg	64–81	65–80	45–50	29–36
Magnesium, mg	3.5–9.5	5.5–9.7	6.0–6.7	4.0 - 5.4
Sodium, mEq (mmol)	1.8–2.0	1.3–1.5	1.1	0.8
Potassium, mEq (mmol)	2.2–3.1	2.1–27	2.0–2.7	1.9
Chloride, mEq (mmol)	2.1–2.8	1.9–2.0	1.6–1.7	1.2
Zinc, µg	1,030–1320	1,200	900	500–680
Copper, µg	104–230	100–200	90	50–60
Iron, mg	0.4–1.5	1.4	1.3	1.2
Vitamin A, IU	1,020–1,350	1,000	340	200
Vitamin D, IU	124–154	120–220	52–60	40
Vitamin E, mg	3.5–4.9	3.2–5.1	2.7–3.0	1.4–2.0
Osmolality, mOsm/L	300–350	250–270	220–255	270
Renal solute load, mOsm	14	15	13	9–10

FHM = Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, IN) and Similac Human Milk Fortifier (Ross Laboratories, Columbus, OH), 4 packets + 100 mL mature human milk; Premie = Similac Special Care with iron (Ross) and Enfamil Premature Formula with iron (Mead Johnson); Enriched = NeoSure (Ross) and EnfaCare (Mead Johnson); Term = Enfamil with iron (Mead Johnson) and Similac with iron (Ross).
CHO = carbohydrate; MCT = medium-chain triglycerides.

products available are considered (Table 28-17). However, the above computations provide the basis on which to select products designed for LBW infants (fortified human milk and preterm formula).

The above studies were conducted using formulations with whole or intact protein. Although fetal nitrogen uptake is composed primarily of amino acids, no data suggest that postnatal formulations include hydrolyzed proteins or free amino acids. Whey-dominant protein formulations are well absorbed, and the provision of hydrolyzed protein formulations, usually casein derived, for the otherwise healthy premature infant is not indicated (Table 28-18).

Protein needs should be considered in conjunction with energy. Protein synthesis requires energy. If energy intake is inadequate, protein synthesis may be depressed and amino acid oxidation may increase.[123] Protein retention, or balance, generally is a function of protein intake if energy intake is adequate.[20] Excessive protein intake is more of a risk if energy intake is limited.

Human Milk Protein Needs The aforementioned studies demonstrated that the lowest plasma concentrations of amino acids, albumin, and urea nitrogen and the slowest rates of weight gain were found in the human milk–fed premature infants.[119,124] These observations suggest that after the early 2 weeks of feeding, the lower protein intakes in human milk–fed premature infants may become a concern. To meet protein needs, the human milk–fed premature infant needs a protein supplement (see Table 28-16). Growth rates and serum protein and urea nitrogen concentrations in premature infants increase when human milk is fortified with protein to achieve a protein intake of at least 3 to 3.5 g/kg/day.[125] This range of protein intake is adequate assuming that no protein deficit has arisen as a result of a prolonged or deficient parenteral nutrition phase. For this reason, greater intakes of protein may be necessary for premature infants to allow for catch-up protein nutritional support. Thus, intakes closer to 4 g/kg/day, with adequate energy and mineral intakes, often may be indicated.

FAT

Human Milk Lipid Composition The lipid system in human milk is structured in a way that facilitates fat digestion and absorption; there is an organized human milk fat globule containing an outer protein coat and an inner lipid core. The pattern of fatty acids (high in palmitic $C_{16:0}$, oleic $C_{18:1}$, linoleic $C_{18:2\ \omega\text{-}6}$, and linolenic $C_{18:3\ \text{-}3}$), their distribution on the triglyceride molecule ($C_{16:0}$ at the 2-position of the molecule), and the presence of bile salt–stimulated lipase.[126] Because the lipase is heat labile, the superior fat absorption from human milk is reported only when unprocessed milk is fed.[126]

The most variable nutrient component in human milk is fat, the major energy source, comprising nearly 50% of the calories. The fat content of human milk varies among

TABLE 28-18 Comparison of Hydrolysate Formula with Premie, Enriched, and Term Formulas, All Prepared to 24 kcal/oz (81 kcal/d)

	Hydrolysate	*Premie*	*Enriched*	*Term*
Volume, mL	100	100	100	100
Energy, kcal	81	81	81	81
Protein, g	2.3	2.2–2.4	2.2	1.7
Whey/casein (%)	0/100	60/40	50/50	60/40
Protein calories (%)	11	11–12	11	8
Fat, g	4.5	4.1–4.4	4.3	4.3
MCT (%)	55	40–50	20–25	2
Fat calories (%)	49	46–49	48	48
Carbohydrate, g	8.3	8.5–9.0	8.7	8.9
Lactose (%)	0	50	40–50	100
CHO calories (%)	40	42–44	42	43
Calcium, mg	76	130–145	97	63
Phosphorus, mg	50	65–80	53	43
Magnesium, mg	8.8	5.5–9.7	6.7–7.4	6.0
Sodium, mEq	1.3	1.3–1.5	1.2	1.0
Potassium, mEq	2.3	2.1–27	2.2–2.9	2.3
Chloride, mEq	2.0	1.9–2.0	1.8	1.4
Zinc, µg	750	1,200	1,000	800
Copper, µg	75	100–200	100	80
Vitamin A, IU	300	1,000	360	240
Vitamin D, IU	60	120–220	65	49
Osmolality, mOsm/L	380	250–270	280	360
Renal solute load, mOsm	20	15	14	11.5

Hydrolysate = Pregestimil (Mead Johnson) is a casein hydrolysate preparation; Premie = Similac Special Care with iron (Ross) and Enfamil Premature Formula with iron (Mead Johnson); Enriched = NeoSure (Ross) and EnfaCare (Mead Johnson); Term = Enfamil with iron (Mead Johnson) and Similac with iron (Ross).
CHO = carbohydrate; MCT = medium-chain triglycerides.

women, changes during the day, rises slightly during lactation, and increases dramatically within a single milk expression (Table 28-19).[127] The variability in total fat content is unrelated to maternal dietary fat intake. Because it is not homogenized, on standing, the fat separates out of human milk. The separated fat may adhere to collection containers, feeding tubes, and syringes. The loss of fat, therefore, robs the premature infant of needed energy. The greatest losses of fat occur from continuous milk infusion systems. Care should be taken when using the continuous milk infusion system to ensure the inclusion of only a short length of tubing. If the system contains a cassette interface, much of the fat will be lost when the tubing system is changed. Milk infusion systems that use a syringe and small infusion pump, where the syringe is oriented upright, will allow more complete delivery of fat.[128] Fat loss was reduced from 48% to less than 8% with the change in methods of continuous infusion.

Manufacturers of infant formulas modify their fat blends to mimic the fat absorption from human milk. This accounts for the differences in the constituent fatty acids between human milk and cow's milk–based formulas. Generally, commercial formulations have a greater quantity of medium-chain fatty acids (MCFAs) to compensate for the absence of lipase and the unique structure of triglyceride in human milk.[126,129] In human milk, saturated fatty acid, particularly palmitic acid, is esterified in the 2-position of the triglyceride molecule. The end product of digestion of the triglyceride is a 2-monoglyceride and minimal free fatty acid. The 2-monoglyceride is absorbed better than with the free fatty acid. This is important because free palmitic acid has a great tendency to bind with minerals to form soaps. In that case, both fat and mineral absorption would be limited. Thus, the overall structure of human milk is designed to provide optimal fat and mineral absorption.

Hindmilk The variability in the fat content of human milk may be made advantageous for the premature infant. Most milk transfer during a feeding occurs in 10 to 15 minutes, but continued milk expression yields a milk with a progressively higher fat content (hindmilk) than the earlier foremilk. The fat content of hindmilk may be 1.5- to 3-fold greater than that of foremilk. The use of hindmilk in selected cases may provide the premature infant with additional energy. Fractionation of each milk expression into two portions, foremilk and hindmilk, is practical if the mother's milk production is greater than needed by her infant. The additional fat and therefore energy intake from hindmilk has been shown to improve the body weight gain in premature infants.[130] The composition of foremilk and hindmilk has been examined (see Table 28-19). No differences between fractions were observed for the contents of nitrogen, Ca, P, Na, or K. Cu and Zn concentrations declined by approximately 5% from foremilk to hindmilk.

The differences between foremilk and hindmilk also should be considered in terms of the distribution of calories. Fat and protein comprised 42% and 12% of calories in foremilk and 55% and 9% of calories in hindmilk, respectively. Theoretically, the long-term feeding of hindmilk could exert a negative effect on protein status. A greater proportion of protein calories (10 to 12%) is recommended for premature infants. Usual commercial human milk fortifiers (see Tables 28-16 and 28-19), when mixed with hindmilk, raise the proportion of protein calories in hindmilk to approximately 12%. The use of hindmilk, therefore, can be recommended for premature infants whose rate of weight gain is low (below 15 g/kg/day).

TABLE 28-19 Composition of Foremilk and Hindmilk (Mean ± SD)

	Foremilk (U/dL)	*Hindmilk (U/dL)*
Energy (kcal)	63 ± 11	82 ± 8
Fat (g)	2.9 ± 0.8	4.8 ± 0.9
Total nitrogen (mg)	210 ± 27	210 ± 32
Calcium (mg)	27 ± 4	27 ± 4.4
Phosphorus (mg)	15 ± 3	16 ± 3
Zinc (μg)	291 ± 88	275 ± 88
Copper (μg)	29 ± 1	27 ± 1
Sodium (mEq)	0.3 ± 0.1	0.3 ± 0.1
Potassium (mEq)	1.1 ± 0.1	1.1 ± 0.1

Adapted from Valentine CJ et al.[130]

Essential Fatty Acids The essential fatty acids, linoleic and linolenic acids, are present in ample quantities in human milk and commercial formula. Without an adequate intake of these fatty acids, essential fatty acid deficiency (thrombocytopenia, dermatitis, increased infections, and delayed growth) develops in 1 week. Approximately 0.5 g/kg/day (~4% of total energy intake) of essential fatty acids will prevent the deficiency.[40] Derivatives of linoleic and linolenic acids are arachidonic acid ($C_{20:4\ \omega\text{-}6}$) and docosahexaenoic acid ($C_{22:6\ \omega\text{-}3}$). The very long-chain polyunsaturated fatty acids (LCPUFAs), which are found in human but not bovine milk, are components of phospholipids found in brain, retina, and red blood cell membranes.[131,132] Arachidonic and docosahexaenoic acids functionally have been associated with body growth, vision, and cognition.[132,133] In addition, the fatty acids are integral parts of prostaglandin metabolism. When their diet was supplemented with LCPUFAs, formula-fed premature infants had red blood cell concentrations of $C_{22:6\ \omega\text{-}3}$ that parallel those of similar infants fed human milk.[131] Follow-up studies of such supplemented infants suggest improvements in visual acuity and short-term neurodevelopmental measures compared with unsupplemented infants but of similar magnitude to infants fed human milk.[133–135] The consensus is that premature infants should receive LCPUFAs via either human milk or supplemented formula.

Medium-Chain Fatty Acids The proportion of MCFAs, here defined as carbon length 6:0 to 12:0, is below 12% of total fatty acids in human milk but approaches 50% in preterm formulas (see Table 28-17). MCFAs are not essential fatty acids. Previous reports suggested that MCFA were absorbed passively and to a greater extent than long-chain fatty acids (LCFAs) and affected growth and mineral absorption positively.[136,137] Data comparing premature infants receiving MCFAs at 42% versus 7% of total fatty acids in a

crossover design demonstrated no differences in either the absorption of fat or weight gain.[138] Similarly, no differences in nitrogen retention, weight gain, and energy digestibility, expenditure, and storage were found in premature infants participating in a randomized, crossover study of formulas with MCFAs at 46% versus 4%.[139] Other reports also confirm the lack of effect of MCFAs on weight gain and mineral absorption compared with exclusively LCFA diets.[140] When used in a high proportion, MCFAs may be incompletely oxidized and contribute to increased urinary dicarboxylic acid excretion and metabolic inefficiency compared with LCFAs.[141,142] When added exogenously to milk, MCFAs have been reported to adhere to feeding tubes and diminish fat delivery to the infant.[143] Thus, there are no compelling data to suggest that a high proportion of MCFAs is needed for preterm formulas. Indeed, formulas containing a very high proportion of MCFAs (> 80%) may produce essential fatty acid deficiency if fed for a prolonged period of time.

Carnitine Carnitine is synthesized from lysine and methionine and serves as an important effector of fatty acid oxidation in the mitochondria. The provision of carnitine in the diet results in improved fatty acid oxidation.[57] Human milk contains abundant carnitine, and all infant formulas are supplemented with carnitine.

Carbohydrate

The carbohydrate fraction of human milk is composed of lactose (90 to 95%) and oligosaccharides (5 to 10%). The lactose content of human milk rises from 55 g/L in colostrum to 70 g/L in mature milk. Although studies in term infants demonstrate a small proportion of lactose in the feces, the presence of lactose is assumed to be a normal physiologic effect of feeding human milk. A softer stool consistency, more nonpathogenic bacterial fecal flora, and improved absorption of minerals have been attributed to the presence of small quantities of unabsorbed lactose in feces.[144] Dietary lactose also has been associated with increased mineral absorption.[145] Theoretic concerns that lactose may not be digested adequately by premature infants less than 34 weeks postnatal age may be unfounded as clinical studies indicate that they tolerate the feeding of lactose-containing milk. Premature infants absorb > 90% of the lactose in human milk.[146] The feeding of milk, in particular human milk, in premature infants stimulates intestinal lactase activity compared with no feeding or formula feeding.[109] Thus, early feeding of human milk also may be beneficial to promote better lactose use.

Because of conflicting data regarding lactose use by premature infants, and as a result of attempts to reduce the osmolality of the milk, preterm formulas contain a large proportion of carbohydrate as corn syrup solids (glucose polymers).[145] The usual lactose-to-glucose polymer mixture is 50:50. Glucose polymers are well absorbed by premature infants.

Calcium and Phosphorus

Ca and P are primary components of the skeleton, accounting for 99% and 85%, respectively, of bone mass. The goal for premature infant nutrition is to achieve a bone mineralization pattern similar to the fetus and to avoid osteopenia and fractures. Preterm human milk contains approximately 250 mg/L and 140 mg/L, respectively, of Ca and P.[147] In contrast, the Ca and P content of enteral products designed for premature infants in the United States is significantly greater (see Tables 28-17 and 28-18). In human milk, Ca and P exist in ionized and complexed forms that are easily absorbed. The salts in commercial formulas, however, are relatively insoluble. Thus, in the design of commercial formulas, greater quantities of these minerals are added to compensate for their poorer bioavailability. However, distinct from the term infant, the premature infant requires significantly greater quantities of Ca and P than can be provided in human milk.

For the human milk–fed premature infant, Ca and P intakes are deficient throughout lactation and far below those necessary to achieve respective intrauterine accretion rates.[148] Skeletal radiographs may reveal poor bone mineralization, rickets, and fractures in the premature infant fed human milk.[149] Deficient intakes of Ca and P are associated with biochemical markers, such as low serum and urine P concentrations, elevated serum alkaline phosphatase activity, and elevated serum and urine Ca concentrations.[150] Usually, serum P concentrations are the best indicator of Ca and P status in human milk–fed premature infants.[151] Prolonged deficiency of these minerals tends to stimulate bone resorption to normalize serum Ca concentrations. This bone activity often is correlated with elevated serum alkaline phosphatase activity. It has been reported that the majority of premature infants having an elevated serum alkaline phosphatase activity were those fed human milk.[152] Moreover, follow-up of the same infants at 9 and 18 months noted that linear growth was significantly lower in the group that had the higher serum activity of alkaline phosphatase in the neonatal period.[152] A high alkaline phosphatase value in the neonatal period is a negative predictor of height in 9- to 12-year-old adolescents.[153]

The supplementation of human milk with both Ca and P not only improves the net retention of both minerals but also improves bone mineral content.[154,155] Current management of human milk–fed premature infants emphasizes the need for supplements of both Ca and P.[156] A linear relationship exists between Ca (or P) intake and net retention in enterally fed premature infants.[157] Premature infants receiving unfortified human milk never achieve intrauterine accretion rates for Ca and P. Intakes of Ca and P of approximately 200 and 100 mg/kg/d, respectively, can be achieved with the use of specialized human milk fortifiers and preterm formulas, thus making it possible to meet intrauterine estimates (see Tables 28-17 and 28-18). However, term infant formulas and specialized (not "preterm") formulas provide inadequate quantities of Ca and P to meet the needs of growing premature infants (see Table 28-18). Several factors affect the absorption of Ca and P, including postnatal age and intake of Ca, P, lactose, fat, and vitamin D. Vitamin D, however, is responsible for only a small component of Ca absorption in premature infants.[158]

The time to supply sufficient Ca and P stores for premature infants is during the initial hospitalization, before their discharge and the beginning of exclusive breastfeeding. However, because of prolonged parenteral nutrition and the inability to provide "catch-up" quantities of Ca and P in milks, some infants may benefit from additional Ca and P after hospital discharge.

Magnesium

Approximately 60% of body Mg is in bone. Preterm human milk contains approximately 30 mg/L of Mg.[147] The absorption of Mg is significantly greater in unfortified human milk (73%) compared with formula (48%).[157] Net Mg retention in human milk–fed premature infants meets intrauterine estimates. Thus, the data from balance studies and biochemical monitoring suggest that Mg supplements are not needed for premature infants fed human milk.[159] Similar studies in premature infants fed preterm formulas indicate that, despite lower absorption compared with human milk, intrauterine estimates for Mg accretion are surpassed.

Trace Elements

Zinc Several factors affect the zinc needs for the enterally fed premature infant. Fetal accretion of zinc is approximately 0.85 mg/kg/day. Growth is a major determinant of zinc needs. The major excretory route is via the gastrointestinal tract. Infants with large gastrointestinal fluid losses may become Zn deficient. Premature infants receiving pooled pasteurized human milk (Zn intake approximately 0.7 mg/kg/day) are in negative Zn balance for 60 days postnatally and never meet the intrauterine accretion rate.[160] In contrast, intakes of 1.8 to 2 mg/kg/day are associated with net retention of Zn that surpasses intrauterine accretion rates.[161–163] The classic signs of Zn deficiency include an erythematous skin rash involving perioral, perineal, and facial areas, as well as the extremities.[123] Although there are limitations to the assay, plasma Zn values < 50 μg/dL are highly suggestive of deficiency.[123] A very low serum alkaline phosphatase activity, a Zn-dependent enzyme, also is suggestive of deficiency. Reports of symptomatic Zn deficiency in unsupplemented human milk–fed premature infants remind us of the decline in milk Zn concentration as lactation advances. The infants reported to be Zn deficient were several months of age.[164]

Copper There are no universally accepted methods to assess Cu status clinically. Balance study data provide only an estimate of Cu retention at one point in time. Premature infants receiving pooled pasteurized human milk (Cu intakes approximately 85 μg/kg/day) are in negative Cu balance for 30 days postnatally and never meet the intrauterine accretion rate.[160] Fortified human milk provides a Cu intake of as much as 180 μg/kg/day, and balance study data surpass intrauterine accretion rates.[163] Cu retention is quite variable from formula providing intakes of 200 to 300 μg/kg/day.[161,163] Several premature infants with those intakes, however, achieve the intrauterine accretion rate. Symptoms of Cu deficiency include osteopenia, neutropenia, and hypochromic anemia. As Cu is excreted in bile, cases of severe cholestasis warrant limiting Cu intakes.

Iron The iron (Fe) needs of the premature infant are determined by birth weight, initial hemoglobin, rate of growth, and magnitude of Fe loss and/or transfused blood.[123] There are three phases of postnatal Fe metabolism. In the first phase, there is decreased erythropoiesis. The hemoglobin concentration declines to a nadir, "physiologic anemia of prematurity," which is at approximately 2 to 3 months postnatal age. In the second phase, the hemoglobin rises as active red cell production is occurring. This phase needs Fe. The third phase is an exhaustion of Fe stores, or "late anemia of prematurity," observed if Fe supplementation is inadequate.[123]

The concentration of Fe in human milk declines through lactation, from approximately 0.6 mg/L at 2 weeks to 0.3 mg/L after 5 months of lactation.[165] The absorption of Fe is affected adversely by blood transfusion.[166] Premature infants fed human milk are in negative Fe balance, which, if untransfused, corrects with Fe supplements.[166] Fe absorption also appears to be facilitated by a modest degree of anemia.[167] Thus, the usual recommendations for premature infants suggest delaying Fe supplementation until 2 to 3 months postnatal age, a time when hemoglobin concentrations are at a nadir.[168] However, the provision of small doses of Fe at 2 mg/kg/day beginning 2 weeks postnatally has been demonstrated, in the absence of blood transfusions, to prevent the development of Fe deficiency at 3 months postnatal age.[168] When recombinant erythropoietin for the treatment of anemia of prematurity is used, higher doses of Fe are needed, in the range of 6 mg/kg/day, to support the more rapid rate of erythropoiesis.[169]

Generally, ferrous sulfate (25 mg/mL, 2 mg/kg/day) drops are used in human milk–fed premature infants beginning soon after the achievement of complete enteral feedings. Formula-fed premature infants should receive Fe-fortified formula from the onset of milk feeding.

Sodium and Potassium Premature infants generally need more Na per unit body weight than term infants.[123] This is attributable to immature renal Na conservation mechanisms. Na wasting is inversely related to gestational age. A comparison of Na intakes of 2.9 and 1.6 mEq (mmol)/kg/day in premature infants suggested that the former intake provided more appropriate serum Na concentrations.[170] Hyponatremia also may occur in premature infants primarily fed human milk because the Na content of preterm milk continues to decline through lactation.[170] The need for these electrolytes may increase during or after diuretic use.

Vitamins Fat-soluble vitamins, A, D, E, and K, are stored in the body, and large doses may result in toxicity. Water-soluble vitamins, thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and vitamin C, are not stored in the body, and excess intakes are excreted in the urine or bile (vitamin B_{12}). The intake of water-sol-

uble vitamins, therefore, should be at frequent intervals to avoid deficiency states. Vitamin A and riboflavin concentrations decline in human milk under conditions of light exposure and after passage through feeding tubes.[79] As a consequence of exposure to air, ascorbic acid concentrations are lower in pooled human milk.[171] Supplementary vitamins are provided in human milk fortifiers and in preterm formulas.[172] There is no indication for additional multivitamin supplements for infants receiving adequate intakes of fortified human milk, preterm formula, or enriched formula. Once the premature infant transitions to unfortified human milk or standard formula, a multivitamin supplement should be added. The supplemental vitamins should be continued until the infant is consuming 300 kcal/day or weighs more than 2.5 kg.

HUMAN MILK

The American Academy of Pediatrics acknowledges that human milk also is beneficial in the management of premature infants.[173] The beneficial effects generally relate to improvements in host defenses, digestion and absorption of nutrients, gastrointestinal function, neurodevelopment, and maternal psychological well-being. However, the special needs of the premature infant that arise as a result of metabolic and gastrointestinal immaturity, immunologic compromise, and associated medical conditions must be considered so that adequate nutrition can be provided to meet the needs for intrauterine rates of growth and nutrient accretion. Human milk is capable of satisfying most of the needs of premature infants if careful attention is given to nutritional status.

Benefits of Unfortified Human Milk

Clinical studies in nurseries throughout the world have suggested a decrease in the rate of a variety of infections, including sepsis, necrotizing enterocolitis, and urinary tract infection, in premature infants fed human milk compared with the feeding of formula.[174,175]

Necrotizing enterocolitis, the devastating acute intestinal inflammatory disease in premature infants, appears less frequently when the prior diet is human milk compared with formula. A large, nonrandomized study of hospitalized premature infants reported that the incidence of necrotizing enterocolitis was significantly lower in infants fed human milk, either exclusively or partially, compared with infants fed formula.[176] That study reported clinical cases as well as cases confirmed at surgery or autopsy, and in both circumstances, the incidence of necrotizing enterocolitis was significantly greater in premature infants solely fed formula. These data provide some encouragement for the potential prevention of necrotizing enterocolitis.

Specific factors such as secretory IgA, lactoferrin, lysozyme, oligosaccharides, cytokines (such as interleukin-10), enzymes (such as acetylhydrolase), growth factors (such as epidermal growth factor), and cellular components may affect the host defense of the premature infant. One of the major protective effects of human milk on the recipient infant operates through the enteromammary immune system. It is reasonable to expect that exposure of the mother to the environment of the neonatal nursery through skin-to-skin contact with her premature infant may be advantageous to the infant. In this manner, mothers potentially might be "induced" to make specific antibodies against the nosocomial pathogens in the nursery environment.

Limitations in the Use of Unfortified Human Milk

A major impediment in advocating human milk for premature infants is the difficulty many mothers experience in providing sufficient quantities of milk. Several explanations have been given for the low milk production, including biologic immaturity of the mammary gland, maternal stress and/or illness, and difficulty maintaining a supply without a suckling infant. Another reason of concern is that nutrient intake is limited by milk volume restrictions imposed on the premature infant because they cannot feed ad libitum and also because their medical condition warrants fluid restriction. The most compelling reason for concern is that nutrient intake is inadequate to meet the very great needs of the premature infant. Unfortified human milk may not supply sufficient quantities of nutrients for several reasons. Because of differences in the methods of milk expression and storage, the feeding of "spot" samples (individual samples of expressed milk from one or both breasts or milk partially expressed from one breast), the use of feeding tubes, and the differences in length of lactation, there is a large variation in the macronutrient composition of human milk used in feeding premature infants. Much of the variation in energy content, for example, is a result of differences in fat content of the unfortified milk (2.2 to 4.7 g/dL).

There also are significant declines in the contents of protein and sodium through lactation.[177] The content of other nutrients (Ca, P) is too low to meet the great needs of the premature infant. In addition, technical reasons associated with the collection, storage, and delivery of milk to the infant also result in a decreased quantity of available nutrients (fat, vitamin C, vitamin A, riboflavin). Given the reasons cited, it should not be a surprise that inadequacies of Ca, P, protein, Na, vitamins, and energy are observed in the premature infant fed unfortified human milk. Thus, the exclusive feeding of unfortified human milk in premature infants, generally infants with birth weights less than 1,500 g, has been associated with poorer rates of growth and nutritional deficits, during and beyond the period of hospitalization.[124,146,150,178,179]

Human Milk Fortification

Growth and nutrient deficits in the premature infant can be improved with the addition to human milk of multinutrient nutrient supplements, or fortifiers.[125,155,180,181] Mineral supplementation during hospitalization prevents a decrease in linear growth and increases bone mineralization during and beyond the neonatal period.[182] Supplementation with both Ca and P results in normalization of biochemical indices of mineral status: serum Ca, P, and alkaline phosphatase activity and urinary excretion of Ca

and P.[156] Na supplementation results in normalization of serum Na.[183] Protein and energy supplementation is associated with improved rates of weight gain and indices of protein nutritional status: blood urea nitrogen, serum albumin, and transthyretin.[124,125]

Current practice suggests the use of multinutrient fortification of human milk. Nutritional outcomes of feeding fortified human milk in the United States indicate that premature infants receive less volume but greater intakes of protein and minerals and experience greater gain in weight and increment in linear growth than infants fed unfortified human milk exclusively.[159,163,181,184] Balance study data indicate that the use of fortified human milk results in net nutrient retention that approaches or is greater than expected intrauterine rates of accretion. Fat absorption, however, with the use of some fortifiers has been lower than expected.[2,156] Fat absorption may be augmented by newer human milk fortifiers, which contain fat.[185]

Questions have been raised as to whether the addition of bovine-derived human milk fortifiers affects feeding tolerance in premature infants. Gastric residual volumes often are used to assess feeding tolerance. When compared throughout hospitalization, the use of fortified human milk was not associated with feeding intolerance, as manifest by abdominal distention, vomiting, changes in stool frequency, or volume of gastric aspirate when compared with control-supplemented human milk.[183] Comparisons with preterm formula also have been made, and no major differences in feeding tolerance have been attributed to human milk fortification.[163,186]

A major concern with human milk fortification is that the added nutrients may affect the complex system of host defense. The effects of nutrient fortification on some of the general host defense properties of the milk have been evaluated.[187] Fortification did not affect the concentration of IgA. Bacterial colony counts do not increase with 24 hours of refrigerator storage of fortified human milk.

The relationship between the feeding of fortified human milk and the incidence of illness (infection and necrotizing enterocolitis) in premature infants has been examined. Human milk–fed infants had a 26% incidence of documented infection compared with 49% in formula-fed infants.[188] The use of fortified human milk was not associated with either confirmed infection or necrotizing enterocolitis compared with control-supplemented human milk.[183] When the latter two events were combined, however, the group fed fortified human milk had more events than the control-supplement group. Although it is difficult to conclude that the use of fortifiers is harmful, these data indicate the need for continued surveillance of these events.[189]

In a comparison with preterm formula, premature infants fed exclusively fortified human milk had a significantly lower incidence of necrotizing enterocolitis and/or late-onset sepsis, fewer positive blood cultures, and less antibiotic use than those fed preterm formula.[163] Infants fed exclusively fortified human milk had more episodes of skin-to-skin contact with their mothers and a shorter duration of hospitalization. These data suggest that feeding premature infants fortified human milk had a marked effect on the cost of medical care. The data further suggest that skin-to-skin contact may promote an enteromammary response in the premature infant. It may well become the practice to encourage mothers to practice skin-to-skin contact to enhance their capacity to synthesize specific factors that counter the pathogens in the nursery environment.

Comparison of Human Milk Fortifiers

Human milk fortifiers are designed to be mixed with human milk. A variety of fortifiers are available globally, but no head-to-head comparison has been published. Most fortifiers are powdered nutrient preparations that contain protein, carbohydrate, Ca, P, Mg, and Na; the contents of Zn, Cu, and vitamins are variable (Table 28-20). Inherent in the design is the adequacy of mother's milk production to meet the needs of the infant. The use of pasteurized donor human milk has not been advocated routinely because of concerns with contamination, lack of sufficient supply, and cost. If there is an inadequate amount of mother's milk, two options currently are available: alter-

TABLE 28-20 Comparison of Selected Fortifiers for Human Milk*

	PrHM	*EHMF*	*SNC*	*SHMF*	*Eo*	*SMAHMF*	*FM85*
Energy (kcal)	70	84	76	84	84	84	88
Fat (g)	4.0	4.65	4.4	4.4	4.0	4.0	4.0
Carbohydrate (g)	7.0	7.2	7.8	8.8	9.8	9.4	10.6
Protein (g)	1.8	2.9	2	2.8	2.6	2.8	2.6
Calcium (mg)	22	112	97	139	72	112	73
Phosphorus (mg)	14	64	50	81	48	59	48
Magnesium (mg)	2.5	3.5	6.3	9.5	5.3	4.0	4.5
Sodium (mEq)	1.3	1.8	1.7	2.0	2.5	1.7	2.5
Zinc (μg)	320	1,040	780	1,320	320	450	320
Copper (μg)	60	104	133	230	60	60	60
Vitamins	Yes	Multi	Multi	Multi	Added A, C, E, K	Multi	No

*Prepared per 100 mL PrHM.
PrHM = Preterm Human Milk (see Table 28-16); EHMF = Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, IN); SNC = Similac Natural Care (Ross Labs, Columbus, OH); mixed 1:1 (vol:vol) with PrHM; SimHMF = Similac Human Milk Fortifier (Ross Laboratories, Columbus, OH); Eo = Eoprotin (Milupa, Friedrichsdorf, Germany); SMAHMF = S-26 SMA Human Milk Fortifier (Wyeth Nutritionals International, Philadelphia, PA); FM85 = (Nestle, Vevey, Switzerland).
Multi = added multivitamins: A, D, E, K, B_1, B_2, B_6, C, niacin, folate, B_{12}, pantothenate, biotin.
No = no additional vitamins added.

nate the feeding of fortified human milk with preterm formula and mix mother's milk with preterm formula.

One study examined the nutrient adequacy of a liquid human milk fortifier mixing a preterm formula 1:1 with human milk.[190] Nitrogen, energy, Ca, and P retentions were below intrauterine rates of accretion. More beneficial outcomes may be observed if preterm formula is alternately fed with fortified mother's milk.

FEEDING TOLERANCE

The ability to tolerate enteral feedings is a major problem for premature infants. Moreover, the infants' tolerance of enteral feeding is a primary concern of neonatologists because it affects their decision to initiate, advance, and discontinue feedings. Because of these concerns, feeding intolerance may be a major factor affecting the duration of hospitalization. The fetus experiences swallowing of amniotic fluid from early gestation, but, postnatally, many premature neonates do not appear to share as "simple" a tolerance for enteral fluid, even dilute fluid mixtures. Several factors affect how feedings are tolerated: immature intestinal motility, digestive enzyme immaturity, medical complications, too great a volume intake, and hyperosmolar medications/feedings.

Despite its importance, there are no universally agreed on criteria to judge feeding tolerance in premature infants. Clinical criteria of feeding tolerance (Table 28-21) generally include physical examination findings of abdominal distention and abdominal tenderness, presence or absence and quality of bowel sounds, and signs of residual gastric fluid aspirated from the feeding tube just prior to the next feeding, emesis, and changes in stool output.[191] There are associated signs that occasionally suggest intolerance to a feeding. These associated signs include increased episodes of apnea and bradycardia, diminished oxygen saturation (desaturation events), and lethargy.

The gastric residual volume, usually measured prior to the next feeding, is an indication of milk remaining in the stomach several hours after a feeding.[192] The gastric residual volume indicates the rapidity of gastric emptying and appears to be a final common pathway, such that changes in the clinical examination may result in decreases in gastric emptying. The nonspecific nature of this assessment is that changes in the clinical examination may or may not be related to intestinal pathology. Gastric residual volume has been quantitated on the basis of body weight (eg, an abnormal sign being > 2 mL/kg per feeding) or on the volume of feeding (eg, > 50% of 3 hours of feeding).[108] Some premature infants have measurable gastric residual volumes before every feeding, whereas others never have any measurable volume. In the latter infants, therefore, any small change might indicate a change in the feeding tolerance. Furthermore, it would be expected that gastric residual volume would be difficult to interpret in infants receiving continuous gastric milk infusions. Such is not always true as these infants generally empty their stomachs rapidly and should still be evaluated every 2 to 4 hours in a similar manner as infants fed by the intermittent bolus technique.[108]

The quality of the gastric residual also has been discussed as a tool to determine feeding tolerance. Gastric residuals that are green, or bilious, could indicate intestinal obstruction but more often indicate overdistention of the stomach and retrograde reflux of bile into the stomach. A blood-tinged residual could indicate an inflammatory process but may indicate a slight mucosal irritation from the indwelling gastric tube.

Unfortunately, the aforementioned criteria have little prognostic significance. Infants having more gastric residuals and emesis episodes were just as likely to reach the milestone of full enteral tube feeding than infants not having any increases in these measurements.[186]

Most clinicians use the pattern of the above criteria, as opposed to a single measurement, as an aid to determine feeding status. Several instances will occur in which infants' feedings are withheld because of one or more of the above signs. Often a single feeding is discarded. Careful assessment and examination prior to the next feeding generally aid the decision to continue feedings. A withheld feeding, however, does not imply that further enteral feeding should be terminated. Too often, feedings are withheld for prolonged periods of time, which hastens the complications of parenteral nutrition and intestinal atrophy. The evaluation of the infant with a large gastric residual, for example, would include the following considerations: Has the medical condition worsened, such that gastric emptying is delayed owing to systemic disease? Is the infant's feeding tube in the correct location? If the feeding tube is high in the esophagus or too small a caliber, then swallowed air may not be evacuated. Large amounts of swallowed air may cause gastric overdistention and displace milk, resulting in emesis and/or large residuals. Body positioning also may play a role. Gastric emptying in some infants is improved by their being in the prone position or in the right lateral decubitus position compared with the supine position. At times, intolerance is corrected by lowering milk intake somewhat.

TABLE 28-21 Potential Indices Used to Assess Feeding Tolerance in Low Birth Weight Infants

Abdominal distention
With visible bowel loops
Without visible bowel loops
Abdominal tenderness
Emesis
Gastric residual volume
> 2 mL/kg
> 50% of 3 h of feeding
Any change from previous pattern
Gastric residual characteristics
Green, bilious
Red, blood tinged
Stool output
Increased frequency
Decreased frequency
Feeding withheld
Document reasons feedings withheld
Assess number of feedings held
Clinical condition
Any worsening in previous medical condition

FEEDING METHODS

Tube feeding is an essential tool in enteral nutrition because the premature infant may be unable to suck and/or coordinate suck-swallow-breathe. There are a variety of methods for tube feeding, continuous or intermittent bolus, and a number of approaches, orogastric, nasogastric, transpyloric, or gastrostomy. The selection of practice relates to the duration of the proposed therapy: premature infants eventually will suckle, so a temporary oro(naso)gastric tube is used; infants with major congenital anomalies may require a semipermanent gastrostomy.

The bolus feeding method mimics the normal adult feed-fast routine and has greater hormonal responses than continuous infusions.[193] The bolus technique does not require an infusion pump. Differences between continuous and intermittent bolus methods have been evaluated. Premature infants had more feeding intolerance and a slower rate of weight gain with continuous infusion compared with the bolus technique.[108] Neither method enhanced nutrient absorption.

Occasionally, intolerance is observed in the bolus-fed premature infant. In some instances, duodenal motility decreases following the bolus feeding.[194] A bolus feeding given over a longer time interval, such as 30 minutes to 120 minutes, results in a return of motility and improved tolerance. The continuous infusion technique has been associated with increased nutrient absorption in infants with gastrointestinal disease.[195] It seems prudent to use this method in infants who have had intestinal surgery and for infants receiving milk via a transpyloric tube. In some infants with persistent gastric residuals or emesis in absence of obvious intestinal pathology, the use of transpyloric feeding has been successful.

FEEDING ISSUES

Enteral feeding and concomitant use of an umbilical arterial catheter have been a subject of much concern. However, most infants had an indwelling umbilical arterial catheter in the recent studies of gastrointestinal priming, and no untoward events were reported.[104,108] Infants were no more likely to develop intolerance or necrotizing enterocolitis if they received enteral feedings while they had an umbilical arterial catheter in place than if they received enteral feeding 24 hours after the catheter was removed.[111] Moreover, fewer evaluations for sepsis and less use of central venous catheters were observed in the group receiving feeding while the catheter was in place. Thus, there appears to be no increased risk of enteral feeding while an umbilical arterial catheter is in place as long as the catheter is functioning optimally.

The use of diluted milks has been suggested for feeding premature infants. In one study, however, intestinal motility responses to feeding were initiated earlier and persisted longer following the use of full-strength formula compared with one-third and two-thirds dilutions of the formula.[196] The use of water for enteral feeding also has been shown not to affect intestinal motility compared with milk.[197] Thus, initiating feedings with full-strength milk appears to be tolerated and appropriate.

The advancement of daily feeding volumes also has been investigated, especially with respect to the development of necrotizing enterocolitis. When compared with matched case controls, infants with necrotizing enterocolitis were more likely to have received enteral nutrition with daily intakes > 20 mL/kg, averaging 46 mL/kg.[198] One study compared the morbidity of low birth weight infants whose daily increment in feeding volume was 15 or 35 mL/kg/day.[199] The infants whose feedings were advanced rapidly had a shorter duration of time to achieve full tube feeding and regain birth weight and no difference in morbidity than infants whose feedings were advanced slowly.

NUTRITION ASSESSMENT

Neonatal nutritional assessment is an emerging interest that requires a knowledge of both nutritional biochemistry and neonatal medical conditions. The nutritionist is a key person to provide input, on a daily basis, that is compatible with the medical condition of the infant.

The nutritional status of the premature infant is monitored by daily assessments of fluid and energy intake and evaluating the rate of growth in weight, length, and head circumference (Table 28-22). Growth parameters are plotted on graph paper or a specific chart for current premature infants' growth. The charts are helpful, but equally important is the computation of the weekly rate of growth (Table 28-23).[200] Once the infant reaches 2.5 kg, a daily weight gain of 20 to 30 g/day is appropriate.

The nutritional status of the premature infant also is monitored by serial evaluations of biochemical indices. These assessments include serum Ca, P, and alkaline phosphatase activity to assess bone mineral status and albumin

TABLE 28-22 Nutritional Assessment of the Enterally Fed Premature Infant

Fluid intake (mL/kg/d)	Daily
Parenteral intake	
Enteral intake	
Nutrient intake (U/kg/d)	Daily
Energy intake (kcal)	
Protein intake (g)	
Specific nutrient (unit)	
Anthropometry	
Body weight (g)	Same time each day
Length (cm)	Weekly
Head circumference (cm)	Weekly
Biochemical monitoring	
Hemoglobin, hematocrit	Weekly
Reticulocyte count	Weekly
Serum electrolytes	Weekly ×2, then every 2 wk*
Calcium, phosphorus	Weekly ×2, then every 2 wk
Alkaline phosphatase	Weekly ×2, then every 2 wk
Albumin, blood urea nitrogen	Weekly ×2, then every 2 wk†
Other assessments	
Renal ultrasonography‡	2 mo

*If infant receiving human milk or diuretics; †add prealbumin if abnormal; ‡to evaluate for nephrocalcinosis.

TABLE 28-23 Growth Guidelines

Weight gain	> 15 g/kg/d for infants < 2.0 kg > 20 g/d for infants > 2.0 kg
Length gain	0.7–1.0 cm/wk
Head circumference gain	0.7–1.0 cm/wk

and urea nitrogen to assess protein status. If more specific indices of protein status are needed, as in the case in which additional protein supplementation is used, the serum prealbumin (transthyretin) is measured before and 1 week after the supplementation. Serum Na, chloride, and bicarbonate are evaluated in infants receiving diuretics, those whose intakes are limited, or those with slow growth. The hemoglobin and reticulocyte count are monitored to assess anemia. Specific determinations of plasma Zn and Cur are not routinely useful, but Zn may be measured in infants with unusual losses, such as after gastrointestinal surgery and from enterostomies. The pattern of changes in biochemical indices may be more reflective of nutritional status than isolated values. Occasionally, renal ultrasonography to determine the presence of nephrocalcinosis and wrist radiography to identify rickets are warranted.

SUMMARY OF NUTRITION SUPPORT

A comprehensive nutrition pathway for LBW infants has been described. The approach is multifaceted, beginning with intravenous nutrition, transitioning via trophic feeding to enteral nutrition, and continuing to full enteral feeding and hospital discharge. This approach does not increase the risks already associated with LBW infants. Indeed, the use of an aggressive approach to nutritional support has resulted in improved growth, with fewer infants falling below the 10th percentile in standard growth charts.[201] Although improvements are found in growth, no increase in sepsis or necrotizing enterocolitis is associated with the more aggressive approach to nutritional support.[201]

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CHAPTER 29

THE TERM INFANT

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GOALS OF INFANT FEEDING

The goals of infant feeding are to meet all nutritional needs, to aid mother–infant bonding, to aid the infant in making the transition from the predominantly liquid diet of the infant to the predominantly solid food diet of the child and adult, and to aid in establishing habits of eating in moderation. The goals can best be met by breast-feeding. However, in industrialized countries, feeding of commercially available infant formulas, although not ideal, is an acceptable substitute. Breast-feeding, besides meeting all nutritional needs, offers protection against infectious illnesses, may foster optimal neurocognitive development, and may offer some protection against conditions in adulthood such as obesity and atherosclerosis. Whether feeding practices during infancy can aid in establishing the goal of eating in moderation is unknown. Nevertheless, in various animal models, habits established during infancy have been difficult to extinguish later in life, and it therefore seems plausible that satiety signals can be reinforced if an infant is encouraged to discontinue nursing from the breast or bottle at the earliest sign of willingness to do so.

TRENDS IN INFANT FEEDING

Historically, in situations in which breast-feeding was not possible, survival of the infant was in jeopardy. The feeding of preparations based on various mammalian milks was associated with high morbidity and mortality. Success at formula feeding gradually improved from the end of the nineteenth century through the first half of the twentieth century. The objective was to make available safe and effective feedings for situations in which breast milk was not available. In the 1920s, the use of evaporated milk for formula preparation together with a number of improvements in formula preparation and storage contributed to successful formula feeding. By the 1950s, formulas reached a point at which they provided adequate nutrition and appeared to be reasonably safe. In the absence of convincing evidence of the inferiority of formula feeding, many parents and physicians adopted formula feeding, presumably because of the supposed greater convenience. The prevalence of formula feeding increased and the prevalence of breast-feeding decreased.

The decrease in the prevalence of breast-feeding was associated with earlier introduction into the infant's diet of beikost (foods other than milk or formula fed to infants) and cow's milk. By the end of the 1950s, feeding of beikost was common during the first month of life, and most infants were fed beikost before the end of the second month of life. Whole- or reduced-fat cow's milk commonly replaced formula by 4 to 6 months of age.[1]

A resurgence of breast-feeding began about 1971 (Figure 29-1).[2] The reasons for the initial increase in breast-feeding prevalence are poorly understood. But enthusiasm for breast-feeding was sustained, at least in part, by the ever-increasing number of reports on the demonstrated or assumed advantages of breast-feeding. As Figure 29-2 indicates, in 2001, about 70% of infants were breast-fed for at least some time.[3] The relatively quick decrease in breast-feeding prevalence with age is at least partially explained by mothers returning to work. Despite the pressures of work, the number of women who breast-feed for 6 months and longer has continued to increase.

In association with the increase in breast-feeding, infants were increasingly fed formula after cessation of breast-feeding (Figure 29-3).[4] Thus, formula feeding largely displaced feeding of cow's milk in older infants (Figure 29-4).[4] Also, beikost was less commonly fed during the early months of life, and it is now very uncommon to see beikost fed before 4 months of age.

TRENDS IN FORMULA COMPOSITION

The formulas fed in the United States in the late 1920s were generally prepared in the home with evaporated milk or fresh cow's milk and sugar. The protein content was considerably greater than that of current formulas, the fat was butterfat, the added carbohydrate was corn syrup or sucrose, and neither vitamins nor minerals were added. Prepared powdered formulas (to be diluted with water before use) were available, but their use was quite limited until the 1950s. With the introduction of concentrated liquid formulas (requiring only the addition of an equal volume of water before use), commercially prepared formulas gradually replaced home-prepared formulas. Over the years, formulas underwent a number of changes: the protein content was decreased, and whey proteins were included to result in a whey-to-casein ratio more like that of human milk; vegetable oils replaced butterfat; the added carbohydrate was lactose rather than corn syrup; and vita-

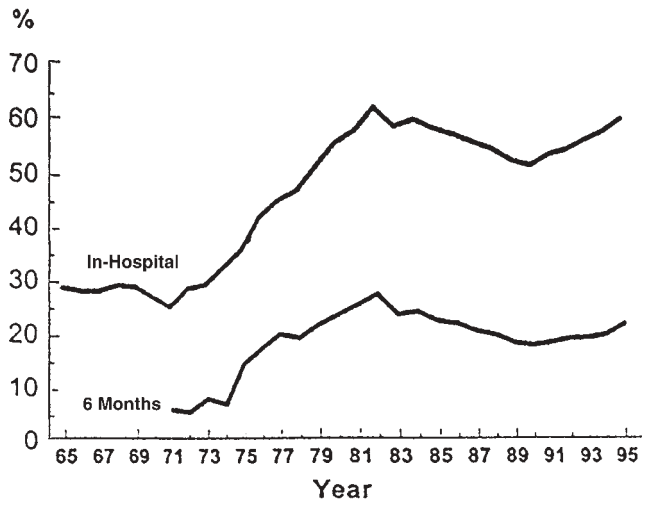

FIGURE 29-1 Prevalence of breast-feeding in the United States 1965 through 1995. Reproduced with permission from Ryan AS.[2]

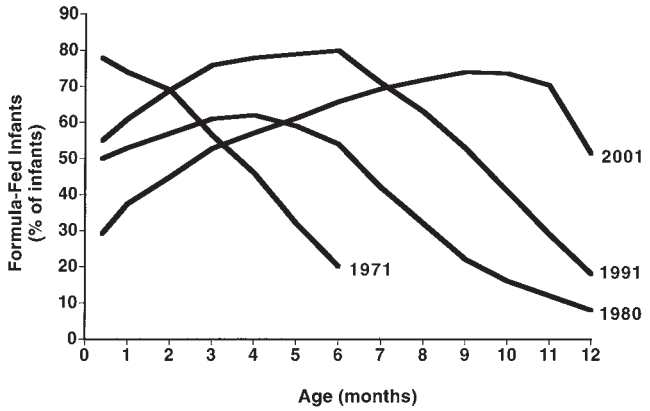

FIGURE 29-3 Formula-fed infants (including infants also breast-fed) as percentage of all infants in 1971, 1980, 1991, and 2001. Data for 1971 and 1980 from Martinez GA et al[4]; data for 1991 based on personal communication from Ross Mothers Survey (Greenbaum S, 1992, Ross Products Division, Columbus, OH); data for 2001 from Mead Johnson Nutritionals, Evansville, IN (J. A. Boettcher, personal communication, 2002).

mins and minerals were included. See below for detailed composition of currently available formulas.

NUTRIENT REQUIREMENTS

The approach to estimating nutrient requirements of the infant differs considerably from that for adults. The normal adult requires regular intake of energy and specific nutrients to maintain the size and composition of the body (ie, requirements for "maintenance"), whereas infants and young children need, in addition, energy and nutrients for growth. The ratio of need for growth to need for maintenance is greatest for the fetus, the rapidly growing preterm infant, and the term infant during the early months of life. Therefore, to obtain reasonable estimates of the requirements for energy and nutrients of the infant, it is desirable to have quantitative data on the increments in energy storage and the increments in specific nutrients needed for synthesis of new tissue. Defining the requirements of energy or nutrients for growth is much less important for children over the age of 2 years and for adolescents because, by then, the requirements for growth are quite small fractions of total requirements.

Thus, from a nutritional point of view, rapid growth is what differentiates infancy from all other ages. Nutrient requirements are exceedingly high primarily because of nutrients needed to support rapid growth. But growth is not only very rapid, it also changes dramatically in velocity as well as in composition. These dynamic changes are illustrated in Figure 29-5, which depicts rate as well as

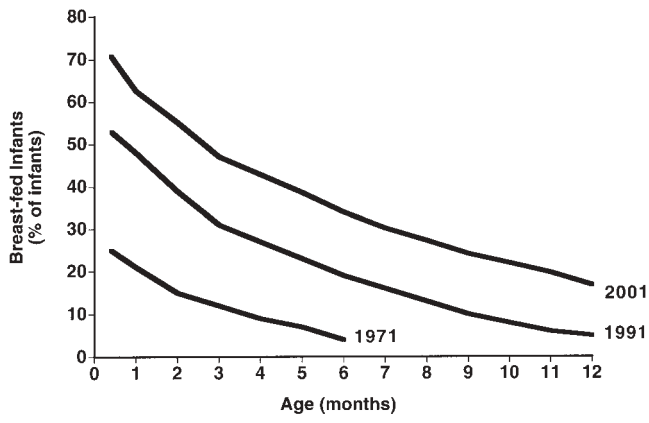

FIGURE 29-2 Exclusively and partially breast-fed infants as a percentage of all infants in 1971, 1991, and 2001. Data for 1971 from Martinez GA and Nalezienski JP[3] and for 1991 based on personal communication from Ross Mothers Survey (Greenbaum S, 1992, Ross Products Division, Columbus, OH); data for 2001 from Mead Johnson Nutritionals, Evansville, IN (J. A. Boettcher, personal communication, 2002).

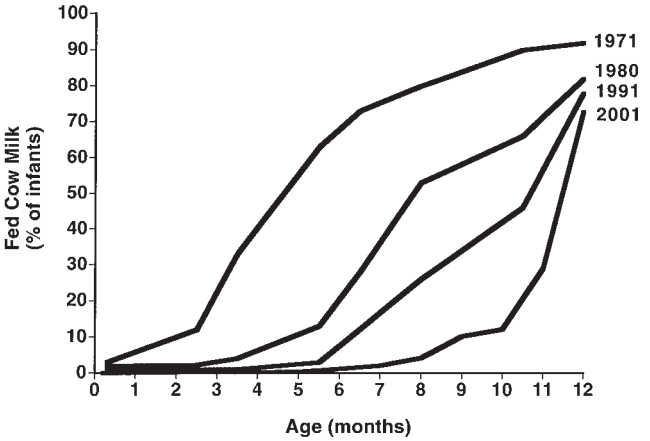

FIGURE 29-4 Infants fed cow's milk (no breast-feeding, no formula feeding) as a percentage of all infants in 1971, 1980, 1991, and 2001. Data for 1971 and 1980 from Martinez GA et al.[4] Data for 1991 from personal communication from Ross Mothers Survey (Greebaum S, 1992, Ross Products Division, Columbus, OH). Data for 2001 from Mead Johnson Nutritionals, Evansville, IN (J. A. Boettcher, personal communication, 2002).

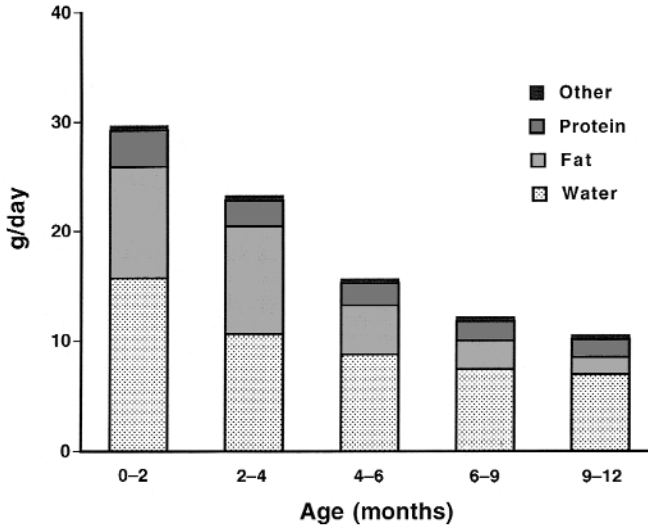

FIGURE 29-5 Gain in weight and in major body components of a "reference infant" (an infant with weight and length and body composition at the 50th percentile for age). Adapted from Fomon SJ and Nelson SE.[5]

composition of growth of a "reference infant."[5] The rapid decline in the rate of growth during the first year of life is readily appreciated. It is also evident that during the first 4 months of life, infants deposit large amounts of body fat. During that period, fat accounts for as much as 40% of weight gain, and the energy necessary for deposition of this fat accounts for about 20% of energy requirements. Toward the end of the first year of life, fat deposition slows down markedly, and so does the proportion of energy requirement explained by fat deposition. Although accretion of protein as a percentage of weight gain increases with age, absolute protein accretion is highest during the first 2 months of life.

Nutrient requirements of infants are obtained chiefly by two methods: the observational method and the factorial method. Each approach has its difficulties and limitations. The observational method relies on the model of the breast-fed infant. The main difficulty with this approach is the determination of representative concentrations of nutrients in breast milk. Concentrations of many nutrients change markedly with the duration of lactation and are in many cases influenced by maternal dietary intakes. Also, the breast-fed infant is not a reliable model in the case of certain nutrients, such as iron, that are not provided in breast milk in amounts that meet the infant's needs. The factorial method yields good estimates for certain nutrients, such as protein, for which estimates of rates of accretion by the infant are available. Nutrient requirements, largely because of the dynamic changes of the needs for growth, are strongly age dependent. Stating nutrient requirements in relation to energy requirements diminishes the age dependency of nutrient requirements somewhat but does not eliminate it completely.

Energy Requirement

Because the infant possesses the ability to self-regulate energy intake, it may be assumed that energy intakes observed in infants receiving feedings with normal energy density represent energy requirements. Table 29-1 presents energy intakes observed in breast-fed and formula-fed infants.[6] The data illustrate the markedly higher energy intakes during the early months of life compared with later infancy, a reflection of the deposition of large amounts of fat as energy stores. The data also show that formula-fed infants consume somewhat more energy than breast-fed infants, especially during the first 3 months of life. Therein may lie (part of) the reason for the somewhat more rapid growth of formula-fed infants. Gender-related differences in energy intake, although quite small, are nevertheless consistently present.

Protein Requirement

Table 29-2 presents estimates of requirements for protein by the factorial method as well as protein intakes observed in breast-fed infants.[7] The close agreement between the factorial estimate and observed intake is striking. During the first month of life, growth accounts for over 50% of protein requirement. But by the end of the first year of life, the proportion needed for growth is less than 20%.

THE BREAST-FED INFANT

Energy and Protein Intakes

The breast-fed infant receives water, energy, and specific nutrients in amounts that meet the needs of the infant at

TABLE 29-1 Energy Intakes (kcal/kg/day) of Infants

	Breast-fed		*Formula-fed*			
	Males	*Females*	*Males*		*Females*	
Age Interval (mo)	*Mean*	*Mean*	*50th*	*10th–90th*	*50th*	*10th–90th*
0–1	115	111	118	99–137	116	96–136
1–2	104	101	113	99–131	111	94–130
2–3	95	93	100	88–116	100	87–114
3–4	91	91	95	83–106	95	83–107
4–5	89	89	94	78–112	97	81–113
5–6	86	85	95	64–113	94	78–113
6–9	81	81				
9–12	92	92				

Adapted from Fomon SJ and Bell EF.[6]

all times, notwithstanding the fact that the needs change with the age of the infant. A prime example is protein. Through a combination of a sharp decrease in protein concentration and an increase in milk volume, a close match between intake of protein and protein requirement is achieved (see Table 29-2). In the case of energy, the content of which in breast milk does not change with the duration of lactation, the match between intake and need (see Table 29-1) is achieved solely through a decrease in volume of milk consumed per kilogram of body weight. Most other nutrients fall somewhere between protein and energy, that is, a match between intake and need is brought about through a combination of concentration changes and volume increase. Formulas, on the other hand, must be designed to meet the highest possible needs, that is, those of the youngest infants in the target age group. Consequently, as the infant grows, nutrient intakes from formulas exceed needs by an increasing margin.

Although it is well established that infants generally do not obtain all of the milk that is synthesized by the mammary gland,[8] the cause of the failure to consume all of the available milk is not known. One possible reason is infant fatigue because the process of obtaining milk from the breast requires considerable effort on the part of the infant. Whatever the mechanism may be, failure to consume all available milk may be one of the reasons why breast-fed infants consistently consume less energy than formula-fed infants, as shown in Table 29-1. It has been surmised that because the milk remaining in the breast is not visible to the mother, contrary to formula remaining in the bottle, she may be more prone to stop feeding at the earliest sign of satiety on the part of the infant than if the infant is fed by bottle.

Growth

Formula-fed infants grow more rapidly than breast-fed infants.[9,10] Differences in energy consumption may explain the difference in growth. However, inconsistent with this explanation is the fact that growth is similar during the first 6 weeks of life and only begins to differ significantly thereafter,[9] whereas the difference in energy consumption seems to be largest during the first 2 months of life. Therefore, there may be other explanations. When the average intake is close to the average requirement for a nutrient, there is the likelihood that for some individuals, intake falls short of requirement. That is the case for protein (see Table 29-2) and also for zinc,[11] a nutrient whose deficient intake can limit growth. Thus, it is possible that inadequate intakes of protein or zinc, or both, occur among breast-fed infants and explain the slower growth. But it must be stressed that the reason for the growth differential is not actually known. By the same token, it is not known whether there are any long-term consequences, beneficial or detrimental, owing to the slower growth of breast-fed infants or to the lower nutrient intake that may be causing it.

Flavor

Breast milk contains a variety of flavoring substances derived from the maternal diet, and there is clear evidence that the infant recognizes flavors and responds to them.[12] Thus, contrary to the formula-fed infant, the breast-fed infant is exposed to a variety of tastes from the earliest age. The nutritional significance of early exposure to flavor variety, perhaps even in the long term, is that it leads to greater acceptance and apparent enjoyment of novel flavors later on.[13,14]

Oligosaccharides

Breast milk contains substantial amounts (5 to 8 g/L) of oligosaccharides, a complex group of substances derived from lactose.[15,16] These oligosaccharides share similarities with epithelial cell surface carbohydrates and adhesion molecules. They exert a number of important functions, from blocking the adhesion of bacteria to intestinal cell surfaces[17] to being responsible for the predominance of the bifidus flora in the breast-fed infant. Consonant with these important functions is the fact that oligosaccharides are only minimally digested in the upper gastrointestinal tract and undergo fermentation in the colon, thereby accounting for much of the hydrogen gas that is exhaled by breast-fed infants.

Iron

Most infants are born with generous iron stores that render him/her independent of an exogenous supply of iron for the first 5 to 6 months of life. Breast milk provides a small amount of highly bioavailable iron that allows the infant to absorb about 0.15 mg each day. Beginning when iron stores are exhausted around 5 to 6 months of age, the infant needs to absorb approximately 0.75 mg each day to avoid iron deficiency. Because breast milk provides only about

TABLE 29-2 Protein Requirements of Infants

Age Interval (mo)	*Growth (g/kg/d)*	*Losses (g/kg/d)*	*Requirement (g/kg/d)*	*Intake of Breast-fed Infant (g/kg/d)*	*Requirement (g/100 kcal)*	*Growth Requirement (%)*
0–1	1.03	0.95	1.98	2.09	1.7	52
1–2	0.78	0.93	1.71	1.59	1.5	46
2–3	0.56	0.90	1.46	1.18	1.5	38
3–4	0.38	0.89	1.27	1.06	1.4	30
4–5	0.30	0.88	1.18	1.00	1.3	25
5–6	0.29	0.89	1.18	0.95	1.3	24
6–9	0.26	0.91	1.17		1.3	22.0
9–12	0.20	0.94	1.14		1.2	18.0

Adapted from Fomon SJ.[7]

0.15 mg/day of absorbed iron, the infant must absorb about 0.6 mg/day from other sources. Except for meat, which provides a highly bioavailable form of iron (heme iron), the natural iron content of most foods fed as beikost is low. Therefore, the breast-fed infant can obtain an adequate intake of iron, besides meat, only from iron-fortified foods such as infant cereals. Other options for securing an adequate iron intake include medicinal iron and iron-fortified formula. Although none of these options have ever been demonstrated to be effective in preventing iron deficiency during prolonged breast-feeding, prudence nevertheless dictates that attention be paid to ensuring an adequate intake of iron for breast-fed infants. Concerns that exogenous iron might exert adverse effects on the infant are theoretic in nature.

Some infants are born with diminished iron stores[18] and may become dependent on an exogenous iron supply sooner than infants born with more generous iron stores. Because these infants may be particularly prone to developing iron deficiency, it is advisable to start ensuring an adequate iron intake for all infants beginning at 4 months of age.

FORMULAS

Formulas provide macronutrients and micronutrients in amounts and proportions that permit infants to grow normally. Like breast milk, formulas provide energy in roughly equal amounts from carbohydrate and fat. Contrary to breast milk, the protein level is fixed and set at a level that meets the needs of the fastest-growing infants within the target age group. Formulas provide water in amounts that allow the infant to dispose of waste products with a satisfactory margin of safety. Owing to the higher potential renal solute load of formulas,[19] that margin is somewhat narrower than in the breast-fed infant, a difference that is not known to be of clinical consequence.

An enumeration of the myriad substances that are provided by breast milk but are absent from formulas is beyond the scope of this chapter (see Chapter 55 and Appendix 3). A number of substances, including macrominerals, trace minerals, and vitamins, are provided in formulas in greater concentration than in breast milk. Some substances that are believed to be biologically important for the infant are added to formulas in amounts similar to breast milk. Some formulas, notably the soy protein–based formulas, provide substances that are not provided by breast milk. Of considerable nutritional importance is the presence of phytate because of its potential to inhibit the absorption of macrominerals and, especially, trace minerals. A group of substances collectively referred to as phytoestrogens is provided by soy formulas.[20] These substances are not nutritionally important but are biologically active, exerting estrogenic as well as antiestrogenic activities. Phytoestrogens are readily absorbed by the infant[20] but produce no clinically or otherwise recognizable effects. When followed into young adulthood, women who had been exposed to soy formulas as infants had somewhat greater menstrual flow and experienced more discomfort with menstruation.[21] Although these effects are not clinically important, they are biologically significant because they demonstrate that relatively brief exposure during a susceptible period can have effects that last for decades.

Carbohydrates

Milk-based formulas contain lactose as the sole carbohydrate and lack the oligosaccharides that make up a substantial proportion of the carbohydrate of breast milk. Oligosaccharides are responsible in large part for the differences in colonic flora between breast-fed and formula-fed infants. Although it is essentially unabsorbable in the upper gastrointestinal tract, the colonic microflora is quite effective in fermenting the oligosaccharides. The fermentation products, acetate and butyrate, are absorbed from the colon.

Fat

The fat of formulas is made up of various combinations of plant oils, selected to provide major fatty acids in approximately the proportions found in breast milk. The absorbability of the fat of formulas is similar to that of breast milk fat. Sometimes formulas contain added polyunsaturated fatty acids (arachidonic acid [ARA] and docosahexaenoic acid [DHA]) from single-cell organisms.

Protein

Although formulas provide bulk casein and whey proteins in approximately the same proportions as breast milk, the individual whey proteins show little resemblance to those provided in breast milk. Manufacturers are able to selectively decrease and/or increase individual whey proteins and thereby alter the biologic quality and amino acid composition of the protein mix. The protein concentration of formulas is set to meet the highest needs, that is, those of the youngest infants in the target age group. Consequently, the older infants in the formula's target group, who have lower protein needs than the younger infants, receive protein intakes that exceed their needs by some margin. In contrast, breast-fed infants receive protein intakes that approximately match needs at all times.

Iron

Formulas fortified with quite large amounts of iron (1.8 mg/100 kcal) were introduced in 1959 and were shown to be effective in preventing iron deficiency. Although non–iron-fortified formulas continued to be used, the use of formulas providing iron at 1.8 mg/100 kcal gradually increased, as illustrated in Figure 29-6. In 1971, iron-fortified formulas accounted for less than 50% of formula sales in the United States, and in the year 2001, they accounted for about 95% of formula sales. At present, all formulas contain added iron. Only some of the routine formulas are available with an iron level of about 0.6 mg/100 kcal. These formulas are not labeled as iron fortified. All other formulas provide iron at 1.8 mg/100 kcal. Iron fortification is not associated with adverse effects on gastrointestinal function.[22]

Composition

The formulas for routine use are rather uniform in composition, as is evident from Table 29-3 (also see Appendix 3). One formula provides partially hydrolyzed whey proteins.

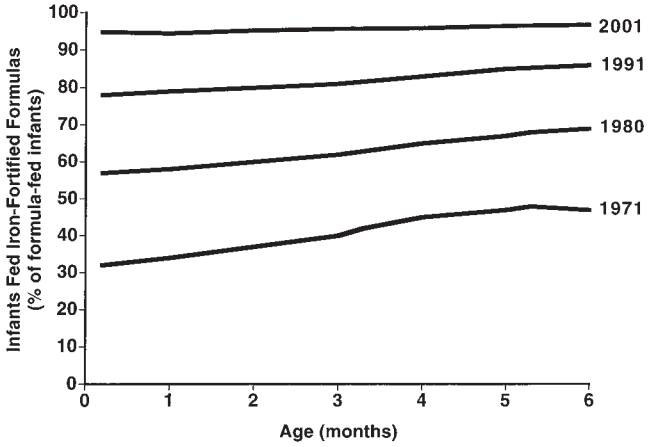

FIGURE 29-6 Infants fed iron-fortified formulas as a percentage of formula-fed infants in 1971, 1980, 1991, and 2001. Data for 1971 and 1980 from Martinez GA et al.[4] Data for 1991 from personal communication from Ross Mothers Survey (Greebaum S, 1992, Ross Products Division, Columbus, OH). Data for 2001 from Mead Johnson Nutritionals, Evansville, IN (J. A. Boettcher, personal communication, 2002).

The latter type of formula is sometimes referred to as "hypoallergenic."

The composition of lactose-free formulas is listed in Table 29-4 (also see Appendix 3). Whereas those based on soy protein isolate (with methionine supplementation) have been available for many years, those based on cow's milk have been introduced more recently. Although the scientific basis for the widespread use of these formulas is uncertain, it is fairly certain that these formulas provide all essential nutrients and support normal growth. The carbohydrates that are provided in lieu of lactose include sucrose and fractions of corn syrup. The protein concentration of soy-based formulas is generally higher than that of milk-based formulas, reflecting the (presumed) somewhat lesser quality (per unit of weight) of methionine-supplemented isolated soy protein. All lactose-free formulas contain iron at 1.8 mg/100 kcal. In the case of soy-based formulas, this includes a substantial amount of iron provided by the soy protein isolate. Little is known about the bioavailability of this iron.

Table 29-5 (also see Appendix 3) lists the extensively hydrolyzed formulas (also referred to as predigested) and one elemental formula. These formulas are characterized by the absence of intact protein as well as lactose. The source of nitrogen is hydrolyzed casein or, in the case of Neocate, free amino acids—hence its classification as elemental formula. Two of the formulas provide a sizable proportion of their fat in the form of medium-chain triglycerides.

Table 29-6 (also see Appendix 3) lists the composition of special formulas designed for specific indications. Enfamil AR is thicker than the usual consistency and is intended use in infants with severe gastroesophageal reflux. Isomil DF is intended for infants recovering from diarrhea. Portagen provides 85% of its fat in the form of medium-chain triglycerides. It is used in infants with chylothorax or chylous ascites. Similac PM 60/40 is low in sodium and phosphorus and is used in infants with renal failure.

Although the concept of age-specific formulas is not widely embraced in the United States, the feeding of unmodified cow's milk to older infants was practiced for many years. A number of formulas are now available for the older infant and toddler (Table 29-7; also see Appendix 3). The scientific rationale for the higher protein content compared with routine formulas is not clear because the protein requirement of the older infant is lower rather than higher than that of the young infant. It appears possible that the higher protein content is designed to ensure an adequate protein intake for those infants who otherwise consume a sizable amount of beikost, which tends to be low in protein content.

Substances Added to Formulas

Of the many bioactive substances that are present in human milk but are contained in cow's milk in lower concentration or are completely absent from cow's milk, some are added to formulas. Evidence that the addition ameliorates an otherwise existing deficiency is not always very convincing. However, it appears reasonable to add a substance when its presence in breast milk seems "intentional" and when its absence from the infant's diet is associated with deficits in serum or tissue concentrations relative to the breast-fed infant. A prerequisite for the addition of any substance is, of course, the availability of the technology necessary for making the addition feasible. The list of substances added to formulas now includes taurine, carnitine, nucleotides, and long-chain polyunsaturated fatty acids (LCPUFAs).

Taurine Taurine is an amino sulfonic acid found in high concentration in certain parts of the developing brain and in the retina. In infants, taurine also plays a role in the conjugation of bile acids and has osmoregulatory functions. Taurine is synthesized from cysteine, and the term infant (but perhaps not the preterm infant) appears to possess ample capacity to carry out the conversion. Breast milk contains appreciable quantities of taurine, whereas the taurine content of cow's milk and hence of cow's milk–based formulas is only a fraction of that of breast milk. However, except for low plasma taurine concentrations, adverse effects owing to low taurine intakes have not been demonstrated convincingly. Nevertheless, all formulas contain added taurine.

Carnitine Carnitine plays an essential role in the entry of fatty acids into the mitochondria and hence is necessary for fatty acid oxidation. Carnitine is derived from endogenous synthesis as well as the diet. Breast milk, cow's milk, and hence milk-based formulas, and meat provide ample amounts of carnitine. When carnitine is absent from the diet, plasma concentrations of infants are low, and certain biochemical abnormalities are observed, the clinical significance of which is uncertain. Carnitine is added to all nonmilk formulas.

Nucleotides Breast milk contains free ribonucleic acid (RNA) nucleosides (adenine, cytosine, guanine, and uridine) as well as their respective nucleotides (ie, nucleosides with one sugar moiety and one or more phosphate groups attached) and some polymeric RNA.[23, 24] For pur-

Table 29-3 Formulas for Routine Infant Feeding

		Protein		*CHO*		*Fat*		*Sodium*	*Potassium*	*Calcium*	*Phosphorus*	*Iron*	
Formula	*Manufacturer*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*mEq/100 kcal (mEq/dL)*			*mg/100 kcal (mg/dL)*		*Osmolality (mOsm/kg)*
Enfamil	Mead Johnson	Reduced minerals, whey, nonfat milk	2.1 (1.4)	Lactose	10.9 (7.5)	Palm olein, soy, coconut, high-oleic sunflower	5.3 (3.5)	1.2 (0.8)	2.8 (1.9)	78 (53)	53 (36)	1.8 (1.2)	300
Similac	Ross	Nonfat milk, whey protein concentrate	2.1 (1.4)	Lactose	10.8 (7.3)	High-oleic safflower, coconut, soy	5.4 (3.6)	1.0 (0.7)	2.7 (1.8)	78 (53)	42 (28)	1.8 (1.2)	300
Good Start	Carnation	Hydrolyzed whey	2.2 (1.5)	Lactose, malto-dextrin	11.1 (7.4)	Palm olein, soy, coconut, high-oleic safflower	5.1 (3.4)	1.0 (0.7)	2.5 (1.7)	64 (43)	36 (24)	1.8 (1.2)	265
Store brand generic	Wyeth	Nonfat milk, whey protein concentrate	2.2 (1.5)	Lactose	10.6 (7.2)	Palm, high oleic safflower, coconut, soy	5.3 (3.5)	0.9 (0.6)	2.1 (1.4)	63 (43)	42 (28)	1.8 (1.2)	280

CHO = carbohydrate.

Table 29-4 Lactose-Free Formulas

		Protein		CHO		Fat		Sodium	Potassium	Calcium	Phosphorus	Iron	
Formula	*Manufacturer*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*mEq/100 kcal (mEq/dL)*			*mg/100 kcal (mg/dL)*		*Osmolality (mOsm/kg)*
Cow's milk based													
Lactofree	Mead Johnson	Milk isolate	2.1 (1.5)	Corn syrup	10.9 (7.3)	Palm olein, high-oleic sunflower	5.3 (3.6)	1.3 (0.9)	2.8 (1.9)	82 (55)	55 (37)	1.8 (1.2)	200
Similac Lactose Free	Ross	Milk protein isolate	2.1 (1.5)	Corn syrup solids, sucrose	10.7 (7.2)	Soy, coconut	5.4 (3.6)	1.3 (0.9)	2.7 (1.8)	84 (57)	56 (38)	1.8 (1.2)	300
Soy protein based													
Alsoy	Carnation	Soy protein isolate	2.8 (1.9)	Maltodextrin, sucrose	11.1 (7.4)	Palm olein, soy, coconut, high-oleic safflower	4.9 (3.9)	1.4 (0.9)	3.0 (2.0)	105 (70)	61 (41)	1.8 (1.2)	200
Isomil	Ross	Soy protein isolate	2.4 (1.6)	Corn syrup solids, sucrose	10.3 (7.0)	High-oleic safflower, coconut, soy	5.5 (3.7)	1.9 (1.3)	2.8 (1.9)	105 (71)	75 (51)	1.8 (1.2)	200
ProSobee	Mead Johnson	Soy protein isolate	2.5 (1.7)	Corn syrup solids	10.6 (7.2)	Palm olein, soy, coconut, high-oleic sunflower	5.3 (3.6)	1.6 (1.0)	3.1 (2.1)	105 (71)	83 (56)	1.8 (1.2)	200
Store brand generic	Wyeth	Soy protein isolate	2.7 (1.8)	Sucrose corn syrup	10.2 (6.9)	Oleo, coconut, soy, high-oleic safflower	5.3 (3.6)	1.3 (0.9)	2.7 (1.8)	90 (61)	63 (43)	1.8 (1.2)	200

CHO = carbohydrate.

Table 29-5 Extensively Hydrolyzed Protein and Elemental Formulas

		Protein		*CHO*		*Fat*		*Sodium*	*Potassium*	*Calcium*	*Phosphorus*	*Iron*	
Formula	*Manufacturer*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*mEq/100 kcal (mEq/dL)*			*mg/100 kcal (mg/dL)*		*Osmolality (mOsm/kg)*
Protein hydrolysate													
Nutramigen	Mead Johnson	Hydrolyzed casein	2.8 (1.9)	Corn syrup solids, modified corn starch	11.0 (7.4)	Palm olein, soy, coconut, high-oleic sunflower	5.0 (3.3)	2.0 (1.4)	2.8 (1.9)	94 (64)	63 (43)	1.8 (1.2)	320
Protein hydrolysate, modified fat													
Alimentum	Ross	Hydrolyzed casein	2.7 (1.9)	Sucrose, modified tapioca starch	10.0 (6.9)	Safflower, MCT (33%), soy	5.5 (3.7)	1.9 (1.3)	3.0 (2.0)	105 (71)	75 (51)	1.8 (1.2)	370
Pregestimil	Mead Johnson	Hydrolyzed casein	2.8 (1.9)	Corn syrup solids, sucrose, modified corn starch	10.2 (6.8)	MCT (55%), soy, corn, and high-oleic safflower	5.6 (3.7)	2.0 (1.1)	2.8 (1.9)	115 (78)	75 (51)	1.8 (1.2)	320
Elemental													
Neocate	SHS	L-Amino acids	3.1* (2.1)*	Corn syrup solids	11.7 (7.8)	Safflower, coconut, soy, MCT (5%)	4.5 (3.0)	1.6 (1.1)	4.0 (2.7)	124 (83)	93 (62)	1.8 (1.2)	342

CHO = carbohydrate; MCT = medium-chain triglycerides.
*Protein equivalent.

Table 29-6 Formulas for Specific Medical Conditions

		Protein		*CHO*		*Fat*		*Sodium*	*Potassium*	*Calcium*	*Phosphorus*	*Iron*	
Formula	*Manufacturer*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*mEq/100 kcal (mEq/dL)*			*mg/100 kcal (mg/dL)*		*Osmolality (mOsm/kg)*
Enfamil AR *Gastro-esophageal reflux*	Mead Johnson	Nonfat milk	2.5 (1.7)	Lactose, rice starch, maltodextrin	11.0 (7.4)	Palm olein, soy, coconut, and high-oleic sunflower	5.1 (3.5)	1.7 (1.2)	2.8 (1.9)	78 (53)	53 (36)	1.8 (1.2)	240
Isomil DF *Diarrhea*	Ross	Soy protein isolate	2.7 (1.8)	Corn syrup solids, sucrose	10.1 (6.8)	Soy, coconut	5.5 (3.7)	1.9 (1.3)	2.8 (1.9)	105 (71)	75 (51)	1.8 (1.2)	240
Portagen *Chylous leak*	Mead Johnson	Sodium caseinate	3.5 (2.4)	Corn syrup solids, sucrose	11.5 (7.8)	MCT (85%), corn	4.8 (3.2)	2.4 (1.6)	3.2 (2.2)	94 (64)	70 (47)	1.9 (1.3)	230
Similac PM 60/40 *Renal disease*	Ross	Whey protein concentrate, sodium caseinate	2.2 (1.5)	Lactose	10.2 (6.9)	Corn, coconut, soy	5.6 (3.8)	1.0 (0.7)	2.2 (1.5)	56 (38)	28 (19)	0.7 (0.5)	280

CHO = carbohydrate; MCT = medium-chain triglycerides.

Table 29-7 Formulas for Older Infants and Toddlers

		Protein		CHO		Fat		Sodium	Potassium	Calcium	Phosphorus	Iron	
Formula	*Manufacturer*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*Source*	*g/100 kcal (g/dL)*	*mEq/100 kcal (mEq/dL)*			*mg/100 kcal (mg/dL)*		*Osmolality (mOsm/kg)*
Cow's milk based													
Follow-up (4–12 mo)	Carnation	Nonfat milk	2.6 (1.7)	Corn syrup solids, lactose, maltodextrin	13.2 (8.8)	Palm olein, soy, coconut, high-oleic safflower	4.1 (2.7)	1.7 (1.1)	3.5 (2.3)	120 (80)	80 (54)	1.8 (1.2)	326
Next Step (> 6 mo)	Mead Johnson	Nonfat milk	2.6 (1.8)	Corn syrup solids, lactose	11.1 (7.5)	Palm olein, soy, coconut, high-oleic sunflower	5.0 (3.4)	1.8 (1.2)	3.3 (2.2)	120 (82)	84 (57)	1.8 (1.2)	270
Similac 2 (6–18 mo)	Ross	Nonfat milk, whey protein concentrate	2.1 (1.6)	Lactose	10.6 (7.2)	High-oleic safflower, coconut, soy	5.5 (3.7)	1.0 (0.7)	2.7 (1.8)	118 (80)	64 (43)	1.8 (1.2)	300
Store brand generic (4–12 mo)	Wyeth	Nonfat milk, whey protein concentrate	2.6 (1.7)	Lactose	10.1 (6.8)	Oleo, coconut, soy, high-oleic safflower	5.4 (3.7)	1.4 (0.9)	3.2 (2.2)	120 (82)	84 (57)	1.8 (1.2)	280
Soy protein based													
Follow-up Soy (4–12 mo)	Carnation	Soy protein isolate	3.1 (2.1)	Maltodextrin, sucrose	13.2 (8.8)	Palm olein, soy, coconut, high-oleic safflower	4.4 (2.9)	1.8 (1.2)	3.0 (2.0)	135 (90)	90 (60)	1.8 (1.2)	200
Isomil 2 (6–18 mo)	Ross	Soy protein isolate	2.4 (1.7)	Corn syrup solids, sucrose	10.3 (7.0)	High-oleic safflower, coconut, soy	5.5 (3.7)	1.9 (1.3)	2.8 (1.9)	135 (91)	90 (61)	1.8 (1.2)	200
Next Step Soy (> 6 mo)	Mead Johnson	Soy protein isolate	3.3 (2.2)	Corn syrup solids, sucrose	11.8 (8.0)	Palm olein, soy, coconut, high-oleic sunflower	4.4 (3.0)	2.1 (1.4)	3.8 (2.6)	115 (78)	90 (61)	1.8 (1.2)	260

CHO = carbohydrate.

poses of quantification, they are collectively referred to as "total potentially available nucleosides."[23] The amount of available nucleosides in breast milk is considerably higher than in cow's milk. It is thought that during times of high demand, that is, during rapid growth, dietary nucleosides are useful and may be conditionally essential. Animal studies have shown nucleosides to enhance T-cell function and gastrointestinal maturation. Fortification of infant formula with the four main nucleotides found in human milk led to enhanced antibody responses to *Haemophilus influenzae* type b and diphtheria.[25]

Long-Chain Polyunsaturated Fatty Acids These fatty acids have received enormous attention in recent years. Although the consequences, especially those in the long term, of a lack of these fatty acids in the infant's diet remain controversial, formula manufacturers are now offering many formulas with and without added LCPUFAs. Formulas with added LCPUFAs are specially designated. The fatty acids in question are DHA and ARA. DHA is a $C_{22:6\ n-3}$ fatty acid with six double bonds. It is derived from dietary α-linolenic acid by a series of chain elongation and desaturation steps. ARA is a $C_{20:4\ n-6}$ fatty acid with four double bonds. It is derived from dietary linolenic acid. Breast milk contains preformed DHA (about 0.2% of fatty acids) and ARA (about 0.5% of fatty acids). The plant oils used in manufacturing formulas do not contain DHA and ARA, and formulas are devoid of DHA and ARA unless they are specifically added from other sources.

Infants, including premature infants, have the ability to synthesize DHA and ARA from their respective precursors, but the synthetic capacity appears to be insufficient to keep up with the high demands, especially for DHA. DHA is needed for incorporation into cortical gray matter and the retina. In infants who are fed formulas devoid of DHA, concentrations in gray matter and retina are substantially lower than in breast-fed infants.[26,27] The same is true for concentrations in plasma and erythrocyte membrane lipids.[28] Infants fed DHA-free formulas show evidence of impaired retinal function during the early months of life.[29] However, this effect seems to be transient and is no longer demonstrable in older infants. The presence of DHA and ARA in formulas is considered desirable because these fatty acids are present in breast milk and because their absence from the infant's diet produces abnormal concentrations in brain, retina, erythrocyte, and plasma lipids.

WEANING AND BEIKOST

Weaning is the withdrawal or displacement of breast-feeding (see Chapter 30). The weaning period begins with the first introduction of a food other than breast milk (water and vitamin-mineral supplements are not considered to be food) and extends until the complete discontinuation of breast-feeding. Beikost is the term for foods other than milk or formula fed to infants.[30] Although we do not apply the term weaning to the withdrawal of formula, beikost is also referred to as weaning food.

Age of Introduction of Beikost

Evidence that infants can tolerate beikost before the currently recommended age of its introduction into the diet was provided by the experience in the 1950s and 1960s, when various beikost items were fed to many infants even during the early weeks of life.[1] However, there is at least a theoretic objection to feeding beikost during the early months of life because, at this time, there is greater permeability of the gastrointestinal tract to macromolecules than later. But the major reason for deferring introduction of beikost until 4 to 6 months of age relates to establishment of eating habits.[31,32] By about 4 months of age, most infants can sit with support and have adequate neuromuscular control of the trunk and neck.[33] At this developmental stage, the caretaker can interact with the infant to permit the infant to discontinue eating at the earliest sign of willingness to do so. Weaning should generally begin within a month or 6 weeks after the infant is developmentally ready. In industrialized countries, there is no compelling argument for delaying introduction of beikost beyond 6 months of age.

Choices of Beikost

There is no evidence that the sequence of introduction of various beikost items is a matter of great importance. It is convenient to begin with cereal because a small amount of the dry powder can be mixed with human milk for the breast-fed infant or formula for the formula-fed infant at quite low expense. Initially, only a small amount, less than a teaspoonful, should be given at one time. Whether pureed fruits or vegetables are then introduced seems of little consequence. However, single foods, rather than combinations, should be offered. It is generally recommended that one food be fed for several days before introducing another. It is desirable to work toward acceptance of variations in tastes and textures.

The exclusively breast-fed infant consumes an adequate intake of protein, but once beikost begins to comprise a substantial portion of the total energy intake, it is important to include some high-protein foods. Deficiency of iron and zinc in breast-fed infants is not rare. Meats, especially red meats, are a good source of protein, zinc, and a highly bioavailable form of iron. We recommend for the breast-fed infant that soft-cooked meats be introduced within the first month or two of beikost feeding (by 5 or 6 months of age). We consider the risk of iron and zinc deficiency to be greater than the risk of sensitization to meat proteins.

With the exception of providing sources of iron and zinc of high bioavailability for the breast-fed infant, the goal of feeding beikost is to begin the transition from the infant's primarily liquid diet to the predominantly solid-food diet of the child. Therefore, as infancy progresses, the variety of flavors and textures offered to the infant should gradually be increased.

Fruit juices should be fed sparingly and only by cup. Fruit juices are associated with adverse reactions[34] and do not provide nutrients that are lacking in the diet of the breast-fed or formula-fed infant.

COW'S MILK

Feeding of cow's milk during the first year of life is undesirable because such feeding is associated with the development of iron deficiency. It is unclear which of the several mechanisms is mainly accountable for the iron deficiency. It has long been recognized that ingestion of large quantities of cow's milk may result in low intakes of other foods that contain more generous amounts of iron. In addition, there is considerable evidence that ingestion of cow's milk causes occult gastrointestinal blood loss.[35–37] Finally, the high intake provided by cow's milk of casein and calcium, potent inhibitors of iron absorption, may contribute to the development of iron deficiency.[38]

The potential renal solute load provided by cow's milk is undesirably high.[19] Feeding of whole cow's milk does not interfere with maintenance of water balance in normal infants under most circumstances. But in a hot environment or during febrile illness, especially if associated with decreased fluid intake, the infant is at greater risk of dehydration if fed cow's milk than if breast-fed or formula fed. The margin of safety is greater with breast-feeding or feeding of infant formulas than with feeding of cow's milk.[19]

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CHAPTER 30

WEANING: PATHOPHYSIOLOGY, PRACTICE, AND POLICY

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DEFINITION

Infant feeding is frequently described by three overlapping periods: (1) exclusive breast-feeding, (2) weaning, which is a transitional period of continued breast-feeding with the introduction of complementary foods, and (3) a modified adult diet.[1,2] The word "wean" is derived from the Anglo-Saxon "wenian," meaning "to accustom (as a child) to take food otherwise than by nursing."[3] In a recent review, the World Health Organization (WHO) defined weaning as "the period during which any nutrient containing foods or liquids are provided along with breast milk."[4,5] In developed countries, weaning has referred to the transition from either breast milk or formula to complementary feedings that are solid foods.[1,2,6] This is the definition used for the purpose of this discussion.

Weaning is a time of life of considerable nutritional, physiologic, and developmental change, requiring transition from a complete liquid diet from a sole nutrient source to a varied diet of complex foods, the sum of which must provide nutritional adequacy. Potential health risks exist for the infant during this process, and these risks differ for infants in the developed versus developing world. Controversy exists as to the optimal timing of the introduction of complementary feeding, and progression through these phases is dependent on the infant's nutritional needs, physiologic maturation, and developmental readiness (Table 30-1). A 2001 WHO review on the optimal duration of exclusive breast-feeding recommends (for populations) exclusive breast-feeding for 6 months, with the introduction of complementary feeding at 6 months of age in conjunction with continued breast-feeding.[7] Despite broad cultural diversity, published recommendations for weaning are remarkably consistent worldwide.[1–6] In summary, they are:

- During the first 4 months of life, breast milk alone provides optimal nutrition for the rapidly growing infant.
- Between 4 and 6 months of age, breast milk alone becomes nutritionally inadequate and physical and developmental capacities mature. Complementary feedings are slowly introduced, and the composition and consistency of the diet advance so that by approximately 12 months of age, the infant is eating a variety of foods from a mixed diet.
- Dietary patterns continue to change rapidly throughout the second year of life as the transition to the family diet continues.

PATHOPHYSIOLOGY: FACTORS AFFECTING RECOMMENDATIONS

Nutritional Need

A primary goal is to meet the infant's nutritional needs during this period of very rapid growth. Human milk differs from the milk of other mammals and is uniquely suited to meet the needs of the growing infant. Nutrient recommendations for the first 6 months of life are derived primarily from the average amount consumed by healthy infants, growing at an optimal rate, exclusively breast-fed by healthy, well-nourished mothers.[8–10] Breast milk also contains components that assist in digestion, the absorption of certain nutrients, and the development of the gastrointestinal tract. In addition to providing optimal nutrition for the rapidly growing infant, breast-feeding promotes bonding between the nursing mother and her infant; breast milk also appears to provide protection against certain diseases such as diarrhea and allergy.[11–13] Because the volume of breast milk an infant consumes is determined by the amount that is needed to satisfy the infant, breast-feeding could play a role in the prevention of obesity.[14] The topics of breast milk and breast-feeding are more fully explored in Chapters 31, 32, and 33.

No specific time for the introduction of supplementary feeding has been universally shown to have positive short- or long-term effects on health.[1] Various investigators have calculated that between 3 and 4 months of age, exclusive breast-feeding becomes inadequate to meet the theoretic energy needs of the normal infant, whereas a more recent review indicates macronutrient but not micronutrient sufficiency.[7,10] Growth patterns and micronutrient intakes of infants exclusively breast-fed by well-nourished mothers indicate that subtle growth faltering, a possible precursor of more serious undernutrition, occurs at about 6 months.[1,8,9] Most of these studies have used growth charts based on predominantly bottle-fed infants, which

TABLE 30-1 Bases of Weaning Recommendations

	Breast-feeding	*Weaning*
Nutritional Need	Birth to 12 mo: appropriate calorie-to-protein ratio in infancy; high bioavailability (zinc, iron, vitamin A)	Four to 12 months: breast milk volume may become inadequate (700–970 mL/d) at 4–6 mo; nutrients of public health concern to emphasize in weaning foods are carbohydrate, fat (calories), protein, zinc, iron, and vitamins D, A, and E
Physiologic maturation		
Renal function capacity	Highly anabolic state, low renal solute load of breast milk; low concentrating and excretory capacity	Increased concentrating and excretory capacity
Gastrointestinal function	Immune factors (SIgA, lactoferrin, lysozyme); enzymes (breast milk amylase, lipase); omega-3 fatty acids; taurine; growth factors (peptides, nucleotides, IGF-I, cortisol, thyroxine, insulin)	Increased gastric capacity, higher-volume, less-frequent feeds; increased bile acid pool; increased pancreatic amylase; increased pepsin; bile-salt conjugation with glycine; matured microvillus membrane structure
Developmental readiness	Rooting; sucking; swallowing; extrusion reflex	Diminished extrusion reflex (4 mo); development of head, trunk, and gross and fine motor control (4–12 mo); development of exploratory behavior; manual dexterity (12–36 mo)

Adapted from Hendricks KM, et al. Weaning recommendations: the scientific basis. Nutr Rev 1992;50:125–33.
IGF = insulin-like growth factor; SIgA = secretory immunoglobulin A.

might be inappropriate. The growth faltering that occurs during weaning in many developing countries is a complex issue and is discussed below.

Mature human milk contains approximately 9 g protein per liter, of which approximately 70% is whey proteins. Protein quantity and quality affect both digestibility and the ability to support growth. The chemical properties of the casein in human milk promote the formation of a soft, flocculent curd, which is easier for human infants to digest than is the casein in other animals' milk. Additional proteins in human milk, such as the important immunologic factors secretory immunoglobulin A (SIgA), lactoferrin, and lysozyme, are active in the gastrointestinal tract but do not contribute nutritionally available protein. Their concentration has been estimated to be 3 g/L. Thus, nutritionally available protein could approximate 7 g/L. This would provide the normal infant consuming 180 mL/kg in the first months of life with approximately 1.3 g of protein per kilogram per day, a figure that agrees with theoretic calculations of protein requirements during early infancy but becomes inadequate to support growth during the second half of the first year of life.[1]

For the mother who cannot breast-feed or chooses not to, iron-fortified infant formula is appropriate for the first year of life.[2,15] The recommended guidelines for the composition of infant formulas have recently been extensively reviewed.[15] Although much progress has been made, certain nutrient issues remain controversial; formula does not provide the same components to the infant as breast milk does. Although all women should be encouraged to breast-feed, the final decision is the mother's. Coercion is inappropriate.[6]

Iron deficiency is the most common micronutrient deficiency in the world, and the weaning period is a particularly vulnerable time.[16] It is estimated that in the United States, 10% of infants and 9% of adolescent females have iron deficiency anemia. Worldwide, it affects 55% of infants and 50% of children. It appears that iron deficiency has both short- and long-term consequences, including lower scores on mental and motor development tests, with continued delayed development scores at age 2 to 3 years[17,18] and even into adolescence. In developed countries, at-risk infants are those born to mothers who are iron deficient because of lowered stores at birth, infants fed unfortified infant formula, and infants fed whole cow's milk early in life. Cow's milk is low in iron and vitamin E and high in protein, sodium, and potassium compared with human milk and infant formulas. In addition, gastrointestinal blood loss is well documented in infants receiving whole cow's milk. Guidelines for primary prevention and treatment of iron deficiency are outlined below.[16]

Milk and Infant Formulas

- Encourage breast-feeding of infants.
- Encourage exclusive breast-feeding of infants (without supplementary liquid, formula, or food) for 4 to 6 months after birth.
- When exclusive breast-feeding is stopped, encourage use of an additional source of iron (approximately 1 mg/kg/day), preferably from supplementary foods.
- For infants aged < 12 months who are not breast-fed or who are partially breast-fed, recommend only iron-fortified infant formulas as a substitute for breast milk.
- For breast-fed infants who receive insufficient iron from supplementary foods by age 6 months (ie, < 1 mg/kg/day), suggest 1 mg/kg/day of iron drops.
- For breast-fed infants who were preterm or had a low birth weight, recommend 2 to 4 mg/kg/day of iron drops (maximum of 15 mg/day) starting 1 month after birth and continuing until 12 months of age.
- Encourage use of only breast milk or iron-fortified infant formula for any milk-based part of the diet (eg, in infant cereal) and discourage use of low-iron milks (eg, cow's milk, goat's milk, soy milk) until age 12 months.

- Suggest that children aged 1 to 5 years consume no more than 700 mL of cow's milk, goat's milk, or soy milk each day.

Solid Foods

- At age 4 to 6 months or when the extrusion reflex disappears, recommend that infants be introduced to plain, iron-fortified infant cereal. Two or more servings per day of iron-fortified infant cereal can meet an infant's requirement for iron at this age.
- By approximately 6 months of age, encourage one feeding per day of foods rich in vitamin C (eg, fruits, vegetables, or juice) to improve iron absorption, preferably with meals.
- Suggest introducing plain, pureed meats after age 6 months or when the infant is developmentally ready to consume such food.

Guidelines for secondary prevention of iron deficiency through screening are outlined below.[16]

Universal Screening In populations of infants and preschool children at high risk for iron deficiency anemia (eg, children from low-income families; children eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children; migrant children; or recently arrived refugee children), screen all children for anemia between ages 9 and 12 months, 6 months later, and annually from ages 2 to 5 years.

Selective Screening In populations of infants and preschool children not at high risk for iron deficiency anemia, screen only those children who have known risk factors for the condition, as follows: (1) consider anemia screening before age 6 months for preterm infants and low birth weight infants who are not fed iron-fortified infant formula; (2) annually assess children aged 2 to 5 years for risk factors for iron deficiency anemia (eg, a low-iron diet, limited access to food because of poverty or neglect, or special health care needs); screen these children if they have any of these risk factors; (3) at ages 9 to 12 months and 6 months later (at ages 15 to 18 months), assess infants and young children for risk factors for anemia. Screen the following children:

- Preterm or low birth weight infants
- Infants fed a diet of non-iron-fortified infant formula for more than 2 months
- Infants introduced to cow's milk before age 12 months
- Breast-fed infants who do not consume a diet adequate in iron after age 6 months (ie, who receive insufficient iron from supplementary foods)
- Children who consume more than 700 mL cow's milk daily
- Children who have special health care needs (eg, children who use medications that interfere with iron absorption or who have chronic infection, inflammatory disorders, restricted diets, or extensive blood loss from a wound, an accident, or surgery)

Physiologic Maturation

At birth, the renal system performs all of its normal functions, but with limited concentrating ability. Functional capacity of the kidneys increases rapidly, and by age 4 months, the ability to handle an increased solute load is adequate for the gradual addition of weaning foods. By 12 months, kidney size has almost doubled, and significant dietary variation is well tolerated. Between 6 weeks gestation and birth, the surface area of the intestine increases nearly 100,000-fold; the length of the small intestine at birth is approximately 2½ times the length of the infant.[19] Gastrointestinal motility increases with advancing fetal age and intestinal transit time at term averages 4½ to 7 hours. During the course of the first year of life, infants rapidly develop rhythm in their feeding patterns. As gastric capacity increases, most infants progress from consuming approximately 180 mL/kg per day at 2- to 3-hour intervals to less-frequent, higher-volume, and higher-density feedings by the end of the first year.[20]

Neurologic Development and Developmental Readiness

In newborns, the neurologic coordination of a rhythmic suck-swallow-breathe pattern is critical in successful feeding.[21] Breast-fed infants usually feed between 8 and 12 times every 24 hours during the first month of life and decrease to 6 to 8 times daily by age 4 to 6 months.[22] At approximately 3 to 6 months of age, the child's oral anatomy begins to change, and central nervous system control of swallowing increases. This allows for an increased range of movement of the oral structures, the development of internal stability, and greater lip control and closure. It also enables the infant to engage in oral-motor play and sensory-motor exploration.[23,24]

Infant motor development occurs at a rapid, sequential pace as part of the overall maturation process. Maturation is dependent partly on the growth of the infant, and physical developmental milestones are linked to the developmental readiness cues given by the infant regarding the introduction of complementary foods. Physical development milestones include a doubling of weight, physical control, sensory awareness, communication attempts, and improved mouth coordination.[24]

Continued refinement of oral-motor skills increases dexterity; cognitive development also prepares the 6-month-old child for more active participation in the feeding process. Development of trunk and shoulder control is a milestone at this stage because it provides the foundation for increased mobility and coordination of the oral structures during eating and playing.[24] By age 7 to 8 months, grasp becomes more refined and progresses from a palmar to a digital grasp; hand-to-hand transfer of objects develops. This facilitates finger feeding. Refinement of oral-motor skills continues and is enhanced through the introduction of spoon feeding (at 4 to 6 months), cup drinking, and self-feeding of finger foods. Characteristic of this developmental stage of feeding is the continued introduction of foods appropriate for biting and chewing. Reaching, grasping and releasing, and eye–hand coordination all improve from 6 to

12 months, allowing for the progression to self-feeding and emerging independence.

The 12-month-old infant is generally independent, mobile, and interactive, allowing for tremendous enthusiasm in the self-feeding process. Refined oral-motor skills lead to an increased ability to accept and manage a variety of food textures, shapes, and tastes. By 12 months, most infants can hold a cup with two hands and handle four or five consecutive swallows without choking. New flavors and textures coming from dietary variety continue throughout the weaning process and should be in forms compatible with developmental abilities.

The progression of feeding skills from 12 to 18 months of age is characterized by continued coordination of chewing, biting, and swallowing skills and by expansion of dietary variety. Important issues during this time are the child's opportunities for sensory-motor feeding experiences and the influence of parental expectations and attitudes about normal feeding and social-communicative experiences during feeding.[24] These factors contribute significantly both to the infant's developmental skills and to behaviors associated with eating. A critical component of the successful transition to complementary feedings is the individual infant's response to the feeding interaction. A positive mealtime and eating environment that leads to the establishment of a healthy attitude toward food and the development of normal eating habits is essential. Factors affecting this interaction include the infant's overall health and growth, the developmental readiness for weaning, the infant's ability to communicate that readiness, and the presence of a caregiver who understands and responds to the child's cues.

This communication between infant and caregiver is an essential component of the successful feeding relationship. Consistent awareness and accurate interpretation of, and appropriate response to, feeding cues strengthen the infant–feeder relationship and facilitate progression of feeding skills at an appropriate pace for the child. The ability of the caregiver to recognize and respond to the child's cues for feeding readiness and the ability of the parent to accept the infant's growing need for exploration and independence are essential to the development of the infant's feeding skills through the weaning period.

Much more is known about behavioral development during early infant feeding than during weaning. However, it is clear that pleasurable sensations associated with taste and ingestion promote exploratory behavior and tolerance for the unfamiliar once the weaning process has begun.[25–27] The original work of Clara Davis in 1928 documented the ability of newly weaned infants to self-select a nutritionally adequate diet when offered a wide variety of animal and vegetable foods that were thought to provide for all known nutrient needs.[25] These infants, who at the start of the study had little experience with the foods offered, showed strong preferences but selected a variety of foods rather than just the most preferred. This balancing of choices resulted in the consumption of nutritionally complete diets.

This confirmed that young children should be offered a variety of foods of high nutritional value and that a healthy young child's energy requirements are controlled by appetite. Research more closely evaluating the energy intakes of 15 children, aged 2 to 5 years, has confirmed this.[28] Food consumption patterns were highly variable from meal to meal, but daily energy intake was relatively constant because the children adjusted their caloric intake at successive meals. Additional research shows that children who have less exposure to variety in foods, who are more likely to be praised or rewarded for eating, and who are punished for not eating are more likely to develop problematic eating behavior.[29,30]

PRACTICE

Many of our recommendations about infant feeding come from observational studies, most of which were cross-sectional in design and used growth as the primary, and sometimes only, outcome. It is unclear whether this provides reliable data on which to base public health nutrition guidelines. More recent studies from developed countries have focused specifically on the weaning period and processes, following infants longitudinally during this period of rapid transition. In addition to reflecting current practice, together these studies provide new information on which to base policy.

Picciano and colleagues followed 55 healthy full-term infants from 12 to 18 months of age. Dietary intake and growth data were collected monthly.[31] Energy intake increased significantly between 12 and 16 months of age. The energy-yielding nutrients (carbohydrate, protein, and fat) increased in relation to increased energy intakes, whereas the percentage of calories supplied by each remained relatively stable, as did dietary diversity. The increase in dietary density from sucrose approached significance. Many children were consuming less than the recommended level of fat (< 30% of calories), despite the common nutrition message not to restrict fat intake until after age 2 years. Decreases in iron and vitamin E intake between 12 and 18 months of age resulted in intakes well below reference standards. No infant consuming less than 30% of calories from fat met the requirement for vitamin E intake at 12 months; only one child did at 18 months. Also, height was positively correlated with both total fat and energy intake at age 18 months. Although zinc intake increased over time, it was approximately half of the recommended intake at each age. Grains (enriched and fortified), whole-milk dairy products, and meats were identified as important sources of the problematic nutrients (iron, zinc, and vitamin E).

Hammer and colleagues followed 191 healthy, full-term infants monthly for up to 60 months.[32] More than 90% of the infants were exclusively breast-fed during the first month of life. This declined rapidly from 31% at 2 months to 14% at 6 months (plus 48% partially) and 7% at 1 year (plus 19% partially). Conversely, bottle-feeding increased from 64% at 2 months to 84% at 1 year. At 24 months, 41% of infants still received bottles; 16% received them at 36 months, 8% at 48 months, and 3% at 54 months. Formula use remained common at 12 to 15 months, after

which use of cow's milk was common. Interestingly, infants fed a combination of breast- and bottle feeds were fed more frequently than those either solely breast-or bottle-fed.

Complementary feeding was infrequent until 4 months of age. After that time, 35% of infants were receiving at least one complementary feeding per day, and by age 9 months, all infants were. The age of introducing complementary feedings was correlated with weaning from the breast but not with weaning from the bottle. Similarly, the mother's return to work was positively correlated with age of breast weaning but negatively with age of bottle weaning. Seventy-four percent of mothers had returned to work by the time their child was 24 months of age. Mothers who returned to work earlier bottle-fed longer and stopped breast-feeding sooner. There was a significant difference between breast weaning, but not bottle weaning, between mothers who worked full time, part time, or not at all. Maternal work status was not correlated with introduction or use of complementary feedings. Maternal age and education were positively correlated with age of introducing complementary feedings and duration of breast-feeding but not with age of bottle weaning. This study raises intriguing questions about the impact of prolonged bottle-feeding on growth and adiposity, which will hopefully be addressed in future research.

A study evaluating the effect of adding complementary feedings on infant growth from 12 to 24 months of age in 94 healthy, full-term infants found earlier-than-recommended introduction of complementary feedings.[33] Eighty-three percent of mothers initiated breast-feeding; 33% were still breast-feeding at 4 months and 18% at 6 months. The median age of introducing complementary feedings fit current guidelines, with cereal added at 4 months, juice at 4½ months, fruit at 5 months, and vegetables at 5½ months. However, two-thirds of all infants had been given complementary foods by 4 months of age (14% by 2 months, an additional 21% by 3 months, and another 29% by 4 months of age); another 9% were fed cereal via bottles. Although introduction of feeding was early, the types of foods initiated (cereal, fruit, then juice) were consistent with recommendations. The age of introducing complementary feeding was not associated with illness scores or growth of the infant.

Kattelmann and colleagues evaluated the impact of early (at 3 to 4 months of age) versus late (at 6 months) introduction of complementary feeding on iron and zinc status of healthy, full-term infants who were formula fed.[34] The infants, who were all fed commercial formulas, had mean iron intakes approximately equal to the Recommended Dietary Allowance (RDA) and mean zinc intakes slightly less than the RDA up to 12 months of age. Mean zinc intakes were 40 to 60% of the RDA between 12 and 36 months; there were no differences between groups. Serum zinc levels were normal, and there were no differences between groups. There were no differences in serum iron parameters at 12, 24, or 36 months between the two groups.

A large study conducted in Scotland of 671 infants, 455 of whom were followed to 24 months of age, reported interesting findings.[35,36] Complementary feeding before 12 weeks of age was associated with heavier infants at 4, 8, 13, and 26 weeks of age but not at 52 and 104 weeks. There was a significant increase in respiratory illness at 14 to 26 weeks and at 27 to 39 weeks in infants given complementary feedings early. The incidence of eczema was greater in these infants; gastrointestinal illness, wheezing, and diaper rash were unrelated to early complementary feeding. Longer-term follow-up (mean age, 7.3 years) of 545 of the initial 671 infants found that infants exclusively breast-fed for 15 weeks had a significant reduction in respiratory illness. Complementary feeding before 15 weeks was associated with increased probability of wheezing, as well as increased weight and percentage of body fat during childhood. Exclusive bottle-feeding was associated with higher systolic blood pressure in childhood. There was no association between timing of complementary feeding and blood pressure. Thus, exclusive breast-feeding and delaying complementary feeding until after 15 weeks of age could have a beneficial effect on childhood health and subsequent adult disease.

In a prospective randomized study, Simell and colleagues evaluated the impact of nutrition and lifestyle education in late infancy on dietary intake and serum lipid parameters and growth during the first 3 years of life.[37] At approximately 7 months of age, infants were randomized either to receive repeated individualized nutrition counseling (n = 540) or to the control group (n = 522), whose parents received a superficial discussion of nutrition. The nutritional intervention promoted a fat intake of approximately 30% and a 1:1:1 ratio of saturated, mono-, and polyunsaturated fatty acids. Results showed that the percentage of calories provided by fat intake was 29.5% for the counseled children at 8 months (29.4% for controls), 26.6% (28.5%) at 13 months, 30.5% (33.5%) at 24 months, and 31.5% (33.5%) at 36 months. Compared with the control children, those in the nutritional intervention group consistently consumed less saturated fat ($p < .0001$). Total cholesterol, high-density lipoprotein (HDL) cholesterol, and non-HDL cholesterol were 3 to 6% lower in the children who received nutritional counseling. The intervention had no effect on height, weight, or head circumference, and fat intake did not predict children's growth patterns. Thus, early childhood nutritional counseling aimed at reduced saturated fat and cholesterol intake did not have an impact on growth and appears safe in children more than 7 months and up to 3 years of age.

A longitudinal study of Swedish infants found that 43% had been introduced to complementary feeding before 4 months of age.[38] The transition to complementary feedings was a lengthy process, averaging approximately 1 month from the introduction of solids to consuming more than 10 mL per day and 1½ months to consuming more than 100 mL per day. The transition process was longer for those infants for whom weaning began at an earlier age. The authors postulate that this could be because of physical immaturity (requiring more time to master the art of eating solids) and to caregiver response to slow acceptance of foods.

Of 74 Caucasian mother–infant pairs in New Zealand, 88% initiated breast-feeding, 42% were exclusively breast-

feeding at 3 months, and 34% were partially breast-feeding at 12 months of age.[39] Longer duration of breast-feeding was seen with higher education of the mother, a finding similar to those in previous reports. Mothers who perceived insufficient breast milk or found breast-feeding in public embarrassing breast-fed for a shorter period. Overall, 95% of infants were given nonmilk feedings before 4 months of age and 69% were given unfortified cow's milk before 12 months of age.

Data from two nationwide, cross-sectional samples of children aged 1 to 2 years in the United States (the Nationwide Food Consumption Survey [NFCS], *N* = 1,045, and the Continuing Survey of Food Intakes, *N* = 1,039) and a longitudinal sample studied from ages 12 to 18 months (*N* = 55) evaluated secular trends in dietary intake.[40] Relationships among portion size, frequency of eating, dietary quality, and growth were evaluated. Portion size remained similar for most foods across decades with the exception of meat portions, which decreased in size in recent years. Portion size was longitudinally stable for most foods, except for milk, bread, cereal, juice, and peanut butter, which together contributed the daily share of children's energy intake. Body weight was positively related to energy intake and portion size but not to the number of times food was eaten daily or the foods consumed. Portion size appeared to be the means by which children self-regulated energy intake when foods offered and the number of meals eaten varied. Although energy intake and body weight were similar among groups, black children ate larger portions but fewer times daily than white children did. Similar results were found for the lowest versus the highest income categories. This study suggests that infants have the ability during the second year of life to consume larger portions if they are fed less frequently. The authors postulate that this behavior could affect energy intake and weight later in life and might in part explain the sociocultural trends in obesity seen on the United States.

Additional research supports the idea that in preschool children, environmental factors become increasingly important determinants of intake. Rolls and colleagues found that 3½-year-old children were not significantly affected by portion size; their intake varied across portion-size manipulation. However, amount of food offered influenced the intake of 5-year-old children, who ate greater amounts when presented with larger portions.[41] This indicated that as children develop, their food intake is increasingly influenced by social, cultural, and environmental factors. This is an important time for the development of dietary patterns related to obesity.

In summary, recent studies reinforce concerns about inappropriate timing of weaning and nutrient deficiency issues and have added new insight into how to optimize nutrition and health beginning in infancy. Although introduction of complementary feeding was frequently early, the types of foods initiated (cereal, fruit) were generally consistent with recommendations. Making the transition to complementary feedings was a lengthy process, and the transition was longer for infants weaned at an earlier age. This could be a result of physical immaturity (requiring more time to master the art of eating solids) and of caregiver response, the long-term impact of which is unknown. Infants fed commercial formulas had mean iron intakes approximately equal to the RDA and mean zinc intakes slightly less than the RDA up to 12 months of age. Zinc, iron, and vitamin E intakes were found to be well below the RDA in older infants. Grains, dairy products, and meats were identified as important sources of those problematic nutrients.

Researchers found a significant increase in respiratory illness at 14 to 26 weeks and at 27 to 39 weeks in infants given complementary feedings early; the incidence of eczema was also greater in these infants. Breast-feeding exclusively and delaying complementary feeding until after 15 weeks of age could have a beneficial effect on childhood health and subsequent adult disease. Despite the common nutritional message not to restrict fat intake until after age 2 years, many children were consuming less than the recommended level of fat (ie, < 30% of calories). This was associated with inadequate intake of vitamin E. Other findings relate to potential effects on long-term health. One study suggests that infants have the ability during the second year of life to consume larger portions if they are fed less frequently. The authors postulate that this behavior could affect energy intake and weight in later life. A well-designed intervention with early childhood nutritional counseling aimed at reducing saturated fat and cholesterol intake showed that counseling did not have an impact on growth but improved diet quality and appeared safe in infancy.

ADDITIONAL ISSUES

Juice: How Much and When?

Fluid that is rich in sugar can pool around the teeth, increasing the incidence of dental decay called nursing bottle syndrome.[42,43] In addition to this well-documented association with dental caries, case reports of high juice intake associated with failure to thrive in infants and short stature in young children have led to the recommendation to limit juice intake in children.[44] Current guidelines are[45]:

- Juice should not be introduced into the diet of infants before 6 months of age.
- Infants should not be given juice from bottles or easily transportable covered cups that allow them to consume juice easily throughout the day. Infants should not be given juice at bedtime.
- Intake of fruit juice should be limited to 125 to 180 mL/day for children aged 1 to 6 years. For children aged 7 to 18 years, juice intake should be limited to 250 to 360 mL, or two servings, per day.
- Children should be encouraged to eat whole fruits to meet their recommended daily fruit intake.
- Infants, children, and adolescents should not consume unpasteurized juice.
- In the evaluation of children with malnutrition (overnutrition or undernutrition), the health care provider should determine the amount of juice being consumed.
- In the evaluation of children with chronic diarrhea, excessive flatulence, abdominal pain, or bloating,

the health care provider should determine the amount of juice being consumed.
- In the evaluation of dental caries, the amount and means of juice consumption should be determined.
- Pediatricians should routinely discuss the use of fruit juice and fruit drinks and should educate parents about differences between the two.

More recent studies have questioned these recommendations. In a longitudinal study of juice intake and growth to 72 months of age in healthy, full-term infants, Skinner and Carruth found that 100% juice was not associated with overweight or short stature in young children.[46] Multiple food records from 37 boys and 35 girls looked at juice, milk, carbonated beverages, and other drinks over time. Overall mean daily beverage intake did not change significantly. However, 100% juice intake decreased, milk intake remained stable, and intakes of both carbonated and other less nutritious drinks more than doubled. Longitudinally, juice intake was not associated with either short stature or overweight. It is unclear whether previous studies specified 100% juice and most were case series or cross-sectional in design. It is likely that the etiologies of failure to thrive and obesity are multifactorial; these conditions are unlikely to be caused solely by a single dietary factor such as fruit juice consumption. Both nutritious foods and beverages are important for child nutrition.

Weaning the Allergic Infant

Weaning the allergic infant can be a slow and complex process. For infants with a family history of food allergy, exclusive breast-feeding is strongly recommended.[13,47,48]

A recent large cohort study examined the issue of whether breast-feeding truly protects against the development of allergy, and actually suggested the opposite; with increased duration of breast-feeding, the incidence of allergy and asthma at ages 13 to 21 years was higher.[49] As with many observational studies, other factors besides the decision to breast-feed could have influenced these results. A family propensity toward allergy might have prompted mothers to breast-feed longer, so reverse causality could have occurred in this study. In addition, most infants received a small amount of cow's milk formula in the neonatal period, raising questions about whether the definition of exclusive breast-feeding was accurate.[49] Recent data have also suggested that dietary supplementation of the nursing mother and infant with probiotics such as lactobacillus could reduce the occurrence of atopic disease.[50]

For the infant with a personal or family history of allergy, prudent recommendations are to delay the introduction of complementary feedings until 5 to 6 months of age. New foods should be added in small amounts, one at a time, ensuring that there are no (or limited) additives. Foods to begin during weaning at 5 to 9 months of age include rice and millet; cooked vegetables, including potato, yam, sweet potato, and squash; and fruits, such as banana, pear, and peach. Lamb and turkey are considered the least allergenic meats. From 9 to 12 months, additional grains such as oats and barley should be tried, one at a time and beginning with small amounts. Chicken, veal, and beef can be added, along with additional cooked vegetables and fruit. From 12 to 24 months of age, stronger vegetables, citrus fruits, berries, and melon are slowly added, as are other grains (specifically wheat). All of the protein-rich foods except shellfish, nuts, and seeds can be added slowly to the diet during the second year of life. The decision to begin dairy products of any kind is an individual one, but this can be done between 12 and 24 months or after 2 years of age, depending on the infant's clinical history.

Because it might be necessary to delay the addition of specific food groups to the weaning infant's diet, close attention should be paid to nutritional adequacy. Important nutrients in the common allergens egg, fish, nuts, and soy are protein, iron, vitamin B_{12}, zinc, and selenium. These nutrients should be met by intake of other rich food sources if possible or if necessary by supplementation.

Weaning Issues in Developing Countries

The importance of weaning is underscored when one considers the consequences of inappropriate weaning in deprived environments (Table 30-2). Too early initiation of weaning displaces breast milk, decreases the mother's milk production, and results in malnutrition, whereas weaning too late leads to growth faltering and depressed immune function.[27] Others have suggested that this association between growth failure and prolonged breast-feeding is not an etiologic one but is more related to poor quality of weaning foods in breast-fed infants, especially those of poor mothers.[51]

Growth faltering and diarrhea that occur at the time of weaning are significant public health problems. The recent WHO Global Database in Child Growth and Malnutrition reports that stunting affects 182 million children and wasting affects 150 million.[52] These growth deficits are associated with more than half of the 10 million annual deaths of children under the age of 5 years, primarily from infectious disease. Breast-feeding protects children from much of this disease burden while they are exclusively breast-fed; growth faltering, diarrheal disease, and progressive malnutrition begin about the time of weaning.[53] In societies where undernutrition, environmental contamination, and social deprivation are common, this has been termed the "weaning dilemma."[27] This occurs because either prolonged, exclusive breast milk intake or eating weaning foods that are contaminated or nutritionally inadequate will lead to the cycle of malnutrition, depressed immune function, and diarrhea. Potential interventions that can help in growth and reduction of morbidity by preventing infections, such as hygienically prepared commercial foods (which are expensive), heating and preparing fresh foods every time (which is expensive and impractical), or better storage with refrigeration, are not always feasible.[54]

There is no clear definition of growth faltering, but it is widely assumed to begin around the time of weaning in developing countries. A 2001 WHO review of the optimal duration of exclusive breast-feeding recommends (for populations) exclusive breast-feeding for 6 months, with the

TABLE 30-2 Weaning Consequences

Time of Weaning	*Consequences*
Too early	Increased diarrhea owing to intestinal immaturity; potential increased allergies in at-risk infants; potential risk of wheezing and respiratory illness; potential prolonged weaning; decreased breast milk production (displaced by weaning foods); malnutrition owing to diarrheal disease; potential risk of obesity
Ideal	Appropriately timed, starting at 4–6 mo; nutritionally adequate, emphasizing calories, protein, iron, zinc, and vitamins E, A, and D; hygienically prepared, cool, covered, clean, cooked; culturally appropriate, available, acceptable to the population
Too late	Growth failure: breast milk alone becomes calorically inadequate; depressed immunity owing to inadequate energy and protein intake; increased diarrheal disease owing to depressed immunity; malnutrition owing to inadequate calories and diarrheal disease; micronutrient deficiencies owing to inadequate dietary intake, increased needs with infection

Adapted from Hendricks KM, et al. Weaning recommendations: the scientific basis. Nutr Rev 1992;50:125–33.

introduction of complementary feedings at 6 months of age in conjunction with continued breast-feeding.[7] The authors also concluded that despite advantages, exclusive breast-feeding to 6 months can lead to iron deficiency and could put infants at risk for growth faltering and other micronutrient deficiencies. More recently, the WHO Multinational Study of Breastfeeding and Lactational Amenorrhea, a longitudinal, seven-country study, evaluated growth patterns and differing durations of breast-feeding and types and frequency of complementary feedings.[53] The infants were living in generally favorable environments. Growth was not sensitive to the differential timing of the introduction of complementary foods between 4 and 6 months or to types and frequencies of complementary feedings. These results do not provide compelling evidence of benefit or risk related to growth and the timing of introduction of complementary foods at a specific time between 4 and 6 months of age. Again, the application to populations living in poorer environments is unclear.

A recent analysis of the WHO Global Database on Child Growth and Malnutrition, containing 39 nationally representative data sets from recent growth monitoring programs in developing countries, attempted to address issues relating to the occurrence of growth faltering.[48] For children in the developing world at birth, in comparison with the National Center for Health Statistics (NCHS) Growth Charts, the average weight for age, length for age, and weight for length are quite close to reference values. Growth faltering then occurs, so that by 18 months, mean weight for age and mean length for age are between 1 and 2 standard deviations below the median reference values. The median weight for length is about –0.6 at 18 months, and the three primary growth parameters (WAZ, HAZ, WHZ) show different patterns. Mean weight starts to falter at about 3 months of age and declines rapidly until 12 months; between 12 and 19 months, this decline slows. Most wasting (WAZ) in children occurs in the period between 3 and 15 months of age. For length, although the mean birth values are close to the NCHS standards, faltering starts soon after birth and lasts well into the third year, and is not recovered thereafter. These processes appear to be independent of each other. The pattern was remarkably similar in many developing countries. It is clear from this new information that weaning is not the only—and might not be the primary—factor in this complex issue.

Prudent Weaning Recommendations

Weaning guidelines are similar for infants in deprived environments, but with several caveats. First, breast-feeding should be continued on infant demand to avoid displacement of breast milk. Variety is needed in complementary foods that are culturally appropriate but follow the basic recommendations summarized below. Special attention should be paid to changes in appetite, growth, or development, which could be indicators of or precursors to nutrient deficiencies or excess.

During the first 4 months of life, breast milk alone provides optimal nutrition for the rapidly growing infant. Between 4 and 6 months, breast milk alone becomes nutritionally inadequate as physical and developmental capacities mature. Complementary feedings are slowly introduced, and the composition and consistency of the diet advance so that by approximately 12 months of age, the infant is eating a variety of foods from a mixed diet. An infant feeding guide for the first year of life is detailed in Table 30-3. Deficiencies of iron, zinc, and possibly vitamin E are the most common micronutrient deficiencies observed during infancy in developed countries, plus vitamin A in developing countries. Examples of sources of these nutrients are listed in Table 30-4. Weaning recommendations have focused on prevention of deficiencies of these nutrients.

As the infant advances to an adult family diet, prevention of nutrient deficiencies can be achieved by eating foods from each of the basic food groups (dairy, grains, vegetables, fruits, and meats) daily. No one food group alone provides all of the essential nutrients, and each group makes an important contribution to a child's daily nutrient needs. A variety of foods from each group ensures an adequate intake of all nutrients. Exposure to many new foods during infancy expands a child's willingness to experiment with foods later, with the aim of achieving a base for long-term healthful eating habits. Current guidelines include the adoption of the American Heart Association Step 1 Diet in children over age 2 years, moderation in restricting fat, and an emphasis on overall dietary quality.

Approximately three to four servings per day of dairy products, such as whole milk, buttermilk, yogurt, cheese, ice cream, custard, or pudding, are appropriate for children ages 1 to 3 years. Dairy products are high in protein, cal-

TABLE 30-3 Infant Feeding Guide

Foods	*0–4 Months*	*4–6 Months*	*6–8 Months*	*8–10 Months*	*10–12 Months*
Breast milk	Short, frequent feedings 8 or more per day	Short, frequent feedings 5 or more per day	On demand 5 or more feedings per day	On demand	On demand
OR iron-fortified formula	500–950 mL, 5–10 feedings per day	700–1,180 mL, 4–7 feedings per day	700–950 mL, 3–4 feedings per day	500–950 mL, 3–4 feedings per day	500–700 mL, 3–4 feedings per day
Cereals and bread	None	Infant cereals, rice, oatmeal, or barley (spoonfed). Mix 10–15 mL with formula, water, or breast milk	Most varieties of boxed infant cereals, 15–60 mL twice a day	Infant cereals or other plain hot cereals, 120–180 mL/d Toast, bagel, or crackers	Hot or cold unsweetened cereals, 60–125 mL/day; bread, rice, noodles, or pasta (125 mL/d)
Fruit juices	None	Infant juice, adult apple juice, vitamin C fortified (avoid orange and tomato juice), 60–125 mL/d	Infant juice, adult apple juice (vitamin C fortified). Offer juice from a cup, 125 mL/d	All 100% juices (orange and tomato juice can be offered), 125 mL/d	All 100% juices from a cup, 125 mL/d
Vegetables	None	None	Strained or mashed dark yellow, orange, or green vegetables (avoid corn), ½–1 jar or 125 mL/d	Cooked, mashed fresh or frozen vegetables, 80–125 mL/d	Cooked vegetable pieces, 125 mL/d
Fruits	None	None	Fresh, cooked, mashed or strained fruits, ½–1 jar or 125 mL/d	Peeled, soft, mashed fruit or fruit wedges, 80–125 mL/d	All fresh fruits, peeled and seeded, 125 mL/d
Protein	None	None	Plain yogurt (can be mixed with soft fresh fruit or applesauce)	Lean meat, chicken, and fish (strained, chopped, or small tender pieces), 45–60 mL/d; egg yolk, yogurt, mild cheese, cooked dried beans	Small, tender pieces of meat, fish, or chicken, 60–75 mL/d; egg white, cheese, yogurt, cooked dried beans, peanut butter

Adapted from Infant feeding guidelines. Boston: Children's Hospital.

cium, vitamins A and D, and riboflavin, and whole milk is high in vitamin E. Low-fat and skim milk products are not recommended until a child is 2 years old.

Meat and meat substitutes include meat, fish, poultry, eggs, and legumes. These foods are generally good sources of protein, iron, zinc, copper, vitamins B_6 and B_{12}, and niacin. Two servings per day, each of approximately 1 to 2 ounces, is appropriate.

The bread and cereal group includes breads, muffins, cereals, rice, noodles, and pasta. Grains are high in thiamin, niacin, vitamin B_6, folate if enriched, and iron if fortified. If they are whole grains, they are generally rich in magnesium and zinc as well. Whole-grain breads and cereals contain significant amount of fiber, which is important in the diet because it aids in normal bowel function and could be important in the prevention of certain chronic intestinal disorders that can occur later in life.

The fruit and vegetable group includes fresh, frozen, canned, and dried fruits and vegetables. Fruits and vegetables are rich in B vitamins, folate, iron, and vitamins A and C. Unprocessed fruits and vegetables are also high in fiber. Between 8 and 10 months of age, as the infant begins to use a cup, juices can be introduced one at a time. Natural juices, particularly those with no added sugar, rather than fruit drinks, are best. It is important for an infant to drink juice from a cup rather than a bottle.

In addition to the type and amount of food offered to infants and children, it is clear that early infant feeding experiences have a profound effect on eating behaviors. Table 30-5 lists common caretaker behaviors that positively influence children's eating patterns and should be encouraged.

TABLE 30-4 Sources of Problematic Nutrients

Vitamin A	*Vitamin C*	*Calcium*	*Iron*
Apricots	Asparagus	Broccoli	Cereals (read labels)
Asparagus	Broccoli	Dairy products	Dried beans
Broccoli	Cabbage	Herring	Dried fruit
Cantaloupe	Cantaloupe	Kale	Eggs
Carrots		Grapefruit	Salmon
Dairy products	Green pepper	Sardines	Greens
Green pepper	Kale	Spinach	Liver
Kale	Lemons	Tuna	Red meats
Liver	Oranges		
Peaches	Potatoes		
Plums	Spinach		
Spinach	Strawberries		
Sweet potatoes	Tangerines		
Tomatoes	Tomatoes		
Winter squash			

POLICY

Recommendations from developed countries for weaning infants, and for the addition of complementary feedings, have not varied significantly over the past 40 years.[55] In a recent review of the rationale for recommendations for feeding normal infants, Fomon[6] outlines them clearly:

- Every mother should be encouraged to breast-feed her infant but not coerced to do so.
- Every infant should be given an injection of vitamin K as soon as feasible after birth.
- While in hospital, every woman who breast-feeds her infant should be given instructions about breast-feeding.
- Follow-up approximately 48 hours after discharge from hospital should be arranged for women who breast-feed.
- Every breast-fed infant should receive a daily supplement of iron and vitamin D.
- Formula-fed infants should receive iron-fortified formulas.
- Actions of caregivers should be conducive to establishing habits of eating in moderation.
- Introduction of complementary feedings (ie, foods other than breast milk or formula) should be deferred until the infant reaches the stage of developmental readiness for such feedings.
- Complementary foods should be thoughtfully selected.
- Cow's milk should not be fed to children before the age of 1 year.

As the focus of public health in developed countries has moved to attaining optimal nutrition for long-term health, current research on infancy has begun to address the significant issues of prevention of diseases such as obesity and heart disease. Currently, data are inconclusive regarding further specific nutrition recommendations on these issues. Future research should focus on these important questions.

TABLE 30-5 Caregiver Behaviors and Children's Resulting Eating Patterns

Caregiver Behavior	*Child's Response*
Exposure	Familiarity increases food acceptance and willingness to try new foods
Modeling	Adults, siblings, and peers provide direct and indirect examples of eating behavior
Positive reinforcement	Happy, safe, relaxed feeding atmosphere; recognition, praise, and approval to reinforce appropriate behavior
Discipline	Consistent, appropriate limit setting; solid family organization in problem solving and guidance in feeding issues
Stimulation	Emotional support, encouragement, and affection around feeding
Caregiver responsiveness	Appropriate, sensitive responses to development readiness and emotional issues involved in feeding

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CHAPTER 31

HUMAN MILK: NUTRITIONAL PROPERTIES

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Breast milk has been the natural and traditional food of human infants for as long as they have existed. Today, it continues to be the optimal source of nutrition for almost all infants worldwide. Breast milk also affords unique immunologic protection and stands alone as a source of nutrition that adjusts to meet the needs of the growing infant.

The volume of breast milk available and its nutritional composition differ among individual mothers based on their infant's demand. Differences are also noted between stages of lactation (colostrum, transitional and mature milk, and weaning) and also within individual feedings (foremilk versus hindmilk).[1] Colostrum, produced from the first to the fifth day of lactation, is rich in many nutrients, particularly proteins. Transitional milk contains increasingly higher concentrations of fats and lactose, until stabilizing by about the fifteenth day as mature milk.[2] The breast milk of mothers who deliver their infants prematurely contains higher concentrations of fats and protein and lower concentrations of lactose than the milk of women who deliver at term (Table 31-1). During weaning, protein and fat concentrations increase as involution of the mammary gland occurs.[3] Although concentrations of proteins, lactose, and other water-soluble components tend to remain similar throughout a single feeding, fat concentrations increase during an individual feeding.[4] This chapter reviews the nutritional properties of breast milk.

Throughout most of human history, infant mortality rates have ranged from 15 to 25% as high as 90% in orphans lacking ready access to a wet nurse. As recently as a century ago, one-quarter of all infants born in the United States died before they reached their first birthday. Many of these deaths occurred because of malnutrition and infectious diarrheal diseases.[5] Breast-feeding was almost a life or death proposition for newborn infants until well into the 1900s. Attempts to simulate human milk by various alterations to cow's milk were the basis for early American pediatric theory and practice. The founding fathers of the field of pediatrics—such as Holt, Rotch, and Jacobi—devoted much of their careers to defining the nutritional needs of young infants and developing safe feedings for infants who were separated from their mother's milk.

Nevertheless, social, cultural, and economic influences have affected maternal decision making regarding breast-feeding, especially in the past century. Beginning in the early 1900s, the United States (and much of the industrialized world) saw a successive decline in breast-feeding initiation.[6] The decreasing trend in breast-feeding was partly attributed to increased advertising for and availability of artificial baby milk, an increased number of women in the workplace, and a newly found belief in science and technology.

Breast-feeding initiation rates reached a low of 22% in the United States in 1972[7] but began to reverse owing in part to changes in childbirth practices beginning in the 1960s. Unmedicated deliveries, infant-directed nursing, rooming-in, and immediate breast-feeding postpartum facilitated an increase in breast-feeding initiation.[8] Maternal education and social class, income level, race, attitude and behavioral intention regarding infant feeding, and social support network are some of the other factors affecting maternal decisions to breast-feed.[9]

Over the past decade, breast-feeding rates have continued to rise overall. As of 1998, the number of mothers initiating breast-feeding has risen to 64%, with 29% continuing breast-feeding at 6 months and 16% at 1 year.[10] These numbers, although improving, still fall far below the Healthy People 2010 target of 75% of mothers initiating breast-feeding, 50% continuing to 6 months, and 25% continuing until 1 year.[11] The Healthy People 2010 report recognizes that "education of new mothers and their partners; education of health providers; changes in routine maternity ward practices; social support, including support from employers; and greater media portrayal of breastfeeding as the normal method of infant feeding are needed to increase breastfeeding rates."[11]

A wealth of literature studying human milk and breast-feeding in the last few decades has highlighted many previously unappreciated differences between human milk and cow's milk–based formulas. Biochemical differences in proteins, vitamins, minerals, enzymes, and fats, along with the availability of anti-infective properties such as secretory immunoglobulin A, lactoferrin, lysozyme, and interferon, set breast milk above artificial baby milk for nutrition as well as immune protection. The 1997 American Academy of

TABLE 31-1 Composition of Term and Preterm Milk during the First Month of Lactation

	3–5 Days		*8–11 Days*		*15–18 Days*		*26–29 Days*	
Nutrients	*Full Term*	*Preterm*	*Full Term*	*Preterm*	*Full Term*	*Preterm*	*Full Term*	*Preterm*
Energy (kcal/dL)	48.00	58.00	59.00	71.00	62.00	71.00	62.0	70.00
Lipid (g/dL)	1.85	3.00	2.90	4.14	3.06	4.33	3.05	4.09
Protein (g/dL)	1.87	2.10	1.70	1.86	1.52	1.71	1.29	1.41
Lactose (g/dL)	5.14	5.04	5.98	5.55	6.00	5.63	6.51	5.97

Adapted from Riordan J.[1]

Pediatrics' (AAP) policy statement outlines the many "diverse and compelling advantages to infants, mothers, families and society from breastfeeding and the use of human milk for infant feeding."[12] The US Surgeon General, in the year 2000, released the *Health and Human Services Blueprint for Action on Breastfeeding*, outlining the action plan for increased breast-feeding education, training, awareness, support, and research in the United States.[13]

In 2001, a call for action for breast-feeding promotion from physicians, based on the advantages of human milk, was made to further advocate breast-feeding as the infant feeding of choice.[14] The AAP currently recommends exclusive breast-feeding for the first 6 months of life, at which point solid foods may be gradually introduced. Breast-feeding should then continue for at least 12 months "and thereafter for as long as mutually desired" between mother and infant.[12]

VOLUME AND COMPOSITION

The total volume of milk production and intake may vary considerably between individual feedings. Although the mean breast milk intake of babies in industrialized societies has often been quoted as high as 750 to 850 mL per day, values may range from 450 to 1,200 mL per day.[15] Milk output in extremely malnourished mothers may drop to as low as 100 to 200 mL per day. In this situation, the protein and lactose content remains surprisingly high, but fat content, total calories, and vitamins may be quite inadequate.

Milk production may not always be synonymous with milk intake. Infants regulate their own intake, which may vary from 360 to 1,000 g per day.[16] The most common method for measuring milk intake involves weighing infants before and after a feeding and estimating their insensible water loss.[17] It is also possible to determine 24-hour milk intakes of infants by weighing their mothers before and after breast-feeding and correcting for maternal insensible water loss.[17] If no correction for insensible water losses is made, then milk intake is subject to overestimation by as much as 15%. Another more technically complex way of measuring human milk production involves using a tungsten-halogen light source to analyze breast topography and calculate the changes in volume of the breast after feeding.[18] However, the biomechanics of such assessments are beyond the scope of most physicians and lactation consultants.

GROWTH

Babies who exclusively breast-feed have been found to grow faster initially than formula-fed infants.[19] However, after 3 to 6 months, breast-fed infants grow more slowly. By 2 years of age, weights of the two may be comparable[20]; by 6 years of age, formula-fed infants are on average slightly taller and heavier than their breast-fed counterparts.[21,22]

Although there has been much discussion about breast-feeding mitigating the risk of later obesity, this has been difficult to establish in good prospective trials that control adequately for socioeconomic, genetic, and cultural factors. In one recent study of 2,500 ethnically diverse children aged 3 to 5 years, investigators were able to compare participants' reports of the length of time children were exclusively breast-fed, age when breast-feeding was completely stopped, and age when solid foods were first introduced with direct measures of children's heights and weights.[23] In this study, the association of breast-feeding and reduced risk of being overweight was not found to be statistically significant. Nevertheless, longer breast-feeding patterns did appear to protect against the development of body mass indexes (BMIs) greater than the 85th percentile.

In a related study, a cohort of approximately 15,000 American children was analyzed to determine whether duration of breast-feeding, exclusivity of breast-feeding, and age at which solid foods were introduced affected later risk of becoming overweight.[24] The study children, aged 9 to 14 years, were asked to self-report their heights and weights, whereas their mothers reported infant feeding practices. The results of this study revealed a significant relationship between less breast-feeding and becoming overweight, even after investigators controlled for age, sex, sexual maturity, energy intake, time watching television, physical activity, maternal BMI, and other variables reflecting social, economic, and lifestyle factors. They also were consistent with a recent European study of 10,000 German children that found a reduced prevalence of obesity among children who were breast-fed.[25]

One of the most important parameters used to assess the nutritional adequacy of breast-feeding is an infant's weight gain. Some authors have noted that the growth rates of exclusively breast-fed infants fall behind rates of those fed formula after about 3 months of age. This has been interpreted as a need for supplemental feeding for some infants before the age of 6 months, but others claim that this "faltering" is actually physiologic and that different growth

standards should be used for breast-fed infants.[26] In 2000, the Centers for Disease Control and Prevention released updated growth charts that include breast-fed infants and are more nationally representative than the version released in 1977 by the National Center for Health Statistics.[27]

The AAP does not recommend giving fluid supplementation to breast-fed newborns without medical indication.[12] Yet there are many reported cases of significant weight loss, failure to thrive,[28,29] and even frank dehydration that have occurred in some breast-fed infants.[30] Recent studies have suggested that the era of short postpartum hospitalizations may increase the risk of neonatal dehydration, especially among first-born children of mothers planning to exclusively breast-feed.[31–33] Breast-feeding failure is still common in first-time mothers, probably more often owing to a lack of environmental stimuli and emotional support of the mother rather than physiologic inadequacy of lactation or biochemical deficiencies in the breast milk.[34]

Nevertheless, the perception of inadequate milk supply has been identified as the major reason that mothers introduce formula or other foods into their infants' diets.[35] Interestingly, although the introduction of formula into infants' diets leads to a rapid and abrupt weaning, the introduction of solids has been found to have essentially no effects on breast-feeding for at least several weeks.[36] The differences between formula and solids in their impact on breast-feeding may be attributed to volume. Whereas infants already have the oral and developmental skills to take in large amounts of formula, they must gradually learn to handle different textures of solids. Infants being introduced to solids will not take enough volume to be satiated and will still depend on the breast.

BIOCHEMICAL COMPOSITION

Breast milk is about 87.5% water. The other constituents of human milk are described in Table 31-2. There is no evidence to suggest that a healthy infant who is adequately breast-feeding needs extra water supplements, even in hot climates[37–39] or during breast milk jaundice.[40] Even among low birth weight infants in hot, relatively humid environments, breast milk alone should be sufficient to ensure adequate hydration status when consumed in quantities that maintain adequate growth.[41] The osmolarity of breast milk is around 286 mOsm per liter,[42] with common infant formulas ranging from 185 to 374 mOsm per liter.[43]

The specific gravity of breast milk is about 1.030, and total solids weigh 10 to 15 g per 100 mL. More than half of this (7 g/100 mL) is carbohydrate, primarily lactose. Another 4 g per 100 mL consists of fat, primarily triglycerides. About 1 g per 100 mL is protein, and 0.2 g per 100 mL is mineral ash. In comparison, cow's milk contains a similar amount of water, slightly less fat (3.7 g/100 mL) and lactose (4.7 g/100 mL), and much more protein (3.5 g/100 mL).

PROTEINS

The protein content of human milk was formerly considered to be somewhat higher, 1.1 to 1.3 g/100 mL, but this was calculated by multiplying Kjeldahl's analysis of total nitrogen by the usual conversion factor of 6.25. Nearly 25% of this nitrogen, however, is nonprotein nitrogen, including urea (27.4 mg/100 mL), creatinine (20.9 mg/100 mL), sugar amines (11 mg/100 mL), and free amino acids (30 mg/100 mL). These values are all at much higher levels than those found in cow's milk, in which only 5% of the nitrogen is nonprotein. Measurement of the protein content of human milk by amino acid analyzer gives the surprisingly low figure of 0.9%,[44] which is much lower than in most other mammalian milks.

The protein composition of human milk is different from that of cow's milk, containing relatively more whey and less casein. "Casein" is actually a group of glycoproteins that are characterized by precipitation at pH 4.6 and 20°C. There are four major families of casein proteins—alpha, beta, gamma, and kappa—each having many genetically determined polymorphic variants.[45] Caseins are rich in phosphorus and proline and low in cystine. They have a tendency to form loose "micelles," which allow them to be more easily digested by carboxypeptidase in the intestinal lumen. The protein content of human milk is only 30% casein (0.4 g/100 mL), primarily β-casein, compared with the much higher (80%) casein content of cow's milk, which is primarily α-casein.

In contrast to cow's milk and most other mammalian milks, the percentage of whey in human milk is an unusually high 70%. Whey is the fluid left after clotted milk contracts. It contains such important proteins as lactalbumin, lactoferrin, lysozyme, albumin, and immunoglobulins. Alpha-lactalbumin contains a component of the enzyme lactose synthetase, and high levels of this protein in human milk (2.6 mg/mL) correspond to the relatively high level of lactose. Although whey-predominant formulas are available, the major whey protein in cow's milk, β-lactoglobulin, is not present in human milk in any significant amount.

Because the estimated average protein intake of the breast-fed infant is only about 1.5 g/kg/day, compared with 2.7 g/kg/day in a formula-fed infant, the protein quality of human milk may be higher, reflecting differences in the amino acid profile. There are only slight differences in the relative amino acid compositions of human milk and cow's milk when expressed as a percentage of total protein. However, plasma and urine concentrations of all amino acids except taurine and cystine are higher after formula feeds than after breast-feeding.[46] This finding suggests that protein intake is in excess of requirements when formula is fed because excess dietary protein is excreted in the urine. This increased metabolic stress is reflected in increased blood urea nitrogen, blood ammonia, and urine osmolarity and may lead to metabolic acidosis, especially in low birth weight infants.[47]

On the other hand, the protein requirement for premature low birth weight infants is generally believed to be higher than that usually provided by mature breast milk.[48] This requirement is estimated to be between 1.8 and 3.0 g/kg/day, depending on whether the ideal growth rate is seen as that matching intrauterine growth accretion rates[49] and whether weight gain or length is

TABLE 31-2 Representative Values for Constituents of Human Milk

*Constituent (per L)**	*Early Milk*	*Mature Milk*
Energy (kJ)[†]		2,730–2,940
Carbohydrate		
Lactose (g)	20–30	67
Glucose(g)	0.2–1.0	0.2–0.3
Oligosaccharides (g)	22–24	12–14
Total nitrogen (g)	3.0	1.9
Nonprotein nitrogen (g)	0.5	0.45
Protein nitrogen (g)	2.5	1.45
Total protein (g)	16	9
Casein (g)	3.8	5.7
β-Casein (g)	2.6	4.4
k-Casein (g)	1.2	1.3
α-Lactalbumin (g)	3.62	3.26
Lactoferrin (g)	3.53	1.94
Serum albumin (g)	0.39	0.41
Secretory IgA (g)	2.0	1.0
IgM (g)	0.12	0.2
IgG (g)	0.34	0.05
Total lipids (%)	2	3.5
Triglyceride (% total lipids)	97–98	97–98
Cholesterol[‡] (% total lipids)	0.7–1.3	0.4–0.5
Phospholipids (% total lipids)	1.1	0.6–0.8
Fatty acids (weight %)	88	88
Total saturated	43–44	44–45
$C_{12:0}$		5
$C_{14:0}$		6
$C_{16:0}$		20
$C_{18:0}$		8
Monounsaturated		8
$C_{18:1\ \omega-9}$	32	31
Polyunsaturated	13	14–15
Total $_{\omega-3}$	1.5	1.5
$C_{18:3\ \omega-3}$	0.7	0.9
$C_{22:5\ \omega-3}$	0.2	0.1
$C_{22:6\ \omega-3}$	0.5	0.2
Total $_{\omega-6}$	11.6	13.06
$C_{18:2\ \omega-6}$	8.9	11.3
$C_{20:4\ \omega-6}$	0.7	0.5
$C_{22:4\ \omega-6}$	0.2	0.1
Water-soluble vitamins		
Ascorbic acid (mg)		100
Thiamin (μg)	20	200
Riboflavin (μg)		400–600
Niacin (mg)	0.5	1.8–6.0
Vitamin B_6 (mg)		0.09-0.31
Folate (μg)		80–140
Vitamin B_{12} (μg)		0.5–1.0
Pantothenic acid (mg)		2.0–2.5
Biotin (μg)		5–9
Fat-soluble vitamins		
Retinol (mg)	2	0.3–0.6
Carotenoids (mg)	2	0.2–0.6
Vitamin K (μg)	2–5	2–3
Vitamin D (μg)		0.33
Vitamin E (mg)	8–12	3–8
Minerals		
Major minerals		
Calcium (mg)	250	200–250
Magnesium (mg)	30–35	30–35
Phosphorus (mg)	120–160	120–140
Sodium (mg)	300–400	120–250
Potassium (mg)	600–700	400–550
Chloride (mg)	600–800	400–450
Trace minerals		
Iron (mg)	0.5–1.0	0.3–0.9
Zinc (mg)	8–12	1–3
Copper (mg)	0.5–0.8	0.2–0.4
Manganese (μg)	5–6	3
Selenium (μg)	40	7–33
Iodine (μg)		150
Fluoride (μg)		4–15

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*All values are expressed per liter of milk, with the exception of lipids that are expressed as a percentage on the basis of milk volume or weight of total lipids.

[†]1 kJ = 0.2389 kcal.

[‡]The cholesterol content of human milk ranges from 100 to 200 mg/L in most samples of human milk after day 21 of lactation.

considered a better measure of growth.[50] Premature milk, like colostrum and transitional milk, contains more protein than mature milk, giving about 1.9 g/kg/day with adequate caloric intake, and breast milk expressed from their own mothers may be sufficient for adequate growth.[51]

Nonprotein Nitrogen

One of the most striking differences between the amino acid profiles of human milk and cow's milk is the relatively small amount of taurine present in the latter. Taurine is a free amino acid that is not incorporated into proteins. It is formed from the sulfur amino acids cystine and methionine. Taurocholate, not glycocholate, is the predominant bile salt conjugate in neonates.

Premature infants have a limited capacity to form taurine because of delayed maturation of the enzymes cystathionase and cystine sulfonic acid decarboxylase.[52] Taurine depletion leads to retinal degeneration in cats, although this effect on vision in humans has not been demonstrated. Nevertheless, taurine may play a role in brain development because its concentration is highest in the developing brain.[53] In preterm infants, taurine supplementation has been shown to result in lower cholesterol synthesis, higher bile acid excretion, and higher fatty acid absorption.[54,55] Therefore, taurine supplementation is recommended in preterm neonates who are not receiving human milk.

In addition to urea, free amino acids, and ammonia fractions, there are several other nonprotein nitrogen constituents of human milk, including nucleotides, nucleosides, and nucleobases, that play important roles in neonatal development. Generally speaking, concentrations of most of these constituents decrease gradually over time with advancing lactation period or nursing time.[56]

Nucleotides, particularly inosine monophosphate, may contribute to superior iron absorption in breast-fed infants and may act as growth factors.[57] Finally, there is growing evidence that nucleotides may have immunomodulating effects on host immune defenses by enhancing antibody responses in infants.[56] Human milk is particularly rich in cytidine nucleotides, whereas only small amounts of adenine nucleotides are found in cow's milk.[58] Polyamines

such as putrescine, spermine, and spermidine are known to be involved in cell proliferation and differentiation, may be present in highly variable amounts in both human milk and formula, and may be related to maternal atopy. Enterally administered polyamines have also been shown to influence intestinal maturation in a number of animal models.[59]

Enzymes and Hormones

Many enzymes are supplied in breast milk in far greater amounts than in cow's milk, including lipases, amylase, catalase, and proteases. Lysozyme has been previously mentioned. Amylase activity is 60 times greater in colostrum and 40 times greater in mature breast milk than in cow's milk, aiding in starch digestion.[60] Many other enzymes are also present in breast milk in higher levels than in cow's milk, including transaminase catalase, cholinesterase, lactate dehydrogenase, proteases, and lipases.

Many hormones, including estrogen, thyroid-stimulating hormone, and growth hormone, are also secreted in breast milk.[61] Additionally, leptin has been shown to be secreted in breast milk, although the physiologic significance of this is less certain.[62] Recent investigation into the bioactivity of phytoestrogens has suggested that soy formulas for infants have isoflavone concentrations that are four orders of magnitude higher than human breast milk.[63] These studies continue to support the notion that human milk may be safest for infants, who, as a group, are undergoing a critical period of growth, bone mineralization, and sexual determination that may be vulnerable to the estrogen-like effects of phytoestrogens.[64]

Growth Factors

Human milk contains gastrointestinal regulatory peptides such as gastric inhibitory peptide, bombesin, cholecystokinin, and neurotensin, which may be important for growth and maturation of the gastrointestinal tract in the neonate.[65] Growth factors such as growth hormone, insulin-like growth factor I, granulocyte-macrophage colony-stimulating factor, and tumor growth factor β have been shown to enhance intestinal function and mucosal defenses. There are also many other growth factors that stimulate DNA synthesis, such as epidermal growth factor and hepatocyte growth factor.[66,67] Tumor necrosis factor (cachectin) and other cytokines, such as interleukin (IL)-1, IL-6, IL-8, IL-10, and interferon, may be produced by stimulation of mononuclear cells in human milk.[68]

Fats

Fats provide the main energy source for newborn infants, supplying 40 to 50% of the total calories in human milk. There are numerous differences between the lipid profiles of human milk and infant formula. A bile salt–stimulated lipase in breast milk complements the immature pancreatic exocrine system of neonates to aid in fat digestion and absorption.

The essential fatty acids, linoleic and linolenic acid, also play a crucial role in brain development as a component of cell membranes. About 98% of the fat in human milk is in the form of triglycerides, consisting of glycerol and three fatty acid esters. Although 167 fatty acids have been identified in human milk (and 437 in cow's milk), the major fatty acids are palmitic (22%), stearic (7%), oleic (36%), and linoleic (9%).[69] Relatively few short-chain fatty acids (C_4 to C_8) are present in human milk (1 to 5%), as opposed to 6 to 9% in cow's milk.

Human milk also contains significant amounts of long-chain desaturation products of n-6 and n-3 fatty acids, including docosahexaenoic and arachidonic acids, that are essential for retinal and neural development.[70] Such long-chain polyunsaturated fatty acids (LCPUFAs) in human milk have been clearly demonstrated to directly impact the chemical composition of brain tissue,[71] as well as enhance retinal and cortical function.[72] The fatty acid composition of depot fat is also affected by dietary intake. It has long been suggested that supplementation of formula with LCPUFAs may be beneficial, especially in premature infants, even if it is not always directly indicated by increased circulating plasma lipid levels.[73,74] Recent studies have also suggested a benefit from LCPUFAs on visual acuity and stereoacuity of full-term healthy infants who are weaned from the breast at 6 weeks.[75]

Human milk has about equal amounts of unsaturated and saturated fats. As cow's milk has more saturated fats, most infant formulas are reconstituted with added vegetable unsaturated fat (corn oil, sunflower oil, or soy oil). Although the total lipid content is higher in hindmilk than in foremilk and higher in the morning than in the evening,[76] the fatty acid pattern has been shown to change little over at least 12 months of lactation.[77] However, the polyunsaturated-to-saturated ratio in breast milk may be influenced by changes in maternal diet (eg, margarine versus butter),[78] with the percentage of linoleic acid varying from 1 to 45%. Colostrum contains a lower amount of total lipids but a higher percentage of LCPUFAs.[79,80] Furthermore, the total lipid content of hindmilk rises more than threefold from colostrum up to the third month and then more slowly up to the twelfth month.[77]

The small amount of nonglyceride lipid in breast milk includes free fatty acids, mono- and diglycerides, phospholipids, sphingolipids, ether-esters, and cholesterol. These are synthesized in the mammary gland and are essential components of cell membranes.[81] The cholesterol content of human milk is greater than cow's milk but varies greatly between time of sampling, among individuals, and from day to day, from 3.1 to 28.8 mg per deciliter.[82]

The high percentage of fat in breast milk and formula is necessary to support rapid growth in infancy. Early infant feeding influences cholesterol metabolism, although breast-feeding has not been shown to reduce the risk of coronary disease in adult years.[64] The cholesterol content of human milk is much higher than in infant formulas, which may decrease endogenous cholesterol synthesis.[83] Increased dietary cholesterol and γ-linoleic acid may contribute to the maturation of high-density lipoprotein particles, which are present in higher levels in breast-fed infants.[84]

Lipases

Although fats provide a major energy source for infant growth, their ability to be absorbed is limited by the relative immaturity of pancreatic lipases and bile acid excretion in the newborn.[85,86] Neonates and infants normally excrete more than 5% of their fat intake in the stool, often up to 30%, which would be considered gross steatorrhea in the adult.[87,88] This is even more pronounced in low birth weight premature infants. Newborns, however, do have a number of compensatory mechanisms to enhance fat absorption, including lingual lipase and breast milk lipase.[89] Breast milk actually contains two lipases. Lipoprotein lipase plays a role in the uptake of plasma lipids by the mammary gland but has no role in digestion. Human milk also contains a bile salt–stimulated lipase that is complementary to pancreatic lipase and has been shown to improve the digestion and absorption of breast milk in vivo.[90] Thus, breast milk not only provides nutrients but also supplies the means to digest them. This enzyme is present in the milk of other primates but not in cow's milk. Adding human breast milk to cow's milk formulas has been shown to improve fat absorption in premature infants.[91]

Prostaglandins

Prostaglandins are derived from the essential fatty acids, linoleic and linnoleic acids. They affect many physiologic functions, including gastrointestinal secretion and absorption, smooth muscle contraction, local circulation, and cytoprotection.[92] Breast milk has been found to contain small amounts of prostaglandins E_2 and F_2, not present in cow's milk. These prostaglandins may play nutritional, immunologic, or hormonal roles in the newborn infant.

Carnitine

Carnitine (trimethylaminohydroxybutyrate) is a major constituent of the enzyme carnitine acyltransferase, which transfers long-chain fatty acids into the mitochondria for oxidation. The higher levels of carnitine (55 to 70 nmol/mL) present in breast milk during the first 3 weeks postpartum correspond to higher plasma levels found in breast-fed infants. This may indicate that ketogenesis and free fatty acid oxidation are major energy sources during early development.[93] The carnitine present in both breast milk and formulas may also aid in free fatty acid oxidation of the absorbed triglycerides.

Vitamins

Vitamin K Although breast milk is an ideal infant food, providing a nearly complete range of all required nutrients, it is recommended that certain vitamins and minerals be supplemented in breast-fed babies to prevent occasional catastrophic deficiency states.[94] This is particularly true of some of the fat-soluble vitamins. Vitamin K is normally produced in sufficient quantities by enteric bacteria, but neonates are susceptible to deficiency before bacterial colonization of their intestines augments their low stores of vitamin K at birth.

Studies have shown that average maternal vitamin K intakes correspond to less than 15% of the recommended infant dietary intake of 10 μg per day.[95] It has been noted for many years that breast-fed infants were particularly susceptible to hemorrhagic disease of the newborn. Breast milk contains less vitamin K activity than cow's milk (15 μg/100 mL versus 60 μg/100 mL), but another explanation may be that the *Lactobacillus*-predominant intestinal flora of breast-fed newborns produces less vitamin K than the *Escherichia coli*–predominant flora of formula-fed babies. Although episodes of severe bleeding are not common, levels of vitamin K in cord blood are very low,[96] and prothrombin levels in breast-fed newborns rise significantly after birth. This disease has essentially vanished since the establishment of routine postnatal administration of 1 mg vitamin K orally or intramuscularly, but cases continue to be reported, especially in breast-fed infants, when this practice is neglected.[97]

Vitamin D Human breast milk contains very little fat-soluble vitamin D. Sufficient amounts of vitamin D can, of course, be obtained by adequate exposure to sunlight, and in prospective studies, the majority of breast-fed infants show adequate growth and bone mineralization.[98,99] However, breast milk supplies much less than the recommended allowance of vitamin D or its active metabolites,[100] and cases of rickets continue to be reported among unsupplemented infants.[101] The AAP recommends that all breast-fed infants (and non breast-fed infants receiving less than 500 mL per day of Vitamin D–fortified formula) be supplemented with 200 IU per day of Vitamin D.[12]

Vitamin E Vitamin E plays an important part in preventing peroxide formation from polyunsaturated fats in the diet. This is particularly important in premature newborns in whom vitamin E deficiency may lead to red blood cell membrane fragility and hemolytic anemia. There has been a gradual but steady increased intake of polyunsaturated fatty acids in American maternal diets over the last 50 years, adding to potential oxidant stress.[102] Fortunately, the vitamin E content of human milk is also higher, particularly in colostrum and early transitional milk.[103] The major portion of vitamin E activity is provided by α-tocopherol, with a small amount of γ- and β-tocopherol.

Vitamin A Breast milk, particularly colostrum, is rich in vitamin A (200 IU/100 mL or 40 to 55 mg/100 mL retinol equivalents) and its dietary precursor, beta–carotene. This amount varies according to maternal diet; however, milk from underprivileged Ethiopian mothers has less vitamin A and retinol binding protein, as well as a lower percentage of retinyl ester, than that from European mothers.[104]

Water-Soluble Vitamins Most of the water-soluble vitamins are well provided in breast milk, but there may be great variation depending on maternal diet. For example, it is estimated that, globally, up to one-third of pregnant and lactating women have some degree of folate undernutrition.[105] Supplementation of water-soluble

vitamins to lactating women will raise levels in breast milk up to a plateau. Although supplementation may be beneficial in undernourished women, it may not be necessary in most well-nourished mothers.[106] Thiamin and riboflavin are usually not a problem,[107] but pyridoxine, vitamin B_{12}, and folate levels may be low in lower socioeconomic groups.[108] Because pyridoxine (vitamin B_6) is critical for early development of the central nervous system, it is of particular concern that breast milk concentrations on the lower end of the range, 100 to 300 μg per liter, may not meet the recommended allowance of 300 μg per day.[109] Pyridoxine supplementation of the maternal diet may adequately increase the concentration of pyridoxine in breast milk.[110] Because the major sources of vitamin B_{12} are foods of animal origin, a strict vegetarian maternal diet can lead to a vitamin B_{12} deficiency. This was reported in a breast-fed infant with severe hematologic, metabolic, and neurologic abnormalities, which recovered rapidly with vitamin B_{12} therapy.[111] Megaloblastic anemia may also occur in folate deficiency, but this is extremely rare in breast-fed infants.[112,113] Although levels of folate in cow's milk and human milk are similar, formula-fed infants are more susceptible to folate deficiency.[114] This may be attributable to the presence of a reducing agent (ascorbate), a regulating folate binding protein, or a greater proportion of the monoglutamate form in human milk.

Minerals

In contrast to vitamins, the mineral content of breast milk is less influenced by recent maternal dietary intake.[115] The mineral composition of breast milk at 1, 2, and 3 months is outlined in Table 31-3. Only small differences are noted over time, maternal age, or parity. Surprisingly, there are no significant effects of maternal nutrient status or dietary supplementation on milk mineral content. Socioeconomic status does affect the concentrations of some minerals in breast milk, but this does not seem to be related to maternal serum levels.[116] There is active regulation of uptake, transfer, retention, and excretion of many minerals. The bioavailability of minerals is generally higher in breast milk than in infant formulas, owing partly to the presence of binding ligands, which enhance absorption.[117] Regulation of certain minerals also occurs through urinary excretion, and simple measurement of dietary intake may not be as accurate as more complex calculations of net retention or tissue accretion.[118]

Calcium Calcium is a major nutrient of milk and contributes not only to skeletal growth but also to muscle contraction, nerve transmission, and blood clotting. Calcium homeostasis is affected by many other nutrients, particularly phosphorus, magnesium, vitamin D, and fats. Although the calcium content of human milk (20 to 34 mg/100 mL) is much lower than that of cow's milk (120 to 134 mg/100 mL), retention of calcium is much higher in the breast-fed infant (67% versus 25%).

Neonatal hypocalcemia and tetany are more often seen in formula-fed infants.[119] One reason may be that cow's milk contains a much higher concentration of phosphorus (93 mg/100 mL) with a calcium-to-phosphorus ratio of 1.2:1.0 (versus 2:1 in human milk). This leads to a decreased absorption and increased excretion of calcium.[120] Another reason may be the formation of nonabsorbable calcium palmitate soaps because of the different types of lipids in cow's milk. To this end, it has been suggested that changing the stereoisomeric structure of calcium palmitate in infant formulas might result in higher bone mineral content, reduced stool soap fatty acids, and softer stools more like those of breast-fed infants.[121] Nevertheless, calcium status in both formula- and breast-fed infants may be marginal, especially in very low birth weight infants. Also, short-term benefits of calcium supplementation to bone mineral density in preterm infants have been demonstrated, although long effects are less clear.[122] Calcium supplements should be routinely given to all premature infants to prevent rickets and hypocalcemic tetany.[123]

Iron Iron deficiency anemia is probably the most common nutritional disease among infants in both developed and developing countries. Both human milk and cow's milk contain low but variable amounts of iron (0.3 to 6.0 mg/100 mL). Breast-fed infants, however, are much less susceptible to iron deficiency. This is because iron absorption in exclusively breast-fed infants is much higher (20 to 50%) than in formula-fed infants (4 to 7%).[124] This may be owing to a number of characteristics of breast milk, including lower protein content, greater lactose, greater ascorbate, lower phosphorus, and different iron binding proteins.[125]

Interestingly, early introduction of solid foods impairs the efficiency of iron absorption in both formula-fed and breast-fed infants.[126] By 6 months of age, when the AAP recommends starting solid foods,[12] iron nutrition in both breast-fed and formula-fed infants may be marginal, and iron should be supplemented to provide the recommended allowance of 10 mg elemental iron per day in any infant with a hemoglobin level less than 11 g/dL.[127,128] Controversy about universal or prophylactic supplementation for all infants remains because excess iron supplements may increase susceptibility to gastrointestinal infections by

TABLE 31-3 Mean Mineral Contents of Human Milk Samples at Months 1, 2, and 3 of Lactation

	*Months**			
Mineral (per L)	*1*	*2*	*3*	*Range*
Copper (μmol)	3.35 (1.07)	3.24 (1.21)	3.26 (1.35)	1.10–11.0
Iron (μmol))	5.87 (2.09)	6.62 (2.17)	7.36 (3.03)	1.61–21.49
Zinc (μmol))	33.8 (19.8)	31.8 (16.8)	29.5 (13.8)	5–118.5
Calcium (mmol)	7.24 (1.52)	7.31 (1.40)	7.14 (1.25)	4.49–11.0
Phosphorus (mmol)	5.04 (0.84)	4.78 (0.84)	4.68 (0.81)	2.58–8.17
Magnesium (mmol)	1.15 (0.25)	1.27 (0.21)†	1.36 (0.21)†	0.53–2.02
Sodium (mmol)	6.57 (2.39)	5.26 (2.18)	5.48 (2.04)	2.18–13.09
Potassium (mmol)	11.92 (2.38)	10.92 (2.23)	10.41 (2.05)	5.17–16.80
Chlorine (mmol)	12.04 (2.37)	11.70 (2.09)	11.96 (2.57)	7.81–19.94

Reproduced with permission from Picciano MF, Calkins EJ, Garrick JR, Deering RH. Milk and mineral intakes of breastfed infants. Acta Paediatr Scand 1981; 70:189.
*Numbers in parentheses represent mean (SD) values.
†Significantly different from month 1 at $p < .05$.

saturating lactoferrin and transferrin, iron binding proteins that have a bacteriostatic effect in the intestine.[129] Also, it must be kept in mind that iron supplements may promote oxidant stress and vitamin E deficiency anemia in premature newborns and should not be empirically prescribed in the first few months of life.[130]

Zinc Zinc is an essential constituent of many metalloenzymes, including alkaline phosphatase, carbonic anhydrase, carboxypeptidase, superoxide dismutase, and DNA polymerase. An inherited form of zinc deficiency, acrodermatitis enteropathica, which is manifested by a rash, chronic diarrhea, irritability, and failure to thrive, was formerly treated with breast milk before specific zinc therapy was recognized.[131] The concentration of zinc in breast milk declines rapidly (60 to 22 mmol/L) over the first 3 months of lactation.[132] As in the case of iron, human milk contains less zinc than cow's milk, but its bioavailability is higher: 60% for breast milk, 43 to 50% for cow's milk, and only 27 to 32% for infant formulas.[133]

Plasma zinc and hair zinc levels are higher in breast-fed infants than in formula-fed infants, suggesting better zinc absorption and nutriture.[134] However, it has been recommended that preterm infants be supplemented with zinc as breast milk from mothers delivering preterm appears to be lower in zinc concentation and their babies appear to be zinc deficient.[135]

Other Minerals The copper content of breast milk varies widely (0.09 to 0.63 μg/mL)[136] and seems not to be affected by maternal supplementation. Selenium is usually higher in human milk (16.3 ng/mL) than in formula (8.6 ng/mL), which may be important because the daily requirement for this element in infants is higher owing to their rapid growth.[137] Much research remains to be done on other essential trace elements in milk, including iodine, manganese, molybdenum, fluoride, chromium, vanadium, nickel, and silicon.

STORAGE OF MILK

The many nutritional advantages of human milk explain the desirability of obtaining expressed breast milk for those infants who are unable to breast-feed. This is particularly true for low birth weight premature infants in critical care nurseries who are at risk for necrotizing enterocolitis and a host of other diseases that might be prevented by optimal nutrition with milk from the mother of the premature infant. Research has shown that human milk is remarkably resilient as long as good food-handling techniques are used.[138] In the storage of expressed breast milk, bacterial contamination by skin flora can present a major problem.[139] *Staphylococcus albus* and *Streptococcus viridans* are the most common organisms, but many samples contain pathogenic *Staphylococcus aureus* and *Enterobacter*,[140] and outbreaks of *Salmonella* have occurred in nurseries.[141] If breast milk is stored for more than 48 hours, it should be frozen or autoclaved.[142] Refrigeration, freezing, and pasteurization are all accompanied by some loss of cellular viability and host defense factors such as lactoferrin, IgA,[143] and vitamin C.[144] Although some studies have suggested that human milk stored in glass retains greater viability and immune function,[145] the bottom line is that these treatments do not markedly affect the nutritional quality of breast milk in terms of nitrogen, calcium, phosphorus, sodium, vitamin A, zinc, iron, or copper.[146,147] Fat absorption may be reduced by destruction of lipases, and several vitamins or their binding proteins may be denatured by heat treatment.

DRUGS AND ENVIRONMENTAL POLLUTANTS

Most medications taken by the mother are excreted into breast milk to some extent but are usually present in trace amounts and therefore not contraindicated in breast-feeding. Decisions regarding maternal medication use should be based on documented levels of medication transfer into human milk, bioavailability of the medication, potential effect to the infant, and effect on maternal milk supply.[148] Acceptable alternative medication for the mother should be considered if the initial medication choice is not preferred. It is important to realize the psychological and physiologic effect on mother and infant if weaning, especially abrupt weaning, is recommended. Telling a mother to arbitrarily stop breast-feeding without researching the medication is not in the best interest of the mother and baby.[149] Medication resources that include product inserts only should be avoided. Preferred are references that detail the medication's effects on breast-feeding.[150] The goal is to protect breast-feeding, not the liability of the clinician, while treating the mother.[151] Although most medications are compatible with breast-feeding, the effect of some to nursing infants is unknown but may be of concern, require temporary cessation of breast-feeding (Table 31-4), or are absolutely contraindicated.[152]

In terms of those drugs that definitively contraindicate breast-feeding, cytotoxic drugs including cyclophosphamide, cyclosporine, doxorubicin, and methotrexate may interfere with the cellular metabolism of the infant via immune suppression, growth, association with carcinogenesis, or neutropenia.[12] Illicit drugs, including amphetamines, cocaine, heroin, marijuana, and phencyclidine, should not be ingested by the mother because of their adverse effects on the infant, as well as the mother's ability to take care of the infant. In comparison, although strict avoidance of nicotine is highly recommended, mothers who continue to smoke should be encouraged to breast-feed. Indeed, breast milk has been shown to offer a protective effect in decreasing acute respiratory illnesses in children whose mothers smoke.[153]

Environmental pollutants are found worldwide in human milk, as well as in cow's milk, milk-based formula, and food. Mothers may not know of their exposure to pollutants, including pesticides (DDT [dichlorophenyltrichloroethane], dichlorodiphenyldichloroethylene [DDE], and heptachlor), polychlorinated biphenyls (PCBs), dioxin, lead, and methylmercury.[154] Maternal occupation, diet, and location of residence may affect exposure to a number of pollutants identified in human milk. Most lactating women are at minimal risk, however, and there is little evidence of consequent illness in their

nursing infants. Therefore, in the absence of known poisonings, breast-feeding is recommended despite the presence of chemical residues.[155]

CONCLUSIONS

As discussed in this chapter, human milk is the ideal nourishment for almost all infants, including those born prematurely. As the volume of research on the nutritional composition and immunologic properties of breast milk grows, so do efforts regarding the support and promotion of breast-feeding within the medical community. Breast-feeding initiation and continuation rates have continued to rise over the last quarter century but remain far below the Healthy People 2010 goals. However, the message in today's industrialized society is clear: breast milk should no longer be regarded as an equal option for infant feeding but as the norm with which artificial baby milks are compared.

Only human milk has the unique ability to change in volume and composition to meet the needs of the growing human infant. Growth patterns of breast-fed infants may demonstrate physiologic growth against which non-breast-fed infants should be assessed. Breast-feeding may also protect against later obesity. Evaluating the success of breast-feeding via careful monitoring of hydration and weight gain in newborns in the first days and weeks of life may prevent unnecessary cases of dehydration and failure to thrive. Should problems occur, enlisting the help of an international board-certified lactation consultant[156] to assess mother and infant will allow for modifications in feeding to improve milk transfer to the infant.

Breast milk is nearly 90% water, providing adequate hydration for an infant who takes sufficient volumes to grow. Fat, which comprises approximately half of the calories in breast milk, also provides essential fatty acids and LCPUFAs. Combined with bile salt–stimulated lipase in the breast milk, fat complements the immature pancreatic exocrine system to aid in fat digestion and absorption. Whey proteins provide not only nutrition but also a host of immune defense factors as well. Hormones, growth factors, and enzymes continue to be discovered and studied for their crucial role in infant growth and development.

Infants who are separated from their mothers, for reasons including hospitalization and mother's return to work, benefit from expressed milk. Proper expression techniques and storage guidelines help ensure that expressed milk is safe for the baby. Maternal medications, if any, should be reviewed to rule out rare contraindications.

Current recommendations in favor of universal breast-feeding by a number of national and international organizations have mirrored a global return of mothers providing ideal infant nutrition and immunologic protection to their babies. Understanding of lactation physiology and breast-feeding practice is warranted to facilitate breast-feeding success.

TABLE 31-4 Radioactive Compounds That Require Temporary Cessation of Breast-feeding*

Compound	*Recommended Time for Cessation of Breastfeeding**
Copper 64	Radioactivity in milk present at 50 h
Gallium 67	Radioactivity in milk present for 2 wk
Indium 111	Very small amount present at 20 h
Iodine 123	Radioactivity in milk up to 36 h
Iodine 125	Radioactivity in milk present for 12 d
Iodine 131	Radioactivity in milk present 2–14 d, depending on study
Iodine 131	If used for treatment of thyroid cancer, high radioactivity may prolong exposure to infant
Radioactive sodium	Radioactivity in milk present 96 h
Technetium 99m (^{99m}Tc), ^{99m}Tc macroaggregates, ^{99m}Tc O_4	Radioactivity in milk present 15 h to 3 d

Consult nuclear medicine physician before performing diagnostic study so that radionuclide that has the shortest excretion time in breast milk can be used. Before study, the mother should pump her breast and store enough milk in the freezer for feeding the infant; after study, the mother should pump her breast to maintain milk production but discard all milk pumped for the required time that radioactivity is present in milk. Milk samples can be screened by radiology departments for radioactivity before resumption of nursing.
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CHAPTER 32

PROTECTIVE PROPERTIES OF HUMAN MILK

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Shortly after cow's milk was introduced commercially as a substitute for breast-feeding in the early twentieth century, it was reported that morbidity and mortality were much lower in breast-fed than in cow's milk–fed infants.[1–3] In the mid-twentieth century and thereafter, these findings were confirmed and extended by epidemiologic investigations in developing and industrialized countries.[4–14] Particularly in developing countries, the incidence of diarrheal diseases and deaths was remarkably higher in non-breast-fed infants, and the protection owing to breast-feeding lasted until weaning was complete. However, it was unclear from those observations whether the observed differences were attributable to an increased number of microbial pathogens contaminating non–human milk feedings or to protective factors in human milk. In that respect, studies in Central America strongly suggested that the protection afforded by breast-feeding was not attributable solely to differences in the degree of exposure to microbial pathogens.[4–6] These investigators found that the frequency of intestinal colonization and diarrhea owing to bacterial enteric pathogens was lower in breast-fed infants, despite the prevalence of carriers of these organisms in the community and the presence of bacterial enteropathogens on the nipples and areola and in maternal milk.

The protective effects of breast-feeding have been more difficult to demonstrate in industrialized countries,[12,13] where advances in sanitation, immunizations, maternal nutrition, and other health care measures led to a decline in morbidity and mortality owing to infectious diseases. In addition, it has been difficult to design studies in which potential confounding demographic variables are controlled.[12,13] Nevertheless, the results in most current carefully designed studies, including one in which breast-feeding education was randomized among several hospitals in one country,[14] suggest that breast-feeding protects against common viral and bacterial enteric infections[4–9,12–14] and possibly against respiratory infections,[10–13] certain allergic disorders such as atopic dermatitis,[13–16] and urinary tract infections during infancy.[17] Further, breast-feeding may have long-term protective effects against certain disorders that have an immunologic, inflammatory, or oncogenic basis.[18–21] These epidemiologic studies provided the impetus to investigate the nature of the immune system in human milk and the effects of the components of that system on the recipient infant.

MAJOR DIVISIONS OF THE IMMUNOLOGIC SYSTEM IN HUMAN MILK

The immune system in human milk consists of three overlapping groups of bioactive compounds. They are direct-acting antimicrobial (Tables 32-1 and 32-2), anti-inflammatory (Table 32-3), and immunomodulating agents (Tables 32-4 and 32-5). Many of these factors in human milk share the following features: (1) they are common to external secretions; (2) they are adapted to protect mucosal surfaces; (3) they often display more than one function; (4) they often act synergistically; (5) they protect by noninflammatory mechanisms; (6) their concentrations in human milk usually decline as lactation proceeds[22,23]; and (7) the patterns of their production are often inversely related to the production of those same factors by the recipient infant (Table 32-6).

Thus, it seems likely that the system evolved in part to augment mucosal immunity of the infant until the defenses of the recipient were fully developed. That proposition has been borne out by a number of observations, including many studies that demonstrate developmental delays in the production of immune factors by the recipient infant (see Table 32–6).[13,24–34] Also in that respect, the immune system in human milk has been found to be different from analogous systems in milks from other species used to feed human infants.

DIRECT-ACTING ANTIMICROBIAL FACTORS

The direct-acting antimicrobial factors in human milk include (1) growth promoters of protective enteric bacteria; (2) factors that interfere with bacterial metabolism; (3) enzymes that lyse bacterial cell walls; (4) antibodies adapted to mucosal sites; (5) certain antimicrobial mucins, oligosaccharides, and lipids; and (6) living leukocytes. A brief description of these agents (see Table 32-1) follows.

Table 32-1 Functions of Antimicrobial Agents in Human Milk.

Agents	*Antimicrobial Functions*
Proteins	
Lactoferrin	Bacteriostasis owing to Fe+++ chelation Bacterial killing owing to lactoferricin
Lysozyme	Lyses bacterial cell walls by degrading peptidoglycans
Secretory IgA	Binds bacterial adherence sites, toxins, and virulence factors
MUC1	Inhibits binding of S-fimbriated *Escherichia coli* to epithelial cells
Lactadhedrin	Binds rotavirus and thus prevents its contact with epithelium
Oligosaccharides and glycoconjugates	Receptor analogues inhibit binding of enteric/respiratory pathogens and their toxins to epithelial cells
Monoglycerides and fatty acids from lipid digestion	Disrupt enveloped viruses, kill certain bacteria, defend against *Giardia lambdia and Entamoeba histolytica*

Growth Factors for Enteric Commensal Bacteria

Human milk, but not cow's milk, promotes the in vitro growth of *Bifidobacterium bifidum var. Pennsylvanicus*.[35] The growth promoters are oligosaccharides, casein and its derivatives,[35,36] and the prebiotic lactoferrin-derived peptide I generated by partial proteolysis of lactoferrin or soluble secretory component.[37] It appears that these components are responsible at least in part for the proliferation of *B. bifidum* and lactobacilli in the lower intestinal tract of breast-fed infants.[38,39] Organic acids produced by those organisms are largely responsible for high hydrogen ion concentrations in stools of breast-fed infants.[40] That acidic environment retards the growth of enteric pathogens such as yeast, *Escherichia coli,* and *Shigella* sp. In addition, these commensal bacteria augment the production of low-molecular-weight, antibacterial peptides by epithelial cells.[41]

Table 32-2 Secretory IgA Antibodies in Human Milk Directed against Pathogens

Bacteria: Toxins Virulence Factors	*Viruses*	*Fungi*	*Parasites*
Escherichia coli	Adenovirus	*Candida* sp	*Giardia lamblia*
Campylobacter sp	Cytomegalovirus		
Clostridium botulinum	Enteroviruses		
Clostridium difficile	Human immunodeficiency virus (HIV)		
Haemophilus influenzae	Influenza virus		
Helicobacter pylori	Respiratory syncytial virus		
Klebsiella pneumoniae	Rotavirus		
Streptococcus pneumoniae			
Vibrio cholerae			
Salmonella sp			
Shigella sp			

Table 32-3 Anti-inflammatory Factors in Human Milk

Categories	*Components*
Cytoprotectives	Prostaglandins E_2, $F_{2\alpha}$
Epithelial growth factors	Epidermal growth factor, lactoferrin, polyamines
Maturational factors	Cortisol
Enzymes that degrade mediators	PAF-AH
Binders of enzymes	α_1-Antichymotrypsin
Binders of substrates of enzymes	Lysozyme to elastin
Modulators of leukocytes	Interleukin-10
Antioxidants	Uric acid, α-tocopherol, betacarotene, ascorbate

PAF-AH = platelet activating factor acetylhydrolase.

Inhibitors of Bacterial Metabolism

Lactoferrin, a ferric iron binding protein common to many external secretions, is largely unsaturated (apo-lactoferrin)[42] and is present in high concentrations in human milk throughout lactation.[21,22] Apo-lactoferrin inhibits the growth of organisms such as *E. coli* by competing with bacterial enterochellin for ferric iron. The chelation is enhanced by bicarbonate, the principal buffer in human milk.[43]

Besides the bacteriostatic effects owing to the chelation of ferric iron, lactoferrin kills certain bacteria such as *Streptococcus mutans* and *Vibrio cholerae* by a chelation-independent mechanism[44] that is attributable to the N-terminal peptide of the molecule lactoferricin.[45] Lactoferricin kills by disrupting cell walls of susceptible pathogens.

Also, there is recent evidence that lactoferrin protects against certain viruses.[46–48] Thus, lactoferrin is a prime example of the multiple functions of certain defense agents in human milk. Moreover, lactoferrin often enhances antimicrobial effects of other agents in human milk.

Lactoferrin is not readily digested by proteolytic enzymes from the gastrointestinal tract.[49] Indeed, a substantial proportion of ingested lactoferrin from human milk remains intact throughout the gastrointestinal tract,[50,51] and some whole lactoferrin molecules and proteolytic fragments of them are absorbed and excreted into the urine of the recipient,[51] where they may protect against urinary tract infections.[17]

Another inhibitor of bacterial metabolism, vitamin B_{12} binding protein, is also found in human milk.[49] Unlike lactoferrin, this protein is readily degraded by proteolytic enzymes.[49] It seems improbable that this binding protein would survive the small intestine, but a role for this agent in the upper portion of the alimentary tract, where proteases are lacking, has not been ruled out.

Lysozyme and α-Lactalbumin

Lysozyme, an enzyme that cleaves peptidoglycans in cell walls of susceptible bacteria,[52] is present in exceptionally high concentrations in human milk throughout lactation.[21,22] In contrast, the quantity of this enzyme is low in other mammalian milks used to feed human infants. Longitudinal changes in the concentrations of lysozyme during

Table 32-4 Types of Immunomodulating Agents in Human Milk

Agents	*Functions*
β-Casomorphin	Activates macrophages
Prolactin	Enhances T-cell development
Anti-idiotypic antibodies	Immunizing agents
α-Tocopherol	Augments cell-mediated immunity
Nucleotides	Enhance natural killer cell, macrophage, T helper activities and antibody formation to certain immunogens
Cytokines	See Table 32-5

lactation are unlike most other immunologic components in human milk. After an initial fall to a nadir at 2 to 4 weeks of lactation, the concentration rises by 6 months to levels three times higher than those found in colostrum. The necessity of these high lysozyme levels in human milk may be related to the low production of the protein by mucosal cells during infancy. The synthesis of this enzyme by cultured epithelial cells from the tracheobronchial tree is lowest during early infancy.[28] It is likely that the attainment of normal intraluminal concentrations of lysozyme in the tracheobronchial tree of infants depends on breast-feeding. This is supported by higher lysozyme activities in stools of breast-fed than in those of non-breast-fed infants.[50]

An evolutionary descendent of lysozyme, α-lactalbumin, enhances the activity of lactose synthase that is found only in the mammary gland. The expression of the protein is essential for lactation.[53] It has also been reported that three domains of α-lactalbumin are antibacterial[54] and that a partially unfolded form of the protein with a specific fatty acid ($C_{18:1}$) increases apoptosis of cultured neoplastic cells.[55] The partial unfolding of the protein and the liberation of the fatty acid from milk lipid may occur in the stomach.[55]

Table 32-5 Potential Functions of Certain Cytokines in Human Milk

Cytokines	*Possible Functions*
Interferon-γ	T helper 1 cytokine. Activates macrophages
IL-1b	Activates T cells and macrophages
IL-6	Enhances IgA production
IL-8	Chemotaxin for neutrophils and $CD8^+$ T cells
IL-10	T helper 2 cytokine
	Inhibits production of many proinflammatory cytokines
IL-12	T helper 1 cytokine. Enhances production of interferon-γ
TNF-α	Enhances production of polymeric Ig receptors
TGF-β	Enhances isotype switching to IgA^+ B cells
G-CSF	Increases granulocyte (neutrophil) production
M-CSF	Increases monocyte production

G-CSF = granulocyte colony-stimulating factor; M-CSF = monocyte colony-stimulating factor; TGF-β = transforming growth factor-β; TNF-α = tumor necrosis factor-α.

ANTIBODIES

Four classes of immunoglobulins are found in human milk (IgA, IgM, IgG, and IgD).[21,22,56] The dominant immunoglobulin in human milk throughout lactation is secretory IgA.[21,22,56] Although the levels of this immunoglobulin decrease during the first few months of lactation, substantial concentrations persist during the first 2 years of lactation.[21,22,56]

There is a wide spectrum of secretory IgA antibodies in human milk directed against enteric and respiratory pathogens (see Table 32-2).[56–63] The heavy, light, and J chains of the immunoglobulin part of the molecules are produced by plasma cells in the mammary gland, which originate from B cells from the small intestines (the enteromammary pathway)[64–66] and the bronchial tree (the bronchomammary pathway).[67] The entrance of these immunologically precommitted mucosal B cells into the pathways is triggered by specific antigens that bind to antibodies on the surface of those cells. As a consequence of the antigenic stimulation and the influence of local T helper (Th) 2 cytokines, B cells in those sites undergo an isotype switch from IgM to IgA.[68,69] The stimulated, antigen-specific B cells migrate first to efferent lymphatics and then enter the systemic circulation through the superior vena cava. In mice, and presumably in humans, lactogenic hormones influence those B cells to home to the mammary gland, where they undergo terminal differentiation to plasma cells that predominantly produce dimeric IgA.[66] This process may be controlled by the mucosal cell adhesion system, for example, mucosal cell adhesion molecule 1 and its counterstructure, α4-β7.[70,71] However, in mice, that has not been found to be the case.[72]

Secretory IgA molecules are assembled as J chain–containing IgA dimers bind to the first domain of polymeric immunoglobulin receptors on the basolateral membranes of mammary epithelial cells.[73–76] The endoplasmic part of the receptor is cleaved from the complex. The ectoplasmic part of the receptor that remains bound to the IgA dimer or trimer is termed the secretory component. The receptor-dimeric IgA complex is transported across the

Table 32-6 Representative Immune Factors in Human Milk Whose Production Is Delayed in Infancy

Agents	*Time of Maturation*
Secretory IgA	~ 4–12 mo
Full antibody repertoire	~ 2 yr
Memory T cells	~ 2 yr
Lysozyme	~ 1–2 yr
Lactoferrin	?
Interferon-γ	?
IL-6	?
IL-8	?
IL-10	?
TNF-α	?
PAF acetylhydrolase	?

Ig = immunoglobulin; IL = interleukin; PAF = platelet activating factor; TNF-α = tumor necrosis factor-α.

epithelial cell.[75,76] After fusion with the apical membrane, the endoplasmic part of the receptor is cleaved away. The remainder of the assembled molecule, secretory IgA, is subsequently secreted into the milk.

The secretory IgA antibodies derived from the enteromammary and bronchomammary pathways protect the recipient infant against infectious agents in the maternal environment. This mechanism is important in early infancy, when there is little production of secretory IgA.[25–27] During that period, about 0.5 to 1.0 g of secretory IgA is transferred daily to the mature infant by breast-feeding.[77]

The ability of secretory IgA antibodies to successfully survive in the gastrointestinal tract of the recipient infant is evidenced by several different lines of investigation: (1) secretory IgA is more resistant than other immunoglobulins to in vitro degradation by trypsin or chymotrypsin[78]; (2) the IgA subclass that is more resistant to bacterial IgA proteases, IgA_2, is more prominent in human milk than in blood[56]; (3) furthermore, secretory IgA antibodies against bacterial IgA proteases are often found in human milk.[79] Thus, the dominant immunoglobulin in human milk is well adapted to persist in environments such as the intestinal tract, where those enzymes are found. In keeping with these findings, concentrations of secretory IgA antibodies in the stools are much higher in infants fed human milk than in those fed cow's milk formulas.[50] Based on in vitro experiments and animal model studies, it is postulated that these maternal secretory IgA antibodies protect by agglutinating and thus immobilizing pathogens, by neutralizing their toxins or virulence factors, or by preventing their adherence to mucous membrane surfaces.

Antibacterial Oligosaccharides and Glycoconjugates

An array of oligosaccharides in human milk is produced by glycosyltransferases in the mammary gland. Many of them act as receptor analogs that inhibit the binding of certain enteric or respiratory bacterial pathogens or their toxins to epithelial cells.[80–87]

The chemistry of these carbohydrates dictates the specificity of their binding to adherence structures of bacterial pathogens or their toxins. In that respect, GM_1 gangliosides are receptor analogues for toxins produced by *V. cholerae* and *E. coli*,[83] whereas the globotriaosylceramide Gb3 binds to the B subunits of Shiga toxin.[84] A fucosyloligosaccharide inhibits the stable toxin of *E. coli*,[85] whereas a different one inhibits *Campylobacter jejuni*.[86] Other oligosaccharides in human milk such as G1cNAc (1–3) Gal-disaccharide subunits interfere with the attachment of *Haemophilus influenzae* and *Streptococcus pneumoniae* to respiratory epithelium.[87]

Certain glycosylated proteins also interfere with bacterial or viral adherence. The prime examples are the high-molecular-weight, heavily glycosylated milk mucins.[88] About two-thirds of the mucin in human milk is membrane bound. The concentration of mucin in human milk is about 50 to 90 mg/mL.

The most prominent mucin in human milk, MUC1, is primarily found bound to membranes of milk fat globules.[88] In that respect, human milk fat globules and mucin from their membranes inhibit the binding of S-fimbriated *E. coli* to human epithelial cells.[89]

Antiviral Factors

In addition to secretory IgA antibodies, other types of antiviral agents have been identified in human milk or are produced by digestion of substrates in human milk. They include human milk fat globules[90] and free fatty acids and monoglycerides generated by the enzymatic digestion of triglycerides in human milk that disrupt enveloped viruses.[91,92] These fatty acids and monoglycerides are also antibacterial[91,92] and kill *Giardia lamblia*,[93] a common intestinal parasite in humans.

Human milk fat globules protect against rotavirus infections in mice[90] and presumably do so in the human infant. The antirotavirus component of the human milk fat globule membrane complex is lactadhedrin, a 49 kDa glycoprotein.[94] Lactadhedrin is thus an important constituent of human milk because rotavirus is the most common cause of infectious enteritis in human infants.[95]

Leukocytes

Living cells are found in human milk.[96–98] In contrast to B cells, which transform into plasma cells that remain sessile in the mammary gland, other types of leukocytes attracted to the site traverse the mammary epithelium and enter milk secretions. The highest concentrations of leukocytes in human milk occur in the first few days of lactation ($1–3 \pm 10^6$/mL). They include neutrophils (40 to 65%), macrophages (35 to 55%), and lymphocytes (5 to 10%).

Human milk lymphocytes are predominantly T cells. Both $CD4^+$ (helper) and $CD8^+$ (cytotoxic/suppressor) T cells are present in human milk.[99,100] In comparison with human blood T cells, there is an increased proportion of $CD8^+$ T cells in human milk.[100] This pattern is similar to that found in other mucosal sites. Virtually all $CD4^+$ (helper) T cells and $CD8^+$ T cells in human milk bear the CD45 isoform CD45RO,[99,100] associated with T-cell activation and immunologic memory.[101,102] In addition, an increased proportion of the T cells display other phenotypic markers of activation.[100]

The ability of leukocytes from human milk to produce certain cytokines has been investigated in in vitro studies. Interferon is produced by virus-infected or phytohemagglutinin-stimulated human milk lymphocytes.[99,103–105] The antiviral agent produced by these mitogen-stimulated cells is interferon-γ,[99] which is consistent with their CD45RO phenotype.[99,100] Other cytokines, such as macrophage migration inhibitor factor and monocyte chemotactic factors, are also produced and secreted by stimulated milk T cells.[105] Additional cytokines are produced by human milk leukocytes,[106] but the extent of their production and secretion is not determined.

In other mammals such as sheep, it has been demonstrated that mononuclear leukocytes from milk enter into the tissues of the recipient's intestinal tract and mesenteric lymph nodes.[107] However, passage of milk leukocytes into the intestinal or lymphoid tissues of the recipient infant has not been demonstrated in humans.[98] There are, however,

observations that suggest that cellular immunity to tuberculosis is transferred from mother to infant during breast-feeding.[108] It is unclear whether that is attributable to the transfer of sensitized T cells or to other immunomodulating mechanisms.

Neutrophils and macrophages in human milk are lipid laden because of the ingestion of milk fat globules and therefore are difficult to distinguish by conventional staining methods. They can be identified, however, by appropriate cytochemical and immunochemical procedures. These cells are phagocytic, and there is some evidence that phagocytosis induces a respiratory burst in milk macrophages.[99,109]

The motility of the neutrophils is decreased,[110] whereas the motility of macrophages in human milk is increased compared with their counterparts in blood.[111] These features are attributable to cellular activation. Indeed, neutrophils and macrophages in human milk display phenotypic markers of activation, including an increased expression of CD18/CD11b and a decreased expression of CD62 (L-selectin).[110] The in vivo fate and role of these activated leukocytes in host defense of the infant are undetermined.

ANTI-INFLAMMATORY PROPERTIES

Human milk protects without clinical manifestations of injury to the recipient infant.[5,6,112] There is evidence that this may be owing to a paucity of many of the initiators and mediators of inflammation and the presence of anti-inflammatory agents in human milk[113,114] More recent in vitro and in vivo animal experiments support the concept that human milk is anti-inflammatory. The in vitro oxidative injury produced by neutrophils is decreased by human milk,[115] and human milk decreases carrageenan-induced inflammation and a chemical-induced colitis in rats.[116,117]

Paucity of Inflammatory Agents

Many of the known inducers or mediators of inflammation are either absent or poorly represented in human milk.[113,114] These include (1) the coagulation system; (2) the kallikrein-kininogen system; (3) major components of the complement system; (4) IgE; (5) basophils, mast cells, and eosinophils; and (6) natural killer cells.

Anti-inflammatory Agents

The anti-inflammatory agents in human milk are (1) antioxidants; (2) protease inhibitors, particularly a_1-antichymotrypsin and α_1-antitrypsin; (3) enzymes that bind to substrates such as lysozyme to elastin[118]; (4) anti-inflammatory cytokines including interleukin (IL)-10[119] and transforming growth factor (TGF)-β[120,121]; (5) soluble receptors that bind to proinflammatory cytokines such as tumor necrosis factor (TNF)-α[122]; (6) enzymes that degrade mediators of inflammation; (7) epithelial growth factors; and (8) cytoprotective agents (see Table 32-3).

The antioxidants include an ascorbate-like compound,[115] uric acid,[115] α-tocopherol,[123,124] and betacarotene.[123,124] In that regard, blood levels of α-tocopherol and betacarotene are higher in breast-fed infants than in artificially fed infants who are not supplemented with those nutrients.[123,124]

The human milk growth factors for epithelium include epithelial growth factor,[125] lactoferrin,[126] cortisol,[127] and polyamines.[128,129] Other hormones and growth factors in human milk[130] may also affect the growth, differentiation, and turnover of epithelial cells and thus limit the penetration of free antigens and pathogenic microorganisms and affect other barrier functions of the intestinal tract. In that respect, there are significant differences between the biophysical/biochemical organization and function of the mucosal barrier system in adults and neonates,[131,132] and the maturation of those functions may be accelerated by human milk.[133–135] In addition, the permeability of the intestinal tract of human infants is decreased in early infancy as a result of human milk feedings.[136–138]

Protection against Necrotizing Enterocolitis

Because human milk appears to protect against necrotizing enterocolitis (NEC) in early infancy,[139] a search has been made to identify the possible agents in human milk that might inhibit intestinal inflammation. Platelet activating factor (PAF) acetylhydrolase, an enzyme that degrades PAF, is a prime candidate. In that respect, PAF plays a role in an endotoxin- and hypoxia-induced intestinal injury in rats that mimics human NEC.[140] Furthermore, PAF acetylhydrolase is present in human milk,[141] and the production of human PAF acetylhydrolase is developmentally delayed.[32]

A role for IL-10 in preventing human NEC is suggested from mice that have been rendered deficient in IL-10 by a targeted gene deletion.[142,143] The mice are asymptomatic until after weaning. Afterward, they develop a fatal enterocolitis that resembles NEC in human premature infants. In keeping with the results of that animal model, stimulated blood monocytes and T cells from human newborn infants produce very little IL-10,[34] whereas high levels of IL-10 are found in milk in the majority of women who deliver at term[119,144] and those who deliver prematurely.[144] Furthermore, it is of interest that high and low producers of IL-10 in human milk have been found,[144] and in the most recent study, very low to undetectable concentrations of IL-10 in human milk were found in most women whose premature infants developed NEC despite receiving maternal milk.[144]

Human Milk and Allergic Diseases

The effects of human milk on the development of allergic diseases have been examined by many investigators, but there is no agreement about the protective effect of breast-feeding,[145] except for two types of allergic disorders. The first is atopic dermatitis,[14–16,145] and the second is diseases such as celiac disease that are provoked by food allergens that are avoided by complete breast-feeding.[146] Much of the discrepancy in the results of the investigations may be owing to confounding variables such as variations in the genetic predisposition to atopic disorders, the sufficiency of breast-feeding, dietary exposures not appreciated by parents, and concomitant exposures to inhalant allergens or irritants that produce respiratory symptoms. Furthermore, there is some evidence that high exposures to certain

infectious agents facilitate Th1 responses and hence the development of cellular immunity, whereas lower exposures engender Th2 responses that lead to antibody formation and possibly to IgE-mediated hypersensitivity.[147] Thus, the effect of breast-feeding on the risk of atopic diseases may well depend on a multiplicity of factors that are not equally represented in all investigated populations.

Moreover, foreign food antigens in human milk are transmitted to the breast-fed infant,[148] and allergic reactions to those antigens may be triggered in some of the recipient infants by this route of exposure.[149] However, only a small subpopulation of breast-fed infants develops atopic diseases. To establish whether a breast-fed infant reacts to a foreign food antigen in human milk, trials of dietary elimination and oral challenge with the food in question should be conducted in the breast-feeding mother.[13,149,150] If those trials suggest that the infant reacts to a foreign food antigen transmitted by breast-feeding, then the problem may be avoided by eliminating the food allergen from the maternal diet.[13,149,150] If the food allergen is a basic food such as cow's milk, the woman must have a diet that supplies the correct types and quantities of nutrients needed during lactation.[13,150] If long-term elimination is impractical, then breast-feeding may be stopped and the infant tried on a hypoallergenic formula.

In addition, the development of allergic disease in breast-fed infants may also be attributable to alterations in the types of fatty acids found in milks produced by mothers of the allergic infants.[13,151,152] The proposition is that some fatty acids that are anti-inflammatory may be reduced, whereas others that are proinflammatory may be increased in those milks.[152]

IMMUNOMODULATING AGENTS

Immunomodulating agents in human milk have only recently been recognized. Certain seemingly unrelated observations provided the basis of this idea:

1. Although the evidence is not completely conclusive, epidemiologic investigations suggested that breast-fed infants may be at less risk for developing type 1 diabetes mellitus,[17] lymphoma,[18] acute lymphocytic leukemia,[20] or inflammatory bowel disease, particularly Crohn's disease,[21] later in childhood. The prevention or lessening of the effects of infections by antimicrobial agents and anti-inflammatory agents in human milk or the avoidance of early introduction of foreign food antigens into the diet may have long-term consequences. However, it also seems tenable that the observed delayed effects may be attributable to agents in human milk that influence the long-term development of the child's immune system.
2. Increased levels of certain immune factors in the infant, levels that could not be accounted for by passive transfer of those substances from human milk, also suggested that human milk is immunomodulating. Breast-feeding primes the infant to produce higher blood levels of interferon-α in response to respiratory syncytial virus infection.[153] Also, the increments in blood levels of fibronectin achieved by breast-feeding are not owing to the amounts of that protein in human milk.[154] In addition, human milk feedings lead to a more rapid development in systemic antibody responses[155] and the appearance of secretory IgA in external secretions,[156–158] including urine, which are far removed from the route of ingestion.[157,158] Therefore, it does not seem likely that the increments were attributable to those same factors in human milk.
3. The third line of evidence developed from the discoveries that all types of leukocytes in human milk are activated (see previous section on the leukocytes in human milk). Further in vitro investigations revealed that human milk enhanced the movement of blood monocytes and that much of that increased motility was abrogated by antibodies to TNF-α.[159] Subsequently, the presence of TNF-α in human milk was verified immunochemically.[160]

CYTOKINES

In addition to TNF-α, many other cytokines have been discovered in human milk, including some that are proinflammatory (IL-1b,[161] IL-6,[162,163] IL-8[164]), anti-inflammatory (TGF-β[164-166], IL-10[119]), growth promoters for hematopoietic cells (erythropoietin,[167] granulocyte colony-stimulating factor,[168] macrophage colony-stimulating factor[169]), chemokines (IL-8,[164] RANTES, [170] eotaxin[170]), Th1 agents (interferon-γ,[171] IL-12,[172] IL-18[173]), and Th2 cytokines (IL-10[119]). Some potential effects of those agents in human milk in the recipient infant have been suggested from in vitro studies (see Table 32-5), but the in vivo sites of action and the extent of their effects on the recipient infant are not determined.

OTHER IMMUNOMODULATING AGENTS

Several other immunomodulating agents have been found in human milk (see Table 32-4), including β-casomorphins from the digestion of β-casein,[174] prolactin,[130,175] anti-idiotypic antibodies,[176] and nutrients including α-tocopherol[123,124] and a host of nucleotides[177,178] that enhance natural killer cell,[179] macrophage,[179] Th cell activities,[180] and antibody formation to certain immunogens.[181]

HUMAN MILK AND TH1 AND TH2 RESPONSES

It is of interest that Th1 and Th2 cytokines are present in human milk and that Th1 and Th2 cells are found in alimentary tract tissues of the recipient infant.[182] The effects of human milk cytokines on the expression of Th1 and Th2 activities in the gastrointestinal tract of human infants are unknown. Furthermore, the types and, in some cases, the intensity of infections dictate the mix of Th1 and Th2 cytokines produced by the host and hence whether cellular immunity characterized by activated T cells, cytotoxicity, and activated macrophages or the production of immmunoglobulins will occur.[147] Antimicrobial agents in human milk often reduce the load of microbial pathogens by killing them, interfering with their replication, preventing their adherence to mucosal sites, or neutralizing their toxins or virulence factors. Thus, it seems plausible that

these agents as well as cytokines in human milk may influence the recipient's T cell helper responses.

Immunologic Tolerance

Another immunomodulating effect of human milk is the induction of immunologic tolerance to maternal human leukocyte antigens. Children breast-fed during infancy have been found to be more tolerant of maternal renal transplants than those who were not breast-fed.[183–185] Furthermore, blood T cells from such children are less likely to react against maternal blood lymphocytes in culture than those from children who were not breast-fed during infancy.[186] The tolerance may be induced by major histocompatibility complex (MHC) class II antigens found on milk fat globules.[187,188] Macrophages and some of the activated T cells in human milk may possibly contribute additional MHC class II antigens[100,110] for the induction of tolerance to those maternal antigens. The natural effects of this tolerance to MHC class II are unknown, but one possibility may be that it may help to establish and maintain residency of maternal human milk T cells or macrophages in the tissues of the alimentary tract or respiratory system of the recipient infant. It is also unclear whether tolerance to other antigens such as foreign food proteins in human milk is induced by breast-feeding.

SUMMARY

There are seven evolutionary outcomes concerning the relationship between the immunologic status of the infant and the immunologic agents produced by the mammary gland:

1. Certain postnatal developmental delays in the infant's immune system are replaced by those same agents in human milk (see Table 32-6).
2. Other postnatal delays in the infant's immune system are offset by dissimilar agents in human milk.
3. Agents in human milk initiate or augment functions that are otherwise poorly expressed in the infant.
4. Agents in human milk alter the physiologic/biochemical state of the alimentary tract from one suited for fetal life to one that is appropriate for extrauterine life.
5. Defense agents in human milk protect without provoking inflammation and by providing some agents that inhibit inflammation (see Table 32-3).
6. Defense agents in human milk have an enhanced survival in the gastrointestinal tract of the recipient infant compared with most foreign dietary proteins.
7. Growth factors in human milk augment the proliferation of a commensal enteric bacterial flora.

Much has been learned about the in vitro activities of the protective factors in human milk, but little is known about how those bioactive agents produce the in vivo effects that are attributed to breast-feeding. The problem is compounded by the interactions between the defense agents in human milk, the many functions of some of the agents, and the dynamic changes in the immune systems of the infant and of the maternal mammary gland during the postnatal period and lactation. Also, the spectrum of bioactive agents such as the cytokines in human milk and the extent of developmental delays in the immune system are not completely known.[189] Furthermore, some consequences of the immunomodulating factors in human milk may not be evident until long after breast-feeding is over. Thus, many investigations will be required to elucidate the immunologic aspects of these maternal–infant interactions. Nevertheless, the uniqueness of the immune system in human milk and its known health benefits are important reasons to encourage breast-feeding.

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CHAPTER 33

APPROACH TO BREAST-FEEDING

Ruth Lawrence, MD, Robert M. Lawrence, MD

The health goals of our nation include a statement regarding breast-feeding. By the year 2010, 75% of women will leave the hospital breast-feeding, at least 50% will continue to breast-feed for at least 6 months, and at 12 months, at least 25% will still be breast-feeding. The goal particularly addresses high-risk women, those from minority, low-income, and undereducated groups.[1]

The Institute of Medicine issued a report on nutrition during lactation as part of a review of nutrition in the perinatal period that stated that breast-feeding was ideal for all infants under ordinary circumstances.[2] It further stated that even women without perfect diets could produce good milk and nourish their young well.[2] Professional medical associations such as the American Academy of Pediatrics,[3] the American College of Obstetrics and Gynecology, and the Academy of Family Practice have developed policies encouraging universal breast-feeding. The World Health Organization and United Nations International Children's Emergency Fund (UNICEF) have taken very strong positions in support of worldwide breast-feeding, including the development of the Baby Friendly Hospital Initiative.[4,5]

Human milk is specifically designed for the needs of the human infant. Its nutritional advantages have been noted to be especially important for brain growth.[6–8] In the first year of life, the brain of the human infant doubles in size.[9] The myelinization of nerves is equally as important and occurs extensively in the first year of life. Taurine, cholesterol, and omega fatty acids are essential to brain growth and are uniquely present in human milk.[10]

The presence of dozens of active enzymes, immunologic properties, infection protection properties, and allergy protection are some of the compelling reasons breast-feeding is superior for human infants.[11–14]

The number of women who elect to breast-feed has continued to increase, and the renaissance of breast-feeding is well established.[15,16] It is important for the clinician to be knowledgeable about the value of human milk, the advantages of breast-feeding, the clinical management of lactation, and the diagnosis and treatment of problems.[17] The current scientific literature provides a large resource of information on these topics, which will be summarized here.

ANATOMY AND PHYSIOLOGY

Lactation is the completion of the normal reproductive cycle. It is a physiologic process triggered by the termination of pregnancy but anticipated both anatomically and physiologically from early development.[10]

The breast bud is present at birth in both sexes but remains dormant until early pubescence, when growth is stimulated by the increase in estrogen and progesterone in the female.[18,19] The ductal system proliferates and the breast matures. This maturation continues with stimulus from each menstrual cycle until age 25. When growth stabilizes, further proliferation does not occur until pregnancy intervenes (Figure 33-1).

Changes in circulating hormones result in profound changes in the ductular-lobular-alveolar growth during pregnancy.[20] There is a marked increase in ductular sprouting, branching, and lobular formation evoked by luteal and placental hormones (Figure 33-2). Placental lactogen, prolactin, and chorionic gonadotropin have been identified as contributors to the accelerated growth.

From the third month of gestation, secretory material resembling colostrum appears in the alveoli. By the second trimester, placental lactogen begins to stimulate the production of colostrum so that a woman delivering immaturely as early as 16 weeks may secrete colostrum, although her baby is not viable. Until delivery, the production of milk is suppressed by prolactin-inhibiting hormone, produced by the placenta. Progesterone produced by the placenta has been recognized as important in blocking milk production in pregnancy. At delivery, the withdrawal of placental and luteal sex hormones and the infant's sucking result in the loss of the inhibiting hormones and the stimulation of prolactin-releasing factors.[21]

The initiation of milk secretion at delivery and the continued production of milk occur because the breast has developed extensively throughout pregnancy.[10] The ductal system has arborized to form an extended network of collecting ducts. The alveoli are richly lined with epithelial cells varying from flat to low columnar in shape, all capable of producing milk. Some cells protrude into the lumen of the alveoli; others are short and smooth. The lumen of the alveolus is crowded with fine granular material and lipid droplets (Figure 33-3). The division and differentiation of the mammary epithelial cells and presecretory alveolar cells into secretory milk-releasing alveolar cells complete the preparation for milk production. The biosynthesis of milk involves this cellular site, where the metabolic processes occur. There are stem cells and highly differentiated secretory alveolar cells at the terminal ducts. The stem cells are stimulated by

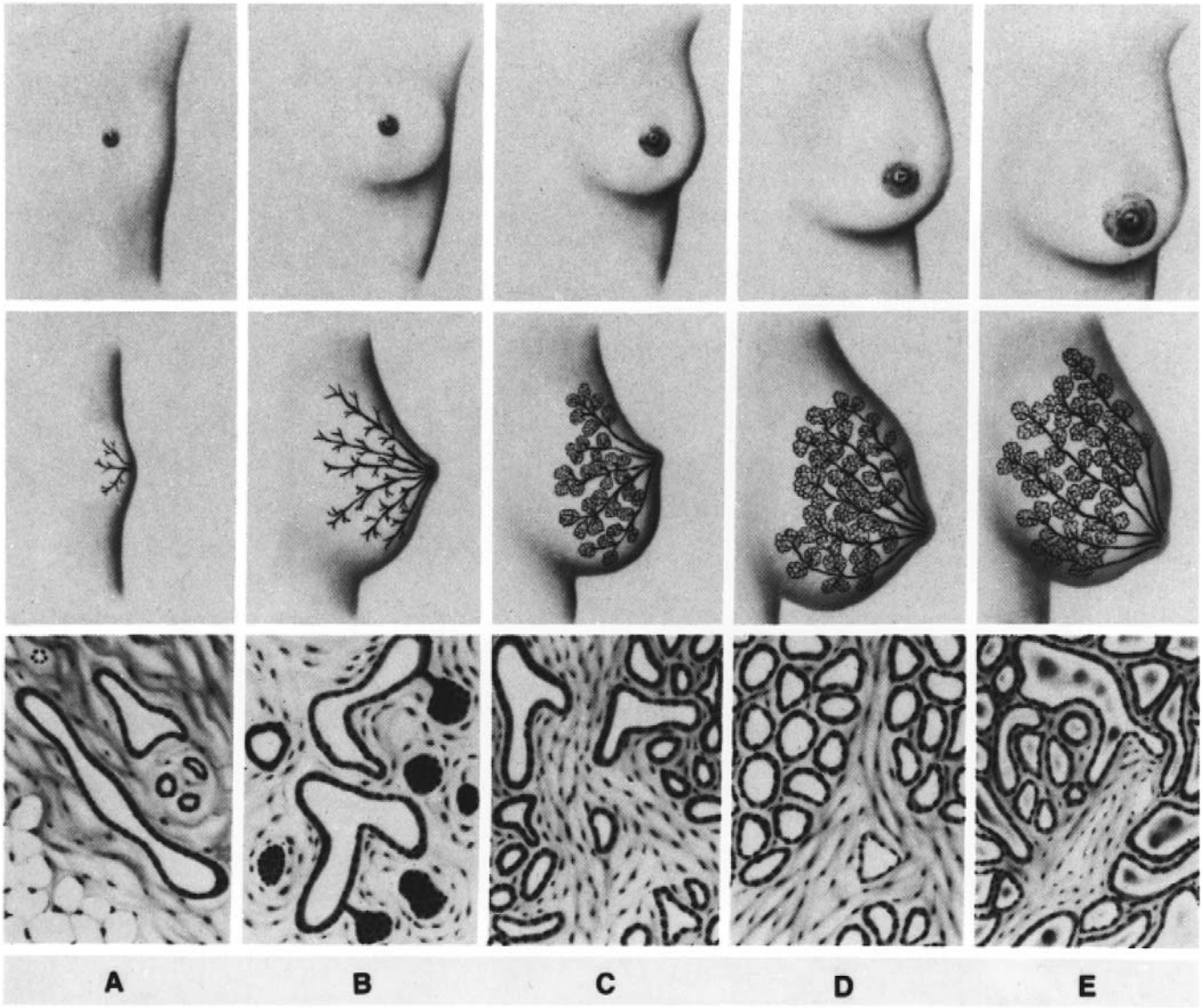

FIGURE 33-1 Female breast from infancy to lactation with corresponding cross-section and duct structure. *A, B, C,* Gradual development of well-differentiated ductular and peripheral lobular-alveolar system. *D,* Ductular sprouting and intensified peripheral lobular-alveolar development in pregnancy. Glandular luminal cells begin actively synthesizing milk fat and proteins near term. Only small amounts are released into lumen. *E,* With postpartum withdrawal of luteal and placental sex steroids and placental lactogen, prolactin is able to induce full secretory activity of alveolar cells and release of milk into alveoli and smaller ducts. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

growth hormone and insulin, which is synergized by prolactin to stimulate the cells to secretory activity. The breast acts in response to the interactions of the pituitary, thyroid, pancreatic, adrenal, and ovarian hormones (Figure 33-4).

The process of milk synthesis involves apocrine secretion for the de novo production of fat and protein and the merocrine secretion of lactose synthesized from glucose.[18] Ions diffuse across the membrane and, in some cases, are actively transported. The primary alveolar milk is then diluted within the lumen to be isotonic with plasma by water that diffuses from extracellular fluid.[22] The pathways for milk synthesis and secretion into the mammary alveolus include (1) exocytosis of protein and lactose, (2) formation of the milk fat globule, (3) secretion of ions and water, (4) pinocytosis-exocytosis of immunoglobulins, and (5) the paracellular pathway (Figure 33-5).

Because lactation is anticipated, the body prepares the breast during pregnancy and also develops additional nutritional maternal stores that will be needed during lactation, in the form of 6 to 8 pounds of body weight apart from the uterus and its contents. When lactation begins, there is a redistribution of blood supply from the uterus to the breast, where there is an increased demand for nutrients and an increased metabolic rate to accommodate the demands of milk production. The mammary gland may have to produce milk at the expense of other organs if stores are inadequate. There are cardiovascular adjustments as mammary blood flow increases. The mammary blood flow, cardiac output, and milk secretion are suckling dependent. In addition, suckling induces the release of anterior pituitary hormones, prolactin and oxytocin, which act directly on the breast tissue and on the uterus.[21]

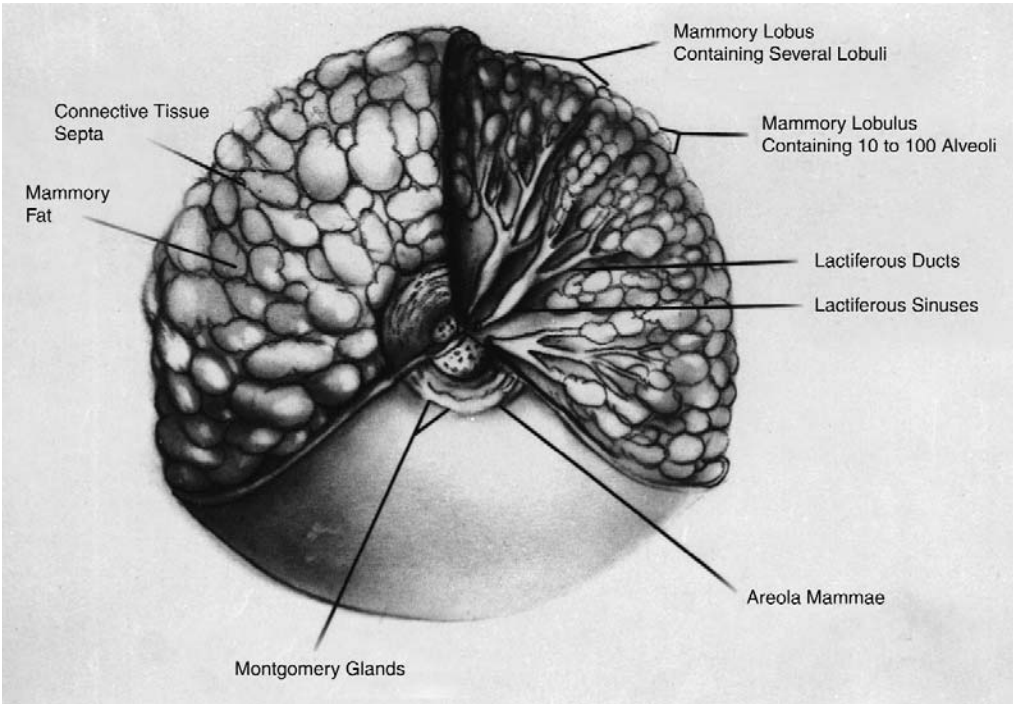

FIGURE 33-2 Morphology of mature breast with dissection to reveal mammary fat and duct system. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

In addition to glandular preparation, the nipple and areola are also preparing for lactation. There is an increase in vascularization. The Montgomery glands, which are sebaceous glands on the areola circling the nipple, become enlarged and begin to secrete a substance that lubricates and protects the areola and nipple during pregnancy and lactation. There are 15 to 25 milk ducts opening in the nipple. Each tubuloalveolar gland arborization, called a lobe, opens separately in the nipple. The collecting duct or lactiferous sinus of the system lies beneath the areola, which is why the infant must have most of the areola in the mouth to "milk" the collecting ductules. The nipple has many sensory nerve fibers, but the areola does not, an important fact in terms of comfort for the mother while nursing. The response to tactile sensation of the nipple increases dramatically at delivery as an adaptation for lactation that enhances the nervous response to suckling by the infant (Figure 33-6).

INITIATION OF MILK SECRETION

Withdrawal of placental and luteal sex hormones and stimulation of prolactin-releasing factor result in the increased prolactin synthesis by the adenohypophysis, which stimulates milk synthesis in the mammary alveoli. The release of milk from the alveolar collecting ductules or lactiferous sinuses depends on the ejection or let-down reflex (see Figure 33-6). The let-down reflex is a simple arc that is initiated by the suckling of the infant. This suckling stimulates the mechanoreceptors in the nipple and areola that send stimuli along nerve pathways to the hypothalamus, which stimulates the posterior pituitary to release oxytocin. Oxytocin is carried via the bloodstream to the breast and uterus.[23] Oxytocin stimulates the myoepithelial cells, which envelop the secretory alveoli and the collecting ductules in the breast, to contract, ejecting milk through the ductule. The oxytocin also stimulates the myoepithelial cells in the uterus to contract, causing the "after pains" a mother associates with lactation. Physiologically, this uterine contraction enhances the uterine postpartum involution so that the uterus of the lactating woman returns to normal more quickly postpartum. Oxytocin release can also be stimulated by seeing or hearing the infant; thus, a woman notices that her milk begins to drip when she sees her infant. Prolactin, however, is released only when the breast is stimulated by suckling or pumping.

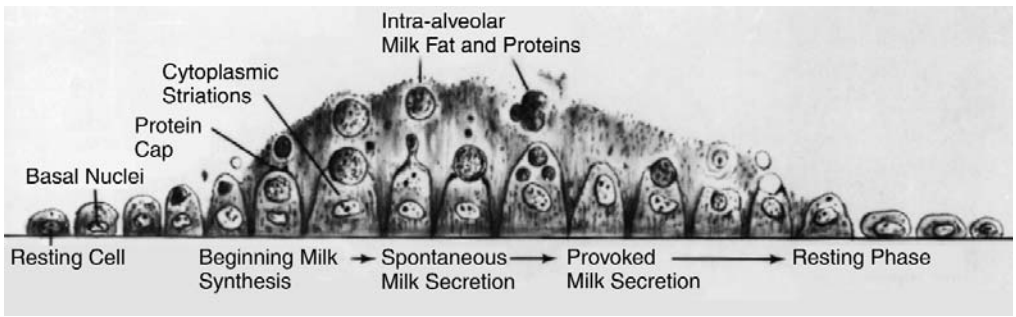

FIGURE 33-3 Cycle of secretory cells from resting stage to secretion and return to resting stage. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

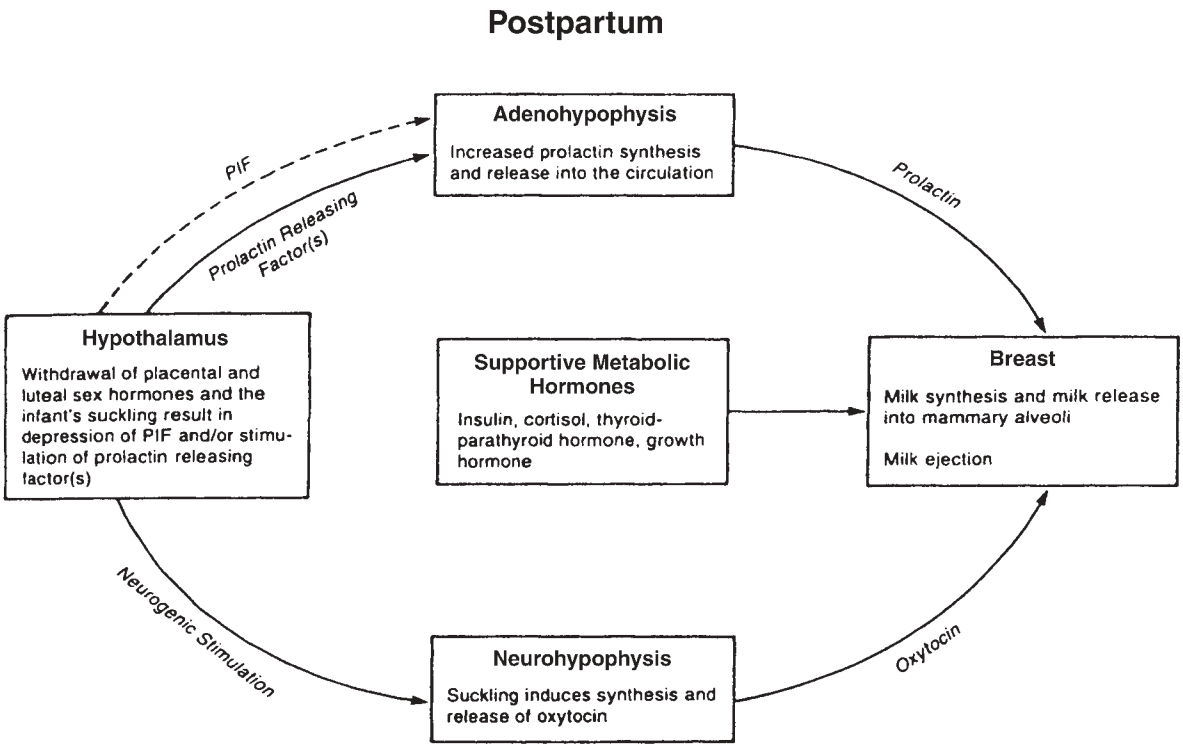

FIGURE 33-4 Hormonal preparation of breast postpartum for lactation. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

Prolactin, which is also released from the hypothalamus during sucking, stimulates the production of milk. Prolactin levels during early lactation are increased 10 to 20 times greater than normal. The technology required to obtain prolactin levels has been available for clinical investigation, but the role of prolactin in the volume of milk produced is still not clearly defined. It is clear, however, that the surge in prolactin to about twice baseline levels is critical to the successful production of an adequate supply of milk. When evaluating prolactin during lactation, a sample of blood is drawn at baseline and then a second sample is drawn after 10 minutes of breast-feeding or pumping with an electric pump.[10]

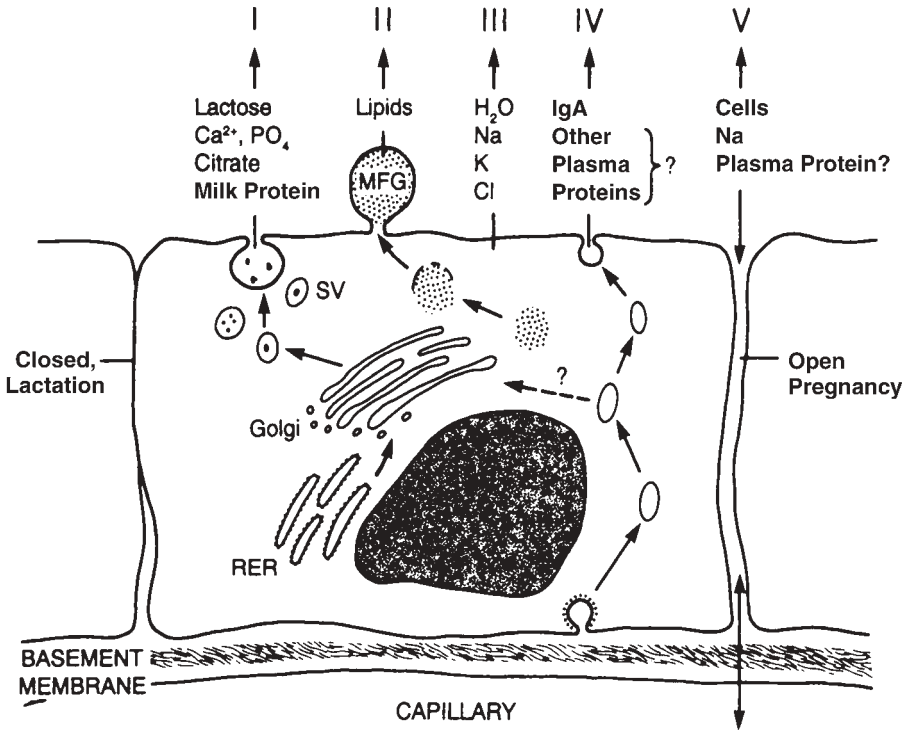

FIGURE 33-5 The pathways for milk synthesis and secretion in the mammary alveolus. (II) Exocytosis of milk protein and lactose in Golgi-derived secretory vesicles. (III) Secretion of ions and water across the apical membrane. (IV) Pinocytosis-exocytosis of immunoglobulins. (V) The paracellular pathway of plasma components and leukocytes. MFG = milk fat globule; RER = rough endoplasmic reticulum; SV = secretory vesicle. Adapted from Neville MC.[18] Reproduced with permission from Lawrence RA and Lawrence RM.[10]

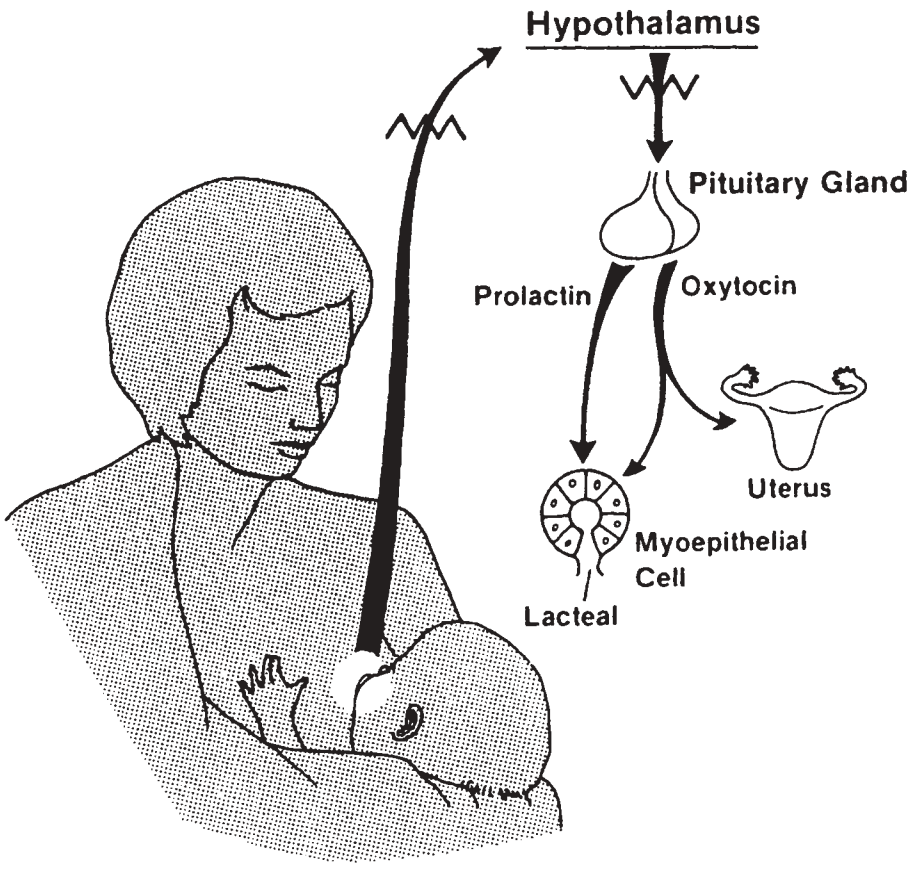

FIGURE 33-6 Ejection reflex arc. When suckling the breast, the infant stimulates mechanoreceptors in the nipple and areola that send a stimulus along nerve pathways to the hypothalamus, which stimulates the posterior pituitary to release oxytocin. It is carried via the bloodstream to the breast and uterus. Oxytocin stimulates myoepithelial cells in the breast to contract and eject milk from the alveolus. It is secreted by the anterior pituitary gland in response to suckling. Stress such as pain and anxiety can inhibit the let-down reflex. The sight or cry of an infant can stimulate it. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

PRENATAL CONSIDERATIONS

Although the breast prepares for lactation independent of the mother's decision to breast-feed, it is important to introduce the question of feeding the infant as soon as possible during pregnancy so that the mother can make an informed choice on behalf of her baby. Although it has been suggested that well-educated mothers have made up their minds about how they will feed their infants long before conception occurs, there are many women who need to be informed about breast-feeding and need to receive reinforcement from their physician.[24] Many women, especially primiparas, will need considerable assistance to lactate successfully. The significant benefits of human milk to the human infant have already been reviewed in previous chapters. The psychological benefits are equally as important to both mother and child.[25]

The nutritional benefits of human milk, although legion, can in part be substituted with a modern prepared formula, but the infection protection, immunologic properties, and psychological benefits of human milk cannot be duplicated.[13,14] In the mid-twentieth century, when bottle feeding was rampant, the single, clear, unchallenged advantage to breast-feeding that was articulated was the special interrelationship between the mother and her baby.[25] The key elements of attachment are said to include early contact, closeness, eye-to-eye contact, and body warmth. Breast-feeding includes these naturally. A woman has a surge of oxytocin and prolactin during each feeding, which has been demonstrated biologically to stimulate mothering behavior.[26,27]

When a mother wishes to be free of the responsibility of breast-feeding, it is often so that she will not be tied down, will not always have to be available, and can have others feed the infant, thus depriving the infant of this special frequent closeness with the mother.

Preparation of the Breasts

Nature prepares the breasts. It is not necessary to manipulate the breasts and nipples prenatally in preparation in the normal woman. Part of the prenatal physical examination should include the breasts with respect to lactation so that any anatomic variations that may interfere with lactation can be discussed.[24] The size of the breast is not related to lactation success and is not a measure of glandular potential. Women who have had benign cysts removed can still nurse successfully. Augmentation mammoplasty does not interfere with lactation if the nipple and duct system have been left intact, that is, the nipple has not been realigned and the implant is placed under the breast tissue on the chest wall. Unless the implant has ruptured and has caused scarring, lactation should be successful. When breast size has been surgically diminished by reduction mammoplasty, the duct system may have been interrupted if the nipple was completely removed and replaced central to the remaining tissue. This may make lactation improbable, and this issue should be discussed with the operating surgeon. If the procedure was done leaving the nipple and areola on

a pedicle, lactation may be successful. Women who have had one breast removed surgically can successfully breast-feed, although when the mastectomy is for malignant disease, it may not be recommended because of the potential effect of continued high levels of sex steroids in the system if pregnancy occurs within 5 years of treatment. It should be discussed with the oncologist. Women who are in the process of treatment for breast cancer during lactation may pump and discard their milk for a few days after chemotherapy and then resume feeding until the next treatment. Length of time for discarding varies with the drug employed. The time for complete clearance can be calculated as five times the half-life of the drug involved.[10]

Inverted nipples are the most common anatomic problem identified (Figure 33-7). Although there are stretching exercises that can be done to pull the nipple out, exercises require time, considerable dedication, and a commitment on the part of the mother to this daily manipulation. Some mothers find nipple exercises distasteful. Nipple stimulus prenatally may trigger uterine contractions and premature labor. Another method of treatment for inverted nipples is wearing specially designed plastic shells (Figure 33-8) inside the normal brassiere daily during the last 6 weeks of pregnancy, beginning with a few minutes a day and increasing time worn to 8 to 10 hours after about 2 weeks. The continued gentle pressure on the areola, stretching the fibrous tissue, will evert the nipple through the central hole. After delivery, these shells can be worn between feedings (but not during) until the eversion is firmly established postpartum and the nipple is easily grasped by the infant. A controlled study by Alexander and colleagues found that neither technique was very effective, and it often discouraged some women from even initiating breast-feeding.[28] Inverted or small nipples may best be everted by using a good hand pump or an electric pump just prior to putting the infant in position to latch on for a feeding in the first few days postpartum. Usually, the nipple will remain erect without pumping in less than a week of these efforts. In subsequent pregnancies, the nipples are more everted, probably owing to the stretching of the fibers that were tying the nipple down.

Only gentle face soap and clear water are needed for breast care. No ointments or lotions are advised prophylactically as they irritate the skin and plug the natural pores, inhibiting the natural secretions. The sebaceous secretions of the glands of Montgomery on the areola are intended to lubricate the areola and nipple. Buffing the tissues briskly with a turkish towel or a toothbrush is neither necessary nor recommended. In a very dry climate, where skin dryness is a problem, a bland ointment such as A and D ointment or purified lanolin might be prescribed in some cases.

Removing colostrum in the last few weeks of pregnancy by manual expression is not recommended as it may irritate the tissues and cause an early mastitis. Because the colostrum is discarded, it wastes a very valuable commodity, which should be left for the infant. Such manipulation of the breast may also stimulate premature contractions of the uterus. Prior to delivery, the mother should purchase and bring to the hospital a well-constructed nursing brassiere to support the breasts, especially as the milk first comes in. This will alleviate the feeling of heaviness and engorgement. Many women wear a nursing brassiere night and day, especially in the first few weeks postpartum.

A new mother may find it helpful to attend breast-feeding classes prenatally and actually see an infant at the breast before she delivers if she is totally unfamiliar with breast-feeding.[29] Many childbirth classes include breast-feeding in the curriculum. If not, the physician may wish to have the office staff provide that educational service or

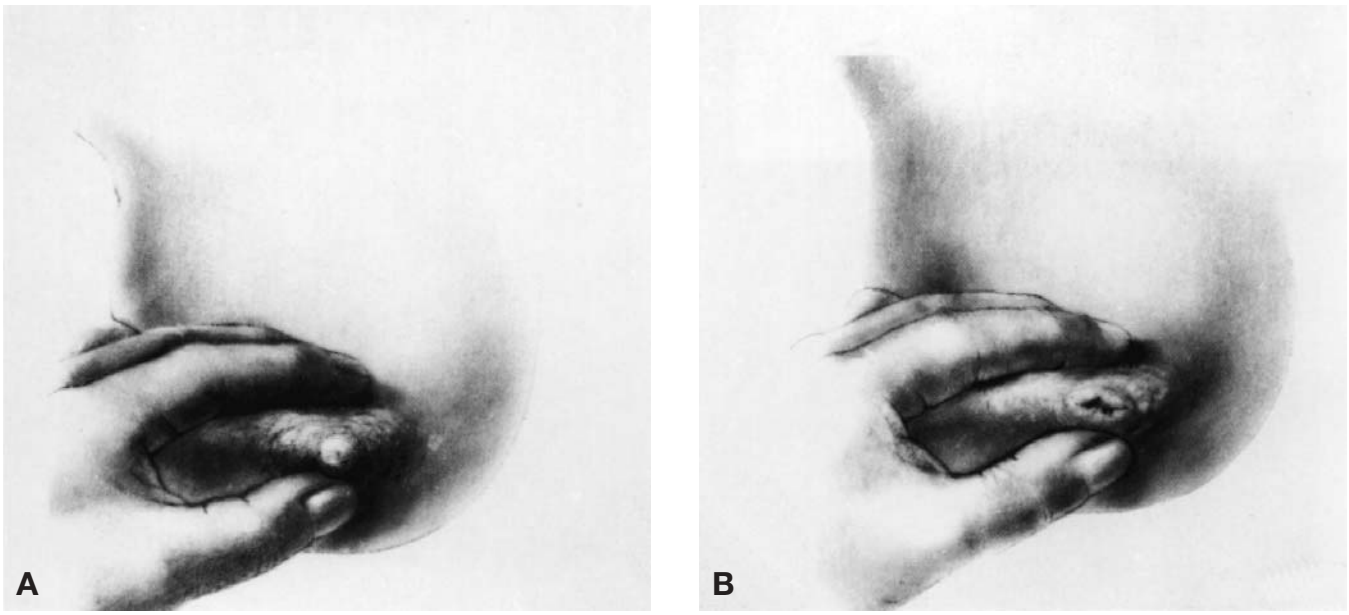

FIGURE 33-7 *A,* Normal nipple everts with gentle pressure. *B,* Inverted or tied nipple inverts with gentle pressure. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

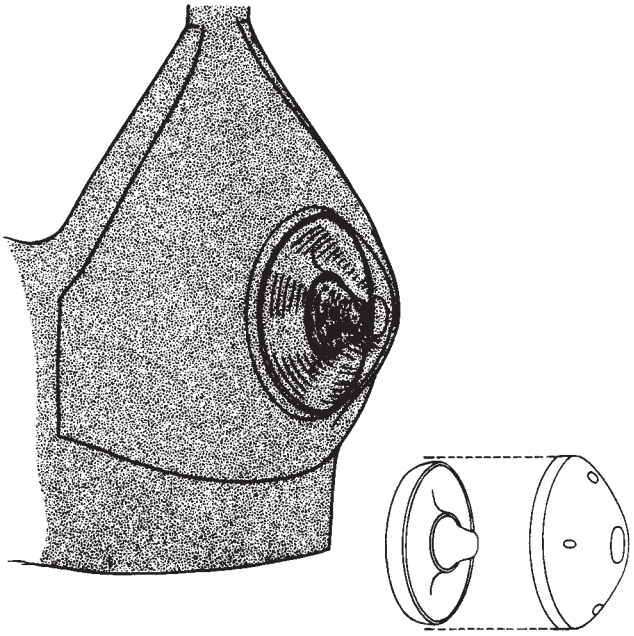

FIGURE 33-8 Breast shell in place inside a brassiere to evert the nipple. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

refer the patient to a community breast-feeding support group, such as La Leche League.

Initiating Lactation: The First Feed

As soon after birth as possible, the infant should be breast-fed.[4,5] Once the infant is stable, with the airway clear and respirations established, he can be offered the breast with the mother lying on her side facing the infant, who is also lying on his side. The infant should be held close to the breast. The areola will be soft and compressible. If the mother strokes the infant's lower lip with the nipple, he will quickly root, open the mouth wide, grasp the nipple and areola, and begin to suckle. The nipple and areola elongate to form a teat as they are drawn into the mouth. The infant should grasp well beyond the nipple to compress the areola and stroke the ampullae of the collecting ductules, which lie under the areola (Figures 33-9 and 33-10). Because nipple size and areola size vary, the infant may not be able to get the entire areola into the mouth. Even at the first feeding, the infant will receive colostrum. The mother should be further instructed in the art of positioning herself comfortably and supporting her breast with her hand. Changing her position at different feedings allows the infant to grasp from different angles.[29,30] This will rotate the point of greatest suckling pressure and will evenly distribute the suckling pressure over the entire areola. A mother may lie down or sit up as she chooses. If the nipple is tender, the baby can be held on the right breast as if he were nursing on the left side, that is, facing the mother's right side with feet to her right (or the reverse on the left breast, with the infant facing the mother's left side). The key to correct positioning is having the infant face the breast. The infant can be brought close by moving the mother's arm that is holding the infant and not by pushing the infant's head toward the breast. Pushing the head toward the breast causes the infant to arch back away from the breast, which is the arching reflex. This results when the back of the head is held. This appears to the mother as if the infant is rejecting the breast.

Initially, a mother may offer both breasts at each feeding to stimulate each breast as often as possible during the first weeks. The infant, however, should nurse long

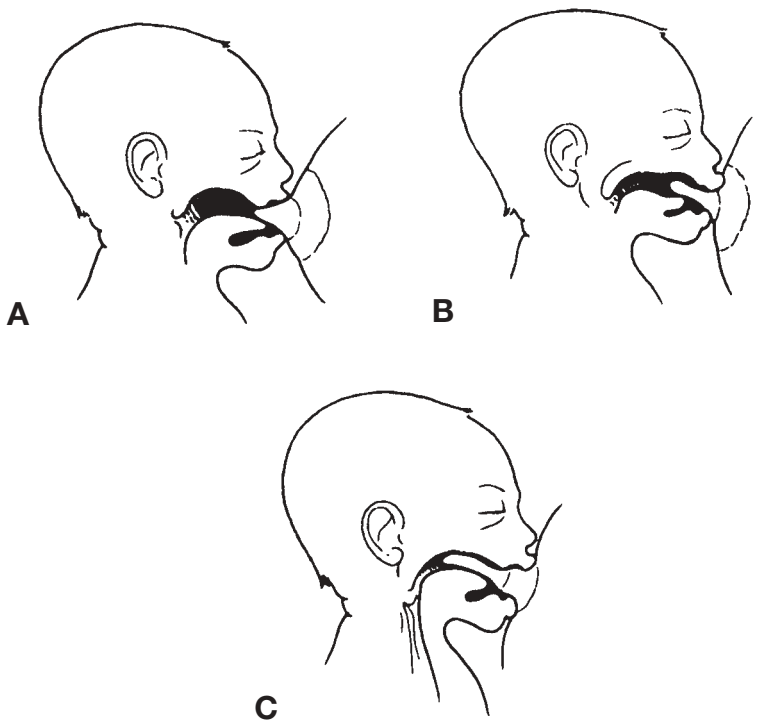

FIGURE 33-9 *A*, As the infant grasps the breast, the tongue moves forward to draw the nipple in. *B*, The nipple and the areola move toward the palate as the glottis still permits breathing. *C*, The tongue moves along the nipple, pressing it against the hard palate and creating pressure. Ductules under the areola are milked and flow begins as a result of peristaltic movement of the tongue. The glottis closes. Swallow follows. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

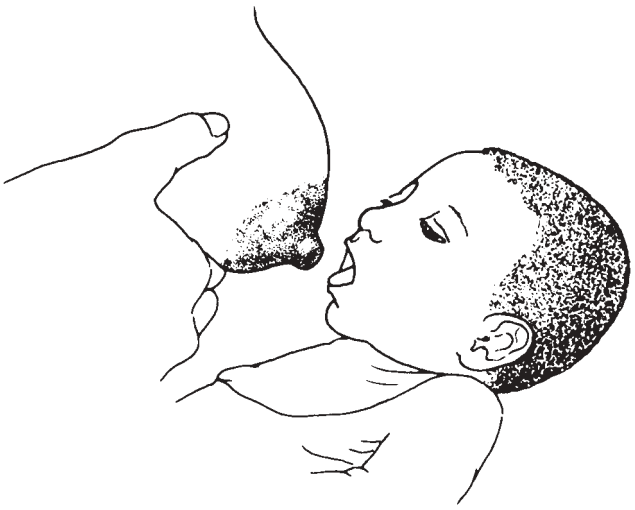

FIGURE 33-10 Latching on. In response to stimulating the infant's lower lip with the nipple, the mouth opens wide. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

enough on the first side to receive the hindmilk, that is, over 5 minutes. In reality, he may drift off to sleep before being switched to the second side. At the next feeding, he should be offered the other breast first. This will balance the stimulus and, thus, milk production. The infant should nurse every time he awakens and is alert and hungry, which may be as frequently as every 2 hours. Intervals between feedings should not be greater than 4 to 5 hours in the beginning, when frequent stimulus is critical to establishing a good milk supply. If the infant sleeps 6 hours, he should be awakened in the first few weeks. Having the mother and baby cared for in close proximity as in rooming-in or by mother-baby nursing staff assignments will facilitate frequent appropriate feeding and will enhance milk production. In programs in which infants are fed more than 6 times daily (average 10 to 12 times), the length of each feeding tends to be shorter. With frequent feeding, there is better milk production, less weight loss, earlier regain of birth weight, and less neonatal jaundice.[31–35] This increase in feeding frequency has not been associated with an increase in sore nipples. Sore nipples are associated with inappropriate positioning at the breast. Care should be taken not to overwhelm the mother with many suggestions for different positions, alternate hand grips, and other angles for the infant. She should find a simple way that works before leaving the hospital. If there is a problem, then different approaches can be suggested. The infant should feed when hungry with no rules for timing or intervals.

Healthy mothers and their infants are being discharged in 48 hours or less in sharp contrast to the 4- to 5-day stay of the past. Mothers with cesarean sections may leave in 36 hours. Having a helpless newborn totally dependent on a mother is an awesome, frightening, and sometimes discouraging responsibility. The mother is no longer an independent person. This responsibility may be overwhelming unless care is taken to "mother the mother" because our culture does not automatically provide maternal support. In fact, our culture programs a superwoman concept in which the new mother must return to her other household chores unless the health professional intervenes. Adequate rest should be prescribed. Discussing the joint responsibilities of parenthood with both parents may facilitate a smoother transition from the sheltered hospital environment to home. Early discharge home also places a responsibility on the physician to see the breast-fed infant in the first week of life at home. Provision for weight checks and assessment of jaundice should involve a home visit or an office visit within 2 days of discharge.[3,34] Many offices have a nurse practitioner skilled in newborn care and breast-feeding who provides this service.

Nourishment for the lactating woman should make sense, but nurturance while providing these nutrients is equally important. Raphael has expressed it as the need for a *doula,* which is taken from the Greek language to mean "a helpful friend from across the street."[36] It means that someone must care for the mother, support her efforts to breast-feed, and make her confident in her ability to mother her infant.

Supplementation with Milk or Water

Careful study of weight loss in breast-fed and formula-fed infants in the first days of life indicates that the breast-fed baby does not lose more weight than the formula-fed baby when breast-feeding is adequately assisted. Furthermore, infants who are fed frequently at the breast in the first few days begin to gain weight as promptly as the formula-fed infants or at least by the fourth day. Studies correlating the method of feeding with the level of bilirubin show no significant difference between breast-feeding and formula feeding.[33,37] Studies comparing the frequency of feeding in the breast-feeding group show that infants who are fed seven or more times per day have significantly lower bilirubins than those fed six or less times per day. Findings were independent of the total number of minutes per day spent nursing.[32,33] In terms of lactation physiology, the breast produces milk in response to suckling and the removal of milk by suckling or pumping. The greatest volume of milk is obtained in the first 5 to 10 minutes at each breast. If the infant feeds more frequently, he receives more milk, and the breast produces more in response. Animal studies by Gartner and Herschel suggest a relationship between elevated bilirubin levels and starvation.[34] Weight loss of greater than 5% requires evaluation of the breast-feeding, as does unexplained hyperbilirubinemia.[3,31]

If, on the other hand, the influence of giving water or milk supplements to babies who are breast-fed is scrutinized, it is noted that supplementation, especially with water, is associated with increased weight loss and increased bilirubin levels in the first few days of life.[32–38] If the influence of water or milk supplements on babies who are breast-fed is investigated from the standpoint of successful establishment of lactation, length of breast-feeding, and reasons for early weaning, it is also noted to be negative. Mothers who add supplements have more difficulty establishing a good milk supply, are more apt to wean early,

and give "insufficient milk" as a reason for weaning. Supplements interfere with successful lactation.[39]

In the first few weeks of lactation, it is important to encourage a feeding program that meets the infant's needs, that is, providing feeding when the infant is awake and hungry (so-called demand or on-request feeding). This may be 12 to 16 times per day. Most babies have a period of a few hours when they want to nurse every hour and that is appropriate for several feedings. There is a relationship between the fatigue and stamina of the mother that has to be balanced against the true needs of the infant. A fussy breast-fed infant who has been well fed may need to be comforted by someone else. This is an important role for the father. Lactating women may not be able to comfort their own infants without offering the breast because the infant smells the milk and will root even though he is well fed. This sometimes leads to incessant non-nutritive suckling, which may be a drain on the mother's energy resources and traumatic to the nipple. Non-nutritive comforting is a significant need of most infants and can be provided by the father.

An additional side effect of supplementation is the use of a bottle and a rubber nipple, which may lead to nipple confusion on the part of the newborn.[40] The sucking mechanism used at the breast is the sucking reflex present at birth. The infant will have much of the areola in the mouth, compressing it against the hard palate as it elongates into a teat, maintaining the seal with the gum and lips. The tongue undulates with a peristaltic motion that also triggers the swallow and initiates peristalsis in the esophagus and the stomach. The nipple is a passive passageway for the milk to exit. When a bottle is used, the infant's jaws do little but hold the nipple in place. There is little undulating of the tongue, and milk flows easily, with a little suction created by the seal. The tongue may even be thrust upward to control the flow from the unyielding rubber nipple. Because this is a different position and action, some babies are confused by switching back and forth between breast and bottle, especially in the first few weeks or when the infant is slightly premature. When the tongue thrusting of bottle feeding is used with the breast, it pushes the human nipple out of the mouth.

The position a mother assumes while nursing should be comfortable and relaxing for her. A rocking chair is often the best for the sitting position. It is recommended that a mother may increase her comfort if she varies the hold and orientation of the baby to the breast. This includes not only lying down and sitting up but also holding the baby under the arm in a football hold or across her body so he is held by the left arm at the right breast or the reverse.[10,30,41] The infant should always be facing the breast directly regardless of the position of the rest of the body, and the back of the head should not be handled.

Management at Home

Adjustments at home for a new baby are often amplified when the mother is breast-feeding because any problem such as fussiness, colic, wakefulness, or night feedings are assumed by the mother to be owing to a problem with breast-feeding. Instilling confidence in the mother's ability to care for and nourish her infant is important. Closer surveillance by the physician in the first few days, however, is necessary to be certain that the new, inexperienced mother does not interpret long sleeping periods with little feeding as adequate for proper growth. Successful breast-feeding results in fewer problems and illnesses later. Review of weight status, number of wet diapers (at least six per day), stool pattern (at least three per day in the first month), and feeding pattern is a further check on successful lactation. When a breast-fed infant does not stop losing weight by 5 days, does not produce a stool every day, does not void adequately, or does not regain birth weight by 14 days, aggressive intervention is indicated. The physician needs to evaluate the infant and the breast-feeding.[41]

Maternal Nutrition

The nursing mother should have a nutrition check to confirm her appropriate food intake. A lactating woman should have 500 extra calories over the prepregnancy baseline, 20 extra grams of protein, and a balanced diet. Mothers who are concerned about losing weight should be counseled to consume no less than 1,800 kcal per day and to consume adequate vitamins and minerals.[2,42] Weight loss after the initial drop should not exceed 1 to 1.5 kg per month in the first 6 months of lactation. The most important dietary increase is calcium and phosphorus, to a total of 1,200 mg per day.[43] The neonatal calcium-phosphorus requirement exceeds that of the fetus in the last trimester of pregnancy. Dairy products are the best source, but if these products are not tolerated by the mother, she needs to seek out additional sources in dark green vegetables, nuts, legumes, and certain dried fruits. Dark green leafy vegetables such as kale, cabbage, collards, and turnip greens contain readily available calcium, whereas the calcium in spinach, swiss chard, and beet greens is bound to oxalic acid and is unabsorbable.[2,42] The amount of calcium in the diet will not influence the amount in the milk, but a deficiency will lead to leaching from maternal bone and significant osteoporosis. A lactating woman does not need added iron for milk but will need to replace stores lost in pregnancy and parturition. A balanced diet should provide all other nutrients. The quality of the milk day by day is balanced by intake and stores (Figure 33-11). The strict vegetarian is in jeopardy, however, of causing vitamin B_{12} deficiency in her offspring unless she takes supplements because vitamin B_{12} is not found in nature except in animal protein.

The lactating woman does have increased needs for fluids and thus increased thirst. If a woman selects beverages that contain caffeine or other active pharmacologic principles, it could affect the infant. Beverages that either contain no caffeine or have been decaffeinated are appropriate. With the increasing interest in herbal teas, attention should be given to the content of such teas.[44] A partial list of products is shown in Table 33-1. Many teas contain very potent glucosides that have pharmacologic properties; others are benign and a few even nutritious, such as rose hips, which contain vitamin C.

Documenting the consumption of herbal teas by the mother or given to the infant directly should be part of the

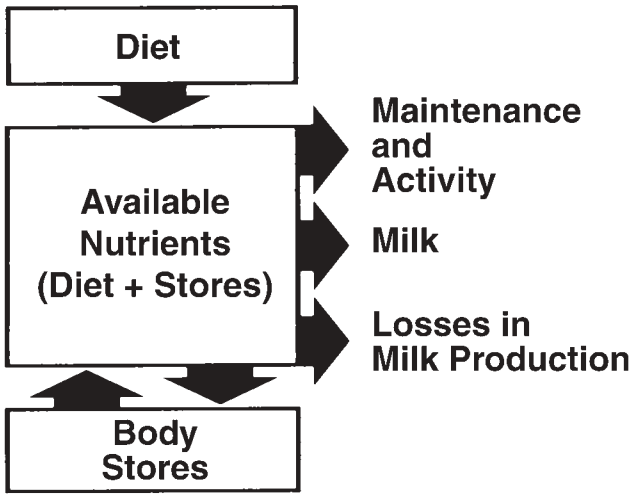

FIGURE 33-11 Energy use in lactation, showing availability of body stores and dietary sources. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

medical history. Some herbs, such as fenugreek, are reputed to enhance lactation. The required dose is large, and soon the milk, all secretions, and the infant smell like maple syrup. It helps some women but not all. There can be a cross-allergy to peanuts and chickpeas that may cause colic in the infant. Comfrey has been widely used in midwifery and in lactation but is banned in many countries. The US Food and Drug Administration has also issued a warning as its use can cause veno-occlusive disease and even be fatal, especially in infants.[45]

STAGES OF BREAST-FEEDING

ADAPTATION

Initially, there is a period of adjustment and adaptation as the mother and baby settle into a reciprocal relationship of supply and demand. The infant can be exclusively nourished at the breast for the first 6 months of life. During that time, there may be gradual changes in the feeding pattern as the infant matures and sleeps longer between feedings and also spends more time awake and socializing. Periods of stress or illness in the infant may be marked with tem-

TABLE 33-1 Herbal Teas

Ingredient	*Botanical Source*	*Pharmacologic Principle*	*Use*	*Effects*
African yohimbe bark, yohimbe	*Corynanthe yohimbe*	Yohimbine	Smoke or drink as stimulant	Mild hallucinogen
Catnip	*Nepeta cataria*	Nepetalactone	Smoke or drink as marijuana substitute	Mild hallucinogen
Gordolobo yerbal	*Senecio douglassi*	Pyrrolizidine alkaloids	Drink	Sore throat therapy, ? tranquilizer
Hops	*Humulus lupulus*	Lupuline	Smoke or drink as sedative and marijuana substitute	? None
Kavakava	*Piper methysticum*	Yangonin, pyrones	Smoke or drink as marijuana substitute	Mild hallucinogen
Kola nut	*Cola* spp	Caffeine, theobromine, kolanin	Smoke, drink, or take as capsules as stimulant	Stimulant
Lobelia	*Lobelia inflata*	Lobeline	Smoke or drink as marijuana substitute	Mild euphoriant
Mandrake	*Mandragora officinarum*	Scopolamine, hyoscyamine	Drink as hallucinogen	Hallucinogen
Mate	*Ilex paraguayensis*	Caffeine	Drink as stimulant	Stimulant
Mormon tea	*Ephedra nevadensis*	Ephedrine	Drink as stimulant	Stimulant
Nutmeg	*Myristica fragrans*	Myristicin	Drink as hallucinogen	Hallucinogen
Passion flower	*Passiflora incarnata*	Harmine alkaloids	Smoke, drink, or take as capsules as marijuana substitute	Mild stimulant
Periwinkle	*Catharanthus roseus*	Indole alkaloids	Smoke or drink as euphoriant	Hallucinogen
Snakeroot	*Rauwolfia serpentina*	Reserpine	Smoke or drink as tobacco substitute	Tranquilizer
Thorn apple	*Datura stramonium*	Atropine, scopolamine	Smoke or drink as tobacco substitute or hallucinogen	Strong hallucinogen
Valerian	*Valeriana officinalis*	Chatinine, velerine alkaloids	Drink or take as capsules as tranquilizer	Tranquilizer
Wormwood	*Artemisia absinthium*	Absinthe	Smoke or drink as relaxant	Narcotic-analgesic

Adapted from Siegel RK. Herbal intoxication.[44]
Reproduced with permission from Lawrence RA and Lawrence RM.[10]

porarily increased suckling, especially non-nutritive suckling for comfort. Human milk meets all of the nutrient needs of the infant for the first 6 months, except for women who live in cold climates with little sunshine, have dark pigmented skin, wear occlusive clothing, or use sunscreen frequently who may be vitamin D deficient.[46] Recommendations from the Centers for Disease Control and Prevention suggest supplementing the infants beginning at 2 months with 200 U vitamin D daily by mouth.[47] Very low birth weight infants may need iron. Healthy exclusively breast-fed infants do not need iron for the first 6 months of life. When weaning foods are added in the second 6 months, they should be iron containing such as iron-supplemented cereal.[48]

Adding Solid Foods

The single nutrient needed to add to solid foods in an exclusively breast-fed infant is additional dietary iron; thus, introduction of iron-fortified weaning foods at around 6 months is recommended, although the exact age is poorly defined.[48] At about 6 months of age, it is appropriate to begin the addition of solid foods to the infant's diet for nutritional reasons (see Chapter 28, "The Low Birth Weight Infant"). Learning to take solid foods is also an important developmental milestone that involves a new use of tongue, jaw, and lips—a use that differs from suckling. Beginning to take fluids from a cup is also a developmental task that should be learned around 7 months of age. The infant who is exclusively breast-fed to this point needs to explore these activities and develop these skills just as a bottle-fed infant would. The fluids can be water, juice, or pumped breast milk. It is probably significant that the composition of human milk gradually changes during this time to provide a lower protein content than previously. If a mother continues to provide her milk, there is no need to introduce formula. Cow's milk when the infant is under 1 year of age is not recommended.

Weaning

To wean is "to transfer the young of any animal from dependence on its mother's milk to another form of nourishment" or "to estrange from former habits or associations," according to the dictionary.[49] The weaning process takes many forms, depending on the mother's schedule and beliefs and the needs of the infant. Some women plan to breast-feed for only a few months "to give the baby a good start"; other mothers wean as soon as solid foods can be started, and some continue to offer the breast for several years, even during a subsequent pregnancy and while feeding a new baby. The appropriate time for weaning should be based on nutritional and psychological needs and developmental milestones. Feeding is an important social as well as nutritional encounter, and eating solids and drinking from a cup are important social accomplishments. This does not mean that the infant is taken completely off the breast. In practice, the mother is usually the instigator of weaning. The process ideally is gradual, replacing one feeding at a time with solids and the introduction of a bottle or cup, depending on the infant's age and stage of development. After the adjustment has been made to substitute one feeding, a second feeding is replaced, usually at the opposite time of day. The process is continued until there is only one nursing at night and one in the morning. These two feedings may be maintained for many months or gradually discontinued over weeks. A mother may be able to express milk from the breast for weeks after the final feeding. An infant who has not weaned by 18 to 24 months usually does not spontaneously wean until 4 or 5 years of age.[10]

Emergency weaning because of a crisis such as illness or separation may be stormy for the dyad. The infant may reject the bottle and refuse all nourishment at first. The mother who abruptly weans may experience severe engorgement, pain, and systemic symptoms attributed to the resorption of milk and referred to as "milk fever." Emergency weaning is facilitated by the assistance of another adult who can initiate the new feeding method and is patient and understanding with the child. Cup feeding with a small medicine cup may be a helpful alternative.

Breast-feeding and the Return to Work

Returning to work has been cited by epidemiologists as a major hurdle in the initiation and duration of breast-feeding.[50,51] Because they need to return to work or to school, women often think it is best not to start. Before the industrial revolution, all women worked on the farm or in a cottage industry, keeping their children with them. In developing countries today, women carry their infants with them to feed them whenever necessary while working. It was the industrial revolution that separated home and work and made parenting a separate role for women.

More women are employed today outside the home than ever before.[52] Women with children under 6 years of age were the fastest-growing segment of the female workforce in 2000 (64.4% of women with a child under 6 years old). Even more startling are the number of working mothers with children under 3 years of age (60.7%).[53] Of the women who work during pregnancy, over 50% plan to return to work by 3 months postpartum. These dramatic statistics make it clear that the decision about infant feeding is an important part of this issue.[51] Child care also presents another consideration for the woman who may well have to choose day care or some form of child care that means that her infant will be in close contact with other children. In modern pediatrics, "day care syndrome" is real. It is the increase in the number of infections, especially diarrhea, respiratory illness, and otitis media, experienced by young infants in day care.

The data are clear that breast-feeding impacts these figures. These illnesses are seen predominantly in bottle-fed infants. A quantitative study has shown that extending breast-feeding from 4 to 6 months of age decreases the risk of respiratory infection, including pneumonia and otitis media, even further.[11] The protective properties in human milk (see Chapters 31 and 32) are even more important for the child exposed to other children early in life while the mother works or attends school. A comparison of mothers' absenteeism showed that those who were breast-feeding had reduced absenteeism.[54] Looking at the illness rates of chil-

dren whose mothers work, 75% of children who were bottle fed were ill and only 25% of those breast-fed had any illness.

The feeding pattern for mothers who work is as follows: Ideally, the mother does not return to work for at least 6 weeks, so she is able to establish her milk supply before having to add work to her schedule. She will have to decide how she will cope.[55] If her job permits her to visit her child several times a day, then she can feed the infant at the usual times. An employer who has a daycare center on the premises makes such an arrangement possible. Professional women who control their own schedules (lawyers, doctors, consultants) may be able to keep the infant on the premises under the care of a baby attendant and feed on demand. For most women, however, their jobs are more rigid, and they may have to settle for an opportunity to pump their milk every 3 or 4 hours on lunch or coffee breaks and store the milk in a cooler to take home for the next day's feedings. Most women practice pumping at home several weeks ahead of time and store up a supply of milk in the freezer so that they do not run out.

Employers such as hospitals, health departments, and family-friendly industries like Amoco, Chicago; Dow Chemical of Midland, Michigan; and the Los Angeles Department of Water and Power, to name a few, have been recognized for their support of "Healthy Mothers and Healthy Babies" and their accommodations for nursing mothers. They provide a room to pump, electric pumps, refrigerators, and, in some cases, lactation consultants to assist with any breast-feeding issues. This support improves the incidence and duration of breast-feeding for the working woman.[56]

Pumping and Storing Milk

If the employer does not provide pumps, a mother should obtain a pump by either renting or purchasing it several weeks in advance of the return to work. All pumps are not equal.[57,58] There are, however, several brands of good portable electric pumps that provide disposable attachments for those parts that contact the breast and the milk. Attachments that allow pumping both sides simultaneously save time and for some women stimulate more milk release. Other women find double pumping overwhelming and choose to do one side at a time. Hand (manual) pumps are good for stimulating milk release and relieving engorgement but not for large-volume pumping for most women. Many hospitals have lactation consultants on staff and a shop or service that rents pumps and sells other breast-feeding devices, such as breast pads and storage bottles. Information about local resources should be available on the postpartum floor. If not, a mother can call La Leche League International (800-LALECHE [800-525-3243]) for a local contact person. After each pumping session, the disposable flanges, tubing, and bottles used for pumping should be rinsed with cool water first and then washed in warm soapy water and thoroughly rinsed and air dried. After rinsing with cold water to remove the milk, the equipment may also be washed in an electric dishwasher.

The pumped milk should be placed in a glass bottle or a firm plastic polypropylene nursing bottle that can be capped with an airtight seal without a nipple and then used to feed the infant later. Polyethylene bags are adequate for term baby use. Storage temperatures and times have been carefully studied.[57] The container, which should be labeled with the name, date, and time, should be placed in a refrigerator immediately or in a cooling bag or container with freezer packs if at work or school where there is no refrigerator. It is safe in a cooler bag as long as the packs remain cold (24 hours). On arrival home, the bottles should be placed in the refrigerator if the milk will be used within 3 days or in the freezer if stored for later use. When milk is pumped at home, it can be placed in the refrigerator (4°C) immediately and kept for 5 days. Actually, when there is no alternative or a bottle has been inadvertently left out, milk can be kept in a sterile container at room temperature for 8 hours and then used immediately or refrigerated for a day.

If milk is placed in the freezer of the refrigerator that has a separate door, it can be stored for 3 months if it is placed in the back to avoid thawing and freezing when the door is opened. If milk is placed in a deep freeze (–20°C), it can be kept for 6 months, or if at –70°C, it is good for a year or longer.[52,56,58] The nutritional impact of freezing on the milk is minimal, destroying only the cells and their function. The effect of refrigeration is also minimal, decreasing the cells and some of their function. Nutrients are unchanged. Storing mother's milk for her own infant does not require pasteurization. Providing donor milk to another infant does require pasteurization by regulation owing to the increase in risk of infection in the present environment. Pasteurization does affect some properties, destroying cells and decreasing lipase activity and some other enzymes (Table 33-2).[52,59]

Day Care for the Breast-feeding Infant

In choosing a daycare service, care should be taken to ensure that breast-feeding and breast milk are welcome. When taking an infant to day care, a mother may wish to nurse the infant just before she leaves her child or she may wish to nurse the infant at day care when she has a break from work. Further, she may wish to feed the child before she sets out for home with the infant in the afternoon. There needs to be a place to sit quietly with the infant out of the mainstream of activity. The staff should be prepared to make these accommodations and delay a feeding if the mother is going to arrive shortly.

The mother will probably wish to provide her stored breast milk for her infant to receive during the day. It is not necessary for the caretaker to wear gloves to handle the milk or feed the infant. It is, however, appropriate to wear gloves to change any babies' diaper. If the milk was frozen, it can be thawed in the refrigerator at day care or thawed by swirling in a container of warm water. It should not be warmed in the microwave because of possible hot spots and scalding the infant. Microwaving interferes with the anti-infective properties as well as decreases the vitamin C content. If the infant does not empty the container, it can be refrigerated and fed later unless it has been microwaved.[10] This is not true of formula, but the protective factors in human milk will keep the bacterial count down. The daycare attendants should save the containers

Table 33-2 Storage and Use of Pumped Milk for Healthy Term Infants

Place	*Length of Time*
Refrigerator (4°C)	5 d at home, 3 d in day care
Freezer section (separate door) refrigerator (–20°C)	3 mo
Deep freeze (manual defrost) (–20°C)	6 mo
Commercial deep freeze (–70°C)	1 yr
Sterile container at room temperature (23°C) (not ideal but milk need not be discarded)	8 h
Stored in cooler bag with frozen packs (as long as packs are still cold)	Less than 24 h
Thawed previously frozen in refrigerator	24 h

for reuse by the mother. Thawed breast milk can be maintained in the refrigerator for 24 hours.

The milk containers should be carefully labeled with the name and date of collection. The attendant should carefully confirm the name on the container before feeding. Mishaps of giving the wrong milk to the wrong infant do occur. It should be reported to both families and the daycare's medical consultant with an incident report. There are no reported cases of injury following such an event.

FAILURE TO THRIVE WHILE BREAST-FEEDING

Paralleling the increasing incidence of breast-feeding, there has been an increase in the number of clinical reports, including one in the *Wall Street Journal*, each describing a few cases of failure to thrive while breast-feeding.[38,60–62] The *New York Times* followed the dramatic story of a teenage mother prosecuted for the death of her 8-week-old breast-fed son from starvation. The event followed a series of misadventures and refusal to see the child at a Medicaid clinic.[63] The majority of these cases have reflected a lack of clinical knowledge on the part of the professionals regarding the basic physiology of lactation and a general failure of the health care system to provide an appropriate safety net for new and inexperienced mothers following the current early postpartum discharge practices (hospital stay ≤ 2 days). As cost drives the health care system to earlier and earlier discharge, the risk of infant problems increases because lactation will not be well established prior to discharge. The American Academy of Pediatrics has recommended that infants be seen by the pediatrician within a week of discharge but in 2 days if breast-fed.[3]

Failure to thrive in children has been thoroughly reviewed, however, there are some critical differential factors when the infant is breast-fed (see Chapter 52, "Failure to Thrive: Malnutrition in the Pediatric Outpatient Setting"). Most cases of significant failure to thrive in the breast-fed infant manifest themselves in the first few weeks or months of life. There is also an important distinction between failure to thrive and the slow-gaining breast-fed infant.[39,64] The weight curve of an adequately nourished breast-fed infant from birth may well include a weight loss of 6 to 8% and the regain of birth weight at 10 to 14 days, in contrast to the formula-fed infant, who may lose only 3 to 4% of birth weight and quickly regain birth weight by 5 to 7 days.

The critical clinical distinctions between failure to thrive and slow gaining are enumerated in Table 33-3. The salient points include the slow increase in weight compared with the erratic gaining and losing pattern in failure to thrive. The slow-gaining infant is alert and active, with good skin turgor and muscle tone. He feeds frequently night and day, wets many diapers with pale dilute urine, and has a normal stool pattern. The infant looks scrawny but well.[64]

Because he sleeps long periods between feeds, the infant who fails to thrive may be mistakenly considered satisfied when actually he has starvation inanition. The infant often fed poorly in the first few days or for various other reasons does not stimulate good milk production. Because breast milk production depends on the supply-and-demand phenomenon, when the infant sucks weakly, he receives little milk and thus remains weak from some degree of starvation. This infant also has few wet diapers; the urine is concentrated and described as "strong" by the mother. There are few and small stools, which are often the color of the green mucus of starvation. The tone and turgor are poor, the cry is weak and infrequent, and the infant looks sick. This may well be a medical emergency requiring hospitalization. The feeding pattern should be evaluated, especially focusing on the length of time spent at the first breast during a feeding to be sure that it is long enough to allow the high-fat hindmilk to be obtained. Sometimes the pattern of slow gaining can be reversed by limiting a feeding to a single breast to ensure high-fat, high-calorie feeds.[65] Switching back and forth between breasts several times during a feeding does not increase milk supply and can reduce the amount of high-calorie fat provided.

The diagnostic workup of these phenomena requires the same clinical assessment that is appropriate when the infant is not breast-fed, and for this, the reader is referred to Chapter 48. Because the breast-feeding infant is part of a synchronous dyad, there are additional considerations in the differential diagnosis.[10] A suggested schema for identifying the cause of the problem is presented in Figure 33-

TABLE 33-3 Differential Diagnosis in Poor Weight Gain

Slow Gainer	*Failure to Thrive*
Alert, healthy appearance	Apathetic or crying
Good muscle tone	Poor tone
Good skin turgor	Poor turgor
At least 6 wet diapers daily	Few wet diapers
Pale unconcentrated urine	"Strong" urine
Stools frequent and seedy (or, if infrequent, large and soft)	Stools infrequent and scanty
8 or more nursings daily lasting 15–20 min	Fewer than 8 feedings, often brief
Well-established let-down reflex	No signs of functioning let-down reflex
Weight gain consistent but slow	Weight erratic (loss may occur)

Reproduced with permission from Lawrence RA and Lawrence RM.[10]

12. The clinician should take a history oriented to the process of lactation. This history should include additional parameters that affect the success of the breast-feeding dyad, such as the mother's perinatal history, general health, diet, habits, psychosocial state, social support system, and the attitudes of the father and family about breast-feeding. Parameters unique to the breast-fed infant include any anatomic or physiologic conditions that would interfere with sucking, which is a critical link in the milk production process.

Difficulties with sucking include anatomic abnormalities that result in mechanical interference with sucking such as cleft lip, cleft palate, hypoplasia of the jaw, macroglossia, ankyloglossia (tongue "tie"), and tumors or cysts of the oropharynx. These abnormalities can be identified by physical examination, which includes observation of the infant's suck. There may be neurologic interference, resulting in a diminished or absent suck. Events at birth, such as maternal anesthesia or analgesia and fetal anoxia or hypoxia, may contribute to poor suckling in the immediate neonatal period and failure to provide adequate stimulus to the breast to initiate lactation. The ensuing lack of nutrition for the infant leads to hypometabolism and continued lack of vigor. Congenital cardiac anomalies may present in this manner. Other causes of neurologic deficit in sucking include trisomy 13 to 15, trisomy 21, and neuromuscular diseases such as Werdnig-Hoffmann, neonatal myasthenia gravis, and congenital muscular dystrophy. Hypothyroidism, prematurity, and congenital intrauterine viral infections contribute to poor suck and lack of vigor. The greatest number of infants, however, are entirely normal but have not had sufficient assistance in establishing the proper grasp of the breast and possibly have been further confused by being given a bottle supplement, which continues to confound their learning experience.[40] In addition to examining the infant and the maternal breast, the clinician should observe the feeding dynamics.

All physicians who counsel breast-feeding mothers should be knowledgeable about normal sucking at the breast so that observation of lactation in a diagnostic situation can be constructive. The style with which the mother approaches a feeding, her body language, may be a clue. If she is relaxed, confident, loving, and gentle with her infant, it suggests that it is not maternal inexperience at fault. Her verbal interaction can be revealing. A baby suckling at the breast brings reflexive eye-to-eye contact, stroking, and verbal nuances that a seasoned lactating woman utters without consideration for the environment. The insecure, inexperienced mother will sit tensely, offering the breast gingerly, with little or no verbal communication to the infant. If the process is mechanical or punctuated by unrealistic commands to the infant, it may suggest an inability to help the infant root, grasp, and suckle properly. Rigidly timed feedings that are scheduled by the clock may result in poor milk production. The treatment rests with frequent on-request feedings that fit the infant's biologic rhythms. A quiet room, a rocking chair, soft music, or a relaxing beverage for the mother may all improve the situation.

The behavior of the infant when offered the breast may indicate an infant with a suckling disorder, not associated with any other neurologic symptom or long-range problem. Sucking inadequately at the breast can be altered so the infant learns the technique. The infant is identified when it is noted that the infant cannot maintain the breast in the mouth unless his mother holds it there. In other words, when she takes her hand away, the breast falls away. A normal infant sucks without help from his mother's hands if the grip is proper and the seal is adequate. When the infant does begin to suck when the breast is held in position, the suck may be a flutter or ineffective

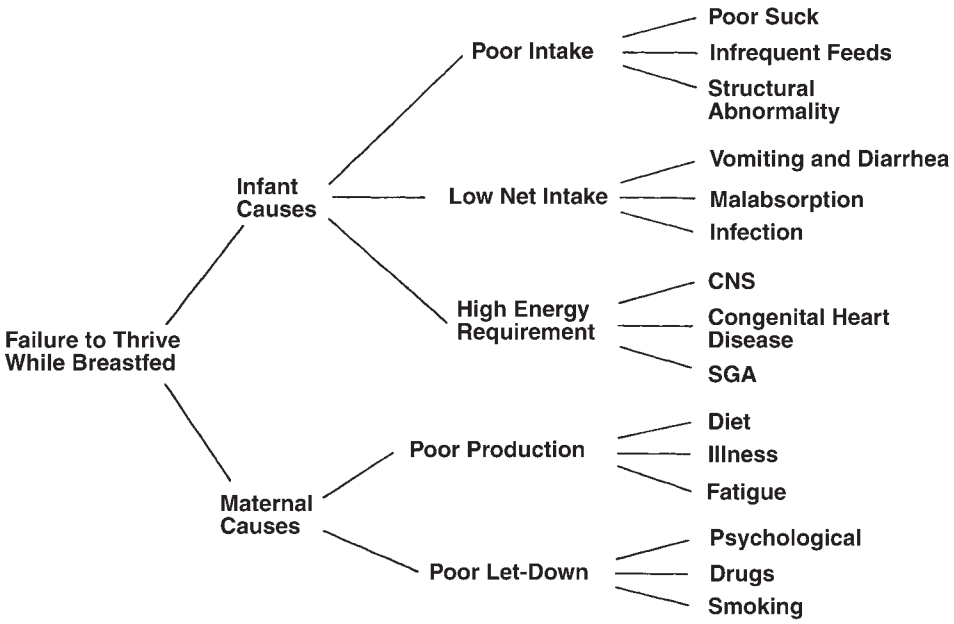

FIGURE 33-12 Diagnostic flow chart for failure to thrive. Reproduced with permission from Lawrence RA and Lawrence RM.[10] CNS = central nervous system; SGA = small for gestational age.

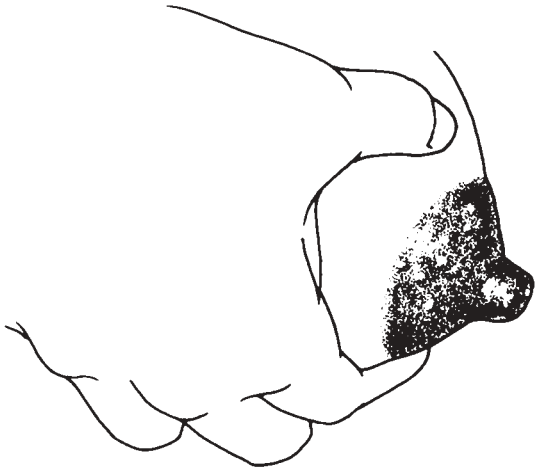

FIGURE 33-13 Palmar grasp (C-hold). When the palm and fingers cup the breast with support and the thumb rests lightly above the areola, the nipple projects straight ahead or slightly downward (correct). Reproduced with permission from Lawrence RA and Lawrence RM.[10]

tongue actions. This may be improved by having the mother hold the breast between thumb and index finger, with fingers under the breast (palmar hold) (Figure 33-13) rather than with the areola compressed between the middle and index finger (scissor hold) (Figure 33-14). The infant's position should be adjusted so his body is turned toward the mother's body (instead of just turning his head). Thus, the breast is centered toward the infant, and this position will improve the effectiveness of the infant's efforts. The mother may have to continue to hold the breast in place for weeks until the infant perfects his technique. The mother may also have to pull his lower lip down to keep the infant from drawing the lip into the mouth and moving it along the lower surface of the breast. The lip should be held as part of the seal holding the breast in place and permitting development of some negative sucking pressure. If the mother stimulates the rooting reflex by stroking the center of the lower lip, the infant will open wide and draw the nipple and areola into the mouth to form a teat.

While the infant is learning to suckle properly, it is urgent to avoid introduction of a rubber nipple on a bottle or a pacifier. This poses a problem if adequate nutrition is critical and the mother's supply needs to be stimulated to be adequate. A trial of frequent feeds, waking the infant every 2 hours, may suffice. Extra calories may be offered by medicine cup or Haberman feeder. When the failure to thrive has reached critical starvation, a more aggressive approach is mandatory. If hospitalization is necessary, intravenous therapy to treat dehydration may also be necessary. Hypernatremia and hypochloremia have been described, and a complete workup, including pH, electrolytes, blood urea nitrogen, and creatinine, are essential.[22,38,41,66,67] While the infant receives intravenous therapy, the mother should be assisted to pump frequently to develop and increase her milk supply. When it is safe to begin oral feedings, the infant should be exclusively breast-fed as far as sucking is concerned, and additional nourishment should be provided by intravenous line, gastric tube, or medicine cup. Thus, the infant avoids the introduction of a bottle. When the crisis has abated and full breast-feeding is appropriate, but the milk production is still inadequate, the use of a nursing supplementer (Lact-Aid) may be useful. This device permits the uninterrupted nursing at the breast while supplementary nourishment is provided via a fine capillary tube that runs along the breast into the infant's mouth (Figure 33-15). The tube brings the supplementary fluid from a reservoir plastic bag that hangs around the mother's neck. The system is carefully engineered. It provides fluid only when the baby sucks; thus, it coordinates with the infant's swallowing mechanism. It is not a siphon or a pump. When used to help establish or increase milk production, as with a premature infant first going to breast, the infant is usually weaned from the supplementer within 1 or 2 weeks by providing smaller and smaller volumes of supplement as maternal production increases. The supplementing device may make the critical difference when the degree of starvation is great and lactation is being preserved. It is important to point out that all too often the infant is quickly weaned to a bottle without any effort to solve the underlying lactation problem, which is unfortunate (see Figures 34-15 and 34-16).

In rare cases of failure to thrive while breast-feeding, the underlying cause is actually metabolic, and the infant does even less well on formula prepared from cow's milk or soy protein. In that case, it is quite possible to have the mother relactate. It is an art practiced in most cultures over the centuries and resorted to when the biologic mother became ill or died and another female (often the grandmother) had to assume the nourishment of the baby. In the case of premature weaning, there has already been the biologic stimulus of pregnancy and early lactation, so reinstituting the milk supply occurs more easily. The lactation

FIGURE 33-14 When the breast is offered to the infant, the areola is gently compressed between two fingers and the breast supported to ensure that the infant is able to grasp the areola adequately. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

FIGURE 33-15 Lact-Aid Nursing Trainer System (Lact-Aid International, Inc.). Reproduced with permission from Lawrence RA and Lawrence RM.[10]

supplementer may be of great value in this situation as the infant can return to the breast and be nourished with donor human milk while the mother builds up her own supply (see Figure 33-16).

Maternal Causes of Failure to Thrive

Poor milk production may be the cause of the failure to thrive. This is usually characterized by an alert, active infant who cries hungrily and is very demanding but never satisfied. This baby demands attention and is usually seen by the physician because of his dissatisfaction. The quiet, sleepy, starved baby gets into serious trouble before he is discovered because his sleeping is interpreted as satiation. It is rare in the United States that diet is the true cause of insufficient milk, although it is appropriate to evaluate the mother's diet and make recommendations for increases or adjustments where needed (see Figure 33-11).[68] An additional 600 kcal or a minimum of 1,800 kcal per day, a balance of foods with 20 g extra protein and 400 mg extra calcium, is minimal for every mother. "Mothering the mother" by caring about her diet may have a positive effect. However, the major factor in poor production is fatigue. It is the single most important element in milk production. The present-day "supermom" model that has been developed by women may be the actual destructive element. A postpartum woman needs rest to recover whether she nurses or not. When she is also nourishing an infant, she needs more rest. This is often neglected when the infant needs care every 3 to 4 hours around the clock and only the mother is involved in the feeding of the infant. When her physician suggests that the mother needs to reorder her priorities and schedule naps for herself, it may be the necessary official approval she needs to do so. A mother may need to be told it is not only okay, but it is also necessary for her to take care of herself to provide for her baby. The physician may need to prescribe rest as well as nourishment.

A small number of women are unable to make sufficient milk. Some of these women have inadequate glandular tissue. Markedly asymmetric breasts, conically shaped breasts, and extremely small ones may be in this category. Even extremely large breasts are occasionally nonfunctional. Failure of the breasts to change and enlarge during pregnancy and/or failure of the breasts to become engorged immediately postpartum are signs of inadequately functioning tissue. These signs prenatally should alert the medical team to extra vigilance as lactation is initiated.

Failure to Let Down Milk

A woman may make milk abundantly but be unable to release it. As the practitioner observes the lactation process, evidence of successful let-down should be sought. If the sucking is interrupted by breaking the suction by putting a finger in the corner of the infant's mouth, milk should continue to flow in a steady drip if not a stream. Although many women describe a tingling and turgescence when the milk lets down, it is possible to have an effective ejection reflex without these sensations. As indicated in Figure 33-6, it is possible for pain or stress to interfere with let-down. If the mother has sore nipples or

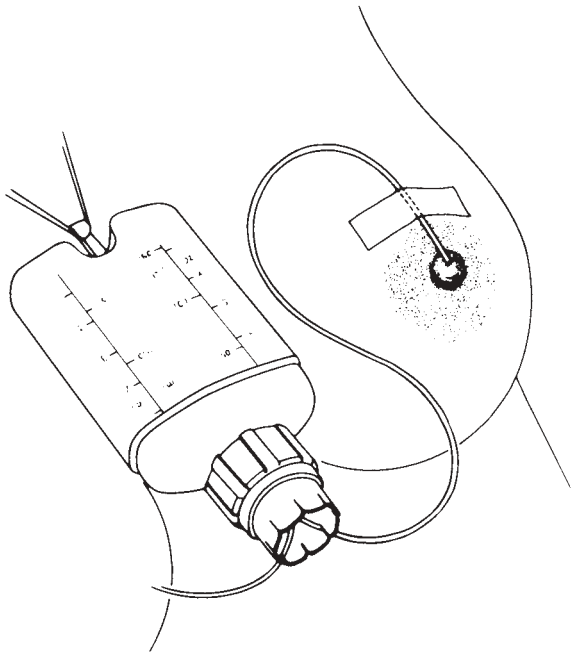

FIGURE 33-16 Lactation Supplementer by Medela, which provides additional nourishment to the infant while it suckles at the underproducing breast. Reproduced with permission from Lawrence RA and Lawrence RM.[10]

the infant has an improper grasp at the breast, the pain may interfere with let-down.[23] If the adjustments and remedial actions to avoid stress and enhance confidence do not result in a change in the release of milk, it may be necessary to temporarily provide the oxytocin needed for the let-down arc.[10] Synthetic oxytocin can be prepared by the pharmacist as a nasal spray for home use using the injectable oxytocin. It is packaged in 5 to 10 mL nasal dropper bottles. It contains 10 USP IU per milliliter of oxytocin, a polypeptide hormone of the posterior pituitary gland. A prescription is required. It is destroyed in the gastrointestinal tract; therefore, it must be used nasally on the mucous membranes, where it is rapidly absorbed. Four to six drops into one nostril followed by having the infant suckle within 2 to 3 minutes is sufficient. This is repeated using the second nares if the infant is switched to the second breast. This may also be used when using a breast pump and collecting for an infant who cannot nurse directly, as in the case of a premature baby. Usually, it is only necessary to use the medication for a few days as the natural process will take over.

A rare finding in lactation failure is the lack of a prolactin surge when the breast is stimulated by the suckling or pumping. The prolactin level should double over baseline on suckling. If prolactin levels are obtained, the samples should be carefully timed so that the baseline sample is drawn from a heparin lock after the mother has recovered from the needle stick. Then she should feed the infant or pump her breasts for 10 minutes, and a second sample should be drawn. The percentage increase in prolactin over baseline should approach 50%. The baseline should be above normal for the laboratory. Replacement prolactin is not clinically available, although prolactin stimulation with fenugreek or metoclopromide or other galactogues may work.[10]

Knowing When to Discontinue Breast-feeding

Although breast-feeding provides species-specific nourishment, infection protection, immunologic protection, and psychological benefits for both mother and baby, there are times when it should be discontinued. The role of the physician is a delicate one, one in which true support of breast-feeding is necessary for credibility. On the other hand, the physician must recognize when other alternatives are medically preferable. The mother will need help in accepting this. Having to wean prematurely or before the planned date is not to be construed as maternal failure. It is still possible to nurture the infant, to be a good mother, and to have a good mother-infant relationship, even though the mother may no longer be able to breast-feed.

The contraindictions to breast-feeding are rare but include severe illness in the mother, severe galactosemia in the infant, and a few maternal drugs such as therapeutic doses of radioactive pharmaceuticals.[69]

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CHAPTER 34

DEVELOPMENTAL DISABILITIES

Babette S. Zemel, PhD, Virginia A. Stallings, MD

Children with moderate to severe disabilities have a markedly increased risk for malnutrition. Neurologic abnormalities—resulting in altered physical activity (voluntary and involuntary), fine motor patterns, and oral-motor patterns—will often significantly affect food intake and nutrient requirements. Chronic undernutrition, characterized by growth failure and reductions in fat stores and lean body mass, is the most common form of malnutrition, but overweight and obesity also occur. Despite these clinical observations, only limited research-based information on the nutrient needs and nutritional status of children with severe disabilities is available. Consequently, recommended nutrient intakes and growth pattern expectations for this group of patients are poorly defined and must be approached on an individual basis.

Nutritional status assessment is essential for identifying the undernourished or overnourished child, estimating the optimum energy intake to promote growth and well-being, and monitoring treatment. In children with moderate to severe disabilities, nutritional assessment is complicated by the interaction of the primary disease process (eg, muscle atrophy, contractures, central nervous system pathology, or movement disorders) and both chronic and acute malnutrition. Cerebral palsy (CP), a common disability with significant risk for malnutrition, will be used as a model to describe the nutritional needs and nutritional status of children with severe disabilities.

The scope of problems relating to feeding difficulties and malnutrition is now being described through community or registry surveys. Studies have revealed that close to 90% of children with neurologic impairment require at least some assistance with feeding or have oral-motor dysfunction.[1,2] A large, multicenter, community-based study in North America reported that 30 to 40% of children with CP had severe feeding difficulties.[3] A recent population-based cohort study in the United Kingdom demonstrated that feeding difficulty at 4 weeks and 6 months of age was associated with subsequent impairment and poor weight gain and developmental outcomes later in childhood.[4] The association of feeding difficulties and nutritional status has been demonstrated in every population studied.[1–7] Nevertheless, a pattern of inadequate food intake, growth failure, and disease-specific nutritional concerns is still evident.

Several important nutritional issues were recognized in these studies. Assistance with feeding, prolonged feeding times, and choking significantly affect food intake.[1,2] In addition, gastrointestinal problems, such as reflux, vomiting, and constipation, and some medications, such as those used to treat seizures, contribute to alterations in both nutritional intake and requirements.[1,8] Food intake low in energy density is of particular concern because of the marked linear growth failure, delayed skeletal[9,10] and sexual maturation,[11] poor weight gain, and reduced energy reserves seen in patients with CP.[12] Abnormal body composition, with reductions in muscle and fat stores, and a high prevalence of undernutrition (failure to thrive, marasmus) and less frequently overnutrition (overweight, obesity) have also been noted.[12–14] Some specific nutrients are also at risk, particularly vitamins C, A, and D; iron; and calcium. Recently, poor bone mineralization,[14–16] associated with degree of immobilization, hypovitaminosis D, feeding difficulties, and lower triceps skinfold measurements in children with CP, also has been reported.

For children with CP, the drug–nutrient interactions of anticonvulsant medications and vitamin D were demonstrated by several investigators in the 1970s. Vitamin D deficiency continues to be a concern in the nutritional care of these children.[17,18] Some classes of anticonvulsants,

through the action of the hepatic microsomal enzymes, cause increased vitamin D catabolism. In a survey of 125 heterogeneous noninstitutionalized children with CP in the United States, nearly 20% had low serum 25-hydroxy-vitamin D levels. However, low vitamin D status was not associated with severity of CP, growth failure, or use of anticonvulsants.[18] Another study of institutionalized children in South Africa found that anticonvulsant therapy was associated with long-bone fracture, and that 3 months of vitamin D and calcium supplementation resulted in marked improvement in serum calcium and phosphate and reduced alkaline phosphatase and fracture rate.[19] Another vitamin D and calcium supplementation study demonstrated improved bone mineral density.[17] Thus, in addition to anticonvulsants, low dietary intake of vitamin D and calcium, limited physical activity, and low sunlight exposure also contribute to rickets, osteopenia, and pathologic fractures in children with CP.[20–23]

Nutritional assessment of children with severe disabilities has several components, including evaluation of dietary intake, growth status, body composition, energy expenditure, and laboratory data in the context of the nutritional risk factors related to the medical history, physical examination, diagnosis, and current therapy. The need for interdisciplinary evaluation and treatment of nutrition and feeding abnormalities for children and adults with CP has been addressed by numerous investigators and position papers.[24–28] Inadequate caloric intake is a primary concern. Children with CP have abnormal growth and body composition. Therefore, conventional methods for estimating caloric requirements based on the Recommended Dietary Allowance (RDA)[29] for age and gender group, or prediction equations that use body weight or surface area, are inappropriate for nonambulatory children with CP.[30,31] The importance of determining energy requirements and meeting those requirements in children with CP is underscored by several nutrition intervention trials in which caloric supplementation by gastrostomy or nasogastric feeding tube resulted in improvements in various components of nutritional status.[32–36]

Another approach to determining energy needs in children with severe CP has been to determine the extent of growth failure and poor nutritional status and their relationship to nutritional and disease-related factors and energy expenditure. In one study, a large group (N = 142) of children ages 2 to 18 years with spastic quadriplegic cerebral palsy (SQCP) participated in a survey of growth and nutritional status.[6,7] Linear growth, assessed by upper-arm and lower-leg lengths, was significantly reduced (z-scores, –1.57 to –2.38) relative to healthy children.[37] Weight and triceps skinfold thickness were, on average, about 65% of age- and sex-specific medians for children in the United States; subscapular skinfold thickness was 81% of the median. Poor nutritional status was evident in children as young as 2 to 4 years of age. Linear growth retardation in upper-arm and lower-leg length was significantly associated with poor nutritional status (arm muscle area, percent body fat), after adjusting for disease severity (diagnosis, cognitive ability, oral-motor function, ambulatory status, gastrostomy feeding, and dyskinetic component) and nondisease variables (age, gender, race, pubertal status, and midparental height). This analysis demonstrated that the effect of poor nutritional status on linear growth was independent of, and additive to, the effects of the severity of the CP and nondisease factors.

Energy expenditure and dietary intake were measured in a subsample of these children with SQCP. Resting energy expenditure (REE), expressed as the percentage of the predicted value from World Health Organization (WHO) prediction equations, was considerably lower than in normal children (91% predicted in CP versus 105% in controls). REE was lowest (88% predicted) among the majority group of poorly nourished children with CP.[38] Total energy expenditure, measured by the doubly labeled water method, was also lower than in control children, in keeping with reduced physical activity in children with severe SQCP. The physical activity factor, or ratio of total to resting energy expenditure, was 1.23 for children with CP as opposed to 1.57 for controls. This is similar to the patterns of resting and total energy expenditure observed in adults[39] with CP. Thus, in children with SQCP, energy requirements are lower than in normal children. However, determination of energy intake proved to be far more difficult. The ratio of total caloric intake, measured by a 3-day weighed food intake diary, to total energy expenditure indicated a large—about 50%—overestimation of food intake by the caregivers of these children with poor oral-motor function.

These findings illustrate the complexity of assessing energy requirements in disabled children. Although total energy requirements are lower in children with severe CP, dietary intake is likely to be grossly overestimated in the clinical setting. The prevalence of chronic undernutrition and growth failure in many children with SQCP indicates that energy needs are not being met. The next sections outline an approach to determining energy requirements in children with CP or other severe disabilities. The first step is the assessment of growth and nutritional status to identify those children whose energy needs are not being met and the degree of past or current undernutrition. Methods for estimating energy requirements based on nutritional status and related factors are reviewed.

NUTRITION STATUS ASSESSMENT

Inadequate energy intake appears to be a major cause of nutrition-related growth failure in children with cerebral palsy. Thus, two clinical management needs arise: (1) methods to assess nutritional and growth status to identify patients who are undernourished or overnourished and (2) methods to determine the caloric requirement of the individual patient. The elements of complete nutritional assessment are based on the standard pediatric medical evaluation and are presented in more detail in Chapter 2 and 3.

The medical history includes assessment of acute and chronic medical problems and medications. In addition, a nutritional history, including review of a "typical" day's

food intake; dietary history; use of caloric, vitamin, mineral, herbal, or other nutritional supplements; and unusual food practices by the child or family are obtained. The past growth patterns, including pubertal history and growth charts, are reviewed. The history includes a review of systems, with emphasis on dental and oral-motor function and on the gastrointestinal tract (emesis, gastroesophageal reflux, diarrhea, constipation).

The physical examination includes current pubertal status[40]; weight; height, length, or alternative linear growth measures; head circumference; midarm circumference; and skinfold measurements. Details of the recommended methods, equipment, and reference standards for the anthropometric measurements are in the following section. (For an overview of some of the physical findings associated with nutritional deficiencies, see Appendix, Table A–12.)

The laboratory evaluation is focused by recognizing the risk factors identified from the history and physical examination for each individual patient. The primary nutritional problem is usually inadequate caloric intake, and laboratory assessment of this pattern of malnutrition is of limited use. Both serum albumin and prealbumin can be indicators of the adequacy of calorie and protein intake, with albumin reflecting the past month (half-life, approximately 18 to 20 days) and prealbumin reflecting the past week (half-life, approximately 2 to 3 days) of nutrient intake. However, these are often in the normal range with the chronic undernutrition associated with CP. Iron deficiency anemia is seen in groups of patients who have limited caloric intake or who have monotonous food intake with few iron-rich foods. Iron status evaluation includes a complete blood count (hemoglobin, hematocrit, and red cell indices) as a screen, followed by other iron studies (serum iron, total iron-binding capacity, transferrin, ferritin) as indicated. Response to iron therapy is monitored by changes in the components of the complete blood count and a reticulocyte count. A summary of common drug–nutrient interactions is given in Table 34-1.

Laboratory tests are selected depending on the patient's history and physical examination and could include serum values for vitamin D, calcium, phosphorus, and alkaline phosphatase and radiologic examination of long bones to diagnose rickets. Clinically significant osteopenia often occurs without rachitic changes and can be diagnosed by determining bone mineral content or bone density (dual-energy x-ray absorptiometry). Bone density of the distal femur has been proposed as a measure for children with CP and contractures who are difficult to position for standard measurement sites.[41] Skeletal age determination is useful for diagnosing nutritional dwarfism in children with a delay of 2 or more years in bone age and for determining the potential for catch-up growth. Blood values for selected vitamins and minerals are available when indicated.

ANTHROPOMETRY

Anthropometric evaluation of growth and nutritional status is an essential component of nutritional care. It is a rapid, inexpensive, noninvasive means of determining both short- and long-term nutritional status. A well-trained anthropometrist is required in order to ensure accurate, reproducible measurements. Numerous anthropometric measures are used in the assessment of nutritional status. Each measure offers different information, and no single measure is sufficient for characterization of nutritional status. Proper equipment should be used, and it should be calibrated regularly to ensure accurate measurements. When accurate measurements are obtained and compared to appropriate reference standards, the clinician obtains a current classification of nutritional status and an opportunity to see changes in status over time. Guidelines for anthropometric measurement techniques are available[42,43] and are summarized below with consideration of the child with developmental disabilities.

Measurement of Growth

Weight, stature or length, and head circumference should be measured at routine office visits and every hospital admission. Current status and increments in growth between visits are very informative, especially for tracking progress in the individual patient. For children with severe disabilities, alternative measures of linear growth—upper-arm length and lower-leg length—are described below for assessment when a length or stature measurement is not possible.

Weight

Because growth retardation is common in children with severe disabilities, it is of extra importance that both weight and linear growth are measured at the same time. Because excess weight can be attributable to excess fat, excess water caused by edema, or organomegaly, other anthropometric measures, such as arm circumference and skinfold thicknesses, are important complements to interpreting a weight measurement.

Equipment, Measurement Technique, and Reference Standards Weight should be measured on a digital electronic or beam balance scale. The scale should be checked weekly with known calibration weights. The measurement should be taken to the nearest 0.1 kg in older children and to the nearest 0.01 kg in infants.

The scale should be reset to zero prior to placing a child on it. Children should be weighed wearing little or no outer clothing and without shoes. Infants should be measured without diapers. Wheelchair-accessible scales are available for older children who cannot stand unattended on a scale. The measured weight of the wheelchair alone is deducted from the weight of the child (with little or no clothing) in the wheelchair.

For reference standards for weight, see the Centers for Disease Control and Prevention (CDC) 2000 growth charts.[44]

Length or Stature

Linear growth is a measure of a child's nutritional history and genetic potential and helps to distinguish between short- and long-term nutritional problems. Length or

Table 34-1 Selected Drug–Nutrient Interactions

Drug	*Nutrient*	*Mechanism*
Antacids	Iron	Decreased absorption
Aluminum hydroxide		
Aluminum phosphate	Thiamin	Unstable in alkaline pH
Calcium carbonate		
Cimetidine	Folate, vitamin B_{12}	Decreased absorption
Magnesium carbonate	Phosphorus	Decreased absorption
Magnesium hydroxide		
Magnesium oxide		
Magnesium trisilicate		
Sodium bicarbonate		
Ranitidine	Vitamin B_{12}	Decreased absorption when administered chronically
Anticonvulsants		
Ethosuximide	Vitamin D	Unknown
Phenobarbital	Folate; vitamins B_{12}, B_6, K, C; calcium	Decreased intestinal absorption, altered vitamin D metabolism, increased renal excretion
Phenytoin	Folate; vitamins B_{12}, B_6, D; calcium	Altered vitamin D metabolism, others unknown
Primidone	Vitamins D, K	Altered vitamin D metabolism
Valproic acid	Carnitine	Unknown; possible causes include decreased synthesis, decreased absorption, or urinary loss
Anti-inflammatory drugs		
Acetylsalicylic acid	Folic acid	Competitive absorption at carrier site
	Vitamin C	Increased excretion
	Iron	Chronic blood loss
Corticosteroids	Protein	Decreased glucose tolerance
	Fat	Increased protein catabolism
	Zinc, sodium, potassium, calcium	Increased excretion/decreased absorption
Antimicrobials		
Clindamycin	Potassium	Unknown
Cycloserine	Vitamin B_6, calcium, magnesium,	Vitamin B_6 antagonist Decreased intestinal absorption
	Vitamin B_{12}, folate	Decreased serum levels
Gentamicin	Potassium, magnesium	Increased urinary excretion
Isoniazid	Vitamin B_6, niacin	Increased urinary excretion of vitamin B_6, necessary for conversion of tryptophan to niacin
Neomycin	Fat; vitamins A, D, K, B_{12}; sodium; potassium; calcium; magnesium; lactose; sucrose	Bile salt precipitation
Penicillin	Potassium	Increased urinary losses
Pyrimethamine	Folic acid	Folic acid antagonist
Sulfonamides	Folate, iron	Decreased intestinal absorption
Tetracycline	Zinc, iron, calcium, protein	Decreased intestinal absorption, increased nitrogen balance
Trimethoprim	Folic acid	Folic acid antagonist
Cardiovascular drugs		
Cholestyramine	Vitamins A, D, K, B_{12}; folate; fat; calcium	Bile salt depletion, increased renal excretion, decreased absorption
Digitalis	Magnesium, potassium, calcium	Competitive inhibition of dehydrofolate reductase
Enalapril maleate	Calcium	Unknown
Hydralazine	Vitamin B_6 depletion (?) trace elements	Vitamin inactivation, possible chelation of trace minerals
Cathartics		
Calomel	Phosphorus	Decreased absorption
Mineral oil	Vitamins A, D, E, K; carotene; calcium	Decreased absorption; solvent interference with micelle formation
Phenolphthalein	Vitamin D, calcium, potassium, riboflavin	Increased transit time
Diuretics		
Furosemide	Zinc	Increased renal losses
General	Thiamin, pyridoxine, magnesium, potassium	Increased renal excretion
Thiazides	Zinc	Increased renal losses
Electrolyte repletion		
Potassium chloride	Vitamin B_{12}	Decreased absorption secondary to decreased ileum pH
Heavy metal antagonists		
Penicillamine	Pyridoxine, copper, zinc	Increased renal excretion
Immune suppressants		
Cyclosporin	Lipids	Absorption altered by dietary lipids

For a complete list, see Allen AM. Powers and Moore's food medication interactions. Tempe (AZ): Ann Moore Allen; 1994.

stature measurements are appropriate for children who can be properly positioned, as described below. For children less than 2 years of age or children older than 2 who are not able to stand erect unsupported, a supine length measurement is taken. Standing height, or stature, is measured at age 2 and older. In older children with developmental disabilities, a length measurement is often required past 2 years of age. When comparing a supine length measurement to a growth chart for stature, the length should be decreased by approximately 2 cm[45] to adjust for the known difference between length and stature measurements.

Equipment, Measurement Technique, and Reference Standards To measure supine length, an infantometer or an inflexible length board with a fixed headboard and a movable footboard should be used. Length is measured to the nearest 0.1 cm. Infantometers and stadiometers with digital counters should be calibrated daily with a calibration bar of fixed length.

Measurement of supine length requires two people to position and hold the child. The head should be placed at the top of the board, with the Frankfort plane perpendicular to the floor. The Frankfort plane extends from the lower margin of the orbit to the upper margin of the auditory meatus (Figure 34-1). An assistant is needed to hold the head firmly in this position. The knees should be flattened to fully extend the legs. The feet should be together and flexed to a 90° angle by the footboard with the infant fully stretched.

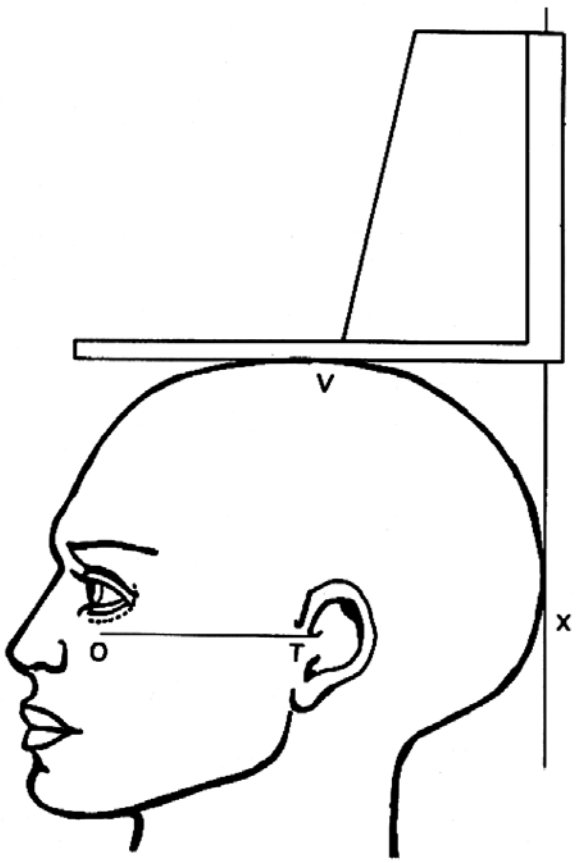

Figure 34-1 The Frankfort plane extends from the auditory meatus to the lower border of the orbit. This plane should be parallel to the paddle or headboard when measuring stature or length. Reproduced from Ross W et al.[61]

To measure stature, the child should stand with the heels, buttocks, and back of the head against the stadiometer. The arms should be down and relaxed and the heels together. The position of the head should be adjusted so that the Frankfort plane is parallel to the floor. Stature should be measured using a stadiometer with a head paddle that glides smoothly but is firmly perpendicular to the back of the stadiometer. Alternatively, a tape measure permanently fixed to a wall or doorframe can be used provided that a head paddle is available that will fit at a 90° angle to the wall. Both length and stature measurements should be accurate to 0.1 cm.

Length and stature measures are inappropriate for children with spinal curvature, contractures, or other conditions that prevent proper positioning for the measurement. Upper-arm length and lower-leg length are alternatives under these conditions (see below).

For both length and stature, measurements should be taken in triplicate, with the measurements in agreement within 0.5 cm, and the mean recorded. Whenever possible, the statures of both biological parents should be obtained and midparental stature computed (the average stature of the mother and father). Adjustment of stature or length measurements using midparental stature charts is a technique that recognizes and corrects for differences in the genetic potential for linear growth.[46]

For reference standards for length and stature, see the CDC 2000 growth charts.[44] Related information is found in Guo and colleagues,[47] Roche and Himes,[48] Himes and colleagues,[46] Berkey and colleagues,[49] and Tanner and Davis.[50]

Weight-for-Height Indices

Weight-for-length and weight-for-height indices are important in the assessment of nutritional status to ensure energy reserves adequate for maintaining growth and overall health. In infants and young children, weight-for-height charts are available[44] to assess nutritional status. For children more than 2 years of age, the body mass index (BMI) can be used. BMI is calculated as weight in kilograms divided by height in meters squared (wt/ht^2). BMI percentile charts are available for children from age 2 to 20 years.[44] Use of these charts is essential for interpretation of BMI in the pediatric range.

Head Circumference

Brain growth is most rapid in the first 3 years of life. Head circumference is a good indicator of brain growth and therefore should be included in the assessment of growth and nutritional status. Because of the high risk of growth failure in children with developmental disabilities, it is important to measure head circumference until age 3, or longer in some children, to determine whether growth of the brain and head is also compromised. However, head circumference is of limited use in nutritional status assessment of patients with central nervous system damage and micro- or megalocephaly of non-nutritional etiology.

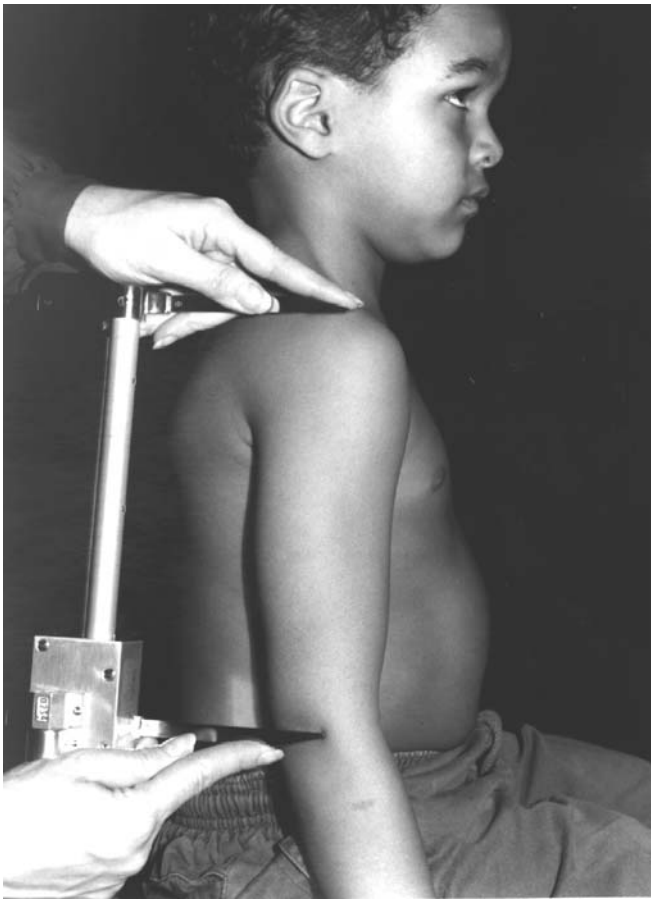

Figure 34-2 Upper-arm length measurement technique.

Equipment, Measurement Technique, and Reference Standards A flexible metal or nonstretch plastic-coated measuring tape scaled to 0.1 cm should be used. The tape is placed over the supraorbital ridge and around the occiput so that a maximum circumference is obtained. Care should be taken that the tape is evenly placed on all sides and is flat against the skull. Three measurements should be obtained and the mean recorded.

For reference standards for head circumference, see the CDC 2000 growth charts.[44,48,51]

Upper-Arm and Lower-Leg Length

Upper-arm length and lower-leg length are alternative measures of linear growth when length or stature measurements are not possible. This commonly occurs in children with developmental disabilities. Both upper-arm and lower-leg length should be measured because they provide measures of upper- and lower-body long-bone growth. Frequently, lower-leg length is more compromised than upper-arm length in children who are nonambulatory.

Equipment, Measurement Technique, and Reference Standards For young infants, sliding calipers (0 to 200 mm) are used. For older infants and children, an anthropometer (50 to 570 mm) is used. All measurements should be taken in triplicate to the nearest 0.1 cm and repeated every 3 months. For infants and young children up to 24 months of age, upper-arm length is measured as shoulder-to-elbow length. With the arm flexed at a 90° angle, the upper arm is measured from the superior lateral surface of the acromion to the inferior surface of the elbow. In children 2 to 18 years of age, upper-arm length is measured from the superior lateral surface of the acromion to the radiale (head of the radius) with the arm relaxed, as shown in Figure 34-2.

For infants and young children, lower-leg length is measured as a knee-to-heel length. With the infant lying supine—with the leg flexed to 90° at the hip, the knee, and the ankle—the lower-leg length is measured from the heel to the superior surface of the knee. For children 2 to 18 years of age, the lower-leg length measure is taken from the lower border of the medial malleolus (sphyrion) to the medial tip of the tibia while the patient is sitting in a relaxed position, as shown in Figure 34-3. The right side should be measured unless there is unilateral involvement affecting the right side. The least-affected side should be measured and thus noted on the growth chart so that repeat measures are always taken on the same limb. Reference percentiles for upper-arm length and lower-leg length for infants are given in Figures 34-4 and 34-5 and for older children (3 to 18 years) in Figures 34-6 through 34-9.

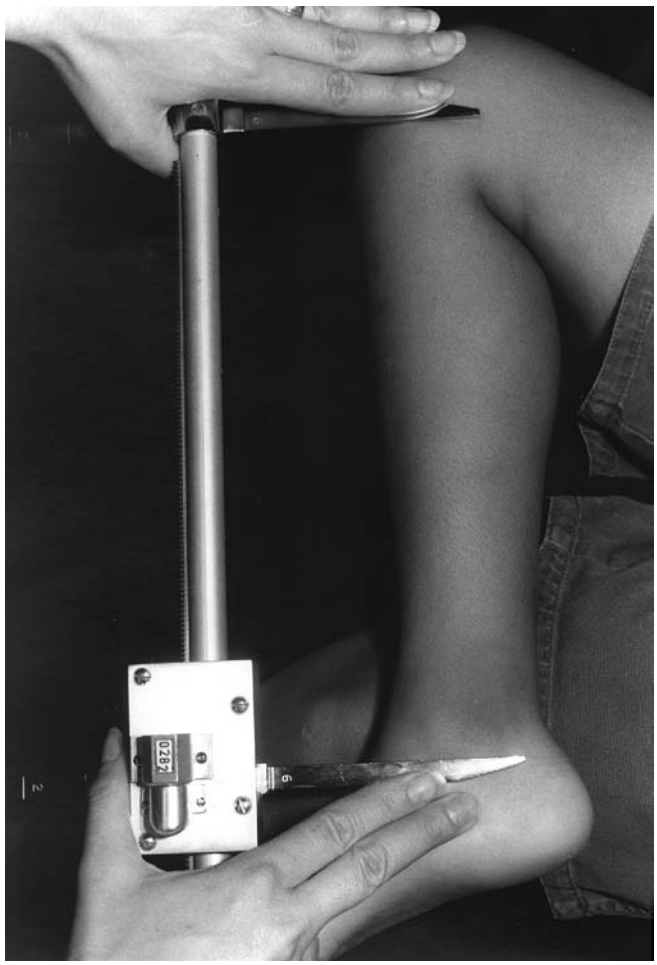

Figure 34-3 Lower-leg length measurement technique.

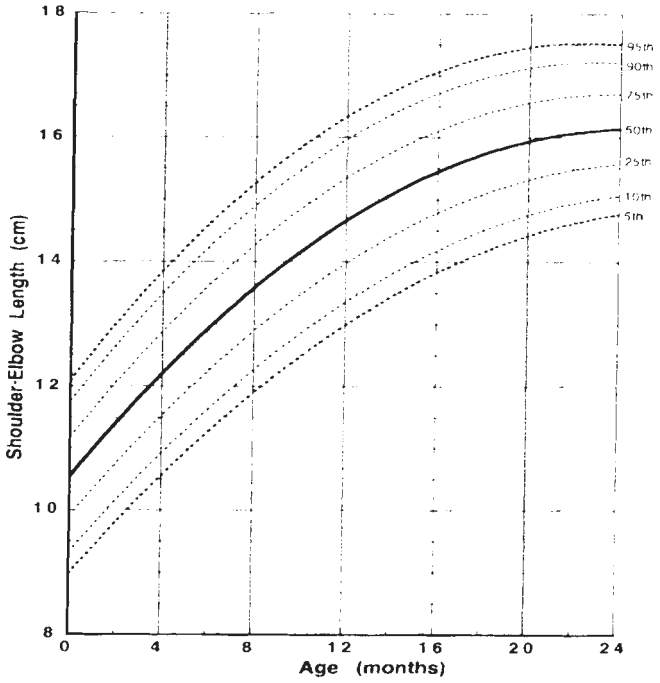

Figure 34-4 Shoulder-to-elbow lengths for boys and girls from birth to age 2 years. Reproduced from Stallings VA and Zemel BA.[62]

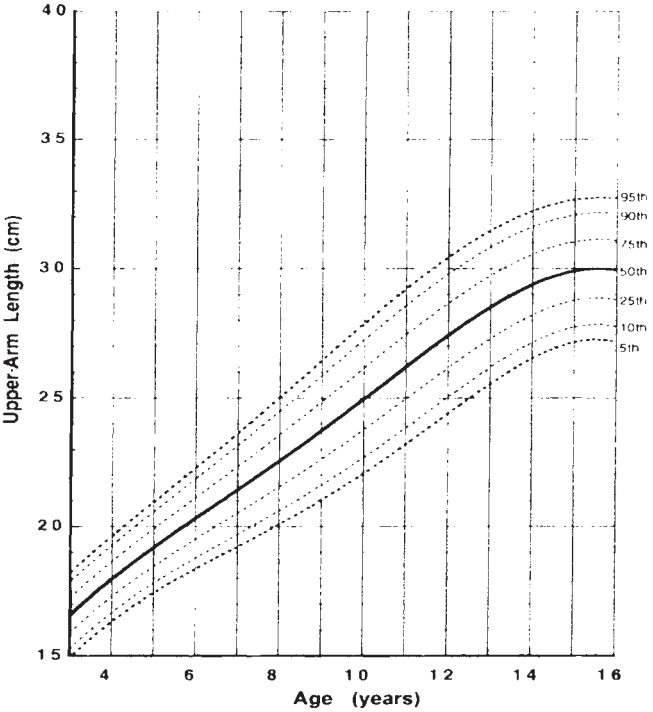

Figure 34-6 Upper-arm lengths for girls 3 to 16 years of age. Reproduced from Stallings VA and Zemel BA.[62]

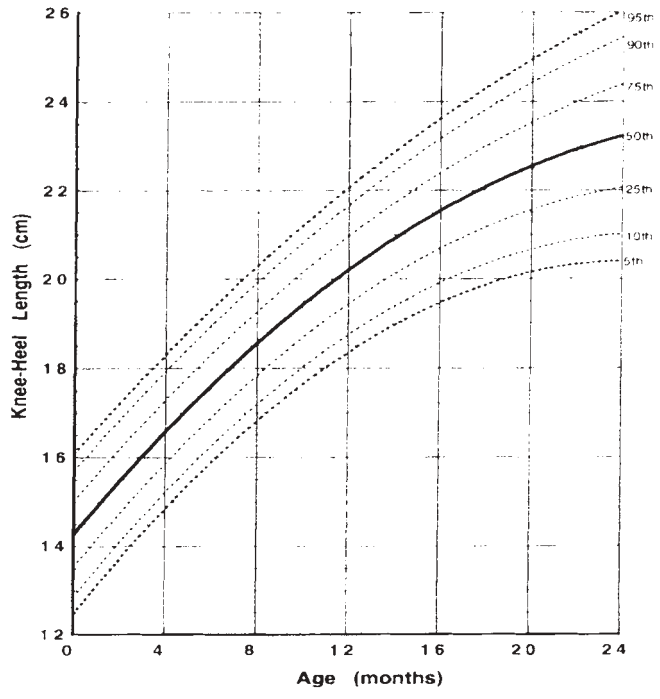

Figure 34-5 Knee-to-heel lengths for boys and girls from birth to age 2 years. Reproduced from Stallings VA and Zemel BA.[62]

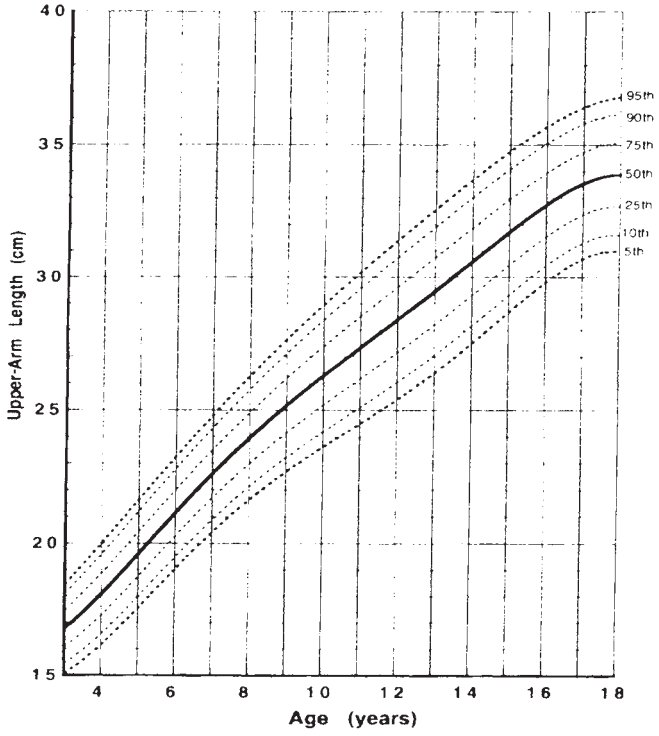

Figure 34-7 Upper-arm lengths for boys 3 to 18 years of age. Reproduced from Stallings VA and Zemel BA.[62]

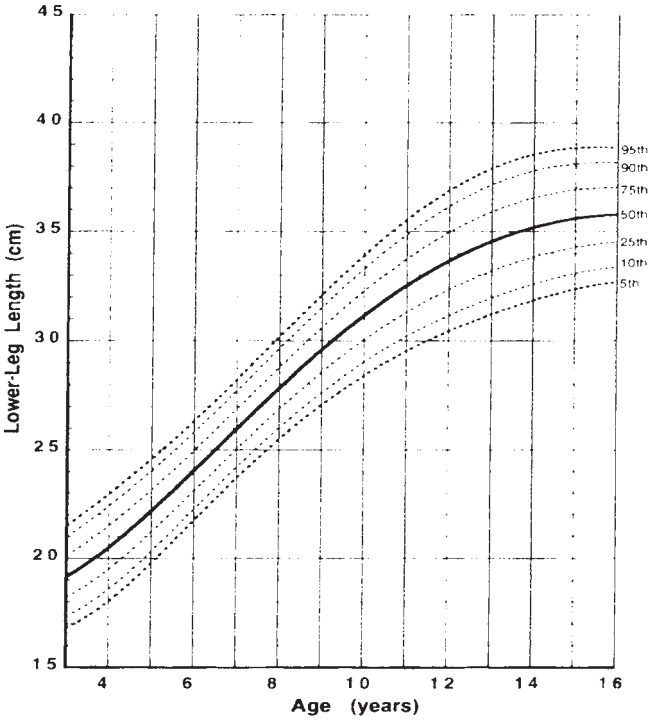

Figure 34-8 Lower-leg lengths for girls 3 to 16 years of age. Reproduced from Stallings VA and Zemel BA.[62]

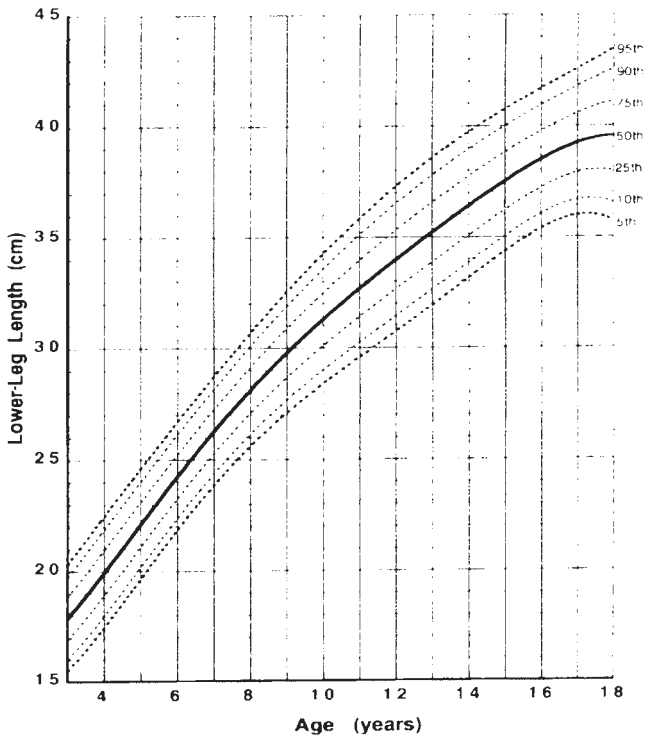

Figure 34-9 Lower-leg lengths for boys 3 to 18 years of age. Reproduced from Stallings VA and Zemel BA.[62]

For reference standards for upper-arm length and lower-leg length, see Spender and colleagues[37] and Snyder and colleagues.[52]

Nutritional Status

Anthropometric indicators of nutritional status consist of measurements of lean and fat tissues at sites known to be sensitive indicators of nutrition and health. Upper-arm anthropometry, the measurement of arm circumference and skinfold thickness, is particularly useful because excellent reference data are available for clinical interpretation. An additional measure of subcutaneous fat on the trunk, the subscapular skinfold thickness measure, is also important because reference data are available and it provides more information for understanding total body fat stores.

Mid-Upper-Arm Circumference

Mid-upper-arm circumference is a composite measure of muscle, fat, and bone in the arm. It is sensitive to current nutritional status and can be used in combination with the triceps skinfold thickness measure to estimate upper-arm muscle area and upper-arm fat area.

Equipment, Measurement Technique, and Reference Standards A nonstretch flexible tape measure is used. All measurements should be taken in triplicate to the nearest 0.1 cm. The midpoint of the upper arm is located by measuring the length of the upper arm (from the acromion to the olecranon with the arm flexed at 90°) and marking the midpoint with a washable ink pen. The midarm circumference is taken with the arm down and in a fully relaxed position. Gently shaking the arm usually ensures that it is relaxed. The tape is placed over the midpoint perpendicular to the long axis of the arm. Care should be taken so that there is no pinching or gaping of the tape as it encircles the arm. This process improves the accuracy and reproducibility of the measure.

For reference standards for mid-upper-arm circumference, see Frisancho.[53]

Skinfold Thickness

Skinfold thickness measures assess subcutaneous fat at specified sites. The triceps and subscapular skinfold measures are indicators of total body fat stores and are sensitive to changes in nutrient intake and nutritional status. Depletion of fat stores at the triceps site is common in children with CP and in other chronically undernourished groups, whereas fatness at the subscapular site is not affected as severely.[6,7,54] Reference data for the sum of these two skinfold measures are available[55] and are used in the research setting as a characterization of total body fat.

Equipment, Measurement Technique, and Reference Standards Holtain skinfold calipers are preferred because they are scaled to 0.2 mm. Lange calipers can be used, but with some loss of accuracy as they are scaled to the nearest 0.5 mm. Calipers that are not spring-loaded and therefore do not provide a constant tension are not recommended.

The triceps skinfold thickness is measured over the triceps muscle, along the back of the arm. The measurement is taken at the same level at which the mid-upper-arm circumference is measured. The patient should be upright with the arm down and fully relaxed for the measurement. The fold of fat and skin is lifted away from the underlying muscle and held throughout the measurement. The calipers are placed on the skin next to the fingers lifting up the skinfold; the skinfold is held in position while the thickness is measured with calipers, and the reading should be taken 3 to 4 seconds after releasing the caliper's handles.

For the subscapular skinfold, the patient should be upright with the arm and shoulder down and fully relaxed. The skinfold is lifted 1 cm below the tip of the scapula at a 45° angle following the natural contour of the body. The fold is held in place, and the calipers are placed next to the fingers holding the fold. The reading should be taken 3 to 4 seconds after releasing the caliper's handles.

For reference standards for skinfold thickness, see Frisancho,[53, 55] Cronk and Roche,[56] and Johnson and colleagues.[57]

Table 34-2 Anthropometric Equations for Prediction of Percent Fat (Ages 8–18 Years)

White males	
Prepubescent:	1.21 (triceps + subscapular) – 0.008 (triceps + subscapular)^2 – 1.7
Pubescent:	1.21 (triceps + subscapular) – 0.008 (triceps + subscapular)^2 – 3.4
Postpubescent:	1.21 (triceps + subscapular) – 0.008 (triceps + subscapular)^2 – 5.5
Black males	
Prepubescent:	1.21 (triceps + subscapular) – 0.008 (triceps + subscapular)^2 – 3.2
Pubescent:	1.21 (triceps + subscapular) – 0.008 (triceps + subscapular)^2 – 5.2
Postpubescent:	1.21 (triceps + subscapular) – 0.008 (triceps + subscapular)^2 – 6.8
All females:	1.33 (triceps + subscapular) – 0.013 (triceps + subscapular)^2 – 2.5
If (triceps + subscapular) greater than 35 mm:	
Males:	0.783 (triceps + subscapular) + 1.6
Females:	0.546 (triceps + subscapular) + 9.7

Adapted from Slaughter MH et al.[58]

Body Composition

Body composition assessment, the measurement of fat and lean body mass stores, is an essential component of nutritional assessment of the disabled child. Whereas linear growth reflects the longer-term nutritional history and genetic potential and is often compromised in children with disabilities, fat and lean body mass stores reflect short-term nutritional adequacy. Body composition can be estimated using the prediction equations of Slaughter and colleagues[58] in children ages 8 to 20 years. These equations use the triceps and subscapular skinfold thickness measures shown in Table 34-2. Specific equations are given based on race, gender, and pubertal status groups.

Body composition values estimated from these anthropometric prediction equations have been compared with measures determined from total body water[59] in children with severe SQCP. Fat mass measured by these two methods is significantly correlated (r = .69), indicating that the anthropometric prediction equations can be used as a clinical, noninvasive method to estimate total body fat in children with CP.[58] Other methods, such as bioelectrical impedance analysis (BIA), total body electrical conductivity (TOBEC), and dual-energy x-ray absorptiometry (DXA), are possible. However, motion artifact and inability to properly position the patient could increase the measurement error and give inconsistent results in children with moderate to severe disabilities. In addition, both TOBEC and BIA require a height measurement. For children whose height can be estimated only from long-bone measures, the measurement error is greatly increased so that these methods become less effective measures of body composition.

ENERGY INTAKE RECOMMENDATIONS

Assessment of energy intake compared to requirement is an essential component of the nutritional care of children with significant disabilities. Undernutrition and overnutrition are the common nutritional pathologies and are the result of energy imbalance. True energy intake is difficult to determine accurately in children with poor oral-motor function and other gastrointestinal problems. Food loss during feeding and regurgitation contribute to the inaccurate estimation of energy intake, even when weighed food diaries recorded over several days are obtained.[38] Daily energy expenditure and its components can be measured in individuals in a research setting (doubly labeled water, 24-hour indirect room calorimetry, REE, thermic effect of food, physical activity). Only REE by indirect calorimetry, a measurement of basal metabolic needs, is available as a clinical evaluation and can be used with estimates of physical activity to predict total caloric needs.

The use of population standards for energy recommendation, such as the RDA from the United States,[29] is not helpful for individual patients with developmental disabilities with atypical body size, body composition, and physical activity. The formulas for energy requirement from WHO[60] are more useful and allow for a more individualized prediction of REE based on gender, age, and body weight, as shown in Table 34-3. Whenever possible, REE should be measured by indirect calorimetry in the early morning with the child fully at rest and in a fasting state. Under these conditions, measurements obtained over 30 to 60 minutes of inactivity can provide an excellent estimate of resting energy needs. The value for REE, whether from indirect calorimetry or a prediction equation, is adjusted by an activity factor to determine total energy expenditure and daily energy requirements. In normally active healthy children and in adults with light or moderate activity, the activity factors range between 1.50 and 1.89 times the REE. Recent work[38] suggests that the physical activity factor for well-nourished children with spastic quadriplegia is much lower, about 1.3 times the REE, and about 1.5 in malnourished children with CP.

Two other methods for estimating caloric requirements have been published. Culley and Middleton developed a

Table 34-3 Equations for Predicting Resting Energy Expenditure from Body Weight (w)

Age, yr	*Male*	*Female*
0–3	60.9 W – 54	61.0 W – 51
3–10	22.7 W + 495	22.5 W + 499
10–18	17.5 W + 651	12.2 W + 746
18–30	15.3 W + 679	14.7 W + 496
30–60	11.6 W + 879	8.7 W + 829
> 60	13.5 W + 487	10.5 W + 596

Adapted from World Health Organization.[60]

method for disabled children that takes level of motor function into account.[59] The caloric consumption based on motor function status was 14.7 kcal/cm of height and 77 kcal/kg for children without motor dysfunction, 13.9 kcal/cm and 75 kcal/kg for ambulatory children with some motor dysfunction, and 11.1 kcal/cm and 64 kcal/kg for nonambulatory children with motor dysfunction. In addition, Krick and Murphy reported a factorial method approach to determining caloric needs in children with CP.[30] This method accounts for caloric intake based on estimated REE needs, muscle-tone alterations, normal growth needs, and catch-up growth or nutritional repletion in malnourished children. The formula is summarized as

kcal/d = resting energy needs × tone factor + growth factor(s).

SUMMARY

Monitoring nutrition and growth status in children and adults with CP and other severe types of developmental disabilities is an essential component of care. This chapter summarizes the previous work in the area and outlines clinical approaches to determining nutritional status and estimating caloric needs. Although data are not available to provide precise definitions of the levels of severity of malnutrition and growth failure and their effect on long-term outcome, it is clear that many patients with moderate to severe cerebral palsy or other disabilities have malnutrition and growth failure as the result of inadequate caloric intake. Nutritional status assessment every 3 to 6 months will enable the clinical care team to identify malnutrition and growth failure and will provide an objective means of following the response to nutritional intervention.

ACKNOWLEDGMENT

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CHAPTER 35

INBORN ERRORS OF FASTING ADAPTATION

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A number of inborn errors of metabolism compromise the child's normal response to fasting. Depending on the enzyme and metabolic pathway affected, the individual will tolerate fasting for a brief or more prolonged period of time. The abnormal enzymatic pathway will also determine which potentially toxic intermediates accumulate, which substrates are consumed, and which products fail to be produced. In general, these derangements in fuel conservation and energy production are characterized biochemically by hypoglycemia and acidosis and by either an abundance or a paucity of ketone bodies. They are characterized histologically by effects on the tissues most involved in fuel metabolism and substrate production during fasting, such as the liver, and those most dependent on the maintenance of adequate substrate for sustained energy requirements during fasting, such as the heart and skeletal muscles. Brain function is intimately linked to an adequate glucose supply and is vulnerable to the accumulation of metabolic toxins. Thus, it is easy to understand why patients with these disorders often present with symptoms of stupor, coma, or even seizures; hypotonia, rhabdomyolysis, or cardiomyopathy; and an enlarged liver filled with fat or glycogen. Accumulation of toxins in the liver, particularly within the mitochondria, can also lead to generalized mitochondrial failure, lactic acidosis, and fulminant hepatic failure.

Normal infants are more likely to develop hypoglycemia and manifest hyperketonemia earlier during a fast than their adult counterparts. This is probably the result of several factors, including decreased hepatic glycogen stores, decreased muscle mass with reduced mobilization of amino acid substrates for gluconeogenesis, and a larger brain mass to body size. This latter factor is important because glucose is the main fuel for the brain. In the rest of the body, free fatty acids (FFAs) replace glucose as the major fuel, but the brain remains the major consumer of glucose during fasting.[1,2] Fasting provocation occurs at several periods during infancy, including the time of placental separation, the time when the infant first sleeps through the night, the time of weaning from the breast, and the time of the first intercurrent illness with fever, vomiting, and catabolic stress. It is at these critical junctures that symptoms and signs of inborn errors in fasting adaptation may present.

This chapter reviews the normal physiology of adaptation to the immediate and prolonged fasting state in infants and children. It then explores specific hormonal and enzymatic abnormalities that disrupt this adaptive process. These include derangements in glycogenolysis, gluconeogenesis, fatty acid oxidation, ketogenesis, or ketolysis. With this background, the nutritional management of these problems is reviewed. Inborn errors of metabolism that are provoked by feeding and the ingestion of substrates that cannot be adequately metabolized are not covered. For a review of these feeding-induced disorders (ie, galactosemia, hereditary fructose intolerance, urea cycle defects, and disorders of amino acid metabolism), the reader is referred to several excellent texts.[3–6]

NORMAL PHYSIOLOGY OF FASTING

In a 24-hour period, a normal man who consumes 1,800 calories per day burns about 75 g of protein, primarily from muscle, and 160 g of adipose tissue triglyceride. Hepatic output of glucose approximates 180 g, of which 144 g is used by nerve tissue (mainly brain) and is completely oxidized to CO_2 and water.[1] Other glycolytic tissues, such as erythrocytes, renal medulla, and normal muscle, metabolize glucose but convert it primarily to lactate and pyruvate. These metabolites are recycled by entering the bloodstream and being converted back into glucose by the liver and kidney (Cori cycle). About 36 g (20%) of the glucose used daily is broken down by anaerobic glycolysis and then remade into glucose. The remainder of the tissues (heart, skeletal muscle, renal cortex) metabolizes either fatty acids released directly into the circulation or ketone bodies derived from fatty acid oxidation by the liver (Figure 35-1).

As shown in Table 35-1, fatty acids stored as adipose tissue triglyceride comprise by far the largest reserve of fuel in the body. Because liver glycogen stores are depleted within only a few hours of a meal, fatty acids then become the predominant substrate for energy production via oxidation in the liver, cardiac muscle, and skeletal muscle. In an adult man, fatty acids provide 80% of caloric requirements after a 24-hour period of fasting.[7] In the muscle, the metabolic end product of fatty acid oxidation is acetyl coenzyme A (CoA), which is further metabolized to CO_2

Table 35-1 Body Fuel Stores and the Potential Length of Time They Could Supply Energy in a 30kg Child Utilizing 1200 cal/day

	Fuel Stores (kg)	*Time*
Tissues		
Fat (adipose tissue)	4.5	34 d
Protein (mainly muscle)	1.5	5 d
Glycogen (muscle)	.09	8.0 h
Glycogen (liver)	.045	3.5 h
Circulating fuels		
Glucose (extracellular fluid)	.010	50 min
Triglyceride (plasma)	.0015	20 min
Free fatty acids (plasma)	.00015	1 min

Adapted from Cahill GF.[1]

via the tricarboxylic acid (TCA) cycle, yielding adenosine triphosphate (ATP) for the energy needs of the cell. In the liver, the primary metabolic product of fatty acid oxidation is β-hydroxybutyrate, a ketone body, synthesized from acetyl CoA and subsequently exported to peripheral tissues as a glucose-sparing fuel.

The predominant hormones controlling hepatic and peripheral glucose metabolism include insulin, glucagon, cortisol, growth hormone (GH), insulin-like growth factors (IGFs), and the catecholamines. Insulin is the primary hormone responsible for lowering blood glucose and protecting the individual from hyperglycemia. A detailed description of insulin release is beyond the scope of this summary; however, a brief overview would be appropriate. The initial response to increased serum glucose is its uptake and metabolism in the beta cell. The rate-limiting step in this reaction involves the catalyst glucokinase. The catabolism of glucose results in an increased ATP-to-adenosine diphosphate (ADP) ratio sensed by the sulfonylurea type 1 (SUR1) receptor. This leads to the closure of the K^+_{ATP} channels and depolarization of the cell membrane. Depolarization leads to the opening of calcium channels and, finally, release of stored insulin.[8] Inappropriate beta cell regulation owing to mutations in critical enzymes and receptors results in uncontrolled insulin secretion and subsequent hypoglycemia. Several groups have published data on specific genetic and receptor defects responsible for congenital hyperinsulinism.[9,10]

During fasting, insulin levels decline and the effects of glucagon produced by the pancreatic alpha cell become predominant (Table 35-2). The primary stimulus for the release of glucagon is a lowering of the blood glucose concentration, although other factors, particularly increased sympathetic neuronal activity, also play a role. Increased glucagon concentrations and changes in the molar ratio of insulin to glucagon have far-reaching effects. These hormonal changes provoke glycogenolysis, gluconeogenesis, fatty acid oxidation, and ketogenesis in the liver; increase lipolysis in peripheral adipose tissue; and stimulate the release of lactate and amino acids from skeletal muscle. These adaptive mechanisms are designed to maintain plasma glucose concentrations, enhance glucose production via gluconeogenesis, allow the consumption of alternative fuels by the bulk of tissues in the body, and preserve glucose for brain metabolism.

GH, catecholamines, and cortisol are other counterregulatory hormones that raise blood sugar in periods of increased demand such as fasting or stress. In the newborn period, deficiency of GH can result in acute hypoglycemia in 20% of cases. Likewise, defects in the GH receptor

Table 35-2 Hormonal Control of Glucose Homeostasis

Substrate	*Enzymes*	*Effects*	
Insulin	Glycogen	↑ Glucokinase ↑ Glycogen synthase ↓ Glucose-6-phosphatase ↓ Glycogen phosphorylase	Stimulates entry of glucose into cells; stimulates storage of glucose as glycogen and inhibits its breakdown
	Glucose	↑ Phosphofructokinase ↑ Pyruvate kinase ↓ Fructose-1,6-diphosphatase ↓ PEP-carboxykinase ↓ Pyruvate carboxylase	Stimulates complete utilization of glucose to CO_2 and H_2O through the TCA cycle; inhibits gluconeogenesis from glycerol, lactate, and alanine
	Fat	↑ Acetyl-CoA carboxylase ↓ Lipase ↓ CPT-I	Stimulates fatty acid synthesis and increases glycerol production for TG synthesis; inhibits FAO and ketogenesis
*Glucagon**	Glycogen	↑ Glucose-6-phosphatase ↑ Glycogen phosphorylase ↓ Glycogen synthase	Increases degradation of glycogen and release of glucose from cells; inhibits glycogen synthesis
	Glucose	↑ Fructose-1,6-diphosphatase ↑ PEP-carboxykinase ↑ Pyruvate carboxylase ↓ Phosphofructokinase ↓ Pryuvate kinase	Promotes gluconeogenesis from recycled lactate and alanine and from glycerol; inhibits glycolysis
	Fat	↑ Lipase ↑ CPT-I ↓ Acetyl-CoA carboxylase	Stimulates lipolysis of TG, FFA release, FAO, and ketogenesis; inhibits fatty acid and TG synthesis

*Other counterregulatory hormones such as epinephrine, cortisol, and growth hormone also act in concert with glucagon on certain enzymes.
CoA = coenzyme A; CPT-I = carnitine palmitoyl transferase I; FAO = fatty acid oxidation; FFA = free fatty acid; PEP = phospho*enol*pyruvate; TCA = tricarboxylic acid; TG = triglyceride.

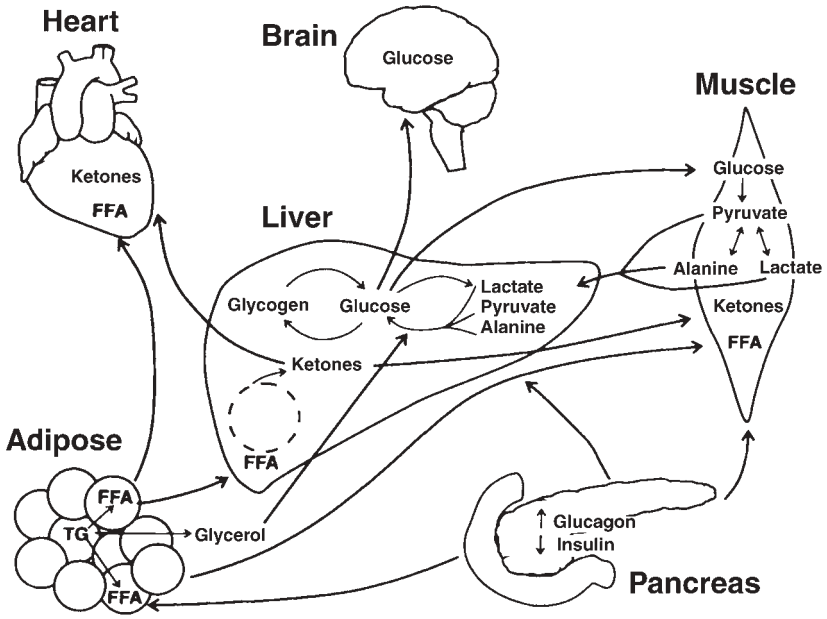

FIGURE 35-1 Organ and substrate interactions illustrating the normal adaptation to fasting. Under the influence of an increased circulating molar ratio of glucagon to insulin, enzymes are activated in the target organs to maintain glucose production, provide alternative fuels in tissues that can use them, and conserve glucose for brain metabolism. Glycogen is degraded to glucose in the liver. Glucose is resynthesized from recycled pyruvate, lactate, and alanine liberated from muscle catabolism and also newly synthesized from glycerol produced by lipolysis of triglycerides (TG) stored in adipose tissue. Free fatty acids (FFA) are mobilized from adipose tissue and exported directly to heart and skeletal muscle for complete oxidation to CO_2. The liver becomes a ketogenic organ and oxidizes FFAs to ketones. Ketones are exported to heart and skeletal muscle for catabolism in lieu of glucose. Glucose is conserved for the metabolic needs of the brain.

(Laron syndrome) may present with hypoglycemia owing to decreased or absent production of IGF-I. Patients with Laron syndrome may present with more profound hypoglycemia when compared with GH-deficient individuals.[11] Glucagon and cortisol play a more crucial role in gluconeogenesis and glucose regulation. Hypoglycemia can occur in the setting of decreased cortisol production or adrenocorticotropic hormone (ACTH) secretion owing to a lack of a counterregulatory response to hypoglycemia.

Glycogen Degradation

Most glucose production during fasting arises from the liver, and this is usually sufficient to provide for the brain's needs. Three elements account for this glucose output: glucose from glycogen, gluconeogenesis from protein and fat, and glucose resynthesized from the products of glycolysis. Hepatic glycogenolysis is the main provider of the body's glucose requirements in the early stages of fasting. In children aged 3 to 5 years, the administration of glucagon or epinephrine injections after 12 to 15 hours of fasting still results in a significant increase in plasma glucose, suggesting that adequate glycogen stores are maintained for at least this period of time.[12] By 24 hours, this effect is no longer seen in fasting infants and children.[13] Glycogen comprises up to 5% of the wet weight of the liver,[14] and approximately one-third of the body's production of glucose is derived from hepatic glycogenolysis during the first few hours of a fast. Although muscle glycogen accounts for a larger tissue reserve than that found in liver, muscle glycogen is depleted slowly over several days and is used primarily for local needs when the external carbohydrate supply is limited. Because the muscle lacks glucose-6-phosphatase, it is also unable to release free glucose into the blood in any significant amount.

In the early fasting state, insulin is decreased, and increased epinephrine and glucagon secretion stimulate glycogenolysis and inhibit glycogen synthesis. These hormones increase the synthesis of cyclic adenosine monophosphate (cAMP) intracellularly, thereby increasing the activity of a cAMP-mediated protein kinase that activates the degradative enzyme glycogen phosphorylase and inhibits glycogen synthetase (Figure 32-2). The phosphorylase reaction cleaves 1,4 straight-chain glucose linkages, producing glucose-1-phosphate, which is subsequently converted to glucose-6-phosphate. Another debrancher enzyme (amylo-1, 6-glucosidase) cleaves the 1,6-glucose linkages found at the branch points of the glycogen molecule, allowing for the continued action of the phosphorylase on the remaining straight chains of glucose polymers. Sequential degradation of glycogen results in the production of approximately 8 to 12% free glucose and 90% glucose-6-phosphate. Further glucose is released through the hydrolysis of glucose-6-phosphate by a reaction catalyzed by the enzyme glucose-6-phosphatase. This complex enzyme is composed of at least five different polypeptides situated in the lumen of the endoplasmic reticulum and is found only in the liver, kidney, and intestinal mucosa.[15]

Gluconeogenesis and Recycling of Glycolytic Metabolites

Gluconeogenesis is the synthesis of new glucose from other noncarbohydrate metabolites such as protein or fat and thus adds to the total body pool of glucose. A quantitatively more important factor in maintaining glucose homeostasis is the conservation of glucose by the recycling of three-carbon fragments generated by glycolysis in the muscle: pyruvate, lactate, and transaminated pyruvate in the form of alanine.[16]

When liver glycogen is depleted, adipose tissue triglyceride (triacylglycerol) is cleaved by a lipase that is inhibited by insulin and activated by epinephrine and glucagon, with the permissive effects of GH and cortisol. This results in the release of large amounts of FFAs and glycerol into the blood, the former serving as substrate for hepatic

ketone production and the latter for gluconeogenesis. Simultaneously, lactate, pyruvate, and alanine liberated from muscle catabolism (glycolysis and proteolysis) are recycled back into glucose synthesis in the liver. Alanine is probably produced by the myocyte because it is released from skeletal muscle in quantities that exceed the amounts stored in these tissues.[17] Transamination of pyruvate to alanine allows muscle to rid itself of ammonia. These recycling processes of alanine (alanine cycle), pyruvate, and lactate (Cori cycle) are responsible for more than half of the glucose produced during prolonged fasting. The energy for conversion of these three-carbon fragments back to glucose is derived from hepatic and muscle fatty acid oxidation. The net effect is that energy derived from fatty acid oxidation is used to spare glucose use in the muscle and regenerate glucose in liver.

The key enzymes responsible for the complete oxidation of glucose during the fed state are phosphofructokinase (PFK), pyruvate kinase, and pyruvate dehydrogenase (see Figure 35-2). PFK activity is increased by insulin and catalyzes a key step in glucose use, the conversion of fructose-6-phosphate to fructose-1,6-diphosphate. Pyruvate kinase is also stimulated by insulin and catalyzes the formation of pyruvate from phospho*enol*pyruvate (PEP). Pyruvate dehydrogenase promotes the entry of pyruvate into the TCA cycle by conversion of pyruvate to acetyl CoA and is stimulated by the availability of pyruvate and free CoA. In the fasting state, stimulated by a decrease in insulin relative to glucagon and by cortisol and epinephrine, pyruvate is preferentially converted to oxaloacetate rather than to acetyl CoA through the action of intramitochondrial pyruvate carboxylase. Oxaloacetate is then converted to malate, and malate is shuttled out of the mitochondria into the cytosol, where it is reconverted to oxaloacetate and metabolized to PEP through the action of PEP carboxykinase (PEPCK). PEP is then ultimately converted to glucose-6-phosphate, which is then hydrolyzed to the free glucose that is released into the blood.

Fatty Acid Oxidation

In the fed state, insulin simultaneously inhibits the enzymes that catalyze triglyceride breakdown, enhances glycerol production via glycolysis, allows for increased esterification of fatty acids as triglycerides, and promotes glucose use by driving conversion of pyruvate to acetyl CoA and eventually to malonyl CoA (see Table 35–2). The accumulation of malonyl CoA inhibits the activity of carnitine palmitoyltransferase I (CPT-I). CPT-I is one of the enzymes responsible for the transesterification of fatty acid ester to carnitine and the transport of the acylcarnitine ester across the inner mitochondrial membrane (Figure 35-3). CPT-I is a major site of regulation that determines whether fatty acids are directed toward intramitochondrial β-oxidation or to resynthesis as triglycerides.[18] The activity, immunoreactive protein, ribonucleic acid (RNA), and transcription rate of CPT-I are increased in high-fat feeding, starvation, and

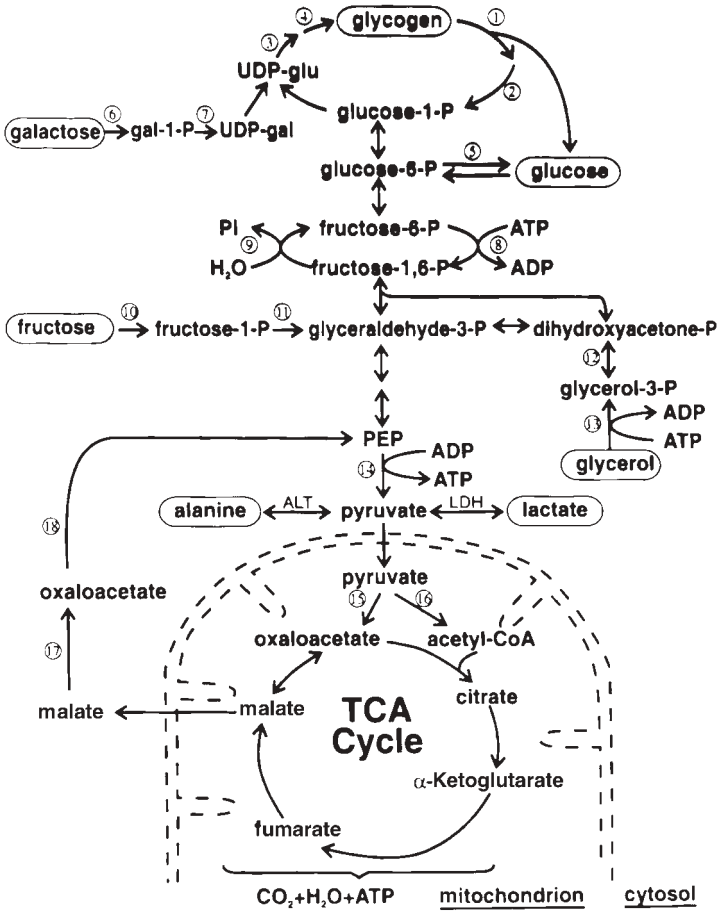

FIGURE 35-2 Pathways of carbohydrate metabolism in the liver including glycogenolysis and glycogen synthesis, glycolysis and gluconeogenesis, and the metabolism of pyruvate. Substrates for gluconeogenesis are circled. Numbers identify major enzymes in the pathways: (1) debrancher, (2) phosphorylase, (3) glycogen synthetase, (4) brancher, (5) glucose-6-phosphatase, (6) galactokinase, (7) galactose-1-phosphate uridyl transferase, (8) phosphofructokinase, (9) fructose-1,6-diphosphatase, (10) fructokinase, (11) fructose-1-phosphate aldolase, (12) glycerol-3-phosphate dehydrogenase, (13) glycerol kinase, (14) pyruvate kinase, (15) pyruvate carboxylase, (16) pyruvate dehydrogenase, (17) malate dehydrogenase, (18) phospho*enol*pyruvate carboxykinase. ADP = adenosine diphosphate; ALT = alanine aminotransferase; ATP = adenosine triphosphate; CoA = coenzyme A; LDH = lactate dehydrogenase; P = phosphate; PEP = phospho*enol*pyruvate; Pi = inorganic phosphate; TCA = tricarboxylic acid.

diabetes and by glucagon, cAMP, aspirin, hypolipidemic drugs, and cytokines.[19] Enhanced glucagon levels during fasting inhibit acetyl-CoA carboxylase, which catalyzes the conversion of acetyl CoA to malonyl CoA. Reduced tissue levels of malonyl-CoA allow increased activity of CPT-I and promote entry of fatty acids into mitochondria for β-oxidation. In the fasting state, ratios of glucagon to insulin are high, lipogenesis is repressed, fatty acid oxidation is enhanced, and the liver becomes a ketogenic organ.

To traverse the inner mitochondrial membrane, long-chain fatty acid esters (long-chain acyl CoAs) must first be transesterified to carnitine to form a fatty acylcarnitine and then transported by a membrane-bound transporter and subsequently reconverted back to long-chain fatty acyl CoAs at the interface of the inner mitochondrial membrane with the mitochondrial matrix (see Figure 35-3).[20] In contrast to long-chain fatty acids such as palmitate and oleate, short- and medium-chain fatty acids can traverse the mitochondrial membrane as free acids without the need for esterification to carnitine. Once inside the mitochondria, the long-chain acyl CoA enters the β-oxidation spiral. Figure 35-3 shows the four enzymes responsible for each turn of the cycle, which results in the shortening of the fatty acyl CoA by two carbons. This cycle results in the production of acetyl CoA, the generation of ATP to support gluconeogenesis and other energy-requiring reactions, and the transfer of two electrons to electron transfer flavoprotein. These electrons ultimately pass to the electron transport chain, resulting in further ATP production via oxidative phosphorylation. Adequate generation of mitochondrial acetyl CoA is crucial to the efficiency of gluconeogenesis because acetyl CoA is the primary activator of pyruvate carboxylase, which converts pyruvate to oxaloacetate.

Ketogenesis and Ketolysis

During times of carbohydrate insufficiency, the body's needs for energy may be partially met by use of ketones derived from hepatic fatty acid oxidation. The liver has a remarkable capacity to oxidize fatty acids and produce the ketones acetoacetate and β-hydroxybutyrate. In one day, the liver can synthesize about half its weight in ketone bodies (about 900 g/day).[21] Although the liver is the major organ for production of ketones, it does not itself oxidize nonthiolated acetoacetate. It exports ketones to many peripheral tissues, including heart, skeletal muscle, kidney, and intestine, where acetoacetate may be oxidized and glucose conserved. Fatty acids and ketones generated during prolonged fasting spare the oxidation of glucose in part by impairing its entry into muscles and by inhibiting the important glycolytic enzymes PFK and pyruvate carboxylase. During more prolonged periods of fasting and starvation, the brain adapts to the use of ketones as a major fuel and derives over half of its energy by the oxidation of ketones.[2] This adaptation results in a marked decrease in the demand for de novo glucose synthesis from alanine and consequently permits the organism to conserve its vital protein stores.

In liver mitochondria, the end product of fatty acid oxidation, acetyl CoA, has the option of entering the TCA cycle by condensing with oxaloacetate to form citrate or, alternatively, of forming 3-methylglutaryl CoA, which can be cleaved to form the ketone bodies acetoacetate and reduced 3-hydroxybutyrate. Thus, the concentration of oxaloacetate at this fork helps to determine the path taken by acetyl CoA. Glucagon and cAMP (through which glucagon exerts its effects) cause a marked diminution of mitochondrial oxaloacetate. This is coincident with decreased synthesis of fatty acids, increased oxidation of fatty acids, and increased ketogenesis.

SPECIAL FEATURES OF THE NEWBORN PERIOD

Glycogenolysis and Gluconeogenesis

As outlined above, maintenance of the plasma glucose concentration in a normal fasted individual depends on (1) a normal endocrine system for modulating substrate mobilization and use; (2) intact enzyme pathways for glycogenolysis, gluconeogenesis, fatty acid oxidation, and ketogenesis; and (3) an adequate supply of endogenous fat, glycogen, and gluconeogenic substrates. In newborns, particularly premature infants subjected to stress, a number of factors combine to render the fasting newborn more susceptible to hypoglycemia (Table 35-3). The adult human is capable of maintaining a normal blood glucose concentration even when totally deprived of calories for weeks. In contrast, the normal neonate and infant exhibit a progressive fall in blood glucose to hypoglycemic levels when fasted for even short periods of 24 to 48 hours.[22–24]

Immediately after birth, the newborn must withstand a brief period of starvation before receiving a new source of nutrients from milk. During this period, the large liver glycogen stores and endogenous fat stores that have accumulated during late fetal life must sustain the infant. In spite of intrahepatic concentrations comparable with those seen in children with glycogen storage disease (GSD), liver glycogen stores in normal newborns are usually exhausted within 12 hours of delivery.[25] At the time of separation of the newborn from the maternal blood supply, there is a relative surge in glucagon secretion. However, the administration of glucagon to neonates has been shown to have little effect on plasma glucose concentrations, implying that the normal glycogenolytic response to endogenous glucagon may be blunted.[26] Marked increases in sympathetic nervous system tone and epinephrine secretion owing to the stress of birth play an important role in initiating glycogenolysis and lipolysis by stimulating glucagon and inhibiting insulin secretion. Prolonged fetal distress, cold stress, or infection accentuates epinephrine secretion and results in a rapid depletion of both fat and glycogen stores, greatly limiting the substrates for subsequent glucose and ketone production.

Although the timing of the induction of the hepatic gluconeogenic enzymes in humans remains to be established, gluconeogenesis is either absent or markedly depressed in the fetus of various experimental animals.[22,27] This activity does not increase until the perinatal period and reaches adult levels only after several hours to days of extrauterine life. Small-for-gestational-age (SGA) infants exhibit a relative functional delay in gluco-

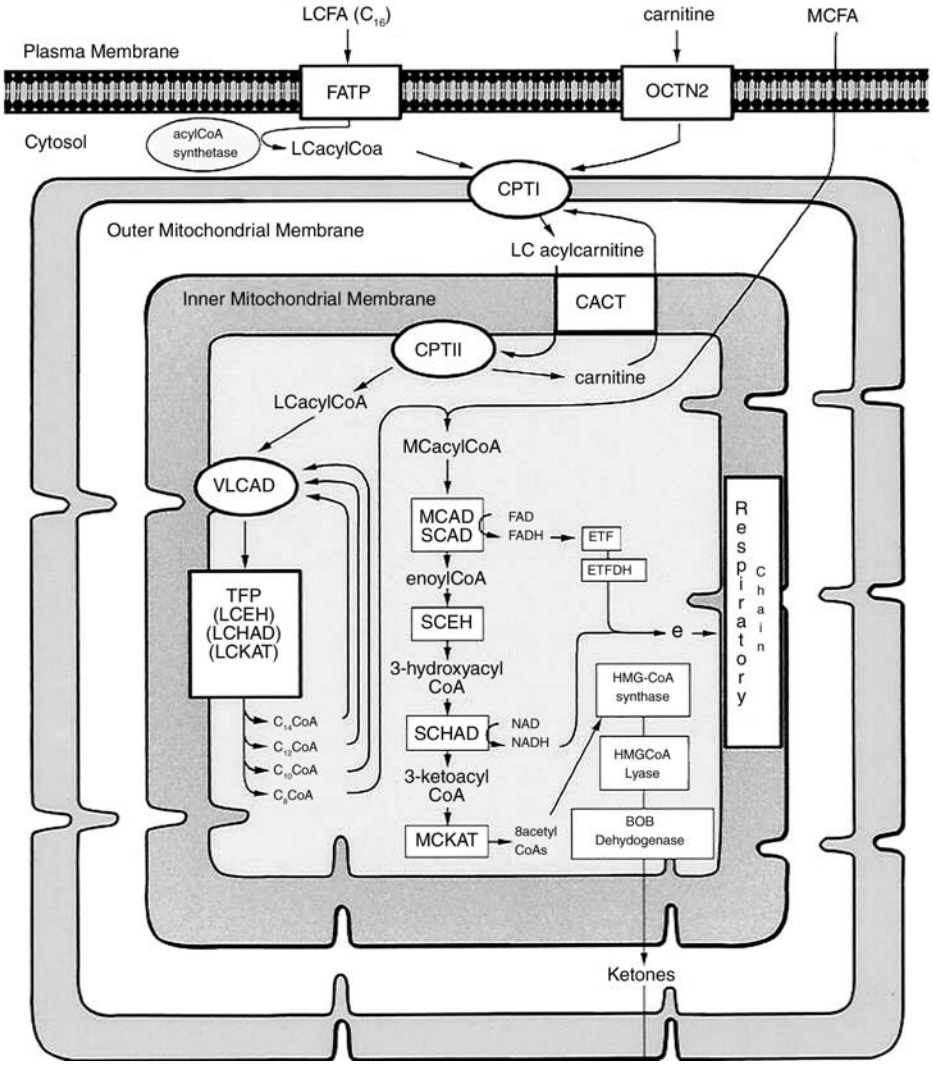

FIGURE 35-3 Pathway of hepatic mitochondrial fatty acid oxidation and ketogenesis. Shown are the steps for the oxidation of palmitate, a 16-carbon (C_{16}) long-chain fatty acid (LCFA). Note that eight-carbon medium-chain fatty acids enter the mitochondria independent of the carnitine cycle. LCFAs are transported across the plasma membrane by a liver-specific LCFA-transporting polypeptide. Carnitine is supplied by a plasma membrane sodium-dependent carnitine transporter (OCTN2). On the outer mitochondrial membrane, carnitine palmityl transferase I (CPT-I) is a major site of regulation that determines whether LCFAs are directed toward β-oxidation to ketones or to the resynthesis of triglycerides. LCFA-coenzyme A (CoA) in the cytosol must first be transesterified to long-chain acylcarnities by CPT-I and then enter the carnitine cycle to be shuttled across the inner mitochondrial membrane. Once across the membrane, the acylcarnitine is re-esterified to an LCacylCoA and enters the β-oxidation cycle. All of the relevant enzymes for LCacylCoAs are bound to the inner mitochondrial membrane (very-long-chain acyl-CoA dehydrogenase, trifunctional protein). At the completion of the four reactions of the β-oxidation cycle, the LCFA has been shortened by two carbons; one molecule of acetyl CoA has been generated for ketone body synthesis, and electrons have been transported to the respiratory chain via flavin adenine dinucleotide and nicotinamide adenine dinucleotide. As the LCFA is shortened, β-oxidation proceeds via enzymes located in the mitochondrial matrix (medium-chain acyl-CoA dehydrogenase [MCAD], short-chain acyl-CoA dehydrogenase [SCAD], short-chain 3-hydroxyacyl-CoA dehydrogenase [SCHAD], medium-chain ketothiolase). Enzymes and transporters are circled. AcAc = acetoacetate; BOB = β-hydroxybutyrate; ETF = electron transport flavoprotein; ETFDH = electron transport flavoprotein dehydrogenase; HMG = 3-hydroxy-3-methylglutaryl; LCEH = long-chain enoyl-CoA hydratase; LCHAD = long-chain 3-hydroxyacyl-CoA dehydrogenase; LCKAT = long-chain ketothiolase; SCEH = short-chain enoyl-CoA dehydrogenase; SCKAT = short-chain ketothiolase.

neogenic activity and have significantly higher blood lactate, pyruvate, and plasma alanine levels than full-term neonates.[28,29] This pattern is already seen in cord blood and is maintained for the first 24 hours of life despite the institution of feeding at the time hypoglycemia is documented. SGA infants do not respond with stimulated hepatic glucose output to the provision of the gluconeogenic substrate alanine as do their appropriate-for-gestational age (AGA) counterparts.[30] These findings suggest a maturational delay in the function of intrahepatic enzymes of gluconeogenesis.

Cytosolic PEPCK is considered to be the rate-limiting enzyme in the gluconeogenesis, with a substantially reduced activity (0 to 25% of adult activity) in the near-term fetus.[31] The rate of PEPCK synthesis increases rapidly after birth, reaching adult values within 24 to 48 hours. Injections of glucagon and cAMP or insulin deficiency caused by streptozocin administration both cause a

marked induction of messenger RNA for PEPCK,[32] suggesting that it is the fall in the plasma insulin-to-glucagon molar ratio that occurs spontaneously after birth that triggers the induction of liver PEPCK. Neonates also exhibit a relative insensitivity of the islet cells to changes in blood glucose, making them more likely to develop hypoglycemia owing to a lack of adequate glucagon secretion in response to falling blood sugar.

Fatty Acid Oxidation and Ketogenesis

The capacity for long-chain fatty acid oxidation and ketone production is low in the fetal liver and markedly increases during the first 24 hours following birth.[33,34] These changes are accompanied by an increase in the activity of key enzymes and substrates in fatty acid oxidation and ketogenesis including CPT-I, hydroxymethylglutaryl CoA synthase, and intramitochondrial free CoA. The shift in the insulin-to-glucagon molar ratio is probably important here as well because both glucagon and cAMP induce fatty acid oxidation in cultured hepatocytes from near-term animals and decrease lipogenesis and intracellular malonyl CoA concentration, leading to increased activity of CPT-I.

The rapid increase in the capacity for intramitochondrial fatty acid oxidation and ketogenesis is of crucial importance within 6 to 12 hours after birth, when glycogen stores are depleted and gluconeogenesis must sustain glucose homeostasis. When the activities of all gluconeogenic enzymes have reached adult levels in the liver soon after birth, gluconeogenesis is mainly controlled by the supply of gluconeogenic precursors—lactate, amino acids, and glycerol—and by the availability of FFAs. The normal baby has a high body fat content (approximately 16% of body weight) and can mobilize FFAs from the periphery, leading to increased gluconeogenic substrate availability in the form of glycerol. In contrast, the SGA infant has a low body fat content at birth and develops hypoglycemia after a short fast. In spite of hypoglycemia, blood β-hydroxybutyrate and acetoacetate levels in SGA babies remain lower than in normal-weight neonates, suggesting inadequate fatty acid stores or a defect in mobilization or oxidation of fatty acids. A deficiency of protein- and fat-derived gluconeogenic substrates also has been implicated as the main factor in the pathogenesis of hypoglycemia associated with severe diarrhea in children.[35]

Table 35-3 Features That Compromise Normal Adaptation to Fasting in the Newborn Period and Predispose to Hypoglycemia

↓ Glycogenolysis in response to glucagon
↓ Gluconeogenesis
↑ Epinephrine (birth stress)
↓ PEP-carboxykinase
↓ α-Butyrobetaine hydroxylase
↓ Carnitine
↓ Fat and glycogen stores (especially in SGA infants)
↑ Brain to body mass ratio
↓ Muscle mass

PEP = phospho*enol*pyruvate; SGA = small for gestational age.

The importance of fatty acid oxidation to the maintenance of the gluconeogenic pathway is further illustrated by experiments in fasting animals and human neonates in whom medium-chain triglyceride (MCT) feeding is associated with an increase in glucose production and the conversion of labeled lactate to glucose.[36,37] Also, inhibitors of long-chain fatty acid oxidation administered to suckling neonatal rats cause an 80% reduction in gluconeogenesis and induce a dramatic fall in blood glucose levels. The administration of MCT to these animals (thereby providing substrate that can bypass the block in long chain fatty acid oxidation) restores a normal blood glucose and a normal rate of gluconeogenesis. In addition to generating substrates and cofactors for gluconeogenesis, enhanced fatty acid oxidation and ketogenesis lead to inhibition of pyruvate oxidation in the peripheral tissues and increased release of recyclable substrates for gluconeogenesis into the blood, namely lactate, pyruvate, and alanine.

Carnitine may be an essential nutrient during the neonatal period owing to a substantially decreased activity of the key enzyme in the synthetic pathway, γ-butyrobetaine hydroxylase.[38] Without an exogenous source of carnitine, such as breast milk or carnitine-supplemented infant formula, neonates who are maintained on carnitine-free total parenteral nutrition develop low plasma and tissue carnitine levels.[39,40] Excessive urinary loss of free carnitine may also contribute to low plasma carnitine levels in premature, stressed, and sick neonates.[41] Exogenous carnitine appears to stimulate fatty acid oxidation and ketogenesis in neonates who are receiving infusions of triglycerides.[42] In some neonates, plasma and tissue levels of carnitine may be reduced sufficiently to inhibit the entry of long-chain fatty acids into mitochondria, thus compromising fatty acid oxidation.

Glucose Use and Brain-to-Body Mass Ratio

Whether expressed on the basis of weight or body surface area, the rate of glucose flux (production and use) is nearly three times higher in infants than in adults, both in the postabsorptive period (4 to 14 hours after eating) and following a more prolonged 30- to 40-hour fast.[43] However, when the data are expressed on the basis of estimated brain weight, the glucose flux is similar in children and adults. The brain of the adult takes up approximately 100 g of glucose per 24 hours. This quantity is disproportionately large because the mass of the adult brain is only 2% of the total body mass, yet it consumes approximately one-fifth of the total calories. The child's brain is larger in relation to body size and must use an even greater proportion of the total calories, predominantly in the form of glucose. This observation supports the hypothesis that the relatively high proportion of brain mass to body size (13% in the newborn versus 2% in the adult) places infants and children at higher risk of hypoglycemia.[44] The ratio of brain to body mass is greatest in premature infants who have an increased glucose flux compared with term infants.[45]

Decreased muscle mass and the subsequent reduction in the provision of substrate for both de novo gluconeogenesis and recycling of three-carbon fragments into glu-

cose are also likely to contribute to the greater susceptibility of the infant and young child to hypoglycemia after glycogen stores are depleted and gluconeogenesis becomes the primary source of endogenous plasma glucose. Several studies have demonstrated an age-related increase in the fasting value of blood glucose and alanine in children and a decrease in fasting blood ketone and FFA levels with increasing age, which is independent of glucose concentrations.[23,46] Comparative studies in normal men, women, and children have determined that after a 30-hour fast, children have the lowest glucose and alanine and the highest β-hydroxybutyrate concentrations.[24] When fasted for 36 hours, children aged 2 to 8 years have lower plasma glucose levels, lower alanine, higher FFAs, and higher β-hydroxybutyrate than older children aged 10 to 18 years whose fasting metabolic profile mimics that of adults.[47] In infants aged 1 to 2 years, the rate and magnitude of substrate changes associated with fasting are even greater.[48] Thus, a combination of more rapid depletion of glycogen stores and decreased availability of substrates for gluconeogenesis results in earlier mobilization of fat in infants and younger children. Their dependency on fatty acid oxidation and ketogenesis during a fast, to maintain glucose homeostasis, is greater and occurs earlier than in older children and adults.[49]

INBORN ERRORS OF METABOLISM LEADING TO FASTING MALADAPTATION

The biochemical hallmark of inborn errors in metabolism that lead to fasting maladaptation is hypoglycemia. Most clinicians define hypoglycemia as a plasma glucose concentration of less than 40 mg/dL (< 2.2 mmol) in infancy (5 days to 1 month) and less than 50 mg/dL (2.8 mmol) in older infants and children.[50] In premature infants, 30 mg/dL is the lower limit of normal. It is important to remember, however, that some normal infants can have low plasma glucose levels and be asymptomatic, and certain infants with inborn errors of metabolism, particularly fatty acid oxidation defects, may manifest symptoms of vomiting, lethargy, or even coma before their blood sugar falls below these levels.[51] The occurrence of hypoglycemia in relation to the duration of the fasting period can give the physician a clue to the metabolic derangement present. The age of the patient will influence the duration of these periods. In infants and younger children, the duration of these periods will be compressed. This classification of inherited metabolic defects leading to fasting maladaptation is not meant to be rigid, and there are numerous patients who will be exceptions to these rules. However, this type of categorization should reinforce in the reader's mind the previous discussion of the sequential steps in the normal adaptation to fasting (Table 35-4).

Hypoglycemia within 0 to 8 Hours of Fasting

Hyperinsulinemia (Increased Glucose Use) Conditions characterized by endogenous insulin excess are probably the most common cause of persistent hypoglycemia in infants, especially in the first year of life. Congenital hyperinsulinism is the predominant cause of persistent hypoglycemia in the neonatal age group, occurring in 1 in 30,000 to 50,000 live births in the general population.[52] Consanguinity increases the incidence to roughly 1 in 2,500. Three subgroups exist based on age of diagnosis. The neonatal form (diagnosed within the first 3 days of life) accounts for 60% of congenital hyperinsulinism, the infantile form for 35% (diagnosed within the first year of life), and the childhood form for 5% (diagnosed after 1 year of age). Other "hyperinsulinemic" states include Beckwith-Wiedemann syndrome, infants of diabetic mothers, infants with erythroblastosis fetalis, and asphyxiated infants.[53] These latter forms are considered transient in nature.

Often these infants are large for gestational age, which suggests that the insulin excess began in utero. An increase in hepatic glycogen synthesis accompanying hyperinsulinism may lead to mild hepatic enlargement; however, hepatomegaly is much less conspicuous than in infants with metabolic defects affecting glycogenolysis, gluconeogenesis, or fatty acid oxidation. Younger patients can present with such nonspecific signs and symptoms as hypotonia, cyanosis, poor feeding, irritability, or hypothermia. Unfortunately, most symptoms are not initially recognized as evidence of hypoglycemia.[10] In addition, 20% will be asymptomatic.[8] The childhood form can present with more specific autonomic symptoms such as perspiration, anxiety, weakness, and reports of palpitations. On the other hand, there are several common features for most patients with hyperinsulinism, including macrosomia at birth and a high risk of hypoglycemic seizure as the presenting event (50% of patients across subtypes).[10] Interestingly, some patients with the childhood form of hyperinsulinism may tolerate hypoglycemia, perhaps owing to decreased central nervous system glucose requirements,[54] and require only increased calories initially for stabilization of blood sugars. These children also respond favorably to medication, principally owing to genetic mutations not affecting the normal expression of critical receptors (SUR1) in this age group.[11] Conversely, neonatal disease is much more difficult to manage.

Excessive insulin promotes increased glucose use, resulting in removal of glucose from the blood. Lipolysis and fatty acid oxidation are inhibited, thus decreasing the availability of FFAs and ketones as alternate fuels. Because of the constant presence of excessive endogenous insulin and resulting inhibition of gluconeogenesis, lipolysis, and ketogenesis, the hypoglycemia that accompanies insulin excess occurs early in the fasting period, is profound, and often requires high rates of glucose infusion for correction.[55] Most patients require a glucose infusion rate greater than the 8 mg/kg/minute generally accepted as the normal newborn requirement to maintain a plasma glucose concentration > 2.6 mmol during fasting, and some even exceed 10 mg/kg/minute, which is considered the maximum amount of glucose needed to maintain an adequate blood glucose concentration in a premature infant or stressed SGA infant.[56] In one study of 12 patients with hyperinsulinemia, the mean glucose requirement was 14.5 mg/kg/minute and the range was 7.1 to 28 mg/kg/minute.[50]

Table 35-4 Inborn Errors of Metabolism Leading to Fasting Maladaptation and Hypoglycemia

Within 0–6 hours of fasting
Hyperinsulinemia: nesidioblastosis, insulinoma
(↑ glucose utilization, ↓gluconeogenesis, ↓ketogenesis)
GSD-I; glucose-6-phosphatase deficiency
(↓ glycogenolysis, ↓gluconeogenesis)
6–12 hours postfasting
GSD-III; debrancher enzyme deficiency
(↓ glycogenolysis)
12–18 hours postfasting
Fructose-1,6-diphosphatase deficiency
(↓ gluconeogenesis)
With prolonged fasting
Fatty acid oxidation disorders
(↓ ketogenesis, ↑glucose utilization)
Ketolysis defects
(↓ peripheral utilization of ketones)

GSD = glycogen storage disease.

Most patients with hyperinsulinemia develop hypoglycemia less than 8 hours after beginning a fast. In one study, 11 patients became hypoglycemic in a mean interval of 2.1 hours, and in another, the mean time of fasting to hypoglycemia was 6.4 hours.[50,57] This contrasts to a mean time of 24.7 hours in children with ketotic hypoglycemia. The diagnosis of hyperinsulinism in both infants and children is made by an inappropriately elevated serum insulin concentration during a period of hypoglycemia (blood glucose < 45 mg/dL). The excessive insulin secretion usually reduces the glucose-to-insulin ratio in the blood to < 4.0. This relative ratio may be used to establish the diagnosis of hyperinsulinism even in the absence of an absolute elevation of serum insulin concentration. A plasma insulin concentration > 10 U/mL with a simultaneous glucose concentration of < 50 mg/dL (2.8 mM) at any time has been accepted as diagnostic of hyperinsulinemia by some authors.[58]

At the time of hypoglycemia, it is imperative to obtain several critical laboratory studies (Table 35-5). Diagnostic clues to hyperinsulinism during a hypoglycemic episode include suppressed ketone formation and low levels of FFAs and IGF binding protein I. However, children under the age of 3 months may lack the apparatus to generate ketones, underlining the importance of serum insulin levels in these children.

Paradoxically, decreased concentrations of ketones and FFAs are often found at the time of hypoglycemia. Thus, patients with hyperinsulinemia present with hypoketotic or nonketotic hypoglycemia. Plasma levels of β-hydroxybutyrate at the time of hypoglycemia may be the best indicator of hyperinsulinemia. In a study by Stanley and Baker, fasted normal control infants and children with ketotic hypoglycemia who developed a plasma glucose < 40 mg/dL had an expected mean level of β-hydroxybutyrate of 2.9 mM with a lower limit (mean 2 SD) of 1.1 mM.[55] However, 10 of the 11 determinations of β-hydroxybutyrate in patients with hyperinsulinemia and plasma glucose < 40 mg/dL were more than 2 SD below the expected level of 2.9 mM. Concentrations of FFAs at the time of hypoglycemia are also a good discriminator of hyperinsulinemia, with a level below 0.46 mM separating these patients from normal infants or children with ketotic hypoglycemia. Cortisol and GH levels are usually elevated; thyroid hormone levels are normal.

Owing to excessive glycogen stores in patients with hyperinsulinemia, the administration of glucagon (1 mg intramuscularly) stimulates hepatic glycogenolysis and results in a marked increase in serum glucose values, exceeding increments of 30 mg/dL.[50] This test differentiates patients with hyperinsulinemia from those with disorders of glycogen synthesis and breakdown, with the exception of glycogen synthase deficiency. This finding is also contrary to what is seen in patients with most other metabolic causes of hypoketotic hypoglycemia, such as fatty acid oxidation disorders. In these patients, the hypoglycemia occurs later in the fasting period when glycogen stores are already exhausted, and there is a blunted or absent glucose response to parenteral glucagon.

Recently, several groups have published data concerning the histologic heterogeneity of congenital hyperinsulism. Histologically, the neonatal and infantile groups are composed of two categories based on the morphology of the affected beta cells. These are the focal adenomatous and the diffuse forms.[10] Focal areas of beta cell hyperplasia, responsible for 25 to 50% of cases, are associated with large islet cell clusters around connective tissue, whereas diffuse disease appears as islets with prominent, enlarged beta cell nuclei.[8] However, the childhood form is predominantly caused by focal adenomas (insulinomas). Most insulinomas are sporadically inherited, whereas some are associated with multiple endocrine neoplasia syndrome. Rarely, children have true islet cell adenomas of the pancreas.[59] When the diagnosis of an islet cell adenoma is made in a child, a search for hyperparathyroidism, hypergastrinemia, and pituitary tumors must be undertaken to exclude multiple endocrine neoplasia syndrome, type I.

Sustained hyperinsulinemia in infants is usually the result of nesidioblastosis, which is defined by diffusely increased numbers of beta islet cells in the pancreas. These cells appear to arise by budding from the exocrine pancreatic ducts and resemble the histologic pattern of early fetal pancreas. The histologic subtypes common to both neonatal and infantile disease are associated with specific genetic mutations of beta cell receptors, which have implications for the patient's ability to respond to current therapy. Most

TABLE 35-5 Studies Needed during Hypoglycemia (< 45 mg/dL)

Serum insulin level
Serum ketones
Serum electrolytes and confirmatory serum glucose
Growth hormone
Cortisol
Serum lactate
Serum acyl carnitine level and total carnitine
Serum amino acids
Urine studies obtained with next void
Urine organic acids

Give glucagon (usually 0.5 mg intramuscularly) after serum samples are obtained and measure serum glucose response every 10 minutes over the next half hour.

mutations discovered to date are found in the neonatal-onset form of hyperinsulinism. Focal lesions are linked to the loss of the maternal 11p15 allele and an alteration in homozygosity of either paternally derived K^+_{ATP} channel subunits, the SUR1 or the inward-rectifying potassium channel KIR6.2.[10] Unfortunately, most patients respond poorly to medical treatment because diazoxide targets the SUR1 receptor. This precludes its use in children with mutations of this receptor and of receptors associated with it (KIR6.2). Diffuse beta cell hyperplasia results from either a mutation in the SUR1 or the *KIR6.2* gene.[10] Dominantly inherited patterns of diffuse hyperinsulinism may likewise have mutations of the glucokinase (GCK) or the glutamate dehydrogenase (GDH) gene.[9] Overactivity of these genes causes an increase in the ATP-to-ADP ratio and subsequent insulin release. In GDH mutations, hyperammonemia is a concurrent finding that rarely causes symptoms or requires therapy.[6] The accumulation of serum ammonium is attributable to decreased levels of *N*-acetylglutamate, an enzyme critical for ammonium catabolism.[9] Lesions owing to GDH or GCK mutations typically present later and respond well to medical therapy.

Transient hypoglycemia associated with hyperinsulinism has been documented in children with Beckwith-Wiedemann syndrome, infants of diabetic mothers, infants with erythroblastosis fetalis, and infants subjected to perinatal asphyxia.[53] Beckwith-Wiedemann syndrome is characterized by macroglossia, macrosomia, omphalocele, and a prominent earlobe fissure.[60] Hypoglycemia typically resolves within the first few months of life but is difficult to control and frequently requires medical intervention. Beta cell hyperplasia has been noted at autopsy. The cause of transient hyperinsulinism in children born to mothers with diabetes has been well defined. These infants are subjected to high serum glucose concentrations in utero, which is amplified during poor diabetes control. This increased serum glucose stimulates pancreatic insulin secretion and beta cell hyperplasia.[61,62] Consequently, the fetus stores large amounts of protein, fat, and glycogen, resulting in the typical phenotype of a large, plethoric infant. In mothers who are able to establish tight metabolic control (mean glucose concentration of 86 mg/dL), the opposite is true: 20% of resulting newborns are SGA. Hypoglycemia in infants of diabetic mothers is the result of postnatal dysregulated insulin secretion and suppressed glucagon release. This classic hormonal profile inhibits the breakdown of stored glucose during periods of fasting (immediate postnatal period). Therefore, these infants may require large amounts of intravenous glucose to stabilize blood sugar, which may normalize within several days. It is, however, not unusual for infants to depend on supplemental glucose for long periods. Hyperplasia of pancreatic islet cells also occurs in infants with erythroblastosis fetalis, which is a hemolytic process in the newborn resulting from the transplacental passage of maternal antibodies to the baby's red blood cells.[63] The cause is uncertain but may be linked to elevated levels of reduced glutathione resulting from hemolysis, which may stimulate insulin release.[64] Infants born SGA and asphyxiated infants are of particular concern during the first few weeks of life. The etiology of the hypersecretion of insulin is unknown; however, these patients may require diazoxide as well as large amounts of glucose to maintain euglycemia (20 mg/kg/minute or more). Although transient in nature, these infants are at increased risk for neurodevelopmental delays from hypoglycemia, as well as their underlying disease.

Glycogen Storage Disease (Impaired Production of Glucose from Glycogen) As opposed to the increased glucose use seen in patients with hypoglycemia owing to hyperinsulinemia, a second major category of conditions causing hypoglycemia is characterized by a deficiency of glucose production during fasting (see Table 35-4). Deficiencies of glycogen synthesis or glycogen degradation can lead to hypoglycemia relatively early during the fasting period. Severe hypoglycemia may be observed in newborns with glycogen synthetase deficiency (type 0 GSD).[65] Other patients have presented later, after nighttime feedings were stopped, with hypoglycemia but without hepatomegaly.[66] Hypoglycemia appears 6 to 10 hours after meals and is accompanied by markedly elevated plasma ketones. The liver biopsy may show little besides a relatively low glycogen content. In contrast, hypoglycemia in response to fasting is distinctly uncommon in another disorder affecting glycogen synthesis, brancher enzyme deficiency (type IV, Andersen's disease, amylopectinosis).[67] Most of these patients present late in the first year or in the second year of life with hepatosplenomegaly, abdominal distention, and failure to thrive. Later, progressive liver dysfunction and cirrhosis dominate the clinical picture. This enzyme defect causes the formation of glycogen with long outer branches that resemble amylopectin, a form of plant starch. The abnormally structured glycogen may act as a foreign body, stimulating a chronic inflammatory reaction in the liver.

The onset of fasting-induced hypoglycemia occurs more slowly (4 to 12 hours into a fast) in some patients with debrancher enzyme deficiency (type III GSD, Cori disease, limit dextrinosis). This is probably owing to the fact that this defect is rarely complete and hepatic gluconeogenesis remains intact. Debrancher enzyme deficiency results in an inability to degrade the 1,6-glucosyl linkages, which form the branch points in glycogen, and in the presence of glycogen with short outer chains.[68] Growth failure and hepatomegaly are prominent early in life.[69] Hepatic fibrosis may lead to the development of splenomegaly in some children by the time they are 4 to 6 years of age. Cardiomyopathy and muscle weakness frequently develop during the second and third decades of life. Moderate elevations in serum triglycerides are common, and liver transaminases are often increased to 200 to 400 U/L. Early on, the liver biopsy may show increased glycogen and fat and varying degrees of fibrosis. Several clinical findings are helpful in diagnosing debrancher deficiency and distinguishing it from the more common glucose-6-phosphatase deficiency (type I GSD [see below]). The rise in plasma glucose following administration of glucagon is usually normal 2 to 3 hours after a meal, when the terminal branches of glycogen are still full of available 1,4-glucosyl linkages. However, 6 to 12 hours

after a meal, there is no response to glucagon because glycogen has already been degraded to its 1,6-glycosyl linkage branch points. Blood lactate levels are normal or low during fasting because there is no defect in gluconeogenesis. Plasma lactate increases abnormally to 4 to 6 mEq/L following an oral glucose load, perhaps owing to an abundance of glycogen stores and disposal of glucose via glycolysis to pyruvate and lactate. Phosphorylase deficiency (type VI GSD) resembles a mild form of debrancher deficiency, with fewer problems with hypoglycemia and growth failure and without the late development of cirrhosis and myopathy.

Deficiency of glucose-6-phosphatase (type Ia GSD) is the most common of the GSDs and is associated with profound hypoglycemia, growth failure, and massive hepatomegaly.[70] Liver biopsy shows markedly increased fat and glycogen, with glycogen levels of 6 to 10 g per 100 g of tissue. A less common form of this disorder is attributable to a defect in the microsomal transport of glucose-6-phosphate (type Ib GSD) and is associated with impaired neutrophil function, neutropenia, recurrent infections, and occasionally inflammatory bowel disease.[71] Because this enzymatic defect is not truly in the glycogenolysis pathway but in the hydrolysis of glucose-6-phosphatase to glucose, this disorder is usually considered with other disorders of gluconeogenesis. Hydrolysis of glucose-6-phosphate is the final common enzymatic event in the hepatic release of glucose from both the gluconeogenic and glycogenolytic pathways. Therefore, deficiency of glucose-6-phosphatase typically results in severe hypoglycemia occurring 3 to 6 hours after a meal and is associated with ketosis and lactic acidosis in early infancy. The mechanism for glycogen accumulation in this disorder is not clear because insulin concentrations are low, glucagon concentrations are elevated, and the in vitro activities of the enzymes responsible for glycogenolysis are normal. Recent studies suggest that accumulating glucose-6-phosphate itself may activate glycogen synthesis and inhibit glycogen degradation via inhibition of the phosphorylase enzyme.[72]

Other metabolic abnormalities encountered in patients with GSD type I are understandable as consequences of a block in gluconeogenesis. Chronic hypoglycemia not only provokes increased secretion of various insulin counterregulatory hormones (catecholamine, glucagon, and cortisol), it also suppresses insulin secretion, resulting in increased glycogenolysis, lipolysis, and muscle catabolism. The lactate generated from increased anaerobic glycolytic processes in muscle and from red blood cell metabolism would normally be removed and reconverted to glucose via the hepatic gluconeogenic pathway. This avenue is blocked, resulting in levels of blood lactate generally 4 to 8 times normal. High levels of lactate can serve as an alternative fuel for the brain, and this is thought to be the explanation for the lack of seizures or other central nervous system manifestations of hypoglycemia in some patients with this disorder. In contrast to type III GSD (debrancher enzyme deficiency [see above]), the administration of intramuscular glucagon does not result in any significant rise in blood glucose but does result in a dramatic increase in blood lactate levels. Ketosis is associated with exaggerated lipolysis and low basal insulin levels. However, the degree of ketonemia observed in these patients is less than that observed in children fasted for 24 to 30 hours, suggesting a defect in ketogenesis.[73] Excessive lipolysis and a relative impairment in ketogenesis may account for the hypertriglyceridemia that is characteristic of this disorder. Hypophosphatemia and hyperuricemia are also common in older patients and result from the sequestration of intracellular phosphate as glucose-6-phosphate and the subsequent reduction in intracellular ATP levels. The decrease in intracellular phosphate levels results in the deinhibition of AMP deaminase and the overproduction of uric acid from AMP.

Hypoglycemia within 8 to 16 Hours of Fasting

Defects in Gluconeogenesis: Impaired Conversion of Gluconeogenic Precursors into Glucose In disorders of gluconeogenesis, fasting hypoglycemia is generally more pronounced the closer the enzyme defect is located to the final common pathway for glucose release via glucose-6-phosphate (see Figure 35-2). Thus, in pyruvate carboxylase deficiency, a disorder of intramitochondrial pyruvate oxidation to oxaloacetate, hypoglycemia is not an obligatory symptom; however, in glucose-6-phosphatase deficiency (GSD type Ia), it is invariably a severe component of the disease. All of these disorders are characterized by elevated plasma levels of substrates at the origin of gluconeogenesis such as lactate, pyruvate, and alanine. In some of these disorders (pyruvate carboxylase deficiency and PEPCK deficiency), the urea cycle may be secondarily compromised, resulting in an increase in plasma levels of ammonia, citrulline, and lysine.

Hepatic fructose-1,6-diphosphatase deficiency results in a defect in the conversion of fructose-1,6-diphosphate to fructose-6-phosphate, which is then converted to glucose-6-phosphate. Patients with this rare enzyme defect usually present during the first year with life-threatening episodes of hypoglycemia provoked by fasting or catabolic stress (eg, infections, burns) and other signs, symptoms, and laboratory findings similar to those of GSD type I. However, in contrast to GSD type I, the timing of the hypoglycemia after 12 to 16 hours of fasting is later, and excessive hepatic glycogen accumulation does not occur because the glycogenolytic pathway is intact. The mild to moderate hepatomegaly is secondary to hepatic steatosis, and liver enzymes are either normal or only mildly disturbed. Between crises of hypoglycemia and metabolic acidosis, the most frequent findings are hyperventilation, mild lactic acidosis, and muscle weakness.

Because glycogenolysis is intact, glucagon administration produces a hyperglycemic response in the immediate postprandial period.[74] Glucose, galactose (lactose), and maltose can be metabolized normally and stored as glycogen. Because fructose (sucrose), glycerol, and alanine enter the gluconeogenic pathway below the level of the defective

enzyme, these substances cannot be converted to glucose. The ingestion of these precursors will result in the accumulation of lactate and may actually precipitate a fall in plasma glucose concentration. However, unlike the more common defect in fructose metabolism, hereditary fructose intolerance (fructose-1-phosphate aldolase deficiency), crises of hypoglycemia, lethargy, coma, acidosis, hypophosphatemia, and hyperuricemia are not solely dependent on the ingestion of fructose.

Two other enzymes are responsible for the recycling of pyruvate and other three-carbon precursors (lactate, alanine) into the gluconeogenic pathway (see Figure 35-2). The mitochondrial biotin-dependent enzyme pyruvate carboxylase catalyzes the conversion of pyruvate to oxaloacetate, which is then converted to malate and shuttled out of the mitochondria to be reconverted back to oxaloacetate. PEPCK then catalyzes the metabolism of oxaloacetate to PEP. Hypoglycemia is an inconsistent finding in patients with pyruvate carboxylase deficiency in whom congenital lactic acidosis, progressive neurologic deterioration, and elevated levels of pyruvate, alanine, and ketones are almost invariably observed. The presentation is more or less severe, depending on whether some enzyme protein is present or there is a complete lack of messenger RNA for pyruvate carboxylase and no residual activity of the enzyme.[75] PEPCK deficiency has only been reported in a few patients and is characterized by hypoketotic hypoglycemia, hypotonia, lactic acidosis, hepatomegaly, and hepatic and muscle steatosis in the first few months of life. Both cytosolic and mitochondrial forms of this enzyme defect have been described.[76]

Hormone Deficiences

Hypoglycemia is also caused by isolated compensatory hormone deficiencies. The presentation of children with panhypopituitarism may be subtle. However, there can be evidence of anatomic abnormalities including midline defects, which provide valuable clues to the diagnosis. Midline defects include structural central nervous system abnormalities (absent corpus collosum, ectopic pituitary), microphallus, cleft palate, and central incisor. One of the most common causes of congenital panhypopituitarism is septo-optic dysplasia, which presents in early childhood with nystagmus (optic nerve hypoplasia), seizures, and developmental delay. These children can develop progressive pituitary dysfunction and may present with hypoglycemia owing to a lack of ACTH and GH. The signs and symptoms of hypoglycemia are similar to those found in children with hyperinsulinism. With this in mind, these children may be ketotic and usually have suppressed serum insulin levels at the time of hypoglycemia. In addition, there is a lack of response to glucagon. Therapy is tailored to provide the missing hormone(s).

Persistent hypoglycemia is a relatively common sign of isolated deficiencies in GH or cortisol, occurring in 11 to 27% of affected newborns. The pathogenesis of hypoglycemia in these children is the inability to stimulate gluconeogenesis (cortisol), a lack of substrate mobilization (cortisol and GH), and increased insulin sensitivity. The most common cause of isolated GH deficiency is the idiopathic form. However, each child should be carefully screened for other hormonal deficiencies and should undergo radiologic studies to ensure an intact hypothalamic-pituitary unit and a lack of mass lesion. One cause of cortisol deficiency in infants is a family of enzymatic defects known as congenital adrenal hyperplasia (CAH). The most common form of CAH is the classic 21-hydroxylase deficiency, which results in electrolyte disturbances (hyponatremia and hyperkalemia), genital ambiguity in female infants, and hypotension. However, hypoglycemia is not the typical presenting sign. Other causes of hypocortisolemia include adrenal hypoplasia, Addison's disease (usually acquired in older children), and ACTH receptor defects. Again, therapy consists of supplementing with the deficient hormone.

Hypoglycemia Occurring with Prolonged Fasting

Fatty Acid Oxidation Disorders There are now at least 24 inherited disorders in this growing family of recently described metabolic defects in the transport and intramitochondrial oxidation of fatty acids. There are three main reasons why these disorders have escaped recognition until recently. First, fatty acid oxidation does not play a major role in energy production until late in fasting, and afflicted individuals may remain asymptomatic until fasting continues long beyond the usual overnight period of 12 hours. Second, the important clue of a paucity of urinary and plasma ketones at the time of hypoglycemia may be overlooked. Third, methods of detecting abnormal fatty acid metabolites in the urine or plasma have only been routinely available for the last decade.

In general, the disorders that affect the most proximal steps in long-chain fatty acid oxidation will result in more profound reductions in ketogenesis, more severe hypoglycemia, and a more precipitous presentation after a shorter period of fasting. Thus, defects affecting the transport of long-chain fatty acids across the mitochondrial membrane (ie, carnitine palmityl transferase deficiency, carnitine transport deficiency) and those affecting the oxidation of long-chain fatty acids (ie, very-long-chain acyl-CoA dehydrogenase deficiency and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency) are most likely to present in the first year of life with potentially life-threatening episodes of hypoketotic, hypoglycemic coma. Patients with defects that allow several turns of the β-oxidation cycle of long-chain fatty acids before encountering the enzymatic block will generate some acetyl CoA, ketones, and ATP from intramitochondrial fatty acid oxidation. Patients with these disorders (ie, medium-chain acyl-CoA dehydrogenase deficiency, short-chain acyl-CoA dehydrogenase deficiency) are likely to tolerate longer periods of fasting and may present later with hypoketotic hypoglycemia, hypotonia, rhabdomyolysis, and failure to thrive.

The hypoglycemia characteristic of these disorders can be explained by two major mechanisms: (1) an increase in

peripheral glucose use owing to the deficient production of ketones, normally the preferred fuel for myocardium and skeletal muscle during prolonged fasting, and (2) the limitation of acetyl-CoA synthesis, which is ordinarily a stimulator of the important gluconeogenic enzyme pyruvate carboxylase. Defective energy production in the skeletal muscle and heart owing to the inability to metabolize long-chain fatty acids leads to fatty deposition, cardiomyopathy, muscle weakness, and rhabdomyolysis, especially during periods of prolonged fasting or catabolic stress brought on by infection, vomiting, dehydration, or other factors. The inability to oxidize fatty acids in the liver results in their diversion into triacylglycerol synthesis and marked hepatic steatosis.

The accumulation of toxic metabolites may be responsible for some of the other metabolic findings in these disorders. Because free CoA does not exchange between the intramitochondrial and cytosolic compartments, blocked fatty acid oxidation leads to intramitochondrial accumulation of acyl-CoA intermediates at the expense of the production of acetyl CoA and the maintenance of the free CoA pool. Hyperammonemia has been attributed to the direct inhibition of key intramitochondrial urea cycle enzymes by accumulating short- and medium-chain acyl-CoA compounds.[77,78] Low intramitochondrial acetyl-CoA levels could also contribute to the hyperammonemia through an inhibition of the production of *N*-acetylglutamate, the allosteric activator of carbamyl-phosphate synthetase, which is the first enzyme in the urea cycle. In an effort to meet the increased demands for gluconeogenesis during episodes of fasting stress and illness, there is accelerated proteolysis and tissue catabolism, which also is likely to contribute to the elevated ammonia, urea, and uric acid characteristically found in these patients.

Alterations in mental status may precede hypoglycemia in some patients with defects in fatty acid oxidation. Accumulating medium- and long-chain fatty acids and dicarboxylic acids are metabolic toxins and have been shown to precipitate mitochondrial damage, uncouple oxidative phosphorylation, cause electroencephalographic changes, and result in increased intracranial pressure in animal models.[79] Long-chain acylcarnitines, another metabolic by-product of inhibited long-chain fatty acid oxidation, have been shown to precipitate myocardial dysfunction, arrhythmias, and cardiac arrest in animals.[80–82] Cardiomyopathy can be a prominent feature in patients with CPT-II deficiency, carnitine transport deficiency, long-chain acyl-CoA dehydrogenase deficiency, and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency.

Although originally characterized as having nonketotic hypoglycemia, most patients with disorders of the fatty acid oxidation continue to produce some ketones even at the time of severe metabolic decompensation. In patients with defects in medium- or short-chain fatty acid oxidation, ketones can be generated from partial β-oxidation of long-chain acyl CoAs to medium-chain intermediates and by continued oxidation of branched-chain amino acids. Even in patients deficient in enzymes of long-chain fatty acid transport or oxidation, peroxisomal oxidation may generate medium-chain intermediates, which can then enter the mitochondria below the block and be further oxidized to ketones.

What is important is that the degree of ketogenesis is inadequate for the degree of fasting, hypoglycemia, and circulating FFAs (Figure 35-4). This dissociation between high plasma levels of FFAs and low plasma levels of ketone bodies can be used as a screening method for diagnosing patients with disorders of fatty acid oxidation or transport. In normal infants, ages 1 to 12 months, the FFA-to-ketone body ratio ranges from 0.3 to 0.7 after a 24-hour fast.[84] When normal children are fasting and blood glucose is less than 3.0 mM (56 mg/dL), plasma ketones are always greater than 1.8 mM. In contrast, in patients with defective fatty acid oxidation, plasma ketones rarely exceed 1.0 mM during fasting, and the ratio of FFA to ketones in the blood always exceeds 1.0 and is often greater than 2.0 when the patient is hypoglycemic. Thus, determination of simultaneous plasma concentrations of glucose, ketones, and FFAs at the time of an acute metabolic decompensation before resuscitation with intravenous glucose can be helpful in making a diagnosis.

Defects in Ketogenesis and Ketolysis Oxidation of fatty acids yields acetyl CoA, the building block for the synthesis of ketones. After condensation of two molecules of acetyl CoA to form acetoacetyl CoA, deacylation is achieved by incorporation of a third acetyl-CoA molecule to form 3-hydroxy-3-methylglutaryl CoA. Cleavage of this molecule by the enzyme hydroxymethylglutaryl-CoA lyase (HMG-CoA lyase) liberates acetoacetate. HMG-CoA lyase also catalyzes the terminal step of the catabolism of leucine to acetyl CoA and acetoacetate. HMG-CoA lyase deficiency has been identified in patients who usually present in the first or second year of life with severe, sometimes fatal, episodes of hypoketotic hypoglycemia, coma, hyperammonemia, elevated aminotransferases, coagulopathy, and marked hepatic steatosis mimicking Reye's syndrome.[85,86] They also manifest severe acidosis from the accumulated intermediates of leucine catabolism (3-hydroxy-3-methylglutaric, 3-methylglutaconic, 3-hydroxyisovaleric, 3-methylglutaric acids). Administration of 3-hydroxybutyrate to a fasting subject with HMG-CoA lyase deficiency resulted in the maintenance of plasma glucose levels. This supports the hypothesis that the hypoglycemia seen in these patients during fasting and catabolic stress is a direct result of the lack of ketone body synthesis.

A functional impairment in the peripheral use of ketones would be expected to mimic a deficiency of ketones and result in increased glucose use during fasting. A few patients have been described with a deficiency of the mitochondrial enzyme acetoacetyl-CoA thiolase (β-ketothiolase), which is responsible for cleavage of acetoacetyl CoA to form acetyl CoA in extrahepatic tissues.[87–89] These patients present in the first or second year of life with episodes of fasting or stress-induced hypoglycemia, often precipitated by a febrile illness or viral gastroenteritis. They are markedly acidotic and ketotic and may accumulate 2-methylacetoacetate, a

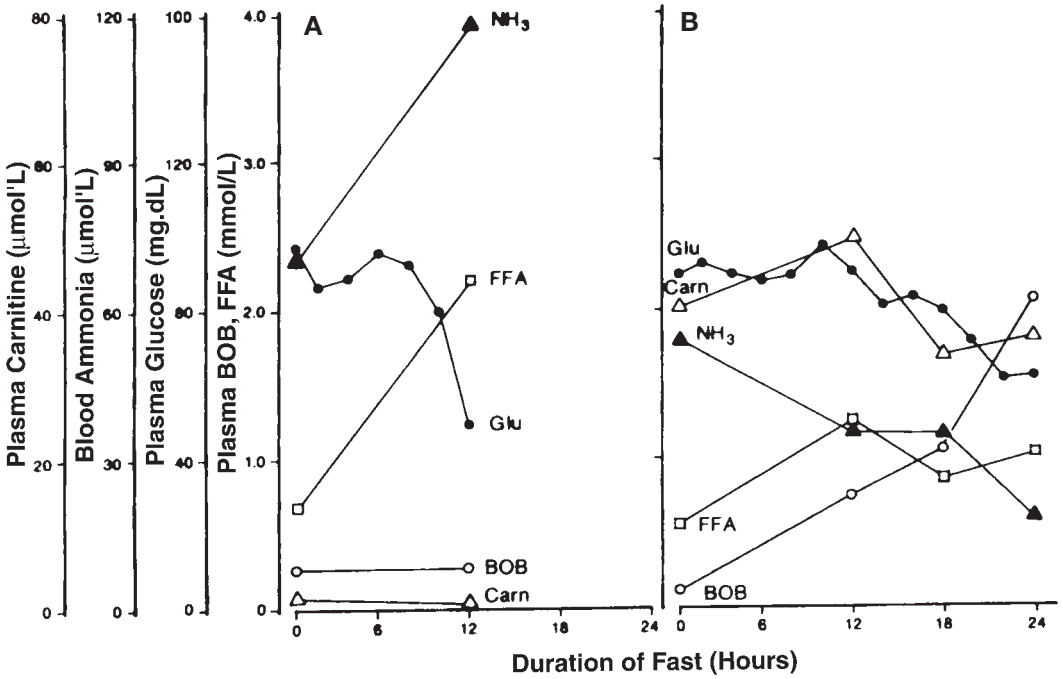

FIGURE 35-4 Metabolic response to fasting in a patient with the carnitine transport defect before (*A*) and after (*B*) long-term oral therapy with L-carnitine. Shown are plasma levels of glucose (Glu), β-hydroxybutyrate (BOB), free fatty acids (FFA), carnitine (carn), and ammonia (NH_3). *A*, The patient's response to fasting before L-carnitine therapy represented clear evidence that hepatic fatty acid oxidation was impaired. Note the falling glucose after a 12-hour fast and the high ratio of FFA to BOB. After L-carnitine therapy (*B*), the defect in ketogenesis was corrected, and a normal capacity for hepatic fatty acid oxidation was restored. Reproduced with permission from Treem WR et al.[83]

metabolite of isoleucine degradation. Several other patients with similar presentations have been reported with a deficiency in succinyl CoA-3-oxoacid CoA transferase activity in extrahepatic tissues. This enzyme is responsible for conversion of acetoacetate to acetoacetyl CoA, which is then cleaved to acetyl CoA by β-ketothiolase.[90] A hallmark of these defects is hyperketosis during fasting owing to the impaired peripheral use of ketones. Fasting studies lasting 20 to 24 hours in these patients result in high levels of ketones in the blood (≥ 4.8 mmol) and very low ratios of FFAs to ketones (≤ 0.3).[84] The product of the plasma ketone body concentration and plasma glucose level (expressed in mM) may also be helpful in separating patients with ketolysis defects from normal infants. Although normal infants and children reach values between 6 and 13 after 20 to 24 hours of fasting, two patients with ketolysis defects achieved markedly elevated levels of 21 and 31.[84]

Typically presenting between 18 months and 5 years, ketotic hypoglycemia is the most common form of low blood sugar, excluding causes related to the treatment of diabetes, during childhood. Being a diagnosis of exclusion, most children presenting with a history of hypoglycemia who are ketotic are evaluated thoroughly for evidence of a metabolic disorder. Initially believed to be secondary to inadequate epinephrine release during times of stress or fasting, there have now been several other hypotheses to explain the pathophysiology. The usual picture is of an acutely ill child who has had poor oral intake. Healthy children are able to withstand 36 hours of fasting before exhibiting signs of hypoglycemia, whereas children with ketotic hypoglycemia are able to tolerate fasting for less than 12 to 24 hours. Blood sugars can be below 20 mg/dL, and hypoglycemic seizures have been reported. Insulin levels are appropriately suppressed, and the counterregulatory hormones (ie, GH and cortisol) are elevated. Alanine levels, on the other hand, are low, indicating a possible defect in protein catabolism or substrate supply. Patients are treated with supplemental intravenous glucose until they are again able to tolerate enteral feeds. Most patients require frequent feedings, and cornstarch supplements at bedtime may be helpful. Parents are advised to monitor urine ketones during illness or fasting as this typically heralds hypoglycemia. This generally benign condition resolves by 9 years of age, suggesting immaturity of the autonomic nervous system and/or of pathways controlling protein catabolism.

DIETARY AND MEDICAL TREATMENT

Because hypoglycemia is a medical emergency, treatment should commence immediately with adequate infusions of intravenous dextrose to prevent seizures and permanent neurologic sequelae. A rate of glucose infusion of 8 to 10 mg/kg/minute or greater in infants should be sufficient to correct the hypoglycemia even in the sickest patients, with the exception of those with hyperinsulinemia, for whom much higher infusion rates may be

needed. The plasma glucose concentration should be maintained above 70 mg/dL (> 4.0 mM). The importance of obtaining plasma and urine samples at the time of hypoglycemia cannot be overemphasized. These samples can be frozen and used for later analysis of insulin, cortisol, GH, thyroid hormone, FFAs, ketone bodies, lactate, pyruvate, ammonia, triglycerides, uric acid, total and free carnitine, acylcarnitines, amino acids, and organic acids.

Once stabilized, the mainstay of therapy for many of these disorders is avoidance of fasting and the provision of adequate amounts of dextrose during periods of catabolic stress. In infants with GSD type I and those with defects in long-chain fatty acid oxidation or transport, this often means continuous overnight intragastric feedings via a gastrostomy or nasogastric tube. In other patients, a late-night feeding with a nutrient that can bypass the metabolic block will be sufficient.

Treatment of Specific Causes of Hypoglycemia

Hyperinsulinemia Medical management of hyperinsulinemia has generally been divided into three strategies: (1) treatments that suppress insulin secretion such as diazoxide[91] and somatostatin analogues[92]; (2) medications that antagonize the effects of insulin on tissues such as glucocorticoids, epinephrine, and glucagon; and (3) therapies that destroy islet cells such as streptozotocin. No single method of treatment has been uniformly successful, and many of them give rise to unacceptable side effects. Specific dietary manipulations in infants have consisted of frequent feedings and a low-protein (low-leucine) diet. Leucine, in addition to a number of other amino acids, has been found to be an insulin secretagogue,[93] and some patients with hyperinsulinemia demonstrate an exaggerated fall in plasma glucose concentration accompanied by a rise in insulin in response to leucine. Most infants (90%) with the onset of symptoms before 1 month of age must undergo subtotal pancreatectomy to control intractable hypoglycemia.[94] These patients often require intravenous glucose infusion rates of 15 to 20 mg/kg/minute along with continuous enteral feeding prior to surgery. If an older infant or child cannot tolerate at least an overnight fast while receiving medical treatment, surgery to remove 85 to 90% of the pancreas is indicated. Even those children who do tolerate such a fast remain at risk for recurrent hypoglycemia during periods of illness and decreased food intake.

Surgical therapy is the only definitive therapy for islet cell hyperplasia. Current computed tomography and magnetic resonance imaging technology rarely allows for the identification of lesions such as islet cell hyperplasia (focal and diffuse) and adenomas. Several centers are now using pancreatic venous catheterization to define the extent of hyperplastic lesions and facilitate surgery, which is currently the only definitive approach. Because diffuse lesions are more common in the neonatal form, a 95% pancreatic resection is often necessary. This increases the risk of developing diabetes later in life. Pancreatectomy, however, is postponed up to 4 weeks in the newborn to exclude transient forms of hyperinsulinism. Therapy should not be delayed; permanent brain damage can be found in 20% of patients with persistent, profound hypoglycemia.

Glycogen Storage Diseases A cessation of the episodes of hypoglycemia and improvement in the metabolic derangements of hyperlipidemia, hyperuricemia, lactic acidosis, and ketoacidosis have been observed in infants and children with GSD type I who were treated with continuous nocturnal intragastric infusion of glucose or glucose polymer–containing solutions.[95] The rate of glucose infused should exceed the normal infant hepatic glucose production rate of 0.25 to 0.5 g/kg per hour (8 mg/kg/minute). This therapy is often continued through adolescence. This is combined with frequent daytime feedings of a high-carbohydrate diet (65 to 70% of calories) containing abundant starch, maltose, and glucose.[96] Most infants will require feedings every 2 to 3 hours. Breast milk may be used, but a formula with glucose polymers and low lactose is preferable if breast milk is unavailable. In patients above the age of 2 to 3 years, feedings of 1 to 2 g/kg of uncooked cornstarch suspensions every 6 hours have been effective as a slowly absorbed form of carbohydrate, allowing greater stability in blood glucose concentrations and a longer interval between feedings.[97,98] Lactose (galactose) and sucrose (fructose) are avoided because galactose and fructose cannot be converted to glucose when glucose-6-phosphate is deficient. Although the liver remains enlarged, many children treated with this aggressive dietary intervention exhibit a sustained increase in growth velocity. Most patients require allopurinol to prevent the formation of renal uric acid stones, and in spite of treatment, many develop focal segmental glomerulosclerosis, nephrotic syndrome, and renal failure in the third to fourth decades of life.[99] They are also at increased risk of developing hepatic adenomas and even hepatocellular carcinoma later in life.[100]

Treatment of type III GSD (debrancher enzyme deficiency) is modified to reflect the intact gluconeogenic pathway. To promote gluconeogenesis from amino acids, frequent feedings of a high-protein, low-carbohydrate diet, together with continuous overnight intragastric infusions of glucose plus protein, are given. Protein intake is increased to approximately twice the normal intake for age. The use of high-protein rather than high-carbohydrate feedings blunts the tendency toward postprandial hypoglycemia. The emphasis on the use of cooked and uncooked starch is similar to that for GSD type I. Fructose and galactose are not excluded from the diet (see Appendix: Table A–24).

Defects in Gluconeogenesis Treatment of patients presenting with fructose-1,6-diphosphatase deficiency early in life consists of frequent feedings to avoid prolonged periods of fasting beyond 8 to 12 hours and the elimination of fructose, sucrose, and sorbitol from the diet. A diet containing 60 to 65% usable carbohydrate (glucose, maltose, and lactose), 10 to 15% protein, and 20 to 25% fat is effective in controlling the chronic lactic acidosis and hypoglycemia. On this diet, patients demonstrate normal

growth. However, at times of infection or other catabolic stress, these patients can develop severe lactic acidosis, ketoacidosis, and hypoglycemia and require parenteral glucose administration. Treatment of patients with pyruvate decarboxylase deficiency has generally been disappointing. It has included dietary supplementation with L-glutamine and aspartate to increase the availability of oxaloacetate and promote gluconeogenesis.[101] Cofactors such as lipoic acid, thiamin, and biotin have been used, especially in patients with some enzyme protein present.[102]

Defects in Fatty Acid Oxidation Infants with defects in fatty acid oxidation or transport may require aggressive nutritional management, particularly if they are hypotonic or have developed cardiomyopathy and do not take adequate oral calories. They will benefit from continuous overnight high-carbohydrate, low-fat formulas administered via nasogastric or gastrostomy tubes. During the day, frequent oral or gastrostomy tube boluses are given. The choice of formula depends on the defect. In patients with long-chain fatty acid oxidation or transport defect, formulas high in MCT are recommended. The advantages of medium-chain fatty acids in this setting include passage into the mitochondria without the need for the formation of an acylcarnitine intermediate and continued availability for oxidation to acetyl CoA by intact intramitochondrial β-oxidation enzymes with substrate specificity for medium-chain substrates.[103,104] In addition, recent work implicating long-chain acylcarnitines and long-chain dicarboxylic acids in disrupting the normal metabolism of cardiac and skeletal muscle myocytes raises the specter of development of cardiomyopathy, muscle weakness, or rhabdomyolysis over time if the provision of long-chain fat is not curtailed. Beyond the age of 2 years, a prebedtime high-carbohydrate snack or a late night feeding of uncooked cornstarch may be substituted for overnight feedings. We continue to recommend a high-carbohydrate, low-fat diet (approximately 20% of calories), supplemented with MCT oil, even for older children.

Patients with medium-chain acyl-CoA dehydrogenase deficiency and other enzyme deficiencies affecting the oxidation of medium- and short-chain fatty acids do not require a special formula, and there is no clear evidence that restricting long-chain fats is necessary. MCT oil is contraindicated in patients with medium- and short-chain fatty acid oxidation defects. Drugs that inhibit intramitochondrial fatty acid oxidation should be avoided in all patients with fatty acid oxidation disorders. These include valproic acid, salicylates, ibuprofen, and amiodarone.

L-Carnitine supplementation at a dose of 100 mg/kg/day is essential in patients with the carnitine transport defect in whom it will maintain plasma carnitine levels in the normal range, restore hepatic carnitine to near-normal levels, correct the defect in fatty acid oxidation in the liver, and increase skeletal muscle and cardiac muscle carnitine levels sufficiently to reverse myopathy and cardiomyopathy in these patients (see Figure 35-4).[83] In other fatty acid oxidation disorders, the benefits of exogenous L-carnitine are not as clear. The administration of large doses of oral L-carnitine to patients with medium-chain acyl-CoA dehydrogenase deficiency results in increased urinary excretion of the medium-chain fatty acid metabolite octanoylcarnitine with restoration of normal plasma levels of total and free carnitine.[105] Some investigators believe that this mimics the situation inside the mitochondria and indicates detoxification of accumulating metabolites, excretion of these metabolites as acylcarnitine esters, and restoration of a normal intramitochondrial free CoA pool. This is the same justification for the use of L-carnitine as that used in the treatment of propionic and isovaleric acidemia.[106,107] Currently, most patients with long-chain fatty acid oxidation defects are supplemented with modest doses of L-carnitine (20 to 50 mg/kg/day) to normalize their plasma carnitine concentrations.

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CHAPTER 36

PERSISTENT RENAL FAILURE

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This chapter outlines principles for the management of nutritional disturbances related to acute and chronic kidney diseases. The relationship between blood composition and nutritional balance is dependent in many ways on the regulatory action of the kidney. The presence of adequate urine volume, although reassuring, does not necessarily indicate the presence of adequate filtering capacity or glomerular filtration rate (GFR). Furthermore, the concentrating and diluting capacity of the kidney depends on a complex set of physiologic factors, which are variably affected by renal disease. Thus, dysfunction of either GFR or urinary concentrating and diluting capacity can affect urine volume.

Understanding the effects of dietary modification on renal function, as well as on renal growth and development, could permit implementation of nutritional therapy that improves prognosis in patients with progressive renal insufficiency. The effects of modifying diet on the progression of chronic renal disease have been examined principally in adult patients; thus, pediatric data are limited. It should be noted that Recommended Dietary Allowances (RDAs) have been developed from observations in normal children and in adults. Because the RDA is generated from normal individuals, it should be used only as a starting point in children in chronic renal disease. Some components of the diet might need to be provided in amounts that seem excessive, whereas others are required in amounts that might seem too small.[1]

We first discuss renal development and function, because both have relevance to nutritional issues. We then discuss the general nutritional needs of children requiring intensive care unit monitoring because such patients often have concomitant renal and nutritional problems. We then consider nutrition in children with various degrees of renal insufficiency and discuss nutritional issues in acute renal failure, followed by chronic renal insufficiency, dialysis, and transplantation. Finally, we include a section that considers specific renal dysfunctions—of glomerulus, proximal tubule, and collecting duct—and describe nutritional adjustments tailored for such patients.

NUTRITIONAL ASPECTS OF RENAL GROWTH AND FUNCTIONAL MATURATION

During gestation, the fetal kidney plays little direct role in metabolic balance, even though fetal urine appears by the third month.[2,3] The placenta regulates fluid and electrolyte balance, even when there is bilateral renal agenesis. Indeed, in the case of unilateral renal agenesis, compensatory hypertrophy occurs following birth, when renal function takes over its regulatory role in metabolic balance, but not before.[4,5] Renal development is influenced by many factors, both genetic and environmental. One important factor is maternal nutrition. Recent data suggest that maternal diet could influence nephrogenesis, with the result that individuals whose mothers have low protein intakes during gestation could have a relatively lower total complement of nephrons at birth.[6] Several large population studies suggest that birth weight is inversely related to hypertension later in life, possibly as a result of nephron endowment, in that fewer nephrons could lead to increased work per nephron, eventual hyperfiltration, and then scarring.[7–9]

Renal function is relatively low at birth and increases during the first months of life.[10] Low birth weight infants have a relatively rapid increase in GFR compared with full-term infants. However, in general, postnatal renal function increases more rapidly than does renal weight, basal metabolic weight, or surface area. An infant's nutritional intake is a major stimulus to both postnatal renal growth and renal functional maturation. A full-term infant exposed to human milk, which has a low renal solute load (25 mOsm/L urine), has a relatively low GFR and a low rate of renal metabolic energy expenditure. In early infancy, protein or amino acid intake can influence renal growth. When premature infants receive a relatively high-protein diet, GFR increases more rapidly than in those who do not.[11] However, a diet too high in protein has been reported to be associated with metabolic acidosis, failure to thrive, and even evidence of renal injury.[12]

GLOMERULAR FILTRATION RATE

Creatinine clearance varies with age and gender secondary both to differences in creatinine production (a function of muscle mass) and actual clearance of creatinine. Serum creatinine can be used to estimate creatinine clearance in children by using an equation that multiplies the child's length or height by a proportionality constant and divides this by the serum creatinine (Table 36-1).[13] A formal endogenous creatinine clearance can overestimate the percentage of residual function because tubular secretion and filtration of creatinine occur and the latter becomes a larger fraction of total urine creatinine as glomerular filtration decreases.

Loss of muscle mass or clearance of creatinine by nonrenal routes also contributes to inaccuracy of serum creatinine and creatinine clearance in predicting residual function. Nevertheless, creatinine clearance assessment remains in common use because of its ease of performance and low cost. The GFR is assessed by measuring total plasma clearance of a substance (eg, creatinine [endogenous], inulin [exogenous]) that is excreted only in the urine and using a timed collection of urine and a serum sample.[14] The formula for calculating GFR is:

$$GFR = U_x \times V/P_x$$

where U_x is the concentration of a substance in the urine (eg, creatinine in mg/dL), V is measured in mL/min, and P_x is the concentration of a substance in plasma (eg, plasma creatinine in mg/dL). GFR is measured in milliliters per minute. This value is corrected to a specified surface area, most often 1.73 m^2 (or 1.0 m^2) to account for differences in body size.

The gold standard for measurement of GFR is inulin, a polyfructosan thought to be freely filtered at the glomerulus; other markers for GFR include ^{125}I-iothalamate, cold or nonradioactive sodium iothalamate, ^{51}Cr-ethylenediaminetetraacetic acid (EDTA), and Tc 99m-diethylenetriamine pentaacetic acid (DTPA). These markers can be used to measure GFR by either standard urine or serum sampling or by the constant-infusion or decay-curve methods. Estimation of GFR from plasma creatinine without a urine sample can be made by using a constant K, which varies with age—preterm infants, full-term infants, children, and adolescents—along with body length or height. The Schwartz formula is:

$$\text{Creatinine clearance} = K \times L/P_{Cr}$$

where L is height in centimeters and P_{Cr} is plasma creatinine in mg/dL. Creatinine clearance is measured in mL/min/1.73m^2. It has also been suggested that GFR be referenced until age 12 to weight and age rather than to surface area (see Table 36-1).[14]

TABLE 36-1 Estimation of Glomerular Filtration Rate

Creatinine clearance may be estimated as $C_{Cr} = kL/S_{Cr}$

C = clearance
k = proportionality constant
L = length (cm)
S_{Cr} = serum creatinine

k values	
Low birth weight babies during year 1 of life	= 0.33
Full-term babies (appropriate for gestational age) during year 1 of life	= 0.45
Children and adolescent girls	= 0.55
Adolescent boys	= 0.79

Note: If a patient's body habitus differs markedly from normal, more standard methods of creatinine clearance should be used.

Adapted from Schwartz GJ, Brain LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children and adolescents. Pediatr Clin North Am 1987;34:571.

The slope of 1/serum creatinine ($1/S_{Cr}$) plotted against time can be used to predict time to end-stage renal disease or need for dialysis.[15] When $1/S_{Cr}$ is less than 0.1, end-stage renal disease care is usually needed,[16] but prediction by this technique can be prone to substantial error.

Renal concentration and dilution are crucial to homeostasis. The kidney is able to achieve a maximum concentration of 1,400 mOsm/L and a minimum of about 50 mOsm/L.[17] However, in renal dysfunction, urine is often isosmotic—300 mOsm/L—with the result that a liter of water must be excreted for each 300 mOsm of renal solute. Thus, solute per 1,000 calories becomes important. Special renal formulas that provide lower mOsm/1,000 calories are preferable in many forms of renal dysfunction.[1]

UNDERNUTRITION AND RENAL FUNCTION

Undernutrition can complicate renal injury from any cause, and this must be kept in mind in the nutritional management of renal disorders. Alterations in renal function have parallels to diverse forms of undernutrition, for example, primary protein-energy malnutrition, iatrogenic malnutrition, or anorexia nervosa. Changes in renal function include decreases in GFR, a decrease in renal plasma flow, poor urinary concentrating ability, decreased ability to excrete sodium, and impaired acid excretion. Significant reductions in GFR are not necessarily accompanied by renal structural damage and are not always explained by hypoproteinemia or edema, which can occur in such states.[18–22]

Protein intake influences both GFR and renal plasma flow.[23] In fact, protein loading can be used to determine renal functional reserve, which is the increase in GFR seen with a challenge to glomerular filtration.[24] Increased intrarenal angiotensin II could play a role both in GFR changes and in lack of urinary concentrating ability.

A number of trace elements are elevated in chronic renal insufficiency,[25,26] including copper, lead, strontium, tin, aluminum, chromium, and silicon, whereas others, such as zinc, can be low. In the 1970s and early 1980s, aluminum phosphate binders were commonly used, with resultant aluminum overload.[27] In polyuric children, water-soluble vitamins can be depleted; this is certainly the case in children on dialysis. Special vitamin preparations are helpful. These include Nephrocaps (Fleming, Fenton, MO), Nephrovite (R and D Laboratories, Marina del Rey, CA), Iberet (Abbott Laboratories, Chicago, IL), and Berocca (Roche, Nutley, NJ). Levels of vitamin A and other fat-soluble vitamins are high in patients with renal insufficiency and do not require supplementation.[28,29] It has been suggested that vitamin C be given very judiciously to avoid elevating serum oxalate levels.[30]

NUTRITIONAL SUPPORT FOR THE CHILD IN INTENSIVE CARE

In addition to treating renal failure per se, any pediatric patient in the intensive care setting with renal concerns requires nutritional support both to minimize the catabolic effects of hypermetabolism, which can follow an acute

injury, and to maintain the positive nitrogen balance necessary for growth and repair. Additionally, prolonged immobilization can alter the fine balance of calcium-phosphorus, vitamin D, and parathyroid hormone (PTH), further emphasizing the need for optimal long-term nutritional planning. Early intervention with protein, calories, and vitamin support can prevent the shifts seen in growth percentiles after an acute stress and, more importantly, can prevent the development of multisystem organ failure. However, no data presently exist that definitively show that nutritional support shortens the need for intensive care or reduces patient morbidity or mortality.

NUTRITIONAL SUPPORT OF THE STRESSED PATIENT

The hypermetabolic response to acute injury results in increased oxygen consumption and significant negative nitrogen balance, depending on the type of stress. Along with the specific injury, renal factors need to be considered in such circumstances. Major burns, sepsis, and skeletal trauma all lead to significant increases in resting energy expenditure and nitrogen excretion as early as the first day of such stress.[31–34] Initially, glycogen and carbohydrate stores can be used for energy production; later, gluconeogenesis and ketone body production, along with consumption of stored fat and protein, provide fuel for the hypermetabolic state. Observations regarding the type of energy source used in critically ill children indicate that more than half the expended calories are derived from fat sources, roughly a third from carbohydrates, and about a tenth from protein sources.[31,35]

Ideally, a nutritional assessment should be made at the time of admission to the intensive care unit. Although influenced by several factors, serum protein levels can provide a quick estimate of the preillness nutritional state. Influencing factors include intravenous (IV) hydration, tissue edema, and metabolic rate.[31] Additionally, and importantly, serum proteins, and albumin in particular, are negative acute-phase reactants. In a stressed and septic patient, a low albumin level (< 2.5 mg/dL) is not uncommon and reflects a compromised overall nutritional status. Planning nutritional care should consider both ongoing needs and preexisting deficits so that calories can be provided with an adequate balance of carbohydrate, fat, and protein sources, along with essential minerals and vitamins. A simple method for estimating such requirements is to multiply the calculated caloric requirements by a ratio of ideal to actual weight. Caloric requirements can also be estimated by weight and type of stress.

Assessing ongoing needs in intensive care patients can be difficult because some patients could have preexisting diseases or specific organ injuries that might prevent adequate use of calories. For instance, a patient with poor liver function might not be able to tolerate lactate or acetate-based parenteral nutrition for acid-base control. Diets for patients with antecedant renal disease or with acute renal dysfunction require further planning.[36–38]

In addition to the number of calories to be provided, the mode of supplementation must be addressed early. Substantial evidence supports enteral over parenteral feeding, if possible. Thus, tube feeding (with gastric or jejunal tube, depending on gastric emptying) should be used whenever possible, depending on the gastrointestinal ability to absorb nutrients.[39–41] Parenteral nutrition is appropriate in conditions such as short-gut syndrome, ileus, severe dysmotility, inflammatory bowel disease, necrotizing enterocolitis, hemolytic uremic syndrome, or Henoch-Schönlein purpura. Other factors that can limit the effective use of enteral feedings include the need for narcotics, benzodiazepines, or high-osmolality formula.

When fluid intake must be limited—for example, during acute renal failure or during interdialytic periods—higher-calorie formula can be useful. Most children will tolerate 24 kcal/oz formula. When further increases in caloric density are needed, the child should be monitored for possible intolerance and need for prokinetic agents. Increasing calories by 3 kcal/oz every 3 to 4 days is usually tolerated.[31] In an acutely ill patient, carbohydrate absorption might be limited, and stool should be checked for reducing substances. Predigested (elemental) formulas might be more easily absorbed than other formulas in patients who are critically ill. The use of medium-chain rather than long-chain triglycerides can also augment absorption.

With parenteral nutrition (whether through central or peripheral venous catheter), care should be taken to provide an optimal mixture of lipid, glucose, and protein. Glucose concentrations above 12.5% should be given centrally, and even so can increase ventilatory requirements or cause hepatic steatosis. Ideally, 1.0 g/kg/day of fat can be given initially and then increased by 1.0 to 1.5 g/kg/day, until 30 to 50% of the calories are derived from fat. Serum triglycerides, cholesterol, liver function (glutamic-oxaloacetic transaminase, glutamate pyruvate transaminase, and bilirubin), and alkaline phosphatase levels should be monitored weekly. Protein should provide 15 to 20% of the calories, calculated on the basis of half the amino acids and half the infused protein products as total protein calories.[31]

Total parenteral nutrition (TPN) solution for patients with renal disease can be modified as needed for individual patients if the concentrations of calcium, magnesium, phosphorus, and potassium need to be altered (often decreased). Branched-chain amino acids, when available, have been used in pediatric patients with chronic liver and acute renal disease with varied success. Patients on dialysis might be helped by receiving a 15% solution of amino acids (0.5 to 1.0 g/kg/day) to maintain adequate nutrition,[42,43] despite fluid restriction.

CALCIUM, MAGNESIUM, AND PHOSPHATE BALANCE

Several aspects of intensive care illness (eg, immobilization, overhydration, or renal tubular damage) can cause several perturbations in the balance of bone formation and bone resorption, especially in pediatric patients because of their relatively high bone turnover rate.[44] Hypercalcemia or hypocalcemia can be found in this setting, along with derangements in phosphate and a low or

high PTH level. Factors that can contribute to these derangements include volume contraction, hypomagnesemia, and malnutrition. Table 36-2 lists sources of calcium, magnesium, and phosphate.

Magnesium is an ion frequently overlooked in the intensive care setting,[45,46] but its importance as an essential nutrient in health and disease should be emphasized. Magnesium deficiency is rarely seen in normal individuals eating a regular diet (containing green vegetables, nuts, grains, seafoods, and meats); however, certain pathologic conditions and medications can lead to disturbances in magnesium balance. Factors that increase renal excretion include extracellular volume expansion, loop diuretic administration, acidemia, proximal tubule dysfunction, and medications such as cisplatin, cyclosporine, and amphotericin B. Factors that decrease intestinal absorption include inadequate intake or prolonged IV therapy, malabsorption, severe diarrhea or inflammatory bowel disease, prolonged nasogastric suction, PTH deficiency, vitamin D deficiency, and acute pancreatitis. Both diabetes mellitus and parathyroid disorders can affect magnesium levels.

Found predominantly intracellularly, magnesium has an essential role there in energy production and use. The availability of magnesium is linked to the gastrointestinal tract, kidney, and bone; regulation is not well understood. Serum levels tend to predict total body stores poorly. Magnesium, like calcium, is highly bound to serum proteins and therefore is affected by hypoalbuminemia and serum pH level. Magnesium and potassium levels tend to change together proportionately. As a result, recalcitrant hypokalemia tends to be aggravated if associated with hypomagnesemia. Concurrent replacement facilitates normalization of both potassium and magnesium.

In the intensive care setting, values for calcium (total and ionized), phosphate, and magnesium should be obtained early, and prompt supplementation can avoid significant depletion. In patients with preexisting low magnesium levels, slow and gradual replacement is preferred unless a patient is symptomatic; in symptomatic patients, IV or intramuscular replacement can be given over 10 to 15 minutes.

Phosphate levels are not invariably monitored, yet phosphate levels are affected by stress. Furthermore, deranged phosphate levels are associated with adverse effects. Factors such as volume expansion, hyperglycemia, mild hypercalcemia, and use of diuretics (especially metolazone) can increase phosphate excretion. Hypophosphatemia (serum levels of 1.0 to 2.5 mg/dL) can indicate phosphorus depletion. Phosphate levels follow a circadian rhythm, peaking at 1 am and ebbing at noon. Simple dietary restriction is unlikely to cause hypophosphatemia, particularly in light of renal phosphate reabsorption and mobilization from bone and soft tissues.

Factors that contribute to moderate phosphate loss include decreased gastrointestinal absorption (because of insulin administration, vitamin D deficiency, malabsorption, or draining fistulas), maldistribution of phosphorus from the blood into bones and cells, and renal tubular loss from various causes (hypokalemia, hypomagnesemia, pharmacotherapy, intrinsic tubular defects, or the diuretic phase of acute tubular necrosis). Excessive use of phosphate binders, diabetic ketoacidosis, parenteral nutrition, catecholamine excess, and respiratory alkalosis can also alter phosphate level, sometimes profoundly. Additionally,

TABLE 36-2 Calcium, Magnesium, and Phosphate Supplementation for Pediatric Patients

Calcium		
Calcium Availability of Calcium Salts		
Calcium acetate	25%	
Calcium carbonate	40%	
Calcium chloride	36%	
Calcium citrate	17%	
Calcium gluconate	8%	
Calcium lactate	12%	
Calcium Supplements	*Product Tablet Size*	*Elemental Calcium Supplied*
Calcium Carbonate	650 mg	260 mg
Calci-Chew	1,250 mg	500 mg
Calci-Mix	1,250 mg	500 mg
Oscal 500	1,250 mg	500 mg
Tums	500 mg	200 mg
TumsES	750 mg	300 mg
Calcium Acetate		
Phos-Lo	667 mg	169 mg
Calcium Citrate		
Citracal	950 mg	200 mg
Magnesium		
Oral Magnesium		
Children: 3–6 mg/kg of elemental magnesium (eMg) divided tid or qid		
Adults: 200–400 mg eMg divided tid or qid		
Magnesium gluconate		
Magonate 500	27 mg eMg per tab	
Magonate Susp	54 mg eMg per 5 cc	
Magnesium oxide		
MgOx 400	241 mg eMg per tab	
UroMag	140 mg eMg per tab	
Magnesium chloride	60 mg eMg per 5 cc	
Antacids		
Maalox Suspension	83 mg eMg per 5 cc	
Laxatives		
Milk of Magnesia	500 mg eMg per 15 cc	
Parenteral Magnesium		
25–30 mg/kg/dose q 4–6 h, maximum 1 g/h		
Magnesium sulfate	24 mg eMg/mL	
	48 mg eMg/mL	
Phosphate		
Oral Phosphate		
Begin with 30–90 mg/kg day.		
Milk (skim, nonfat, dried)	255 mg/230 mL*	
Neutra-Phos†		
Sodium phosphate	250 mg/pkt	
Potassium phosphate	250 mg/pkt	7 mEq K^+/pkt
Fleets Enema	31 mg/mL	14 mEq K^+/mL
Fleets Phosphosoda	125 mg/mL	6 mEq K^+/mL
KPhos	114 mg/tab	3.7 mEq K^+/tab
KPhos-Neutral	250 mg/tab	2.0 mEq K+/tab

*If supplementing with calcium, make sure these are not given together as they can neutralize each other.

†Milk contains calcium, so phosphate availability is lower; however, the palatability of milk is much better, particularly when mixed with chocolate. The taste of phosphate products is reminiscent of soap.

many of these factors can be additive. For example, a severely burned patient 4 or 5 days post trauma could have elevated levels of catecholamines, respiratory alkalosis, and elevated cortisol secretion and could be receiving parenteral nutrition, all of which lead to hypophosphatemia.[44]

Hypophosphatemia in the stressed patient should be treated; however, it is somewhat difficult to predict the response.[31] Attention should be directed to signs and symptoms of hypophosphatemia (eg, proximal muscle weakness or pain, difficulty in weaning from respiratory support, anorexia, hypoglycemia, hypercalciuria, hypermagnesuria, or bicarbonaturia). The type of phosphate support should be gauged by the duration of IV support and timing of resumption of oral intake. For serum phosphate levels of less than 1 mg/dL, treatment should commence immediately with slow administration of parenteral neutral phosphate (5 to 10 mg/kg/dose or 15 to 45 mg/kg/day IV; for adults, 1.5 to 2 g/day) because as IV administration can produce weakness, bradycardia, and dyspnea.

Additionally, hyperkalemia can occur because phosphate is typically delivered with potassium. If the serum phosphate is greater that 2 mg/dL, parenteral treatment should be initiated if a prolonged course is expected. If enteral supplementation is possible, it is the preferred route. When phosphate is administered, it is important to consider the potential effects on other electrolytes, particularly calcium, because IV phosphate can decrease serum calcium as a result of calcium-phosphate complexing. In a hypocalcemic patient, this phenomenon can lead to tetany. Finally, attention should be given to situations that predispose to significant phosphate binding (eg, concomitant antacid treatment).

Conversely, hyperphosphatemia can be seen in the intensive care setting in stressed patients with either acute or chronic kidney disease and in those with increased phosphate loads (caused by laxative ingestion, excessive vitamin D intake, hyperpyrexia, burns, neoplasms, hemolysis, or respiratory acidosis). In hyperphosphatemia, calcium-phosphate salts can precipitate into soft tissues such as kidney, muscle, or vessels. This can occur acutely but is an even greater risk with chronicity. Monitoring the calcium-phosphate product can be useful as precipitation begins typically with a calcium × phosphate product greater than 70. Treatment of hyperphosphatemia includes the use of gastrointestinal phosphate binders, reduction in oral and parenteral phosphate intake, and, in extreme instances, hemodialysis.

Calcium is a predominantly intracellular cation found mainly in bone (99%).[30] Plasma calcium exists in two phases, one bound to albumin (40%) and the other free and ionized (60%). At least three biologic processes regulate calcium homeostasis: gastrointestinal absorption of calcium, bone turnover, and renal calcium reabsorption in conjunction with the actions of PTH and vitamin D. Hypocalcemia is seen more often than hypercalcemia in the intensive care setting. In a symptomatic child with tetany, especially a child with seizures, calcium should be provided at a dose of 10 mg/kg (0.5 mEq/kg) as elemental calcium over 10 to 20 minutes via slow, steady IV infusion (with electrocardiographic monitoring for bradycardia and QRS complex changes). Calcium should be added at 20 to 40 mg/kg/24 hours or by oral supplements given at 60 to 100 mg/kg/24 hours. Providing vitamin D might also be helpful if longer-term calcium supplementation is needed. Severe hypercalcemia, though rare, should be treated with aggressive saline diuresis with furosemide, followed by restriction of calcium intake and cessation of any calcium or vitamin D supplements. Calcitonin (salmon calcitonin, 4 IU/12 hours intramuscularly or subcutaneously) can also be used for severe hypercalcemia, as can bisphosphonates.

NUTRITION IN ACUTE RENAL INSUFFICIENCY

Children with acute renal failure are extremely catabolic. Urea nitrogen appearance, used as a surrogate for assessing catabolic states, has been found to be elevated in children with acute renal failure (levels of more than 180 mg/kg/day).[47] Although the reasons are not well understood, patients with acute renal failure require higher caloric input to balance the increased metabolic rate associated with the renal insult and to reduce accumulation of nitrogenous wastes, acids, and potassium.

A number of studies have evaluated the potential benefits of nutritional therapies in acute renal failure. For example, in one double-blind study in adults, a combination of 50% glucose and amino acids (compared with glucose alone) improved renal recovery.[48] However, another similar study was unable to show any difference in renal recovery.[49] In practice, the optimal nutritional prescription should be tailored to the individual patient, providing adequate protein and caloric energy. Marked protein restriction in pediatric patients with acute renal failure is unwise. In considering the therapy for acute renal failure in oliguric patients, the clinician often must choose between marked fluid restriction or early dialysis or ultrafiltration. Early dialysis seems most reasonable and is currently recommended.[36–38]

Various continuous renal replacement treatments can permit nutritional support but concomitantly contribute to nitrogen losses as amino acids and small peptides are filtered across the dialysis membranes. Recently, Maxvold and colleagues determined that both continuous venovenous hemotiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHD) lead to losses, but these are offset by the ability to feed the very ill child with acute renal failure.[38] Glutamine, lysine, proline, alanine, and arginine were lost in the greatest amounts, representing more than 50% of amino acid losses.[38]

In the child subjected to marked fluid restriction, nutritional support via oral feedings fortified with Polycose and medium-chain triglycerides can be accomplished. However, it is not uncommon for children with acute renal failure to be nauseated and anorexic. In such patients, enteral feedings given continuously through a nasogastric tube using specially designed renal diets,[6] which are initially diluted and then gradually increased to full strength as tolerated, might be a better alternative. These formulas can also be augmented with Polycose and medium-chain triglycerides for added calories. Alternatively, parenteral nutrition using a high glucose concentration (25%), 20% lipid emulsion,

and essential amino acids can be given through central lines to supply partial or full nutritional support.

Protein intake in the nondialyzed child with acute renal failure should be at least 0.6 g/kg/day and increased while daily electrolyte, glucose, calcium, magnesium, phosphate, blood urea nutrigen (BUN), and creatinine levels are monitored. Patients can be started at a protein intake of 1.5 g/kg/day if on dialysis and 2.5 to 3.0 g/kg/day during continuous renal replacement therapy (along with folic acid and water-soluble vitamins).

The active form of vitamin D is also recommended, that is, 1,25 dihydroxyvitamin D_3 (calcitriol) or 19-nor-1(alpha), 3(beta), 25-trihydroxy-9,10-secoergosta 5(Z),7(E),22(E)-triene (paricalcitol), because renal conversion will be reduced in acute renal failure, and the half-lives of active vitamin D or paricalcitol are relatively shorter than that of the monohydroxylated form.[50] It is also important to note that paricalcitol is not yet approved for children by the US Food and Drug Administration (FDA).

Metabolic acidosis is frequently found concurrent with acute renal failure and can be treated with the enteral or parenteral addition of acetate as a sodium salt. If an elevated anion gap is present, suggesting increased lactate production or hepatic insufficiency, oral or parenteral bicarbonate can be used instead of acetate. However, for positive anion gap metabolic acidosis, the clinician is obligated to search for and treat the etiology of the metabolic acidosis (eg, sepsis or hypoxia). The clinician must remember that with hyperalimentation containing calcium, bicarbonate must be given through a separate line (eg, Y-tubing connections) or with low calcium concentration to avoid calcium precipitation. Many of the considerations for nutritional management of the child in the intensive care unit apply in acute renal failure.[51]

NUTRITION IN CHRONIC KIDNEY DISEASE

Renal insufficiency creates a state of metabolic imbalance proportional to the decline in renal function. Pediatric patients face not only the challenge of maintaining metabolic homeostasis in the face of renal dysfunction but also that of achieving somatic growth. Growth, in turn, is ultimately dependent, in part, on overall nutritional status. Metabolic requirements for improving growth are multifactorial and are affected by disparate factors, including patient compliance, genetics, psychosocial issues, infection, dialysis, and side effects of medications.

Chronic kidney disease (CKD), defined as a reduction in GFR to less than 70 mL/min/1.73 m^2, often occurs long before end-stage renal disease develops (defined as filtration of less than 12 mL/min/1.73 m^2). CKD in children can originate from a variety of causes, but all children with CKD require attention to nutrition. Depending on the degree and etiology of nephron loss, nutritional therapy can play a role in either slowing or stabilizing the decline in renal function or could serve to improve overall quality of life. Furthermore, when glomerular filtration is severely compromised, limitations and alterations in dietary intake can help to prevent metabolic disturbances.

The nutritional goal for the child with advancing CKD is to maximize growth and development. Table 36-3 is a partial list of supplemental formulas. Because infants, especially, demonstrate poor catch-up growth, protein and calorie intake should not be restricted; this can lead to stunting. Other specific abnormalities, such as metabolic acidosis, renal osteodystrophy, and hormone unresponsiveness, can further affect the growth failure seen in children with CKD.

Growth failure is the major manifestation and primary nutritional management problem for the child with CKD. Table 36-4 provides a summary of specific dietary recommendations for children of different ages with various degrees of CKD. For those children with renal insufficiency from infancy, in which one-third of a child's growth normally occurs, growth decline can result in a permanent loss of growth potential and result in a decrease in ultimate height.[52,53] Infants with CKD present an especially difficult situation. Even with successful conservative management of the renal failure, growth sufficient for transplantation with an adult kidney might not be achieved. Despite the emphasis on nutritional support, our lack of a complete understanding of how the uremic condition inhibits growth prevents optimization of nutritional prescription and results in empiric supplemental feeding.

Growth deficits are most dramatic in infants who have had renal insufficiency from early in life. A few months of delayed therapy in such infants can result in severe growth stunting, with a poor chance for recovery and catch-up growth. Nutritional requirements for these children are thought to be altered to some degree by uremia. Only limited data are available for this special group of patients. A study of 12 infants with renal insufficiency showed that forced feeding regimens augmented the weight velocity curve after age 2 years but did not improve length velocity curves.[54] In this study, protein-calorie supplementation was given orally or enterally through nasogastric tube or gastrostomy using 30-calorie Similac PM 60/40 (Ross Laboratories) with Polycose (9% protein, 36% fat, and 55% carbohydrate). This supplementation gave 141% of the RDA for protein intake. Despite this supplementation, the babies still demonstrated loss in length and head circumference, even into the second year of life. Hyperparathyroidism was demonstrated in this group and was believed to contribute overall to the short stature.[54]

Many children with chronic renal failure have polyuria, and nutritional support should include both sodium and water supplementation, which can help to maintain or improve the growth rate. For example, Parekh and colleagues[55] supplemented 24 children who had chronic renal failure with a dilute, sodium-supplement, high-volume regimen (enteral formula diluted with water to a caloric density of 0.3 to 0.5 kcal/mL, supplemented with 2 to 4 mEq of sodium as NaCl, $NaHCO_3$, or both, per 100 mL of formula). The regimen resulted in stabilization or improvement in their growth.[55] The formulas that were used included Nepro, Suplena (both Ross Laboratories), Similac PM 60/40, and SMA (Wyeth-Ayerst Laboratories) and were provided in volumes of 180 to 240 mL/kg in each

TABLE 36-3 Some Enteral Supplements for Patients with Renal Disease

Infant Formulas

- For increased energy requirements and/or fluid restrictions, fortify by increasing formula concentration and using modular components.
- Optimize digestibility using similar proportions of fat, protein, and carbohydrate. Begin by adding 2 kcal/oz from Polycose and 2 calories from medium-chain triglycerides, gradually increasing as tolerated.
- Osmotic load of high-calorie formula should be less than or equal to 450 mOsm/kg H_2O renal solute load.
- Maximize calcium-to-phosphate ratio (1.4:1) using infant formula such as Similac compared with Similac PM (2:1).
- Modular components
  - Polycose: 2 kcal/cc liquid, 23 cal/tbsp powder. Note that glucose polymers in Polycose increase osmolality slightly
  - Promod: 28 cal/scoop (5 g protein, < 44 mg calcium, < 15 mg sodium, < 65 mg potassium, and < 33 mg phosphorus (whey protein concentrate)
  - Vegetable oil: 8 cal/cc, not well tolerated in higher amounts (> 2 tsp/oz)
  - Medium-chain triglycerides: 7.7 cal/cc, stays in solution better than vegetable oil and is usually better tolerated in larger amounts

Formulas for Older Children

- Aminaid: very low-protein formula (19 g/L), 2 cal/cc, no added vitamins or minerals, short-term use only, expensive
- Suplena: low-protein formula (30 g/L), 2 cal/cc, with vitamins, low in phosphorus, magnesium, and vitamins A and D
- Nepro: moderate protein (69 g/L), 2 cal/cc, with vitamins, low in phosphorus, magnesium, and vitamins A and D
- NuBasics: relatively high-protein, palatable formula
- NutriRenal: calorically dense (2.0 kcal/mL); 14% of calories as high biologic value protein
- Renalcal: calorically dense, low electrolyte

Oral Supplements for Caloric Support in Patients with Progressive Renal Failure

Shake

6 oz sorbet/sherbert	16.2 g protein
4 oz nondairy creamer	115 mg phosphorus
2 tbsp chocolate syrup	70 mg calcium
	206 mg sodium
	544 kcal/300 cc

Enteral Nutrition Supplements

Predialysis patients

Suplena, Ensure, Isocal

Hemodialysis and peritoneal dialysis patients

- Underweight: Nepro, Isocal HCN,* Magnacal (2.0 kcals/mL); if not tolerated, try lower-osmolarity formulas, such as Ensure Plus/Plus HN,* or Sustacal HC*; monitor K levels
- Overweight with protein malnutrition: Replete, Sustacal,* Isocal HN, Ensure HN, Comply*
- With protein malnutrition: Sustacal*, Isocal HN, Ensure HN
- With protein-energy malnutrition: Nepro, Magnacal, Isocal HCN,* Ensure Plus HN,* Sustacal HC

For manufacturers and composition, see American Dietetic Association. Clinical guide to nutrition care in end-stage renal disease. 2nd ed. American Dietetic Association; 1994.

*For older children.

24-hour period. This led to an intake of 100 to 160 kcal/kg per 24 hours and about 2 to 2.5 g/kg of protein daily. Thus, these were intakes at or higher than the RDA for age.

Ledermann and colleagues showed that enteral feeding prevented or even reversed weight loss and growth retardation in children with chronic renal failure and end-stage renal disease.[56] Others had similar results.[57] Kari and colleagues showed that enteral feeding did not worsen lipid subfractions in chronic renal failure.[58,59] Additional studies are supportive of the concept that enteral feeding is very helpful in this group of children.[60,61]

Protein Handling in Chronic Kidney Disease

As noted above, a normal protein intake is tolerated under the right circumstances in a child with CKD. But can a low-protein diet slow progression of renal disease? Dietary protein reduction has been shown to slow the progression of renal decline in adult animals and humans, whereas it appears that, at least in immature uremic animals and renal-insufficient infants, decreases in protein intake retard growth more than excessive protein intake does.[62,63] Few studies in which protein intake was decreased in children are available. In one multicenter, prospective, controlled clinical trial of 24 infants with chronic renal insufficiency, randomized either to a low-protein or a control diet, linear growth was compromised in the low-protein group.[62] Neither group had increases in GFR, but the low-protein group did not achieve energy intakes equivalent to those of the control group, and this in and of itself could have stunted growth.[61] Success in this study was also limited by anorexia, parental and patient interactions, and primary care resistance to nasogastric feedings. Caution must be exercised with institution of low-protein diets and careful attention paid to growth parameters.

Protein-energy malnutrition often occurs in the course of CKD. This can affect renal function in several ways, independent of hydration status. In renal failure, renal tubular concentrating ability is decreased, as is the capacity to eliminate sodium and acid. Renal diluting capacity is also decreased, and malnutrition can worsen this problem, leading to fluid overload. However, malnutrition reversal is not easily effected, even in a child without intrinsic renal disease, in whom caloric intake might need to be between 140 and 160 kcal/kg/day and as high as 200 kcal/kg/day.[16,64,65] Despite aggressive nutritional management, the uremic child does not have the same response as does a child with simple protein-energy malnutrition.[64,66] Additionally, there is some evidence to suggest that certain types of caloric supplementation could be counterproductive as carbohydrate supplementation can reduce the child's ingestion of other foods, in effect without net protein-energy ratio change.[53] Nevertheless, we strongly advocate the early and consistent use of protein-calorie supplementation to attempt growth restoration, if not catch-up growth.

Carbohydrate Handling in Chronic Kidney Disease

Although no simple explanation is available, uremic children are often carbohydrate intolerant. Glucose use abnormalities in renal insufficiency include relative insulin resistance and hyperinsulinemia, prolonged insulin and glucagon clearance, and elevations of other hormones, such as PTH, glucagon, and catecholamines. These are all related in part to reduced GFR and, therefore, clearance by the kidney. When protein intake is reduced or dialysis is initiated, glucose intolerance can be seen to improve.[64]

TABLE 36-4 Daily Fluid and Nutrient Recommendations for Children with End-Stage Renal Disease

	Energy	*Protein*	*Sodium*	*Potassium*	*Calcium*	*Phosphorus*	*Vitamins*	*Trace Minerals*	*Fluids*
Predialysis (> 15% GFR)									
Infants	Min. of RDA for statural age	RDA for statural age	1–3 mEq/kg	1–3 mEq/kg	Supplement as needed	Restrict high-content foods, use low-content formula	1 cc multivitamin drops + vitamin D metabolite	Supplement Zn, Fe, Cu if needed	Min. maintenance level
Children/ adolescents	Min. of RDA for height age	Min. of RDA for height age	1–3 mEq/100 kcal expended	Unrestricted until K rises	Supplement as needed	—	Multivitamin, vitamin D	Supplement Zn, Fe, Cu if needed	With edema, insensible loss + urinary output
Predialysis (< 15% GFR)									
Infants	Min. of RDA for statural age	1.5–1.6 g/kg	1–3 mEq/kg	1–3 mEq/kg	Supplement as needed	Restrict high-content food; use low-concentration formula	1 cc multivitamin drops + vitamin D metabolite	Supplement Zn, Fe, Cu if needed	With edema, insensible loss + urinary output
Children/ adolescents	Min. of RDA for height age	Max. of RDA for height age	1–3 mEq/100 kcal expended	Unrestricted until K rises < 10% GFR	Supplement as needed	500–1,000 mg	Multivitamin, vitamin D	Supplement Zn, Fe, Cu if needed	With edema, insensible loss + urinary output
Hemodialysis									
Infants	Min. of RDA for statural age	RDA for statural height	1–3 mEq/kg	1–3 mEq/kg	Supplement as needed	Restrict high-content food; use low-concentration formula	1 cc multivitamin, 1 mg FA, vitamin D	Supplement Zn, Fe, Cu if needed	Insensible loss + ultrafiltration capacity + urinary output
Children/ adolescents	Min. of RDA for height age	RDA for height age	1–3 mEq/100 kcal expended	25–50 mEq if needed	Supplement as needed vitamin C, Bc, vitamin D	500–1,000 mg	1 mg FA, 50–100 mg	Supplement Zn, Fe, Cu if needed	Insensible loss + urinary output
Peritoneal Dialysis; IPD									
Infants	Min. of RDA for statural age	2.5–3 g/kg	1–3 mEq/kg	1–3 mEq/kg	Supplement as needed	Same as for HD	Same as for HD	Same as predialysis	Insensible loss + ultrafiltration capacity + urinary output
Children/ adolescents	Min. of RDA for height age	Usually halfway between HD and CAPD	1–3 mEq/100 kcal expended	25–50 mEq if needed	Supplement as needed	Same as for HD	Same as for HD	Same as predialysis	Insensible loss + urinary output
Peritoneal Dialysis; CAPD									
Infants	Min. of RDA for statural age	3–4 g/kg	3 mEq/kg ± depending on edema and BP	1–3 mEq/kg; may not be needed	Supplement as needed	Liberalize based on serum levels	Same as for HD	Same as predialysis	Insensible loss + ultrafiltration capacity + urinary output
Children/ adolescents	Min. of RDA for height age	3 g/kg 2–5 yr; 2.5 g/kg 5–10 yr; 2 g/kg 10–12 yr; 1.5 g/kg > 12 yr	Usually unlimited; 85–174 mEq	Usually unlimited; 25–50 mEq	Supplement as needed	240 cc milk or equivalent milk product	Same as for HD	Same as predialysis	Not needed
Transplant									
Infants	RDA for statural age after ideal weight/length achieved	3 g/kg	1–3 mEq/kg	Unlimited	Ad libitum	May need very high intakes; supplement as needed	Usually not needed unless malnourished prior to transplant, vitamin D possible	Not needed	Not needed
Children/ adolescents	RDA for height age; no concentrated sweets for 6 weeks post transplant	2–3 g/kg	130–174 mEq, less if edema and BP elevated	Unlimited	Unlimited	May need high intakes; supplement as necessary	Usually not needed unless malnourished prior to transplant, vitamin D possible	Not needed	Not needed

Adapted from Nelson and Stover.[43]

BP = blood pressure; CAPD = continuous ambulatory peritoneal dialysis; FA = folic acid; HD = hemodialysis; GFR = glomerular filtration rate; IPD = intermittent peritoneal dialysis; RDA = Recommended Dietary Allowance.

Carbohydrate supplementation can also increase triglyceridemia and lead to obesity without increasing lean body mass or growth. Patients should be encouraged to eat complex rather than simple carbohydrates.

Lipid Handling in Chronic Kidney Disease and Renal Insufficiency

Children with chronic kidney disease and renal failure often have lipid derangements, most commonly similar to those seen in type IV hyperlipidemia or in familial endogenous hypertriglyceridemia.[67–76] Thus, elevated triglyceride and elevated very-low-density lipoprotein (VLDL) levels occur; high-density lipoprotein (HDL) levels are low. Although the significance of these abnormalities is not fully known, their presence is thought to represent an increased risk of atherosclerosis. Possible reasons for the abnormalities include increased fat in the diet, decreased lipoprotein lipase, and hepatic triglyceride lipase activity. Carnitine deficiency, often present in renal insufficiency, theoretically could decrease fatty acid transport from the cytoplasm of cells to the mitochondria.[72]

There is recent experience in treating children with hyperlipidemia. The abnormal lipoprotein metabolism seen in renal disease reflects interactions among many factors—the disease itself, medications that affect lipids (eg, glucocorticoids and immunosuppressive medications such as sirolimus), diet, obesity or malnutrition, and familial factors. Conclusive data about efficacy compared to safety have led to a lack of certainty about therapy. However, use of dietary manipulation, statins, fibrates, and resins that bind bile acids is gaining favor.[73]

Practical Aspects of Nutritional Management in Renal Insufficiency

Major reasons for dietary intervention include dehydration, sodium depletion, metabolic acidosis, and preexisting malnutrition. The worsening of anorexia by metabolic acidosis can further inhibit nutritional intake. Thus, treating chronic acidosis is important.

Growth quantification can be conveniently achieved by monthly measurements of length, weight, and head circumference and permits early identification of growth failure and slowed height velocity. Table 36-5 provides a list of data that should be obtained and compiled at each visit to develop or modify the dietary prescription.

Calcium-phosphate homeostasis is altered in CKD by changes in PTH and vitamin D levels. Metabolic acidosis leads to a decrease in bone mineralization, release of bone buffers, and changes in protein conformation and can inhibit linear growth. Many factors can alter the balance of ionized versus bound plasma calcium, including acidosis and hypoalbuminemia (which are commonly seen in both chronic renal failure and nephrotic syndrome). Additionally, these renal diseases, which affect renal function, also cause increases in PTH and vitamin D metabolism. With progressive renal insufficiency, defective bone mineralization and secondary hyperparathyroidism or renal osteodystrophy require attention to plasma concentrations of calcium, phosphorus, 1,25-dihydroxyvitamin D, and PTH.[77,78]

The active form of vitamin D is 1,25-dihydroxyvitamin D. The 25-hydroxylation takes place in the liver, and 1α–hydroxylation takes place in the kidney. Active vitamin D has been available for some years as calcitriol, and its therapeutic use has increased in recent years. Dihydrotachysterol (DHT) becomes biologically active because of a 3-OH group that can rotate, making a pseudo 1α-OH group. Once 25-hydroxylation occurs in the liver, resulting in 25-OH-DHT, transport of calcium across the intestine increases. DHT has a shorter duration of action and greater potency than vitamin D_2 and is recommended over vitamin D_2. Vitamin D_2 has a narrower therapeutic window and is highly lipophilic; thus, it promotes adipose retention and poses problems for treatment of hypercalcemia.

Hypercalcemia can occur with any vitamin D preparation and is commonly seen with calcitriol, although it is usually mild and quickly reversible because active vitamin D has a short half-life. Although some early studies suggested that calcitriol therapy might hasten renal failure, this concern has largely been disproved by subsequent studies. Indeed, children do well with calcitriol, and bone histomorphometry results greatly improve.

Maintenance of normal serum calcium and phosphorus levels becomes extremely important in preventing renal

TABLE 36-5 Data Obtained for Dietary Prescription Adjustment

Measurements
Weight (for peritoneal dialysis or CAPD, weigh with full abdomen)
Height
Head circumference
Skinfold thickness
Estimated midarm muscle area
Pubertal stage
Three-day dietary history
Biochemical profile
Electrolytes, BUN, creatinine
Calcium, magnesium, phosphate
Alkaline phosphatase
Cholesterol, trigycerides
Total protein, albumin
Assessment of contributions of medications to biochemical balance
Calcium binders can contribute potassium:
Kphos 3.7 mEq K^+/tab;
Fleets PhosphoSoda 6 mEq K^+/mL
Potassium adsorbants contribute 100 mg sodium/g
Acetates contribute sodium (1 mEq/cc) or potassium
Phosphate supplements may contribute potassium:
Neutra-Phos (potassium phosphate), 14 mEq K^+/packet;
sodium phosphate, 7 mEq K^+/packet
Assessment of phosphate binder status
Calcium-containing: see Table 36-2
Phos-Lo
Renagel
Assessment of vitamin prescription
Vitamin D analogs
Water-soluble vitamins
Assessment of anemia and iron status
Assessment of dialysis efficacy if applicable
Hemodialysis: URR or Kt/V and protein catabolic rate
Peritoneal dialysis PET
CAPD-urea nitrogen appearance

BUN = blood urea nitrogen; CAPD = continuous ambulatory peritonial dialysis; PET = peritoneal equilibration test; URR = urea reduction ratio.

osteodystrophy. Calcitriol is now commonly used, with starting dosages of 0.01 to 0.05 μg/kg/day. DHT has been used for more than 25 years at dosages beginning at 15 mg/kg/day (in the morning) and can be given either in tablet form (0.1 to 0.2 mg tablets) or as a capsule (0.25 mg/mL). For children who weigh less than 15 kg, the capsule can be diluted in corn oil, and a tuberculin syringe can be used to give dosages of less than 25 mg/day. Calcium supplements, as calcium carbonate or calcium citrate, can be given to improve serum levels at dosages shown in Table 36-2 (400 to 1,200 mg/day, depending on age); Table 36-2 provides a short list of calcium supplements together with the available calcium supplied by each when given in supplemental form.[18]

Prevention of renal osteodystrophy is accomplished only with frequent monitoring of serum phosphorus, calcium, alkaline phosphatase, and PTH levels; adjusting vitamin D supplementation; and following monthly growth parameters. Normalization of serum calcium values can take several weeks. Current recommendations based on studies in adults have advised the limitation of calcium supplementation to provide sufficient amounts to achieve a "normal" value but not to exceed it because coronary artery calcifications have been seen in patients in their early twenties.

Because intestinal phosphate absorption is also increased with the use of calcitriol, the addition of phosphate binders might be needed to control serum phosphate levels. Many phosphate binders can also contribute to oral calcium intake. Calcium carbonate or calcium citrate, when used as phosphate binders, needs to be taken with meals and for supplementation between meals. It should be noted that when other active vitamin D preparations that have less effect on the gut—for instance, paricalcitol[50]—are shown to be safe and effective in children, they might be preferable.

Phosphorus levels can be controlled simply by limiting dietary phosphate intake when there is still only a moderate decline in GFR (eg, when GFR falls below 50% of normal). Although phosphorus is present in nearly all foods to some extent, milk products, nuts, nut butters, dried peas and beans, and whole grains (such as whole wheat, bran, and corn meal) are relatively high in phosphorus. Patients can be instructed to aim for a phosphorus intake of 1 g/day. As GFR falls toward end-stage disease levels, phosphorus can be restricted to 600 mg by prescribing a low-protein diet, which is not advised for growing children.

Phosphate excess must be treated, but phosphate binders that contain aluminum, which can lead to bone disease, should be avoided.[79,80] Preparations that contain calcium carbonate or calcium acetate bind phosphate in food when given with meals and also act as a source of calcium supplementation when given between meals to promote optimal absorption. These compounds can also be given at bedtime if the patient is not on nighttime feeds. Sevelamer can lower phosphate without concomitant calcium and can be helpful in individuals with high calcium levels.[81,82] There are presently no liquid formulations of either calcium acetate or sevelamer. It should be noted that sevelamer combined with liquids creates a sticky "glue" that can clog gastrostomy tubes.

As renal function declines, particularly below 25% of normal, dietary potassium intake often must be adjusted by avoiding certain foods high in potassium (eg, apricots, bananas, cantaloupe, dates, figs, orange juice, avocados, beans, potato with skin, spinach, tomatoes, nuts, certain cereals, and milk products). Salt intake might also need to be curtailed by limiting high-sodium foods such as prepackaged and processed foods (eg, lunch meats, frankfurters, canned foods, soups, certain sodas, certain cereals, salted nuts, nut butters, some cheeses, and milk products). An exception is the infant or child with tubular sodium and potassium wasting, who might need supplements even as renal function is markedly decreased.

Obviously, the list of foods to be avoided increases as renal failure worsens, and such restrictions progressively make the diet less palatable. Being presented with lists of foods that can no longer be enjoyed can be overwhelming. Dietary advice should be focused on specific areas that need adjustment for the particular child. The dietary prescription should be evaluated with each visit. Not only are children with renal failure restricted by dietary prescription, but as they lose renal function, many have poor appetites, an altered sense of smell, early satiety (with delayed gastric emptying), and weight loss, despite increased nutritional requirements and higher protein catabolic rates. In this setting, oral supplementation with a variety of preparations tailored for the patient with chronic renal failure can be helpful (with choice based on cost, convenience, and palatability).

Children who are not yet on dialysis should have nutritional intake that provides calories for both maintenance and catch-up growth (Table 36-6). Ideal caloric intake for children with renal failure is not known but can begin at 90 to 100 kcal/kg/day or even higher for infants—98 to 110 kcal/kg/day. Adolescent girls might need 40 to 47 kcal/kg/day and adolescent boys 45 to 55 kcal/kg/day (caloric and protein recommendations are based on height and age). Infants might need 2.2 g/kg/day of protein, and the protein requirement can increase to between 2.4 and 4.0 g/kg/day in the infant on peritoneal dialysis (see below).

Concentrating infant formulas can result in very high renal solute loads and lead to obligate water losses. It is advisable to add vegetable oils, medium-chain triglycerides, and carbohydrate supplements (Polycose) to increase the number of calories in standard formulas (carbohydrate and fat should be in similar proportions) to maintain palatability. Formulas such as SMA, Similac (Ross Laboratories), and Similac PM 60/40 have lower renal solute loads and higher calcium-to-phosphate ratios than most other formulas do. Use of formulas such as these is advisable over breast-feeding, which can be difficult in infants who are poor feeders and require volume determination. If oral feedings do not provide adequate caloric intake, continuous overnight nasogastric feedings are indicated to achieve adequate intake.

For older children, blenderized shakes or enteral nutritional supplements can be used to achieve adequate caloric intake. Table 36-3 provides a short list of high-

calorie supplements that can be given daily as needed for caloric support. Additionally, depending on the level of renal function and electrolyte stability, sweet foods such as cake or donuts; bagels with cream cheese; Popsicles; fruit in heavy syrup; margarine, butter, or jam on bread; white sauce on cooked vegetables; and whipped cream can be tried. Adding Polycose powder or liquid to drinks, hot or cold cereal, or puddings might also be effective in raising caloric intake.

Despite all efforts, poor appetite often persists in the child with renal failure. The decreased appetite commonly seen in uremic children is not readily explainable, although children with failing kidney function frequently maintain proportionate height for weight and body mass. One contributing factor could be changes in taste (eg, sweet and sour foods can taste bitter to uremic children).[83–85] Eating frequent small meals; keeping favorite snacks or hard candy on hand; adding flavorings such as lemon, garlic, or pepper to improve taste; and avoiding cooking odors can help overcome anorexia and nausea.

NUTRITION IN DIALYSIS PATIENTS

For the undersized child with end-stage renal disease, height age rather than chronologic age should be used to determine adequate dietary allowance. The daily dialysate glucose should be incorporated into the oral intake for determination of daily calories in the child on continuous ambulatory peritoneal dialysis (CAPD) or other forms of peritoneal dialysis. This intake is estimated to be about 10% of the total calories for children 2 to 10 years of age.[78] Even though synthetic diets can maintain uremic adults for long periods of time, there seems to be no advantage to using synthetic diets over appropriate conventional diets in children. Whether increased energy consumption can promote nitrogen sparing in children is not clear, and this might not be an ideal way to replenish lean body mass. Thus, the initiation of early dialysis, provision of additional calories, and prescription of recombinant human growth hormone can benefit some children, particularly anorexic ones,[64] and

TABLE 36-6 Predialysis Fluid and Nutrient Recommendations for Children with Near End-Stage Renal Disease

Age	*Infant (0–1 yr)*	*Toddler (1–3 yr)*	*Child (4–10 yr)*	*Adolescent (11–18 yr)*
Energy (kcal/kg)	0–0.5 yr: ≥ 108 0.5–1 yr: ≥ 98	102	4–6 yr: 90 7–10 yr: 70	Girls 11–14 yr: 47 Girls 15–18 yr: 40 Boys 11–14 yr: 55 Boys 15–8 yr: 45
Protein (g/kg)	0–0.5 yr: 2.2 0.5–1.0 yr: 1.6	1.2; as much as tolerated	4–6 yr: 1.2 7–10 yr: 1.0	11–14 yr: 1.0 15–18 yr: 0.9
Sodium (mEq/kg)	Generally unrestricted; 1–3 if edema or HTN present	Generally unrestricted; 1–3 if edema or HTN present	Generally unrestricted; 1–3 if edema or HTN present	Generally unrestricted; 1–3 if edema or HTN present
Calcium (mg/day)	0–0.05 yr: 400 0.5–1.0 yr: 600 (provided that hypercalcemia does not occur and calcium-phosphorus product does not exceed 70)	800 (provided that hypercalcemia does not occur and calcium-phosphorus product does not exceed 70)	800 (provided that hypercalcemia does not occur and calcium-phosphorus product does not exceed 70)	1,200 (provided that hypercalcemia does not occur and calcium-phosphorus product does not exceed 70)
Potassium (mEq/kg)	(Usually not required until GFR is < 10% normal) 1–3 if needed	1–3 if needed	1–3 if needed	1–3 if needed
Phosphorus (mg/d)	Use low-content formula if serum levels of phosphate are elevated; restrict high-content foods	Usually 600–800	Usually 600–800 when serum levels are elevated	Usually 600–800 when serum levels are elevated
Vitamins	1 mL multivitamin drops; vitamin D metabolite if needed, based on serum calcium, PTH, and alkaline phosphatase	Multivitamin, 1 mg folic acid, and vitamin D metabolites as needed based on serum calcium, PTH, and alkaline phosphatase	Multivitamin, 1 mg folic acid, and vitamin D metabolites as needed based on serum calcium, PTH, and alkaline phosphatase	Multivitamin if needed; vitamin D metabolite if needed, based on serum calcium, PTH, and alkaline phosphatase levels
Trace minerals	Supplement zinc, iron, or copper if needed	Supplement zinc, iron, or copper if needed	Supplement zinc, iron, or copper if needed	Supplement zinc, iron, or copper if needed
Fluid	Unrestricted unless needed; then replace insensible loss + urinary output	Unrestricted unless needed; then replace insensible loss + urinary output	Unrestricted unless needed; then replace insensible loss + urinary output	Unrestricted unless needed; then replace insensible loss + urinary output

GFR = glomerular filtration rate; HTN = hypertension; PTH = parathyroid hormone.

certainly is worth trying in a child whose growth velocity and weight gain are declining.

Uremia is associated with anorexia and consequent decreased caloric intake, depression, changes in taste perception,[83–85] and a susceptibility to infections, all of which worsen preexisting malnutrition.[64] This can be compounded by severe preexisting malnutrition, especially in patients in whom protein restriction is used to prolong the time to dialysis.[86–90] Nutrient metabolism can be impaired by endocrine and metabolic changes (eg, insulin resistance and impaired glucose use, alterations in lipid metabolism, and a relatively high protein catabolic rate).[91–93] Uremic patients have been found to have an insulin growth factor inhibitor that is thought to diminish the anabolic effects of growth hormone. Additionally, PTH is thought to contribute, in a yet undefined way, to net negative nitrogen balance. Metabolic acidosis, even in the absence of renal failure, is a strong curtailer of growth and contributes to protein breakdown, despite an adequate protein-energy supply. During the dialysis process, between 2 and 15 g of amino acids can be removed per day, depending on dialysis modality.[94,95]

It is important to quantify dialysis delivery on a regular basis as Kt/V (measurement of dialysis adequacy) has been shown to correlate with dietary protein intake.[91] Reliance on predialysis BUN level as an indicator of adequate nutrition is no longer considered sufficient because a low BUN level can be the result of poor intake as well as adequate dialysis.

Nutritional Aspects of Peritoneal Dialysis

Nutritional aspects of peritoneal dialysis have been incorporated into the recommendations of the Dialysis Outcomes Quality Initiative, which examines evidenced-based data to develop standards for the care of persons with renal disease.[96] Although peritoneal dialysis can substitute for many aspects of renal function, it also creates new metabolic and nutritional problems for the patient with end-stage renal disease.[97–100] Whereas some patients do show improved appetite and nutritional status, others, despite the lowering of BUN and creatinine levels, have persistent anorexia and nausea, compounded by inefficient removal of small molecules, abdominal distention, and discomfort with dialysate fills. Furthermore, appetite suppression owing to glucose in the dialysate can occur (dialysate glucose can supply up to 700 kcal and represents an absorption of 100% of glucose per dialysate fill).

Protein loss via the dialysate will occur—5 to 15 g of albumin per day, depending on whether the child's peritoneal membrane transport characteristics are high or low.[99] Albumin losses during episodes of peritonitis can increase dramatically, to as much as 10 to 30 g/day, and can persist for several weeks.[99] Dialysate glucose concentration, along with dialysate lactate and acetate, can also exacerbate hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and weight gain.[95] The amount of glucose a patient can be expected to absorb over a daily cycle can be estimated with the following formula[99]:

$$y = 11.3\,x - 10.9$$

where y is glucose absorbed in grams per liter and x is the average dialysate concentration of glucose in grams per deciliter.

Malnutrition in patients on peritoneal dialysis can be demonstrated by muscle wasting; by low levels of serum albumin, transferrin, and other liver-derived proteins; and by abnormal amino acid levels.[95] Of all of the chemistries determined in the clinical laboratory, serum albumin and creatinine are best correlated with increased morbidity,[99] reflecting the fact that peritoneal dialysis cannot replace full renal function. Hypoalbuminemia or poor dialysis, reflected by inadequate Kt/V, might not be seen during the first year of treatment but are common after a longer time on chronic peritoneal dialysis (18% in the first year versus 42% after 1 year).[91] Less adequate dialysis with time is not significantly different from that experienced by patients on hemodialysis (see below).

The cause of hypoalbuminemia in patients on peritoneal dialysis is not thought to be a result of renal failure per se but rather of a separate process, protein malnutrition. Nevertheless, nutritional supplementation does not always seem to restore body stores of albumin. Other processes, such as endocrine imbalance involving growth hormone, cortisol, or thyroid hormone levels, can affect albumin synthetic rates. Additionally, inflammation, which can affect the proportion of acute-phase reactants, as well as albumin losses in urine or across dialysis membranes, can affect levels. In a recent study in adults,[97] hypoalbuminemia was found to be secondary to reduced albumin synthesis and not related to dialysis prescription, protein intake, or albumin losses. It appeared that decreased albumin synthesis was, in part, a response to inflammation involving acute-phase components, including insulin-like growth factor (IGF)-I.

Practical Aspects of Nutrition in Peritoneal Dialysis

Fluid and nutrient recommendations for children on peritoneal dialysis are listed in Table 36-7 according to age group. To achieve positive nitrogen balance, an adolescent might need 0.75 g/kg/day of "high-quality" protein (for nondialyzed, nonuremic patients); with CAPD, protein requirements increase to 1.2 g/kg/day.[98] Although many authors discuss "high-quality" protein supplementation, what high-quality protein is and whether it makes a difference has not been established. It might be more important that the taste of the food be acceptable.[64] Protein requirements should be balanced with concurrent caloric intake and the level of physical exercise. For infants, protein requirements can vary depending on how they are dialyzed and how much protein is lost in the dialysate. As one would expect, higher protein intake is required with more exchanges per day.

Sodium, potassium, and fluid intakes tend to be more liberal in peritoneal dialysis patients than in hemodialysis patients. Infant formulas tend to be low in sodium; therefore, supplementation with sodium chloride or sodium bicarbonate, depending on the presence or absence of systemic acidosis, can be provided. For infants whose fluid intake needs to be restricted, formulas can easily be concentrated to 24 kcal

per ounce. Monitoring of serum phosphorus and potassium is advised when concentrated formulas are used.

As an infant grows, the formula used can be advanced to one with higher caloric and protein contents (such as Pediasure, Nepro, or Suplena). We do not recommend the use of cow's milk as formula because it contains higher amounts of phosphorus and potassium. Recommendations for appropriate formulas for nutritional support for infants and children undergoing routine peritoneal dialysis can be found in Table 36-3. For phosphorus control, formulas such as Similac PM 60/40 and SMA, and for control of both phosphorus and potassium, S-29 (Wyeth-Ayerst Laboratories) can be used. If used long term, S-29 needs to be supplemented with sodium, chloride, calcium, vitamins B_6 and B_{12}, and folic acid. Sodium chloride or sodium bicarbonate can be used for supplementation, particularly in infants with residual renal function who waste sodium in their urine and for those with renal tubular acidosis.

For children on peritoneal dialysis, micronutrient needs, especially resulting from vitamin losses, are expected to be greater than for those on hemodialysis because large molecules and proteins are lost in the peritoneal dialysate. This finding is largely based on information from adult patients on CAPD. Water-soluble vitamins (vitamins B_6 and C, folic acid, and thiamin) are lost in dialysis. Vitamin C and folic acid intakes are usually low with potassium-reduced and low-protein diets. Vitamin C replacement should be used with caution to avoid the possibility of oxalate deposition in organs such as heart and kidney and in blood vessels. The fat-soluble vitamins are not as readily dialyzable and additional supplementation is generally not recommended, except for the active form of vitamin D. Commercial formulas for infants and children are supplemented with vitamins; however, additional supplementation using liquid or chewable forms is routinely used.

A unique study of pediatric patients on peritoneal dialysis showed that serum levels of vitamins A, B_1, B_2, B_6, and B_{12} and folic acid were elevated.[101] Indeed, the peritoneal dialysate contained large amounts of vitamin C. The authors questioned the need to supplement with multivitamins while these children (6 to 13 years of age) were asymptomatic.[101] There are several vitamin supplements available now[101,102] that are designed for dialysis patients; Nephrocap (Fleming and Company) and Nephro-Vite (R&D Laboratories) have no vitamin A or D. Carnitine, a water-soluble amino acid, is important in the transport of long-chain fatty acids across mitochondrial membranes, ultimately providing muscles with energy.

In peritoneal dialysis, low carnitine levels have been observed, and supplementation at 30 mg/kg is recom-

TABLE 36-7 Fluid and Nutrient Recommendations for Children on Peritoneal Dialysis

Age	*Infant (0–1 yr)*	*Toddler (1–3 yr)*	*Child (4–10 yr)*	*Adolescent (11–18 yr)*
Energy (kcal/kg)	0–0.5 yr: ≥ 108 0.5–1 yr: ≥ 98	102	4–6 yr: 90 7–10 yr: 70	Girls 11–14 yr: 47 Girls 15–18 yr: 40 Boys 11–14 yr: 55 Boys 15–18 yr: 45
Protein (g/kg)	2.5–4.0	2.0–2.5	2.0–2.5	1.5
Sodium	1–3 mEq/kg if needed	Same as for predialysis	Same as for predialysis	Same as for predialysis
Calcium	Same as for predialysis	Same as for predialysis	Same as for predialysis	Same as for predialysis
Potassium (mEq/kg)	1–3 if needed	1–3 if needed	1–3 if needed	1–3 if needed
Phosphorus (mg/d)	Use low-content formula if serum levels of phosphate are elevated; restrict high-content foods	Usually 600–800	Usually 600–800	Usually 600–800
Vitamins	1 mL multivitamin drops, 1 mg folic acid, vitamin D metabolites (in most cases)	Multivitamin, 1 mg folic acid, vitamin D metabolites as needed	C and B-complex vitamin containing 1 mg folic acid, 10 mg pyridoxine, 60 mg ascorbic acid, 5 mg pantothenic acid, 1 mg thiamin, 1.2 mg riboflavin; 3 μg B_{12}, 300 μg biotin, 15 mg niacin; active form of vitamin D as needed	C and B-complex vitamin containing 1 mg folic acid, 10 mg pyridoxine, 60 mg ascorbic acid, 10 mg pantothenic acid, 1.5 mg thiamin, 1.7 mg riboflavin; 6 μg B_{12}, 300 μg biotin, 20 mg niacin; active form of vitamin D as needed
Trace minerals	Supplement zinc or copper if needed; iron is usually needed with EPO	Supplement zinc or copper if needed; iron is usually needed with EPO	Supplement zinc or copper if needed; iron usually needed with EPO	Supplement zinc or copper if needed; iron usually needed with EPO
Fluid	Provide insensible loss + urinary output + ultrafiltration capacity	Unrestricted unless needed	Unrestricted unless needed	Unrestricted unless needed

Adapted from Nelson P and Stover J.[133]
EPO = erythropoietin.

mended to improve the response to cardiac contractility, improve erythropoietin therapy, and reduce triglyceride levels (see Table 36-7). Additionally, in regions where the water supply contains less that 0.77 ppm of fluoride, supplementation is routine. Children on peritoneal dialysis should not have fluoride supplementation because this puts them at risk for fluorosis and damage to their permanent teeth.[78]

A number of recent studies examine the effects of using amino acids in dialysis fluids to promote growth and also consider peritoneal transport properties because these affect growth.[47,103–107]

Nutritional Aspects of Hemodialysis

Dialysis Outcomes Quality Initiative recommendations for hemodialysis also comment on nutritional aspects of hemodialysis.[108] As is the case for peritoneal dialysis, the recommendations for children are largely based on opinion and consensus rather than on hard data.[108] Many of the nutritional considerations for peritoneal dialysis are the same for the child on hemodialysis. Thus, the foregoing discussion about nutritional aspects of peritoneal dialysis in children will not be repeated. Table 36-8 lists fluid and nutrient recommendations for children of various ages receiving chronic hemodialysis treatments.

Hemodialysis can contribute to amino acid losses when glucose-free dialysate is used (up to 8 g of free amino acids per session in an adult). This loss is further exacerbated by the choice of membrane, which contributes to the negative nitrogen balance seen in these patients. Synthetic polyacrylonitrile membranes have decreased losses relative to cellulose membranes.[100] The inflammatory reaction could be initiated by dialyzer membrane choice (biocompatible to bioincompatible), which activates the complement system.[109] However, many authors believe that hemodialysis-associated protein catabolism is not a simple function of increased protein degradation or a function of cuprophane membranes. As a result, recommendations for protein intake are higher: 1.2 g/kg/day of high-quality biologic protein, in combination with a minimum of 35 kcal/kg/day (see Table 36-8 for age-specific guidelines).

The balance of carbohydrate to lipids should be one-third carbohydrate and two-thirds fat, with a 2:1 ratio of polyunsaturated to saturated fat. As mentioned earlier, serum albumin provides a marker for nutritional evaluation. With improved caloric intakes, serum albumin does rise. However, other markers (eg, transferrin) are dependent on a number of other factors, such as iron stores, that might not reflect an accurate nutritional picture and can make interpretation difficult.[108]

Malnourished Dialysis Patients

As long as reversible causes of malnutrition have been addressed and treated, oral or parenteral supplementation is not necessary. However, nutritional intervention should be considered in patients who, for whatever reason, cannot take in the recommended protein and calories. As in other types of malnourished children, enteral feedings are preferable to parenteral routes. Table 36-3 lists oral supplements that can be used to augment deficient diets. In the pediatric population, interdialysis supplemental

TABLE 36-8 Fluid and Nutrient Recommendations for Children on Hemodialysis

Age	*Infant (0–1 yr)*	*Toddler (1–3 yr)*	*Child (4–10 yr)*	*Adolescent (11–18 yr)*
Energy (kcal/kg)	0–0.5 yr: ≥ 108 0.5–1 yr: ≥ 98	102	4–6 yr: 90 7–10 yr: 70	Girls 11–14 yr: 47 Girls 15–18 yr: 40 Boys 11–14 yr: 55 Boys 15–18 yr: 45
Protein (g/kg)	0–0.5 yr: 3.4 0.5–1.0 yr: 1.6	≥ 1.8; as much as tolerated	4–6 yr: ≥ 1.8 7–10 yr: ≥ 1.5	≥ 1.3–1.5; as much as tolerated
Sodium	1–3 mEq/kg if needed	Same as for predialysis	Same as for predialysis	Same as for predialysis
Calcium	Same as for predialysis	Same as for predialysis	Same as for predialysis	Same as for predialysis
Potassium (mEq/kg)	1–3 if needed	1–3 if needed	1–3 if needed	1–3 if needed
Phosphorus (mg/d)	Use low-content formula if serum levels of phosphate are elevated; restrict high-content foods	Usually 600–800	Usually 600–800	Usually 600–800
Vitamins	1 mL multivitamin drops, 1 mg folic acid, vitamin D metabolites (in most cases)	Multivitamin, 1 mg folic acid, vitamin D metabolites as needed	C and B-complex vitamin containing 1 mg folic acid, 10 mg pyridoxine, 60 mg ascorbic acid, 5 mg pantothenic acid, 1 mg thiamin, 1.2 mg riboflavin	Multivitamin if needed; vitamin D metabolite if needed, based on serum calcium, PTH and alkaline phosphatase levels
Trace minerals	Supplement zinc, iron, or copper if needed	Supplement zinc, iron, or copper if needed	Supplement zinc, iron, or copper if needed	Supplement zinc, iron, or copper if needed
Fluid	Unrestricted unless needed; then replace insensible loss + urinary output	Unrestricted unless needed; then replace insensible loss + urinary output	Unrestricted unless needed; then replace insensible loss + urinary output	Unrestricted unless needed; then replace insensible loss + urinary output

PTH = parathyroid hormone.

amino acids and carnitine do not result in improved amino acid or lipid profiles.[54,110,111] The institution of tube feeding for enteral supplementation is recommended for children who cannot consume the "required" calories and for those who are growing poorly, more than two standard deviations below the mean (below the 3rd percentile for height and weight).

Although tube feeding can impose an additional complication on an already busy care schedule, growth outcome can be improved in infants when tube feeding is begun early. Recent reports from several centers indicate that normal growth can be obtained in children who receive tube feedings.[56,112–115] Either nasogastric or gastrostomy tubes can be used to deliver supplemental calories. Chronic placement of nasogastric tubes has been used successfully by some; however, complications (eg, frequent removal by the child, vomiting, gastroesophageal reflux, aspiration, sinusitis, recurrent otitis media, and gastric irritation with possible perforation) can occur.[115] Gastrostomy tubes might be preferable to chronic nasogastric tube placement and can be placed percutaneously with a minimum of anesthesia. Adverse complications of gastrostomy tubes are leakage at the exit site, blockage, malabsorption or diarrhea, and infection at the exit site. Additionally, reliable use of nasogastric tubes might be difficult because it is a major undertaking for all involved.

The method for giving enteral supplementation consists of either a continuous drip or repeated bolus feedings during the day. For infants on CAPD, drip feedings can be organized for dialysis periods, balanced with bolus feedings.[78] Other factors that can modify the net monthly caloric intake and growth gain include psychosocial factors: economic and social situation of the parents, the age and number of siblings, the relationship and availability of the support system, including primary care medical staff and family, and the ease of access to the hospital or clinics. Parenteral nutrition can be given to patients who cannot tolerate oral feeds, whether because of gastrointestinal intolerance or intercurrent illness. Total parenteral composition for patients on dialysis should include 10 to 15% concentrated mixture of essential and nonessential amino acids, along with 20% lipid infusion, providing up to one-third of the caloric intake. Potassium, phosphorus, and magnesium might need to be added, with caution, to the TPN and monitored closely.

Patients with metabolic acidosis who are treated with acetate- and lactate-based dialysates and TPN solutions can become acetate intolerant secondary to systemic acetate transfer exceeding their maximal metabolic capacity, generally in the setting of intercurrent illness; this can contribute to decreased oxygen delivery to tissues and disturb hemodynamics.[116] Provision of bicarbonate, either by using specially composed dialysate or adding bicarbonate to the TPN (use caution with calcium-containing fluid) can treat this. Trace minerals and water-soluble vitamins should also be provided.

Intradialytic parenteral nutrition (IDPN) provides parenteral nutrition during regular hemodialysis sessions. Overall, the success of this type of supplementation has not been impressive. Most studies that show a benefit do so only marginally, with small improvements in weight and amino acid profiles.[117–120] No study has shown a change in morbidity or mortality. Under special circumstances in which there is moderate malnutrition, poor appetite, and low serum albumin, a short course of IDPN might be helpful. The goals of IDPN therapy are to provide maximum caloric and protein substrates in conjunction with enteral feedings so as to improve protein synthesis, prevent weight loss, improve appetite, and provide a sense of well-being.[96] IDPN formulations provide concentrated dextrose solutions (D50 to D70) and concentrated amino acid solutions (10 to 15%). Lipids usually are not introduced in the initial administration but are added later in either 10 or 20% forms. IDPN is very expensive and so should be carefully considered.

An interesting alternative for patients on CAPD is to use amino acids instead of dextrose dialysate. In one prospective, randomized, crossover study of seven malnourished children on CAPD,[116] appetite and serum albumin levels improved with amino acid dialysate, and there was effective ultrafiltration and creatinine clearance. However, there was no additional proven nutritional benefit. Qamar and colleagues reported that using a dialysate that contained amino acids was helpful in a small group of children ($N = 7$) on continuous cycling peritoneal dialysis who participated in a prospective, randomized, crossover study in which they received either amino acid dialysate or dextrose dialysate.[103] Each modality was used for 3 months and then subjects crossed over to the alternate regimen for another 3 months. The amino acid dialysis was comparable to the dextrose dialysis with respect to creatinine clearance and ultrafiltration, and plasma urea was higher during amino acid dialysis. Additionally, appetite and total body nitrogen increased in at least half the patients. Further study might be needed to identify a subset of patients who could benefit from this sort of substitution.

In another (short-term) study, 10 children on chronic hemodialysis were provided with IV amino acid supplementation at 0.25 g/kg during dialysis thrice weekly for a month, taken off for a month, and then given supplements plus carnitine at 25 mg/kg at the end of each session. No child was on recombinant human growth hormone (rGH), and all had dietary intakes of at least 75% of the RDA. Nine patients gained weight during the study, although one lost weight. Carnitine had no effects on plasma amino acids or lipids. No results of long-term studies are available.[111]

Despite progress made by dialysis as a means of controlling the impact of end-stage renal disease, growth in children on dialysis still remains a problem. The factors that contribute to this are many and include calorie-protein deprivation, intermittent and persistent metabolic acidosis, electrolyte deficiencies, uremic toxins, renal osteodystrophy, hormonal disturbances, pyschosocial issues, age at onset, and the natural history of the primary disease.[121] Dialysis modalities, including hemodialysis, continuous peritoneal dialysis, and CAPD, have been examined with respect to their effects on growth nutrition so that children can receive the most beneficial maintenance dialysis until transplantation. It is clear that dialysis

alone is not able to prevent the growth failure seen frequently in children with end-stage renal disease.

In several studies, CAPD has been shown to facilitate better growth relative to hemodialysis.[121–127] Some children receiving hemodialysis are found to grow normally (at predialysis rates) and another two-thirds are found to have moderate to severe growth impairment (catch-up growth is not seen).[123] In a recent study, 80 children on CAPD did show improved growth when there was improvement in metabolic parameters and metabolic acidosis, additional caloric supplementation from dialysate glucose (5 to 10% of the RDA), and lower BUN levels. Disappointingly, in this study, despite aggressive nutritional management and high protein intake for all modes of dialysis, the percentage of calories that patients actually took in was 100% of the RDA.

Regardless, aggressive nutritional support for infants and children on chronic dialysis is recommended and provides for maintenance of growth or improved growth while awaiting transplantation.[63,78] All efforts should be made to diagnose and treat chronic renal failure as early as possible and to integrate the family into a well-designed program of routine visits for biochemical, dietary, and clinical review.

TRANSPLANTATION

Nutritional intervention in patients with renal transplantation might at first seem unnecessary. Indeed, the onset of a normal GFR increases appetite and sense of well-being. However, changes in body composition are common and are modulated by multiple factors, including gender, age, income, energy intake, and, in particular, glucocorticoids and immunosuppression, which affect fluid retention and fat accumulation. Recent studies have added to the growing body of data indicating that cardiovascular disease is accelerated in transplant recipients in concert with the acquired weight gain and other cardiovascular disease risk factors. Indeed, elevated body mass index is a strong independent risk factor for patient mortality and allograft failure, at least in adults.[128]

Drug-induced metabolic issues, in addition to weight gain, often include hyperlipidemia, hyper- or hypokalemia, hypertension, interference with metabolism and action of vitamin D, glucose intolerance, hyperuricemia, and hypercatabolism of protein. Additionally, exacerbation of preexisting disease processes (eg, calcium malabsorption, hyperparathyroidism, hyperlipidemia) can also be found. Nutritional management for the transplantation patient can be divided into three periods: pretransplantation, acute post-transplantation, and long-term post-transplantation. The goal for all phases is to improve the new graft's longevity by careful attention to nutritional and metabolic states.

In the pretransplantation period, the patient's nutritional status should be optimized to minimize surgical risk, complications, and length of hospital stay.[129] Patients range from those who will undergo preemptive transplantation to those who have been treated with dialysis for varying periods of time. Nutritional assessment can expose aspects of undernutrition requiring supplementation or correction before transplantation. Specifically, calcium-phosphate balance should be adjusted as needed, with larger doses of phosphate binders and the addition of, or increase in, vitamin D supplementation. Ideally, metabolic and nutritional issues should be addressed as the patient approaches the time of transplantation. However, despite best efforts, optimal nutrition often is not achieved.

Acute post-transplantation management focuses on stabilizing an allograft that functions well.[129–132] The use of corticosteroids, a virtually universally used class of medicine, stimulates appetite and can make weight control difficult. Counseling at this stage with advice about total caloric intake, desired percentage of carbohydrates, possible behavior modification techniques, and exercise can be beneficial. Many patients who have renal transplants are entering puberty or are already in puberty. A number of medications can lead to changes in body or facial appearance, such as puffy cheeks or jowls caused by corticosteroids. Such changes can be detrimental to ego stability and lead to poor compliance. The effect of corticosteroids on carbohydrate metabolism, including increases in insulin and insulin resistance, along with glycosuria, is well known.[130] Minimization of carbohydrate intake (40 to 50% of caloric intake in pediatric patients) has been shown to help reduce the cushingoid side effects of corticosteroids. Curtailing intake of dessert-type items, some cereals, and additives (syrup, ketchup) is helpful; juices and fruits, which are considered complex carbohydrates, can be used in moderation.[132–134]

Ultimately, a plan can be formulated that prescribes protein intake for early and later phases of transplantation, lipid intake and composition, and calcium, phosphate, and vitamin D use. Additionally, if patients have been on corticosteroids (eg, for treatment of nephrosis or systemic lupus erythematosus) prior to allograft placement, attention should be given to carbohydrate metabolism. Iron intake should be assessed, and, if needed, supplementation should be given, along with sodium restriction and supplementation with water-soluble vitamins.

Immunosuppressive drugs (eg, cyclosporine, azathioprine, and corticosteroids) decrease protein anabolism through diminished uptake of amino acids,[133] inhibit deoxyribonucleic acid (DNA) and ribonucleic acid synthesis,[135] and increase protein catabolism by augmenting hepatic gluconeogenesis.[136] Immediately post transplantation, high doses of glucocorticoids are given, the effects of which combine with stress from surgery. If rejection occurs, treatment with high-dose IV methylprednisolone might be given, leading to marked protein catabolism. In combination with preexisting protein depletion, problems such as poor wound healing and susceptibility to infection can be seen.

Protein intake should begin at 2 to 3 g/kg/day immediately following transplantation, along with sufficient calories and a low intake of carbohydrates, which can be tapered over the next several months to the RDA for the appropriate age group[129] (Table 36-9). Although higher-protein diets are indicated for the early post-transplantation period, optimal dietary prescription on maintenance

immunosuppression might conflict with issues such as long-term renal function, stability, and growth. Some data suggest that even patients on low-dose maintenance corticosteroids (0.15 to 0.2 mg/kg/day) with optimal allograft function have elevated protein catabolism—as evidenced by muscle wasting, poor wound healing, and delicate skin—and dietary intake of more than 1.0 g/kg/day of protein is necessary to reduce signs of protein depletion.[136]

It is not uncommon to find elevated blood pressures during the immediate post-transplantation period, when drugs such as cyclosporine and corticosteroids are used in high dosages. Sodium, therefore, should be restricted (no salt added to the diet, maximum 2 g sodium per day) and liberalized carefully as the medications are tapered.

Although cyclosporine can result in mild elevations of potassium secondary to renin and aldosterone suppression, patients can experience acute post-transplantation diuresis. Additionally, diuretic and corticosteroid therapy, together with hypomagnesemia, the possible presence of renal tubular dysfunction, and ileal conduits with gastrointestinal losses, can all contribute to elevated potassium levels. Typically, potassium levels can be managed without dietary intervention or reduction in cyclosporine dosage.

A large diuresis is characteristic of the post-transplantation period and begins at about the time of the vascular anastomosis. Even though large volumes of fluid are given postoperatively, the etiology of this diuresis is not completely understood. Contributing factors include preoperative and interoperative expansion of extracellular fluid volume, osmotic diuresis caused by urea, diuresis and natriuresis owing to denervation of the transplanted kidney, proximal tubular dysfunction, resetting of glomerulotubular balance, or medullary ischemia. Nevertheless, judicious fluid replacement must be achieved, adjusting volume and type of fluid administered based on urinary composition. It is not uncommon to find significantly elevated fractional excretion of sodium, along with glucosuria and aminoaciduria. Most commonly, for living-donor transplants, hypotonic solutions (0.45% normal saline) can be administered without potassium. In some patients, elevated magnesium losses, the administration of diuretics, or both can precipitate potassium losses and will require changes in therapeutic strategy as the type of loss changes.

Concurrent hypomagnesemia will require magnesium replacement to correct hypokalemia. A strategy for volume control can be anticipated, and fluid should be replaced at twice maintenance with close monitoring and appropriate treatment of hemodynamic and homeostatic changes, including daily weights. Patients receiving cadaveric renal transplants present a somewhat different problem, particularly because of their higher incidence of delayed graft function. This situation precludes planning preset replacement fluids; however, the usual of maintenance fluid plus urine output volume can be used to start.

Pediatric patients who receive transplantation are commonly on vitamin D supplementation. As mentioned earlier, despite maximal efforts, alterations in calcium-phosphate-PTH balance are not uncommon, together with a range of

TABLE 36-9 Fluid and Nutrient Recommendations for Pediatric Transplant Recipients

Age	*Infant (0–1 yr)*	*Toddler (1–3 yr)*	*Child (4–10 yr)*	*Adolescent (11–18 yr)*
Energy	Same as for predialysis after ideal weight and length achieved	Same as for predialysis after ideal weight and height achieved	Same as for predialysis after ideal weight and height achieved	Same as for predialysis after ideal weight and height achieved
Protein (g/kg)	Usually 3 initially; RDA after approximately 3 mo	Usually 2–3 initially; RDA after approximately 3 mo	2–3 initially; RDA after approximately 3 mo	2 initially; RDA after approximately 3 mo
Sodium	1–3 mEq/kg initially	1–2 g initially; unrestricted when HTN and edema no longer present	Usually 2–3 g initially; unrestricted when HTN and edema no longer present	Usually 2–4 g initially; unrestricted when HTN and edema no longer present
Calcium	Ad libitum; supplement if necessary to RDA	Ad libitum; supplement if necessary to RDA	Ad libitum; supplement if necessary to RDA	Ad libitum; supplement if necessary to RDA
Potassium	Unrestricted unless needed	Unrestricted unless needed	Unrestricted unless needed	Unrestricted unless needed
Phosphorus	May need very high intakes; supplement as necessary	May need very high intakes; supplement as necessary	May need very high intakes; supplement as necessary	May need very high intakes; supplement as necessary
Vitamins	Usually not necessary unless severely malnourished prior to transplantation; vitamin D as needed, depending on phosphorus-calcium balance	Usually not necessary; vitamin D as needed	Usually not necessary; vitamin D as needed	Usually not necessary; vitamin D as needed
Trace minerals	Generally unnecessary; supplement iron as needed	Generally unnecessary; supplement iron as needed	Generally unnecessary; supplement iron as needed	Generally unnecessary; supplement iron as needed
Fluid	Ad libitum	Ad libitum	Ad libitum	Ad libitum

Adapted from Nelson and Stover.[133]
HTN = hypertension; RDA = Recommended Dietary Allowance.

accompanying renal osteodystrophy. In our experience, pediatric patients often have pronounced hypophosphatemia following transplantation. They develop hypocalcemia and hypomagnesemia secondary to post-transplantation diuresis, have a renal tubular phosphate leak (either PTH dependent or PTH independent), and have gastrointestinal losses. This occurs in both cadaveric and living-donor kidney transplant recipients. This hypophosphatemia can still be seen even 6 months following graft placement.[44]

Early supplementation with vitamin D_3 for patients with PTH-independent hypophosphatemia can ameliorate and prevent further decrements in phosphate and calcium; the vitamin D can later be tapered according to response. Even though the transplanted kidney is capable of dihydroxylating vitamin D, corticosteroid treatment can contribute to a renal phosphate leak via its effect on vitamin D metabolism.[136] The active form of vitamin D is recommended because its half-life is significantly shorter than that of the monohydroxylated form (3 to 7 days versus 6 to 18 weeks), which facilitates management.

Persistent post-transplantation hyperparathyroidism (PTH-dependent hypophosphatemia, normocalcemic or mildly hypercalcemic) can be managed with oral phosphorus supplementation. Consuming skim milk (1 g phosphorus per liter) is an easy and cost-effective way of replacing phosphorus. Whole milk, with its higher fat content, can aggravate diarrhea and hyperlipidemia, and phosphate supplements, in addition to inducing diarrhea, might provide an acid load that might not be buffered appropriately (some patients continue to have urine bicarbonate wasting). In some cyclosporine-treated patients, addition of potassium and sodium loads from phosphate supplements can aggravate hypertension and parathyroid balance.

Obesity or weight gain and hyperlipidemia are not uncommon among renal transplantation patients. Not only do patients feel better after transplantation, but they are encouraged to consume more calories. The concurrent use of corticosteroids stimulates appetite, and insufficient exercise can persist as a carryover of the pretransplantation phase. Thus, the caloric expenditure might be insufficient for the actual intake, resulting in rapid weight gain. Exercise programs should be advised to restore normal energy expenditure.

Intake of dietary fats should include both monounsaturated and polyunsaturated fats, with the overall intake being between 30 and 50% of total calories to minimize the hypercholesterolemia and hyperlipidemia described during this period.[136] Generalized hyperlipidemia can be seen with patients treated with azathioprine and prednisone, and hypercholesterolemia is found in patients receiving cyclosporine. Therefore, on most post-transplantation medical regimens, patients are likely to exhibit elevations in both cholesterol and triglyceride levels. Prednisone is strongly associated with hyperlipidemia, related in large part to insulin resistance in peripheral tissues with impaired synthesis of lipoprotein lipase and lipoprotein synthesis.[137] Other factors that can adversely affect serum lipid levels include diuretics and beta-adrenergic agents used to treat hypertension.

Elevations of uric acid can be found following transplantation concomitantly with cyclosporine or azathioprine treatment. This is particularly so with cyclosporine administration, especially if diuretics are used. It is believed that the decreased excretion of urate explains the elevation of uric acid seen with cyclosporine use. Despite levels of urate in the range of 8 to 14 mg/dL, gouty arthritis is uncommon, and adequate management consists of limiting dietary purines, reducing or eliminating diuretic treatment, and administering colchicine.

Frequently, elevations of serum calcium are found following transplantation, either early, transiently, persistently, or a combination of these. Persistent secondary hyperparathyroidism (correlating with serum PTH levels and the extent of renal osteodystrophy), along with phosphate deficiency and abnormalities in vitamin D metabolism, contributes to the observed hypercalcemia. Despite the brisk diuresis seen following transplantation, many patients have sustained PTH elevations, some even 3 years after transplantation. It could be that gastric absorption of calcium and renal tubular leak are aggravated by corticosteroid treatment. Management of mild to moderate post-transplantation hypercalcemia should include oral phosphate supplementation (Table 36-2), magnesium administration (Table 36-2), vitamin D administration, and hydration. Subtotal parathyroidectomy should be reserved for refractory, severe hypercalcemia.

Synthesis

The challenge of maintaining maximal nutritional standards for patients with renal insufficiency in all stages is formidable, and the best achievements can be less than ideal. One must consider that surgical intervention and dialysis (either peritoneal dialysis or hemodialysis) are not without risk and inconvenience for families. The actual benefit of caloric maximization for predialysis patients is endorsed. Clearly, the emphasis should be on growth, particularly for infants with chronic renal failure, in whom catch-up growth is so rare. Increasingly, our experience with growth hormone administration to patients at the predialysis, dialysis, and transplantation stages has expanded; results have shown significant improvements—for some, in both height and weight percentiles. Nevertheless, our expectations of growth for patients with renal insufficiency should be tempered by the need for further research and study of the ideal plan for all children with renal insufficiency.

NUTRITIONAL CONSIDERATIONS IN GLOMERULAR DISEASE: NEPHROTIC SYNDROME

Nephrotic syndrome is an example of a glomerular disease in which dramatic nutritional alterations occur. Nephrotic syndrome results from increased glomerular permeability to albumin and other macromolecules of intermediate molecular weight, leading to massive proteinuria (1 g/m^2/day or 40 mg/m^2/hour or more), hypoproteinemia, hyperlipidemia, and edema. Systemic manifestations and consequences of nephrotic syndrome are responsible for much

of the morbidity and mortality seen with this condition.[138] The most common form of nephrotic syndrome in children is minimal-change disease, which is usually responsive to corticosteroid administration. The management of nephrotic syndrome involves treatment of acute symptoms concomitant with the administration of corticosteroids (with or without other medications), fluid control, and diet modification.[139]

Acute Management of Nephrotic Edema

Many patients tolerate considerable proteinuria and moderate hypoalbuminemia without developing massive edema.[140] However, severe generalized edema can occur with profound hypoalbuminemia (albumin level below 1.5 g/dL). Massive ascites and pleural effusion can occur, and occasionally painful scrotal or labial edema occurs. Any of these situations can cause much discomfort, together with difficulty in carrying out daily activities. Marked fluid overload, severe intravascular depletion, or infection are indications for hospitalization.

If blood volume is normal, 25% albumin (1g/kg over 3 to 4 hours) is given, followed by IV furosemide (1 to 2 mg/kg) either halfway through or after the albumin infusion. This can be repeated once a day for 2 or 3 days until an adequate diuresis occurs. Albumin infusion must be given with great care, owing to potential adverse effects from sudden fluid shifts, which can lead to pulmonary edema. Albumin should be infused during the daytime, when sufficient staff are present to monitor the patient closely. Albumin infusion should be reserved for very severe edema with problems as noted (never for cosmetic reasons only) because it leads to only temporary improvement of serum albumin level when a patient is nephrotic. It is crucial to limit fluid intake during and after albumin infusion so that weight loss will occur.

There are two contraindications for 25% albumin infusion. The first is increased blood volume, as assessed by elevated blood pressure, distended jugular veins, signs of pulmonary edema, or congestive heart failure. The infusion of 25% albumin can lead to rapid fluid shift from the interstitial to the vascular space in such patients and can lead to pulmonary edema, congestive heart failure, and possible death.

The other contraindication is decreased blood volume, as assessed by the presence of orthostatic hypotension (a drop of 15 to 20 mm Hg in systolic blood pressure with postural change from supine to upright), tachycardia, decreased capillary refill, decreased urine output, or low random urine sodium (less than 20 mmol/L). Patients with decreased blood volume should receive 5% albumin at 10 cc/kg over 1 to 2 hours, prior to more concentrated infusions. This solution contains normal saline as the solvent (130 to 160 mEq/L). However, 5% albumin is expensive and not always on hand, and 0.9% NaCl alone, although easily available, rarely stays in the intravascular space. In nephrotic patients, infusion of normal saline alone will lead to worsening edema and will not expand vascular volume, except transiently. Thus, if 5% albumin is not available, a patient with volume depletion should receive 10 cc/kg of a 1:5 dilution of 25% albumin (diluted in normal saline). For example, in a 20 kg child, the dose of 10 cc/kg = 200 cc; thus, 40 cc of 25% albumin is added to 160 cc of 0.9% NaCl to provide a total volume of 200 cc.

Dietary Management of the Nephrotic Child

Fluids and Electrolytes After stabilization of intravascular volume, the nephrotic patient needs to have fluid restricted to insensible losses (400 cc/m^2) plus urine output (or less, for weight loss) for several days until onset of diuresis or until stable. If salt intake is limited, the urge to drink is limited to some extent. Thus, sodium intake both during relapses and during corticosteroid therapy should be restricted with a no added sodium diet. Severe sodium restriction, equivalent to 1 to 2 mEq Na/kg/day or 23 to 46 mg/kg/day (maximum 30 mEq/day or 690 mg/day), is necessary for patients who have poor response to diuretics. It can initially be difficult to persuade a child that food with no added salt tastes good; it can take up to 3 months to change taste preference. Because the majority of nephrotic patients have relapses, a no added salt diet should be continued even when the patient is in remission and off corticosteroids.

The edematous nephrotic patient might have hyponatremia on laboratory evaluation, despite sodium retention. Low values of sodium are not an indication for increased sodium supplementation as this will lead to a vicious cycle of increasing edema.

Dietary Protein Although endogenous protein synthesis can be augmented by increased intake of dietary protein, urinary protein losses also increase with increased intake. Additionally, changes in glomerular hemodynamics resulting from increased dietary protein intake can accelerate the progression of the possible underlying renal disease.[141] The dietary protein intake in the nephrotic child should meet the RDA for age, which should provide enough intake to avoid an impact on growth curve in the developing child. Recently, a soy protein diet has been reported to limit proteinuria in adult nephrotic patients.[142,143] This has not been studied in children, but adding soy protein to meals is not harmful.

Lipids Hyperlipidemia in nephrotic syndrome is caused, at least in part, by an increase in hepatic cholesterol synthesis in response to increased hepatic albumin synthesis. Persistently elevated serum cholesterol can lead to atherosclerotic disease and hasten the progression of renal disease.[141] In experimental animal models of nephrotic syndrome, hyperlipidemia promotes mesangial damage, glomerular sclerosis, and permeability of the glomerular capillary wall.[144]

Nonpharmacologic treatment of hypercholesterolemia in childhood nephrotic syndrome is suggested as most patients enter periods of remission and normalize their cholesterol. In the nephrotic child, 20% of energy should be delivered from protein; total fat intake should be limited to 28% of total caloric intake (with 8% from saturated, 8% from polyunsaturated, and 12% from monounsaturated fat), as suggested by the National Cholesterol Education Program.

Pharmacologic therapy for hyperlipidemia is not needed in most nephrotic children as hyperlipidemia usually corrects itself when the level of albumin increases during remission. In individuals with corticosteroid-resistant nephrotic syndrome, hyperlipidemia can present a long-standing problem. In these rare cases of prolonged hyperlipidemia with abnormal high-density lipoprotein (HDL) to low-density lipoprotein (LDL) ratio and high triglyceride levels, treatment with antilipogenic drugs might be indicated, especially if there is a concomitant family history of hyperlipidemia.

A soy-based vegetarian diet can be somewhat effective in treating hyperlipidemia.[142–144] Soy protein ingested in amounts of 20 to 50 g/day is associated with decreasing serum concentrations of total cholesterol, LDL cholesterol, and triglycerides but does not significantly affect HDL cholesterol. Such effects are significantly related to the initial serum cholesterol values, with the best result (reduction of cholesterol by 19.6%) when used in severe hypercholesterolemia (cholesterol level above 335 mg/dL). The soy diet has been reported to have an additional favorable effect on nephrotic proteinuria (which could be a direct consequence of partial correction of the hypercholesterolemia). However, the soy protein vegetarian diet should be used with caution in children because of its decreased content of vitamin B_{12}, vitamin D, and other important nutrients. It might be useful to implement soy protein as the primary protein element of the diet (eg, 230 mL of soy milk contains 4 to 10 g of soy protein, 28 g of soy flour has 10 to 13 g of soy protein, and 1,103 g of tofu has 8 to 13 g of soy protein).

Because omega-3 fatty acids found in coldwater fish have some lipid-lowering effect,[144] they can also be added to the daily diet. Although therapy with lipid-lowering agents is presently being attempted in children with unremitting nephrotic syndrome, few data exist.[145–149] In one brief report of 12 children,[148] statins appeared to be effective in a marked reduction of total and LDL cholesterol, although no overall change in the course of the nephrotic syndrome was noted. Recently, eight children were reported as having responses to gemfibrozil,[149] although the course of their disease did not appear affected either. Long-term controlled studies with statin therapy are needed to further document or negate their renoprotective role in refractory nephrotic syndrome.

Calcium and Phosphate Metabolism In prolonged, corticosteroid-resistant nephrotic syndrome, some patients have urinary losses of vitamin D binding protein and its accompanying vitamin, leading to a vitamin D–deficient state with resulting mild impairment of intestinal absorption of calcium and reduction of plasma ionized calcium concentration. This can lead to secondary hyperparathyroidism. Adding 400 IU of cholecalciferol (vitamin D_3) plus 800 mg of calcium to the diet per day will meet the FDA dietary requirements for children and should be sufficient for most nephrotic patients. In cases of suspected deficiency, serum levels of calcium and vitamin D must be measured and the supplemental dose of vitamin D adjusted.

NUTRITIONAL ISSUES IN RENAL TUBULAR DISORDERS

The renal tubules reabsorb the vast majority of filtered plasma water as well as solute, amino acids, and sugars. In addition, the tubules secrete numerous substances. For this reason, renal tubular disorders, depending on the tubular segment involved, can affect nutritional balance. An example of a proximal tubular dysfunction (cystinosis) and one of a collecting dysfunction (nephrogenic diabetes insipidus) serve to illustrate the problems that can ensue from such imbalances.

Cystinosis

Cystinosis, a rare autosomal recessive storage disease resulting from defective transport of cystine across the lysosomal membrane, is the most common cause of secondary Fanconi syndrome in children.[150,151] The stored cystine is poorly soluble and crystallizes within the lysosomes of many cell types, leading to widespread tissue and organ damage. In the infantile nephropathic form of cystinosis, which is the most common form, the kidney is severely affected early in life owing to stored cystine crystals within the proximal tubule, leading to deformation and damage with subsequent uncontrollable wasting of sodium, potassium, phosphate, calcium, magnesium, bicarbonate, tubular proteins, carnitine, glucose (without leading to hypoglycemia), and water.

Patients with the infantile nephropathic form of cystinosis present with the initial symptoms in infancy, frequently before the age of 1 year. Initial symptoms include polydipsia, polyuria, vomiting, loss of appetite, and subsequent failure to thrive. The first signs might go unrecognized for several months, until patients present dramatically, often during the course of a mild viral illness, with severe dehydration, serum electrolyte imbalance, and metabolic acidosis. Initially, many patients might be misdiagnosed with diabetes mellitus, diabetes insipidus, dwarfism, rickets, or failure to thrive.

Management of Acute Dehydration The initial management of dehydration in a cystinotic child requires the administration of large amounts of fluids and electrolytes, often exceeding any known or so-called acceptable limits. The intravenous fluid requirements in this situation might be more than twice that expected for the patient's size. In cystinotic children, the obligate urine volume is often several liters per day and must be meticulously measured and replaced during hospitalization. The initial reconstitution of wasted nutrients should be performed with the use of large-vein access, preferably a central line if the patient is severely affected.

The IV rehydration fluid should contain glucose, isotonic saline, potassium, and bicarbonate, in amounts generously exceeding the standard IV fluid composition. A good starting infusion consists of 5% dextrose in 0.45% NaCl with 40 mEq/L KCl and 80 mEq/L sodium bicarbonate. This mixture can be adjusted, depending on serum laboratory values: sodium, potassium, chloride, bicarbonate,

and glucose should be measured every 6 hours and calcium, phosphorus, magnesium, total protein, albumin, BUN, and creatinine once daily. Aggressive management is advisable to prevent nutritional deterioration with each episode of dehydration. As soon as the dehydration is under control, efforts should turn to increasing caloric intake.

Caloric preparations should follow RDAs: carbohydrates at 60 to 65%, protein at 10 to 15%, and lipids at less than 30%. Caloric intake should aim to achieve weight gain. The formula used to calculate catch-up growth in patients with failure to thrive can serve as a useful initial guideline:

$$\text{Catch-up growth (kcal/kg)} = \frac{120 \text{ kcal/kg} \times \text{median weight for current height}}{\text{current weight (kg)}}$$

Free access to water or other fluids is of great importance because cystinotic patients easily become dehydrated. For example, a water container should be placed at the bedside during the night.

When the patient becomes free of acute gastrointestinal symptoms (no longer having frequent episodes of vomiting, gagging, abdominal pain, or diarrhea) and eats well, a regular diet should be restarted, supplementing individually determined amounts of sodium, potassium, bicarbonate, and phosphate to achieve normal serum levels. Supplementation with the active form of vitamin D and with carnitine if serum total carnitine level is below 20 μmol/L is helpful.[150,151]

If the patient is a poor eater and oral feeding is unsuccessful, high-calorie oral supplementation in the form of shakes, puddings, or Polycose (up to 15 mL added to 30 mL of water [15 mL = 6 g of Polycose; 1 g of Polycose gives 3.8 kcal]) should be given. If the patient fails to take supplements or has an inappropriately low intake because of poor appetite or vomiting, gastric tube placement can be helpful. The decision to use gastric tube feeding needs to be made quickly (within 6 to 8 weeks) so that patients can meet their caloric needs for age without further delay. This permits improvement in linear and ponderal growth, while still allowing daytime oral feeding to the patient's preference. Prior to the placement of a gastric tube, the upper gastrointestinal tract should be evaluated with an upper gastrointestinal series, nuclear medicine studies of gastric emptying, a pH probe, or a combination of these. If severe or complicated reflux is documented, fundoplication should be considered during gastric tube placement.[152]

If a patient already has a gastrostomy tube in place, high-calorie formula (30 kcal/oz) should be resumed slowly after an acute illness, increasing by tolerable increments daily. The choice of formula for cystinotic patients can be divided into three categories, based on the patient's status:

1. For patients with abnormal gastrointestinal tract function, Peptamen, which is an elemental/semi-elemental formula, is appropriate.
2. For patients who are not in renal failure, a high-calorie, moderate-protein formula is recommended, such as Ensure Plus, Sustacal HC, Resource Plus, Nutren 1.5, Comply, Isocal HN, Ensure HN, Isosource, Osmolite HN, or Isosource HN.
3. For patients with constipation or chronic diarrhea, a formula containing fiber is recommended, such as Jevity, Newtrition Isofiber, Enrich, Sustacal with Fiber, or Compleat.[153]

If a cystinotic patient cannot tolerate any form of enteral feeding, TPN is indicated. The hyperalimentation should consist of RDA amounts for protein, carbohydrate, and lipids (see above), supplementing required electrolytes in increasing amounts depending on the patient's serum levels. Frequently monitor serum levels (initially daily, then twice a week, then weekly when the patient is stable) and the patient's weight, adjusting the volume and caloric content. Such patients might need double the volume required for maintenance of normal patients of the same weight. To achieve catch-up growth, the caloric requirements are in general higher than calculated for age.

Chronic Management Chronic management of nutritional needs in the cystinotic child should address the method of feeding (oral, gastric, or jejunal tube or central line hyperalimentation), type of diet, electrolyte supplementation, and medications. Our data[154] suggest that there are gastrointestinal abnormalities even in very young children with cystinosis, although earlier reports have suggested that such problems were found only in older patients.[155] There is at least a subgroup of cystinotic patients who present before age 1 year with severe gastrointestinal involvement manifested by daily episodes of vomiting, poor oral intake and subsequent growth retardation, frequent alternating episodes of diarrhea and constipation, and recurrent abdominal pain with flatulence. Some of these patients have been diagnosed as having swallowing dysfunction and gastrointestinal dysmotility (gastroesophageal reflux, delayed gastric emptying, or episodes of pseudo-obstruction).

Many other patients have not been evaluated, as these symptoms are ascribed to cystinosis and β-mercaptoethylamine therapy itself. In any young cystinosis patient presenting initially with gastrointestinal problems, we strongly advocate early formal evaluation for gastrointestinal dysmotility with pH probe, upper gastrointestinal studies, and manometry followed by a trial of management with gastrointestinal acid production antagonists (H_2 blockers, dyspeptic agents) and gastrointestinal prokinetic agents (metoclopramide, cisapride, erythromycin). We also advocate early consideration of gastric tube placement and initiation of high-calorie formula feeding, optimally overnight for 12 hours while allowing ad libitum feeding during the day.

Cystinosis patients have been found to have predilections for salty and spicy foods, along with specific food texture preferences, which are unique for each patient. They are very picky eaters with poor appetites, who as young children (less than age 2) have cravings for foods such as spicy Mexican food, hot sauce, hot peppers, hot dogs,

American cheese, pizza, popcorn, potato chips, lemon juice, sauerkraut, and pretzels and refuse more nutritious foods. Encouragement to eat well-balanced diets might be unsuccessful and create many unnecessary arguments, leading to total food aversion.

Overnight tube feeding can dramatically improve weight and height gain in these children. When there is severe feeding dysfunction (including strong gagging at the sight of food), aid from a feeding team, which should include a psychotherapist, to evaluate and manage swallowing dysfunction is needed. To teach the child that eating is a social event, it is important to have the child sit with the family at mealtimes and slowly introduce small amounts of food. Gastric tube dependence is common in this group, at least for the first few years. As the patients mature, their feeding dysfunction improves, and with the use of medications and socialization, tapering gastric tube feeding might be feasible. Some parents prefer to retain the tube even after the child's feeding pattern is improved so that it can be used for medications because these patients need to take many different medications that have a bad taste, and gastric tube delivery makes life easier for the child and the family.

There are also a few cystinotic patients with severe gastrointestinal dysmotility who cannot tolerate even gastric tube feeding, despite therapy with many prokinetic agents. These patients need to be carefully managed with IV hyperalimentation for months to years until subsequent trials of gastric or jejunal tube feedings are successful. In our center, we have one patient who required several years of TPN via the central line. Jejunal tube feeding was eventually restarted with the use of epidural anesthesia and IV erythromycin to counteract visceral hyperalgesia and episodes of pseudoobstruction. The patient was gradually weaned off the epidural anesthesia and continued on gastric tube erythromycin therapy, cimetidine, and cisapride.

Indomethacin, a prostaglandin synthetase inhibitor, is reported to have marked beneficial effects on appetite improvement by decreasing polyuria and, subsequently, polydipsia.[156,157] Indomethacin might be a helpful adjunct to nutritional management. Its use should be limited to patients with normal or stable renal function, and the patient should be monitored closely during therapy because indomethacin can lower GFR, although this is reversible by decreasing the dose. Indomethacin can also induce gastritis or stomach ulcers. Because cysteamine is also ulcerogenic, patients begun on indomethacin must be carefully monitored.

NEPHROGENIC DEFECTS IN URINARY CONCENTRATION

In the collecting duct of the renal tubule, antidiuretic hormone binds to receptors in the basolateral cell membrane and leads to an increase in water permeability.[158] Although antidiuretic hormone has effects in other segments of the nephrons, its primary effect is in the collecting duct. A variety of disease processes can lead to lack of responsiveness to antidiuretic hormone. These range from hereditary nephrogenic diabetes insipidus to chronic renal insufficiency and drug effects. Prompt recognition of this type of defect, especially in the neonate with hereditary nephrogenic diabetes insipidus, is very important.

The nutritional issues relating to nephrogenic defects of urinary concentration stem from the solute load needed for growth in the face of an inability to concentrate the urine. For example, a 10 kg infant receiving a standard diet of 30 mOsm for each 100 kcal metabolized will require about 300 mOsm as a minimal solute load. If normal, this infant is likely to produce urine of 600 mOsm/kg water and thus excrete 500 mL of urine per 24 hours. However, if such an infant cannot produce a urine more concentrated than 100 mOsm, the volume needed would be 3 L. An obligate urine volume of this magnitude leads to the need to drink vast quantities of water, leading to inadequate caloric intake. However, a reduction in solute intake can also be difficult to accomplish and still provide adequate calories. For infants, low-solute formula or breast milk should be used. Sodium intake should be kept to a minimum in the older child.

The use of thiazide diuretics can be helpful in decreasing urine volume by as much as 50%, although mechanisms of action remain elusive. It is thought that thiazides work in these conditions by increasing proximal NaCl and water resorption in the proximal tubule, and thus decreasing distal tubular flow. Furthermore, thiazides block resorption of NaCl in cortical diluting segments. Patients taking thiazides for this indication should also reduce sodium intake. Adjunctive medications have included amiloride hydrochloride, especially in lithium-induced polyuria. Nonsteroidal anti-inflammatory drugs, such as indomethacin, suppress renal prostaglandin synthesis and, by as yet unknown mechanisms, decrease polyuria. Because nonsteroidal anti-inflammatory drugs can adversely affect renal function in the face of volume contraction, these agents should be used with care in children with concentrating defects.

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CHAPTER 37

INFLAMMATORY BOWEL DISEASE

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From the earliest clinical descriptions of children with Crohn's disease, it was clear that significant undernutrition is a major feature of the disease. Furthermore, growth retardation, which may have a nutritional component, is a common clinical manifestation. Although, on occasion, undernutrition and short stature may be a feature of chronic ulcerative colitis (UC) in children, these manifestations are less prominent in this disease.

Early reports of nutritional therapy in children with inflammatory bowel disease (IBD) were thus aimed at the restoration of normal nutrition. More recently, a body of evidence has shown that in children with Crohn's disease, nutritional therapy has a specific anti-inflammatory action in addition to its ability to restore their nutritional status to normal. Unfortunately, there is no such firm evidence in children with UC, yet here also the provision of adequate nutrition still remains important.

The value of nutritional therapy in Crohn's disease chiefly centers on the use of exclusive enteral nutrition in the treatment of active disease. Enteral nutrition may be defined as the provision of a liquid formula diet by mouth or by tube into the gastrointestinal tract.[1] Bottle feeding of normal infants is excluded from this definition. Although it is now clear that oral feeding may be highly effective, research began with liquid formulas administered by intragastric tubes. The technique of tube feeding goes back at least as far as 1872, with a report by Clouston in *The Lancet* on forcible feeding,[2] whereas the work of Widdowson in 1947 drew attention to the adverse effect of malnutrition on human disease in general.[3] The advent of effective parenteral nutrition then made clinicians aware how dramatic the benefits of nutritional rehabilitation from malnutrition could be. The development of a range of complete formula diets of varying compositions, designed for a range of situations, has now made enteral nutrition a highly desirable and practical alternative to parenteral nutrition.

It was Giorgini and colleagues in 1973 who first suggested that treatment of malnutrition could lead to resolution of inflammation in a child with Crohn's disease.[4] They described resolution of terminal ileal inflammation on barium follow-through after a period of elemental diet. In adults with Crohn's disease, Logan and colleagues produced evidence that protein and lymphocyte loss from the gut decreased during feeding with an elemental diet.[5] Then, in Quebec, Morin and colleagues described four children with Crohn's disease whose growth failure responded to an elemental diet,[6] and this was confirmed in larger studies.[7,8] In France, an elemental diet was given to children with Crohn's disease by continuous nasogastric infusion. This was called constant rate enteral alimentation (CREN), but it was a cumbersome technique that was not popular with the children. They used a complex regimen using oligopeptides, whereas others reported the use of a high-osmolality amino acid–based elemental formula. At St. Bartholomew's Hospital in London, a semielemental diet using extensively hydrolyzed milk protein given intragastrically was shown in a small study to be as effective as conventional steroids in the induction of a clinical remission.[9] Most importantly, however, this study showed that there was no short-term growth while the patients were on steroid therapy, whereas enteral nutrition led to short-term growth acceleration. In subsequent follow-up studies, it was shown that this could, on occasion, be sustained for some time if the child remained in remission even when back on a normal diet after the period of nutritional therapy.[10] Central to this approach to therapy was the concept of a period of 6 to 8 weeks of enteral nutrition followed by a graded return to a normal diet.

ROLE OF DIET IN THE ETIOLOGY OF INFLAMMATORY BOWEL DISEASE

The etiology of IBD remains one of the greatest challenges in gastroenterology today. The presence of unexplained gut inflammation has inevitably led researchers to try to identify factors in our diet that may trigger, or even cause, IBD. Although it appears highly likely that there are several environmental factors involved in the etiopathogenesis of IBD,[11,12] the evidence that some of these may be dietary remains tempting.

It was initially suggested that the adoption of an urban lifestyle may lead to an increase in the incidence of IBD, with increases occurring much more rapidly than could be explained by genetic factors alone.[13,14]

Patients with a recent diagnosis of Crohn's disease have been shown to consume greater quantities of sucrose

than control groups,[15] although this was not confirmed in patients with UC.[16] Whether a diet low in fiber leads to an increased risk of Crohn's disease remains in dispute.[17] Many of these studies have had methodologic problems and, as a result, make it difficult to confirm that dietary differences antedated the development of disease. Reif and colleagues, however, again showed that a high level of sucrose intake (> 92 g/day) occurred before symptom onset in patients with both UC and Crohn's disease (odds ratio [OR] = 5.3 and 2.8, respectively); in contrast, fructose and fiber consumption were both negatively associated with a risk for IBD.[18] This carefully controlled study also reported an increase in fat consumption prior to a diagnosis of IBD. These findings were mirrored by Geerling and colleagues, who reported an increased risk of developing UC in those with a high consumption of monounsaturated and polyunsaturated (mainly n-6 polyunsaturated fatty acids) fats as well as vitamin B_6.[19] Overall, these findings suggest nothing more than that a low-residue, highly refined diet is associated with the development of IBD, whereas a high-fiber diet, rich in fruit and vegetables, may be more protective. Large, prospective, epidemiologic studies will be necessary to adequately control for the many confounding variables that could affect this type of data.

Conflicting evidence is also available on the role of butyrate in the pathogenesis of UC. Data suggest that butyrate levels decrease in the distal colon,[20] with the ability of colonic mucosa to use butyrate being reduced even in macroscopically "normal" mucosa of patients with quiescent UC.[21] However, the response of distal UC and so-called diversion colitis to butyrate enemas has not been striking.[22,23] Dietary sulfates have been implicated in reducing the ability of colonocytes to use butyrate by their conversion to toxic sulfides such as H_2S,[24] although luminal levels of sulfides do not appear to be significantly higher in patients with UC than in normal controls.[25] However, along with a putative role of oxidant injury in the pathogenesis of UC, all of these mechanisms appear more likely to be involved as mediators of the injury in UC rather than primary etiologic factors.

It is also of note that researchers have been accumulating evidence over a number of years implicating the food-borne pathogen *Mycobacterium avium* subsp *paratuberculosis* in the pathogenesis of Crohn's disease. Although detailed discussion of this is beyond the scope of this chapter, the presence of this organism in the food chain and its persistence in milk, despite pasteurization, along with the characteristic T helper 1 immune response it evokes, continue to hold interest.[26] However, well-controlled clinical trials have failed to show any benefit of antituberculous therapy.[27] Larger, population-based cohort studies are still needed to better define the importance of this and other specific dietary risk factors.

NUTRITIONAL COMPLICATIONS OF IBD

The chronic and relapsing nature of intestinal inflammation inevitably impacts on a patient's nutritional status. However, nutritional state is determined not only by the dietary intake but also by the patient's age, type of disease, and disease distribution, as well as disease activity. These factors all contribute to the wide range of nutritional complications seen, from almost none in a child with mild distal UC to the most severe nutritional consequences of chronically active disease in a child with panenteric Crohn's disease. Nutritional complications are rarer in children with UC, although a severe pancolitis may present with acute weight loss and significant iron deficiency anemia.

Caloric Deficiency and Growth Failure

The mechanisms surrounding the anorexia and undernutrition seen in IBD are complex and still poorly understood. As well as food avoidance as a result of abdominal pain or diarrhea, the reduction in caloric intake is attributable to the consequences of the systemic inflammatory response.[28] Protein-energy malnutrition may occur as a result of unchecked disease activity, with the associated anorexia being largely mediated by the proinflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF). The activity of these cytokines leads to lean tissue loss,[29] reduced voluntary motor activity,[30] and protein synthesis, with a concomitant increase in protein catabolism.[31] This state of increased need may not be met during active inflammation and thus leads to chronic undernutrition. Protein intakes up to 1.5 g/kg body weight may be required per day to achieve adequate nutrition, with excessive supplementation perhaps even being counterproductive during the acute inflammatory state.[32] Increased protein oxidation and worsening of the nitrogen balance may result if overfeeding occurs during inflammation.[33] Calorie intake in children with Crohn's disease has been reported to be 43 to 82% of recommended values, yet with adequate calorie supplementation, improvements in linear growth can be achieved.[34–36] However, simple nutritional restitution may be insufficient to achieve adequate growth, suggesting that other factors are also important in mediating growth retardation.[37] An elegant study by Azcue and colleagues demonstrated an inappropriately maintained resting energy expenditure (REE) in children with moderately active Crohn's disease when compared with children with anorexia nervosa and similar degrees of malnutrition.[38] This relative increase in energy expenditure, together with the voluntary reduction in intake, further compromises nutritional status and hence optimal growth. Careful animal experiments, which did not look at body composition, suggest that it is the reduced caloric intake that is largely responsible for the weight loss seen in active colitis. However, in this animal study, although able to restore calorie intake and body weight to normal, nutritional supplementation was unable to restore linear growth. At least in this animal model, 30 to 40% of growth impairment is likely to be a direct result of the inflammatory process.[39]

Particularly in children with Crohn's disease, active disease can have a profound and lasting effect on long-term growth,[40] and this is covered in greater detail later in the chapter. Although it is well documented that up to 90% of children with Crohn's disease may present with impaired height velocity,[41] Hildebrand and colleagues also reported

a subnormal growth velocity (< –2 SD) in 24% of prepubertal children with UC compared with 40% in those with Crohn's disease.[42]

Osteoporosis

Owing to the fact that this complication is largely a problem of adult life, it is easy to forget that the accumulation of peak bone mass occurs during adolescence and early adult life. The implications of a substantial interruption in this process are only now becoming clearer as better long-term bone density data are becoming available.

Much attention has focused on trying to tease out the relative importance of the factors that lead to reduction in bone mineral density (BMD) in patients with IBD. As the most important determinants of peak bone mass appear to be age and genetic potential, these confound almost all studies in IBD trying to identify possible predictors such as nutritional status, disease duration, activity and distribution, and steroid therapy. However, despite these shortcomings, it appears that up to 40% of adults with established IBD have osteopenia (T ≤ –1.0; –1 to –2.5 SD from the mean of young adults), whereas around 10% have osteoporosis (T ≤ –2.5; > 2.5 SD from the mean of young adults) when compared with age- and sex-matched controls.[43] The relative importance of disease activity, nutritional status, and cumulative steroid consumption remains debated. A large adult study did identify chronic steroid exposure as the only significant risk factor for the staggering 40% increased risk in osteoporotic fractures in adults with Crohn's disease.[44,45] Furthermore, it appears that BMD is no different to healthy age-matched adult controls within the first 6 months following symptom onset.[46] Interpretation of BMD in the pediatric IBD population remains a problem in the face of significant pubertal and bone age delay.[47] However, up to 30% of children are still likely to have a significantly reduced BMD,[47,48] with children with Crohn's disease tending to be more affected. Overall, therefore, both unchecked inflammation and chronic steroid exposure lead to loss of bone mass.[49]

The impact of nutritional status is unclear as the correlation with BMD may well be confounded by disease activity. Although aggressive nutritional restitution is likely to minimize the chance of nutritionally dependent bone loss, whether supplementation with vitamin D and/or calcium provides added benefits remains to be determined by placebo-controlled studies. Identification of children at greatest risk is important as urinary calcium excretion, plasma 25-hydroxyvitamin D levels, and a baseline bone density scan allow monitoring and subsequent supplementation of documented deficiencies. There is great potential for bone remodeling if children are in good clinical remission. Following presentation with osteoporotic vertebral fractures and in a good nutritional state, a 16-year-old patient with Crohn's disease displayed a dramatic recovery of vertebral height within 3 years of largely steroid-free therapy that controlled his disease activity.[50]

The fact that the consequences of osteoporosis occur so long after the diagnosis of IBD in childhood makes it imperative for pediatricians to be aware of the BMD data now accumulating on adults with IBD. Several larger series are now reporting the clear association with lifetime steroid dose and the increased risk of osteoporotic fractures.[44] An ideal combination may be enteral nutrition and azathioprine or 6-mercaptopurine in the treatment of children with more severe Crohn's disease. It is now clear that treatment regimens minimizing steroid therapy and relying on nutritional therapy or other steroid-sparing agents do not lead to the reduction in BMD seen in patients receiving corticosteroids. Patients with a lifetime steroid exposure of 12.9 g have a significantly lower BMD than normal controls, whereas those with < 2 g lifetime exposure are comparable to age-matched healthy controls.[51] However, it is also clear that osteopenia does occur in steroid-naive patients.[52] Unchecked inflammatory activity may lead to calcium and vitamin D malabsorption, which, in turn, increases parathyroid hormone secretion and further bone resorption.[53] Patients with small bowel disease and/or resections are therefore also at risk of long-term osteoporosis.

Micronutrient Deficiencies

Identifying and treating macro- and micronutrient deficiencies are problematic for two main reasons. There is the initial difficulty of finding an accurate and reliable measure for each specific nutrient deficiency, followed by the inherent variability of a disease characterized by a remitting/relapsing course. There is also the impact of medical therapies and surgical interventions on nutrient status, for example, sulfasalazine inhibiting folate absorption and corticosteroids limiting calcium absorption. Clinically relevant micronutrient deficiencies in patients with IBD are unusual, and most are likely to occur when receiving long-term total parenteral nutrition (TPN).[54] Nonetheless, significant subclinical deficiencies in vitamins and certain trace elements have been reported.

Vitamin B_{12} deficiency occurs most often in patients with active terminal ileal Crohn's disease or following a resection of this part of the intestine. In addition to the usual consequences of these deficiencies, low serum vitamin B_{12} and folate levels may result in an elevation of homocysteine and hence contribute to a hypercoagulable state,[55] with folate supplementation leading to a reduction in homocysteine levels.[56] Patients with IBD are also at risk of developing fat-soluble vitamin deficiency. A significant deficiency of both vitamins A and E has been documented in 16% of children with IBD, with moderate to severe disease activity leading to a deficiency in over 40% of children.[57] Whether this was a consequence of a poor dietary intake or disease activity was not made clear. The range of vitamin deficiencies in patients with long-standing IBD is wide. Two comprehensive studies documented deficiencies in biotin, folate, betacarotene, thiamin, and vitamins A, E, and C in 40 to 90% of adults, despite inactive disease and adequate dietary intakes.[58,59]

Iron deficiency anemia is difficult to diagnose in children with Crohn's disease. Both the anemia of chronic disease and the variability in serum ferritin as part of the acute-phase response make clear guidelines impossible. Low values of serum ferritin (< 15 μg/dL) certainly confirm iron deficiency, but this may also be present at much higher values. Combining the more stable serum transferrin receptor with serum fer-

ritin has been of benefit in adults,[60] whereas a small pediatric study suggested that basic red cell ferritin was a more reliable measure in the presence of inflammation.[61] Variable absorption and the common gastrointestinal adverse effects of oral iron also make the response to treatment difficult to interpret.[62] This, together with the potential exacerbation of colitis by the oxidative stress of oral iron supplementation, has led to successful trials of parenteral iron and erythropoietin use.[63,64]

Trace elements are reduced in up to 50% of patients with active IBD,[59] with zinc deficiency being the most common.[65] The latter has been implicated in the maintenance of intestinal barrier function by regulating tight-junction permeability, with supplementation leading to a reduction in gut permeability in both animal models of colitis and adults with active Crohn's disease.[66]

Many micronutrients are also antioxidants (vitamins A, E, and C and selenium); thus, adequate supplementation may help counteract some of the oxidative stress that contributes to ongoing gut inflammation. Both serum selenium and erythrocyte glutathione peroxidase activity have been inversely correlated to plasma TNF-α levels in patients with active Crohn's disease.[67]

Other Nutritional Consequences of IBD

Patients with long-standing IBD may, of course, also suffer the nutritional consequences of their therapies. Sulfasalazine is most notable for its impact on folate metabolism by competitively inhibiting dihydropteroate reductase, but folate rarely requires supplementation. Patients with severe ileitis or a significant ileal resection may develop steatorrhea, which, in turn, binds available free calcium, thus preventing calcium from binding to oxalate. High concentrations of luminal oxalates may lead to hyperoxaluria and renal calculi.

INDICATIONS FOR NUTRITIONAL TREATMENT

The indications for nutritional intervention differ among the different types of IBD. However, adequate nutritional support is an essential part of the long-term management of any chronic inflammatory disorder. In most cases, this involves the provision of nutritional supplements to complement an otherwise inadequate intake and may involve anything from overnight nasogastric feeds to long-term support on home parenteral nutrition. For UC, no exclusively nutritional therapy has been shown to be therapeutically effective. In contrast, over many years, patients with active Crohn's disease have responded well to exclusive enteral nutrition. There have only been anecdotal reports of patients with indeterminate colitis responding to exclusive enteral nutrition, although the responders are likely to be those with a more Crohn's disease–like phenotype.

Ulcerative Colitis

There have been no studies showing that any form of nutritional intervention, used as sole therapy, can induce a remission in patients with active UC. Two randomized, prospective studies clearly showed that there was no role for exclusive TPN and bowel rest in the management of acute UC.[68,69] Although there were some nutritional advantages in the group on TPN, these were outweighed by the complications reported at the time.

Although often not as severe as in patients with Crohn's disease, malnutrition does occur in children with UC.[70] However, although exclusively nutritional therapies are of no benefit in treating acute UC, nutritional support plays a vital role in minimizing further morbidity. Up to 10% of children with UC present with weight and height z scores ≤ -2,[71] and, inevitably, nutrition is compromised in acute disease, both by a reduced oral intake and by increased losses of both protein and blood from the gut mucosa.[72] Although the concept of continuing enteral feeds during an episode of acute colitis may raise concerns in some, the evidence clearly suggests that equal nutritional improvement occurs with TPN and total enteral nutrition in active colitis.[73] Not only does the latter lead to fewer complications, it is also less costly, more physiologic, and much simpler to provide. However, there continue to be absolute contraindications to enteral nutrition (Table 37-1).

Although dietary supplementation plays a role in acute UC, there is no evidence that specific dietary exclusions are of benefit in the long term. Well-balanced, healthy diets that include normal amounts of dietary fiber are to be encouraged. Short-term studies suggest improved gastrointestinal symptoms on isphaghula husk,[74] although initial data that suggested that diets low in fiber were linked to an increased risk of colon cancer have now been refuted in large epidemiologic surveys in women.[75]

Crohn's Disease

In children with Crohn's disease, there are several reasons for nutritional intervention (Table 37-2).

Exclusive Enteral Nutrition Exclusive enteral nutrition is indicated as a first-line therapy in any child with acute Crohn's disease, provided that there are no absolute contraindications to enteral nutrition per se. The issue of whether enteral nutrition is as effective as steroid therapy at inducing a remission has been hotly debated for some time. However, what is clear from the pediatric literature over the last 20 years is that an exclusively nutritional therapy can be highly effective at inducing a remission from active disease.[76–78] The best results appear to be in those children with newly diagnosed disease,[79] although the pediatric evidence does remain limited in terms of the number of children reported. Large adult studies,[80,81] as well as some of the smaller pediatric studies,[78] suggest that disease distribution does not affect the efficacy of the treatment. Colonic disease appears to respond as well as terminal ileal disease, with a

TABLE 37-1 Contraindications to Enteral Feeding

Massive hemorrhage
Intestinal obstruction
Bowel perforation
Toxic dilatation

TABLE 37-2 Indications for Enteral Nutrition in Crohn's Disease

Exclusive enteral nutrition for active disease
Perioperative parenteral nutrition and bowel rest
Supplemental enteral nutrition for maintenance of disease remission
Nutritional support to maintain adequate weight gain
Dietary supplementation of specific vitamins/minerals

similar reduction in inflammatory markers, disease activity, and improved mucosal histology.[77] More recent retrospective data, however, suggest that clinical remission with isolated colonic disease may only be about 50%, compared with about 75 to 80% in the presence of any macroscopic ileal involvement.[82] Although there is only anecdotal evidence on the response of oral and perianal Crohn's disease to exclusive enteral nutrition,[83] the authors have made use of exclusive enteral nutrition as an adjunct in treating severe perianal Crohn's disease.

Adverse effects to using exclusive enteral nutrition in Crohn's disease are very rare. However, we reported a case of refeeding syndrome in a child following her presentation with severe Crohn's colitis. A rapid loss of weight over the preceding 4 weeks, followed by treatment with exclusive polymeric nutrition, led to a dramatic fall in serum phosphate and signs of hypervolemia in the first few days of treatment.[84] It is important to remain aware of this complication when refeeding previously malnourished children with Crohn's disease as adequate supplementation in the first few days can prevent serious complications.

Perioperative Nutritional Support Preoperative undernutrition has long been known to adversely affect surgical outcome. Although surgical outcome is related to the nutritional state of the patient,[85] short-term preoperative use of TPN is insufficient to dramatically improve the nutritional status. Even 7 to 10 days of preoperative parenteral nutrition in malnourished "cancer" patients achieved only a 10% reduction in postoperative complications.[86] Parenteral nutrition may replace acute nutritional deficits in the immediate perioperative period and may also reduce the length of small bowel resection in adults with Crohn's disease.[87,88] Uncontrolled studies in adults with IBD also suggest that there is a reduction in postoperative complications following preoperative parenteral nutrition,[89] yet it appears most effective in patients with severe malnutrition and highly active disease.[90]

Improvements in the medical management of children with IBD are likely to continue reducing the need for surgery, yet recent studies still suggest that almost 60% of adults with Crohn's disease will require an operation.[91] Older pediatric data showed that up to 80% of children with Crohn's disease were needing surgery in the 15 years following diagnosis.[92] Emergency surgery may be unavoidable in a small number of children who present with fulminant colitis; however, the majority will require surgery for treatment-resistant disease.

Although children with acute, severe UC will require close monitoring of fluid and electrolytes in the perioperative period, they are less likely to have had a long period of active disease leading to chronic malnutrition.

Despite persistently active, treatment-resistant disease, surgery can often be planned some weeks in advance. In these circumstances, optimizing nutrition over a period of 4 to 6 weeks is likely to result in a much better postoperative course. Provided that inflammatory activity and symptoms allow, several weeks of exclusive enteral nutrition in children with severe Crohn's disease can lead to nutritional restitution prior to surgery. In isolated cases, the use of TPN for several weeks may also be justified in preparation for surgery if enteral access is impossible. However, clinicians can be forced to compromise in the face of severe treatment-resistant disease, for which disease activity does not allow time for any improvement in nutritional state, and surgery should then not be delayed.

Postoperative support for all children, irrespective of the type of abdominal/perianal surgery, should involve institution of enteral feeds as soon as possible. Adult evidence demonstrates no increase in complications when patients are fed enterally within 48 hours of colectomy.[93] Very early use of enteral supplements reduces early postoperative complications even in undernourished adults and leads to a better weight gain, as well as an improvement in physical and mental quality of life.[94] Routine use of postoperative TPN in well-nourished patients should be discouraged as it increases complication rates.[95] However, provision for TPN should still be made if enteral feeding is likely to be delayed for more than 1 to 3 days in any undernourished child who is likely to suffer a long convalescence without achieving full enteral feeds.

NUTRITIONAL TREATMENT OF ACTIVE CROHN'S DISEASE

In severe malnutrition, there is clear evidence of a secondary immune dysregulation.[96] Both T cell numbers and secretory immunoglobulin A levels are consistently reduced, and there are also defects in bacterial phagocytosis, lysozyme, and interferon (IFN) production. Although today's children with Crohn's disease are not often severely malnourished, they are certainly well below their expected percentile for weight.[97] It is therefore quite clear that this degree of malnutrition does little to attenuate tissue damaging immune responses.

Parenteral Nutrition

The advent of parenteral nutrition in the early 1970s proved useful in managing intractable cases of Crohn's disease,[98] and its use became more widespread as an alternative primary therapy for severe disease.[99] As would later be clearly demonstrated for enteral nutrition,[40] it was parenteral nutrition that was first shown to reverse growth failure in children and adolescents with active Crohn's disease.[35,100] However, as awareness of the septic and thrombotic complications associated with an indwelling line increased, the use of parenteral nutrition in Crohn's disease declined. Although it still appears to be as effective as elemental nutrition in the short-term treatment of acute disease,[101] its complications, practical difficulties, and

expense limit its use. Furthermore, TPN induces mucosal atrophy and increases bacterial translocation,[102] something that is entirely preventable by luminal nutrition.

The combination of intravenous nutritional support and complete bowel rest has not been shown to be more effective in treating active disease than either exclusive enteral nutrition or TPN with oral feeding.[103] In a controlled study, 58 to 71% of all groups achieved a clinical remission, indicating that bowel rest per se has no added effect on the disease but that improved nutrition in any form has clinical benefit. However, there have also been a number of case series suggesting that exclusive parenteral nutrition may be of significant benefit in severe Crohn's colitis,[87] with at least one study documenting endoscopic healing of mucosal ulcers on exclusive parenteral nutrition.[104] Despite this, the preference for nutritional support in most cases remains an enteral feed.

There has been limited success (35%) in achieving fistula closure on exclusive TPN,[105] with any improvement not being sustained once the patient is back on a normal diet. In view of other therapies, such as octreotide and anti-TNF-α antibody, TPN now has only a very limited role in the management of these fistulae.

Children only rarely have bowel resections large enough to require long-term home parenteral nutrition support. However, if in adults less than 100 cm of jejunum or less than 50 cm of small bowel with an intact colon remain, long-term parenteral nutrition is often necessary.[106] Yet over 70% of these patients will be on a full oral diet within 12 months of starting home parenteral nutrition.[107]

Enteral Nutrition

Elemental Diet An elemental feed is a chemically defined diet whose protein source is amino acids or short-chain peptides, with short-chain carbohydrates and added fat, minerals, and vitamins. The National Aeronautics and Space Administration (NASA) had initially designed elemental diets for astronauts.[108] This was with the intention of providing a nutritionally complete diet of which as much as possible would be absorbed. However, although absorption was limited mainly to the upper small bowel, the diet did not prevent the production of stool, as had been hoped.

Nutrition was initially used in IBD as an adjunct in malnourished patients with growth failure. Elemental diets were developed and first used as sole therapy for IBD in adults in the 1970s.[109] It was then shown that nutrition had a beneficial effect on disease by reducing the increased gut permeability characteristic of Crohn's disease.[5] Logan and colleagues studied seven adults with extensive jejunoileal Crohn's disease.[5] They showed a reduction in both gut protein and gut lymphocyte loss during a period of elemental feeding. This was the first report demonstrating that an elemental diet could directly improve gut function, probably by reducing bowel inflammation.

In 1973, Giorgini and colleagues reported the first successful use of enteral nutrition in treating a child with acute Crohn's disease.[4] It was then shown that enteral nutrition was effective in treating a series of children with Crohn's disease. Successful use in combination with drug therapy led to a further study by the same group, which first showed exclusive CREN to be as effective as steroid therapy in inducing a remission.[110] Although both of these studies had few patients, they gave the first insights into the possible benefits of nutritional therapy as treatment for childhood Crohn's disease. In addition to achieving disease remission, nutritional therapy was also found to have beneficial effects on inflammatory masses and fistulae.[6,110] Simultaneously, both Morin and colleagues and O'Morain documented that an elemental diet improved linear growth in several children with active Crohn's disease.[6,111]

A variety of devices, formulas, and regimens were then used to feed patients intragastrically. Continuous feeding and then overnight feeds predominated for the induction of remission.[7–9] Supplementation of an elemental diet with glutamine, a gut-specific metabolic fuel, did not further improve efficacy, although the small numbers in this study make conclusions difficult. [112]

Semielemental Diet Once elemental diets had achieved their first successes, short-chain peptide–containing diets were suggested as a better nitrogen source than amino acids.[113] Silk and colleagues refuted previous evidence that free amino acids were better absorbed than di- and tripeptides.[113] By using an intestinal perfusion technique in adults, they were able to demonstrate better absorption of amino acids from both casein and lactalbumin hydrolysates than from an equimolar feed of free amino acids. Not only was there a more uniform absorption of amino acids, but the hydrolysates had a beneficial effect on jejunal absorption of water and electrolytes. There followed the first small randomized study of seven to eight children in each group, in which overnight nasogastric feeding of a semielemental diet was compared to prednisolone treatment in children with predominant small-bowel Crohn's disease.[9] A four- to five-chain amino acid–based diet was as effective as steroids at achieving a remission in active Crohn's disease. It again confirmed the North American finding that there was a clear acceleration in growth in the group not taking steroids.[6]

Polymeric Diet It therefore appeared that steroids may have an efficacy similar to semielemental feeds in the induction of remission. Several adult studies reported the efficacy of a whole-protein diet compared with both that of elemental diets and steroids. Raouf and colleagues and others all found polymeric diets to be as effective as an elemental diet in inducing remission.[114–117]

Polymeric diets were also shown to be as effective as conventional steroid treatment. Gonzalez-Huix and colleagues confirmed this in adults and Ruuska and colleagues and Beattie and colleagues in children.[76,78,118] Ruuska and colleagues, in a well-planned but small study (N = 19), showed a polymeric diet to be as effective as steroids in inducing a remission in children with acute Crohn's disease.[78] A further great advantage in using a polymeric diet then became clear. Although almost all children previously required feeding by intragastric tube,

whole-protein formulas such as AL110 (Nestlé-Clintec), used by Beattie and colleagues,[76] and Nutrison Standard (Nutricia, Finland), used by Ruuska and colleagues,[78] were palatable enough for daily oral consumption. Children rarely required a nasogastric tube to complete their entire nutritional needs. This provided a considerable improvement in the quality of life for children on several weeks of nutritional therapy.

The most recent and most definitive cohort study to date, by Fell and colleagues,[77] shows that a whole-casein, polymeric diet (Modulen IBD, Nestlé Clinical Nutrition), rich in transforming growth factor (TGF)-β, is well tolerated and achieves a clinical and histologic remission. Twenty-nine consecutive patients were treated with the exclusive enteral diet for an 8-week period. Although over half had mild disease, 12 had moderate to severe disease with a pediatric Crohn's disease activity index (PCDAI) > 30.[119] A nasogastric tube was required only in one patient for the first 2 weeks of treatment. Only 2 of 29 patients failed to show any clinical response, one with severe colonic disease and the other with an inflammatory mass requiring surgery. Twenty-three of 29 patients achieved a complete remission on PCDAI scoring. The PCDAI fell dramatically within 2 weeks of starting the diet but continued to fall until 8 weeks of treatment. There was significant macroscopic and histologic improvement after treatment, with mucosal healing occurring in the terminal ileum and colon of 8 and 2 patients, respectively. Serum TNF-α and mucosal messenger ribonucleic acid (mRNA) for IL-1β and IL-8 were significantly reduced in both the terminal ileum and the colon after treatment. IFN-γ was significantly reduced and TGF-β was elevated in the terminal ileum alone. There is no direct evidence that the TGF-β in the enteral formula is responsible for the up-regulation of mucosal TGF-β. Nonetheless, this study strengthens the findings by Breese and colleagues that polymeric enteral nutrition alone can achieve an improvement in histology and a complete normalization of some of the mucosal mRNA of proinflammatory cytokines involved in tissue damage.[120]

The lipid composition of some polymeric diets has been held responsible for some of the variability in their efficacy.[121] High long-chain triglyceride concentrations have been associated with a poorer response in treating active Crohn's disease, with suggestions that the high linoleic acid concentration may be responsible,[122] although high concentrations of medium-chain triglyceride in the feed do not affect its short-term efficacy.[123] However, the only two randomized studies have been unable to show a difference in efficacy between formulas containing either low or high amounts of long-chain triglyceride.[124] Only one randomized study appeared to show a significant difference in remission rates depending on the fatty acid composition of the polymeric feeds. Gassull and colleagues reported a significantly better clinical remission rate in adults after 4 weeks of an exclusive enteral feed rich in n-6 fatty acids compared with one high in monounsaturated fats (52% versus 20%, respectively).[121] Why this conflicts with previous evidence remains unclear,[114] although the high percentage of synthetic oleate (79% of total fat) in this study may mask beneficial effects previously seen with formulas containing different fatty acid profiles.

There is limited evidence of milk intolerance in adults with active Crohn's disease. True lactase deficiency is an unusual cause of symptoms in adults with active Crohn's disease[125]; however, up to 46% complained of gastrointestinal symptoms related to milk intake. In contrast, exclusive enteral feeding with lactose-free, whole-casein diets has not been associated with intolerance in children with active disease.

Steroids versus Enteral Nutrition Contrary to these striking pediatric findings, large adult trials and meta-analyses of the adult data have found steroids to be more effective than enteral nutrition at inducing remission in active Crohn's disease.[80,81,115,126] The meta-analysis by Griffiths and colleagues, although including both children and adults, excluded most of the smaller pediatric studies.[126] This large review ($N = 413$) reported that steroids were significantly more effective in achieving a remission than enteral diets (OR = 0.35, 95% confidence interval = 0.32 to 0.58). Like other analyses, this study also relied on clinical disease activity indices to document clinical remission rates, but these tended to favor steroid therapy by their reliance on a patient's general feeling of well-being. As a result, conclusions from these studies are frequently and inappropriately applied to children, despite there being clear differences between adult and pediatric patients. Most children have had much shorter disease duration and tend to be much more compliant with therapy. Furthermore, no comment is made on the differing adverse effects and abilities of the two treatments to heal gut mucosa, with steroids having been well documented to have limited effects on gut inflammation.[127] As yet, no analysis has detected a significant difference in efficacy between elemental or polymeric diets.[128]

Despite the several small pediatric studies that suggest a useful role for enteral nutrition in active Crohn's disease, the view has thus prevailed that enteral nutrition is less effective than steroid therapy. A meta-analysis of pediatric data was performed to maximize the available pediatric data.[129] Despite limited numbers of truly randomized children, sensitivity analyses allowed the authors to arrive at valid and important conclusions. The summary data clearly showed enteral nutrition to be as effective as steroids in the treatment of children with active Crohn's disease. Furthermore, to overturn this finding and demonstrate that steroids were significantly more effective than enteral nutrition would be close to impossible given the outcomes of the pediatric studies reported to date. All of these studies principally address efficacy as their primary outcome measure, largely ignoring the very different side-effect profiles of each therapy. Corticosteroids have many significant adverse effects, whereas oral enteral nutrition has almost none.

Enteral Nutrition and Crohn's Colitis There remains the further question of whether enteral nutrition is less effective at treating Crohn's colitis than Crohn's ileitis. Early use

of enteral feed was limited to children with predominantly small bowel disease,[130] with a suggestion that colonic disease was unresponsive to nutritional management.[131] More recent evidence from Thomas and colleagues, Ruuska and colleagues, and Fell and colleagues, however, supports the value of nutritional therapy in large bowel and small bowel disease.[77,78,132] The improvement in colonic mucosal cytokine profiles after enteral nutrition provides hard evidence that there is an effect on colonic disease.[77] Larger studies in adults also confirm that disease location does not appear to influence the response to treatment.[80,126,133]

However, a more recent retrospective analysis of 60 children treated with exclusive enteral nutrition suggested that disease distribution may be relevant in the response to nutritional therapy. Children with any macroscopic ileal inflammation were significantly more likely to achieve a clinical remission than those children with colonic involvement alone (75% versus 50%).[82] Despite this, many individuals with Crohn's colitis continue to respond extremely well, still making exclusive enteral nutrition the first choice for any child with Crohn's disease, irrespective of their disease distribution.

Food Reintroduction

There has long been uncertainty as to the best way of reintroducing adults and children to their "normal" diet after a period of exclusive enteral nutrition. The evidence for any of these different practices is very limited, with most approaches having been selected by experienced clinicians on the basis of theories prevalent at the time.

The best-described reintroduction program is based on the stepwise introduction foods, starting with the least allergenic.[134] One new food is introduced every 48 hours and, if not tolerated, reintroduced at the end of the program. This systematic but quite laborious program not only allows individual foods to be identified if causing immediate symptoms but also gives the patients several more weeks on reasonable quantities of enteral nutrition while their normal diet is re-established. The most frequently implicated foods causing discomfort in adults are cereals, dairy products, and yeast,[134] although in children only a very small minority require exclusion of specific items from their diet. In a 2-year follow-up study of about 100 adults, the relapse rate was only just significantly lower in the group excluding dietary products that caused symptoms compared with those maintaining a normal diet ($p = .048$). However, in a randomized controlled trial of an exclusion diet following a remission induced with an elemental diet, subsequent rechallenge and double-blinded challenges in adults with Crohn's disease proved that specific dietary exclusions did not persist.[135] There is thus insufficient evidence to routinely suggest exclusion of specific food items in children with Crohn's disease.

Other units use less evidence-based but more practical reintroduction programs, which range from the immediate introduction of a full diet to a graded introduction over 3 weeks, with the ad libitum diet increasing by 25% each week, along with the simultaneous reduction in enteral nutrition.

ENTERAL NUTRITION AS MAINTENANCE THERAPY IN CROHN'S DISEASE

There has been much interest in whether dietary modification may prolong a remission in Crohn's disease.

Initial studies suggested that intermittent use of exclusive enteral nutrition for 1 month in every 4 could not only reduce steroid requirement and reduce disease activity but could also increase the long-term growth rate in children with Crohn's disease.[136] Although this intermittent use of exclusive enteral nutrition may have had a role in managing patients with otherwise intractable disease and a previous good response to enteral nutrition, repeated and prolonged use of exclusive enteral diets in most adolescents is difficult and mostly unnecessary. Given the availability of other, currently more effective maintenance agents, compliance with supplements of enteral nutrition is likely to be much greater if these can be shown to be effective.

Low-residue diets are not indicated in the maintenance of remission in Crohn's disease. Unless required as a dietary modification in the presence of fibrosing/stricturing disease, they have not been shown to prevent disease relapse.[137]

A retrospective study in which a normal ad libitum diet of children with Crohn's disease was supplemented with an additional 30% of the recommended daily calorie intake as polymeric feed led to the halving of relapse rates within the first 12 months.[138] Small controlled studies also suggest an advantage to simple long-term calorie supplementation per se,[139] although larger, more definitive studies are still awaited. However, it is highly likely that a long-term nutritional supplement, in combination with a well-tolerated immunosuppressant, will provide the optimal maintenance therapy for most children with moderate to severe Crohn's disease.

Attempts at supplementing diets with specific anti-inflammatory agents continue, with fish oils receiving particular attention. Their effects on reducing mucosal eicosanoids (particularly leukotriene B_4 and thromboxane A_2) have been widely reported.[140] The n-3 fatty acids present in fish oils may also inhibit IL-1β and TNF production.[141] In addition, they also decrease platelet responsiveness and thus may act to reduce the multifocal gastrointestinal infarctions that have been reported as early pathogenic steps of Crohn's disease.[142,143] Several large placebo-controlled randomized studies have been performed on adults with both Crohn's disease and UC,[144;145] but, unfortunately, many of the data remain conflicting. Although different methodology makes generalizations difficult, several important issues are raised. Although low-dose regimens cause no appreciable adverse effects,[146] compliance with high-dose fish oils in adults is poor, making long-term maintenance therapy in children even less attractive. Belluzzi and colleagues found that supplementation with 2.7 g of n-3 fatty acids reduced the relapse rate in adults with Crohn's disease,[144] whereas another large study failed to confirm any benefit over placebo in using either > 5 g/day of n-3 fatty acids or maintaining a diet low in carbohydrate (84 g/day).[145] However, despite no clear-cut clinical benefits, significant changes are reported on a mucosal

level. Colonic inflammatory cell infiltrates are reduced and the synthesis of leukotriene B_4 and thromboxane A_2 is downregulated after supplementation with n-3 fatty acids.[145] It may therefore be that further refining of the composition, formulation, and dose is required before fish oil supplements become an accepted part of maintenance therapy.

Other, more specific dietary interventions have been reported to prolong remission in Crohn's disease. Although none of these have been assessed in larger, placebo-controlled studies, they offer interesting clues to the role dietary modification may play in maintaining disease remission. A small study randomizing patients to a diet low in microparticles suggested significant benefits in disease activity and remission rates after 4 months when compared with 10 patients on a normal diet.[147] Diets low in refined sugars have not been found to prevent relapse rates in adults with Crohn's disease.[148] Similarly, the presence of yeast in the diet of patients with Crohn's disease may potentiate disease relapse, but larger studies are necessary before firm conclusions may be drawn.[149]

As the importance of gut microflora in the etiology of IBD is increasingly recognized, so has the prospect of modulating it by means of "functional foods" gained much support. Although discussion is beyond the scope of this chapter, the mechanisms of action and potential implications of this exciting new field are great for patients with chronic intestinal disease driven by enteric flora. It is quite clear that, over the next few years, we are likely to see larger, placebo-controlled trials of both pro- and prebiotics. Prebiotics are the complex sugars such as fructo-oligosaccharides and inulin, which pass into the colon undigested, where they may be selectively fermented by certain probiotic species.[150] Attempts to maintain remission in both UC and pouchitis with combined probiotic combinations have proved quite successful,[151] although *Lactobacillus GG* alone may have a role in improving gut barrier function and clinical status in children with Crohn's disease.[152]

If long-term nutritional support is required, most children will tolerate a more palatable polymeric formula by mouth. However, some children will require supplementation by tube. Although short-term support can be given via a nasogastric tube, longer-term needs should be met via a more permanent device. Where nutritional support is needed for several months, placement of a percutaneous endoscopic gastrostomy (PEG) is ideal. Despite initial reservations about possible complications from the formation of fistulous tracts, PEG placement has now been documented to be uncomplicated in selected adults and children with IBD.[153] In patients receiving corticosteroids, adhesion of the gastric to the abdominal wall may be delayed; thus, early "pulling" of the PEG could lead to tract disruption.

ROLE OF ENTERAL NUTRITION ON GROWTH AND DEVELOPMENT

Epidemiology of Growth Failure

After the onset of symptoms but before a diagnosis of Crohn's disease is made, up to 46% of children will have a reduced height velocity, with only 12% having a normal height velocity up to the time of diagnosis.[41] In contrast, only 3 to 10% of children with UC may present with reduced height velocities at diagnosis.[42] Although many of these data are now over 10 years old, and an accurate diagnosis may now be made more quickly, it is clear that untreated Crohn's disease has profound implications on a child's growth potential. Motil and colleagues reported in a cross-sectional study of their pediatric IBD patients that 23% had a z score < –1.64, with 50% of these having a bone age delayed by > 1 year over their chronologic age.[151] Physicians caring for children with IBD, particularly Crohn's disease, therefore have the unique opportunity to try and modify the impact that both disease and therapy have on the growth rate of their patients.

A delay in presentation is associated with a significantly greater degree of growth impairment at diagnosis.[71] Despite management within tertiary centers, 49 to 65% of children with Crohn's disease have a reduced height velocity in early puberty, with growth velocity remaining less than 4 cm/year during the first 1 to 2 years of therapy.[42,154] Hildebrand and colleagues reported a mean z score for height of –0.6 2 years after diagnosis in 46 consecutive children with Crohn's disease.[42] Griffiths and colleagues reported that of 67 consecutively diagnosed children with Crohn's disease followed to maturity, about two-thirds maintained or increased their z scores for height.[155]

The outcome of many of these studies reflects management in which the mainstay of therapy was often corticosteroids and so does not include the more recent move to the earlier use of steroid-sparing agents.

Etiology of Growth Failure

The growth failure seen in children with IBD is multifactorial, with inflammation, undernutrition, and steroid therapy being its principal determinants.

Initial evidence suggested that chronic undernutrition was the main factor in the growth failure seen in children with IBD,[35] with studies confirming that simple nutritional restitution improved the linear growth of children with Crohn's disease.[34,36] Children with active Crohn's disease have a relative insufficiency of dietary intake when compared with children of the same age,[132] although they may compensate with an increased intake between disease relapses.[154] However, simply increasing the calorie intake, as seen in patients on steroids, does not confer the same benefit on growth as a lower calorie intake received on exclusive enteral nutrition.[132] The presence of low levels of insulin-like growth factor I (IGF-I) in children with active Crohn's disease strengthens this association as the relationship between IGF-I and malnutrition is now clear.[156] Both IGF-I and its carrier protein, IGF binding protein 3, are increased significantly by treatment with exclusive enteral nutrition.[157,158] Further evidence that inflammation, not only nutritional factors, plays a role in determining growth can be seen in studies of children undergoing surgery for active IBD. Although postoperative catch-up growth is not documented by all authors, several authors show a clear growth spurt occurring after the removal of an

inflamed segment of bowel.[159] Although this is most striking in prepubertal children, the benefit is still substantial if surgery is carried out before the final stages of puberty.[160] This response may, of course, in part be the result of improved postoperative nutrition. However, Varille and colleagues neatly documented that even children undergoing localized resections for stricturing disease had a significant reduction in REE and an increase in nitrogen use 4 weeks after surgery, despite maintaining preoperative nutritional and steroid regimens.[161]

There now seems little doubt that ongoing inflammatory activity plays a key role in the inhibition of growth.[162] Down-regulation of proinflammatory cytokines by enteral nutrition may partly improve growth by reducing IL-6, a potent inhibitor of IGF-I. [163] There is a dramatic reduction in C-reactive protein, with a concomitant increase in IGF-I and IGF binding protein 3, within 14 days of commencing exclusive enteral nutrition.[76,77] This clearly indicates that enteral nutrition also has a more rapid, direct anti-inflammatory action in addition to its longer-term nutritional benefits. As has been confirmed in children with rheumatoid arthritis, systemic inflammation, as well as malnutrition, reduces IGF-I.[164] Direct inhibitory effects of proinflammatory cytokines such as TNF-α on developing growth plates and a down-regulation of IGF-I by IL-6 are both likely to contribute to growth retardation.[165,166] The additional suppression of appetite by TNF-α, the failure to down-regulate the REE during malnutrition in Crohn's disease, and the exacerbation of bowel symptoms by food intake all add to the final reduction in height velocity.[38,167]

Enteric losses during active disease can also contribute to the decline in nutritional state. Children with small bowel Crohn's disease have varying degrees of malabsorption, with some of the hypoalbuminemia occurring as a result of enteric losses.[168] The most important determinant of hypoalbuminemia is the systemic inflammatory response. Although protein loss through an inflamed mucosa does occur, it is usually modest and nonspecific and occurs in association with loss of globulins. The hypoalbuminemia seen in Crohn's disease is more frequently associated with the hypergammaglobulinemia occurring as a result of the acute-phase protein synthesis. The latter is principally mediated by IL-6.[169] Furthermore, a sustained protein intake of less than 0.4 g/kg/day is necessary to achieve any reduction in serum albumin.[170]

Bile acid malabsorption may occur not only in children with active terminal ileitis as systemic effects of ileal inflammation may lead to malabsorption in the proximal small bowel.[171] As a result, fat malabsorption may occur in some children with Crohn's disease. In addition, low concentrations of vitamins A and E and zinc have been shown to correlate more with disease activity than nutritional state,[57,172] suggesting that depletion occurs during the acute inflammation rather than as a result of chronic malabsorption.

Ongoing growth failure in the first years after diagnosis may be attributable to several factors. Growth velocity can be delayed well beyond nutritional restitution and normalization of inflammatory indices. This, together with the frequent use of high-dose steroids to achieve the initial remission, up to 85% of children in some studies,[152,173] may arrest normal growth for many months after diagnosis. However, the most recent data suggest that it is neither the disease distribution nor the pubertal stage at diagnosis that determines final adult height but rather the use of corticosteroids during puberty.[174] Children who were diagnosed with Crohn's disease during puberty and were treated with corticosteroids were significantly shorter as adults when compared with those who did not receive corticosteroids. In this study, this was the only independent predictor of final adult height.

Nutritional Treatment of Growth Failure

Over 20 years ago, several small studies confirmed the central role of nutrition in the long-term management of growth failure in children with IBD. Motil and colleagues concluded that neither low-grade chronic inflammation nor low-dose corticosteroid use reduced whole-body protein synthesis and that it was adequate dietary supplementation that led to a significant increase in growth velocity of children with growth failure.[175,176] This was confirmed by others as nutritional therapies became more practical for the treatment of acute Crohn's disease.[6,34] Sanderson and colleagues were the first to establish the benefit of enteral nutrition over steroid therapy on short-term growth in children with newly diagnosed Crohn's disease.[9]

MECHANISM OF ENTERAL NUTRITION

Despite the wealth of information that exists about the benefits of enteral nutrition, the mechanisms of action remain largely unclear (Table 37-3).

The most frequently advanced theory is that the bacterial flora within the gut lumen is modified by enteral nutrition. The clinical evidence of any difference in flora between patients with Crohn's disease and normal controls remains slim. It was shown in the late 1970s that there are higher bacterial counts within the terminal ileum of patients with active disease.[177] Studies at that time also suggested a reduction in fecal flora after enteral nutrition.[178] It is now clear that increasing severity of systemic disease is associated with an increase in the adherence of fecal bacteria to the enterocytes,[179] and this does not appear to be related to the degree of local mucosal inflammation. The response of acute Crohn's disease to antibiotic therapy further implicates the bacterial flora in the disease pathogenesis,[180] although antibiotics such as the quinolones and metronidazole have other immunomodulatory effects in addition to their antimicrobial actions.[181] The organisms that appear to be increased in the lumen of patients with Crohn's disease include *Bacteroides*, *Eubacterium*, and *Peptostreptococcus*.[182] Elegant work on mice that develop spontaneous colitis (T-cell receptor α knockout) has confirmed that feeding with an elemental diet prevents bowel inflammation.[183] Unlike the mice fed the elemental diet, the mice that are fed regular chow and then develop colitis are colonized by *Bacteroides vulgatus* in > 80% of cases. Furthermore, instilling this strain into the rectum of the elementally fed mice led to development of a

TABLE 37-3 Mechanisms of Enteral Nutrition

Alteration in bacterial flora
Reduction in antigenic load
Whole-body nutritional restitution
Provision of enterocyte nutrition
Direct immunoregulatory effect
Increased concentrations of transforming growth factor β
Low lipid and fiber content

typical T helper 2–type T cell–induced colitis. Further animal work has shown that an elemental diet may reduce the progression of granulomatous enteritis by modulating the activation of T cells, the production of nitric oxide, and the generation of oxygen free radicals.[184,185]

The reduction in antigenic load that accompanies exclusive enteral nutrition may also contribute, at least in part, to bowel rest. However, a whole-protein diet, and even an ad libitum diet together with some parenteral nutrition, appears to be as effective as an exclusive elemental diet at inducing a remission.[76-78,103] The efficacy of polymeric diets and recent evidence that dietary supplementation with enteral nutrition may prolong a remission both suggest that reducing luminal antigens may play only a modest role in the efficacy of this therapy.[135]

Whether enteral nutrition per se has a direct and/or indirect immunoregulatory effect remains speculative. Degrees of moderate protein malnutrition have been associated with poor immune function. In rodents, protein deprivation leads to impairment of the mucosal immune response, as well as depletion of a population of T cells that control oral tolerance.[185,186] This would suggest that poor nutrition inhibits T cells that down-regulate the gut's response to foreign antigens. Enteral feeding may therefore have an indirect effect on the immune response by restoring an adequate nutritional status.

More recently, the direct influence of luminal content on immune function has been studied. Sanderson provided evidence that luminal content can influence epithelial cell gene expression within the gut.[187] Short-chain fatty acids, such as butyrate, are bacterial metabolites from unabsorbed carbohydrates. Butyrate induces secretion of IGF binding proteins by a complex process involving histone deacetylation.[188] Butyrate has also been shown to potentiate the secretion of IL-8 by intestinal epithelial cells (Caco-2) if these are stimulated with either lipopolysaccharide or IL-1β. Lipopolysaccharide was able to induce IL-8 secretion only if these cells were preincubated with butyrate, implying direct effects of the latter on gene regulation.[189] Epithelial cell gene regulation by luminal products thus appears to be able to influence intestinal inflammation through release of inflammatory cytokines. Up-regulation of the chemokine macrophage inflammatory protein 2 increases local neutrophil recruitment.[190]

It has also been suggested that the presence, or absence, of individual components of enteral feeds is important in immune regulation. The putative advantage of high TGF-β levels in both AL110 and CT3211 (~ 24 ppm) is based on the large body of experimental evidence that this cytokine has the ability to down-regulate other proinflammatory cytokines.[191] Fell and colleagues demonstrated mucosal up-regulation of TGF-β within the terminal ileum after an 8-week course of TGF-β-rich CT3211.[77] It is still unclear whether this is related to the increased luminal presence of TGF-β or is simply an epiphenomenon of tissue repair.

It may also be that enteral nutrition plays a direct role in promoting the mechanisms involved in epithelial healing. There are numerous peptides involved in the restoration of a disrupted epithelial barrier. The ulcer-associated cell lineage secretes cytoprotective peptides that promote epithelial healing. Among them are epidermal growth factor, TGF-α, human spasmolytic peptide, and the family of trefoil peptides.[192] The trefoil peptides in particular have been shown to be vital in protecting against mucosal damage.[193] Enteral nutrition may contribute toward the maintenance of mucosal integrity by boosting the proliferation of the ulcer-associated cell lineage.[194]

Although the theory of "bowel rest" has its supporters, others continue to feel that adequate nutrition alone can induce remission and growth in these patients.[195] Kirschner and colleagues demonstrated improved growth in children simply fed an extra 1,000 kcal/day.[34] The same group later confirmed that improved nutrition not only increased linear growth but also returned previously low levels of IGF-I to normal in children with active Crohn's disease.[196] Thomas and colleagues confirmed this finding with an elemental feed, which was as effective at increasing IGF-I as prednisolone yet better promoted linear growth.[157]

There are likely to be many mechanisms responsible for the clinical efficacy of enteral nutrition. It is clear, however, that the luminal environment is crucial to the expression of mucosal disease. Our ability to regulate specific aspects of this environment by nutritional or other means remains a great challenge. The multitude of variables that may be important in achieving a disease remission makes identification of single factors extremely difficult. Current attention is focused on modifying enteral formulas in line with the recent evidence on dietary fats, while continuing to ensure their clinical efficacy and tolerability.

Mucosal Healing

Greater emphasis has recently been placed on the ability of treatments to achieve mucosal healing of the gut mucosa.[197] Breese and colleagues gave an initial indication that enteral nutrition was able to down-regulate intestinal mucosal inflammation.[120] Enteral nutrition was as effective as cyclosporin and steroids in reducing the percentage of IL-2-secreting cells in the terminal ileum after treatment, whereas it appeared to be more effective than steroids at reducing the percentage of IFN-γ-secreting cells. Furthermore, it was only the enterally fed group that showed significant histologic improvement. Despite being only a small study, Breese and colleagues raised two important issues: that enteral nutrition may be able to heal mucosa and that mucosal cytokine analysis following treatment did not necessarily correlate with either clinical or histologic indices of remission.[120]

The mucosal cytokine responses of a much larger cohort of children were reported by Fell and colleagues.[77] Although clear clinical and histologic remission was achieved in over 70% of children, cytokine profiles also dramatically improved with a polymeric diet alone. The dramatic down-regulation of the potent proinflammatory cytokines IL-1β, IFN-γ, and IL-8 is the most concrete evidence to date that enteral nutrition acts at the mucosal level (Table 37-4).

The issue of whether clinical, endoscopic, histologic, or immunologic remission should be the gold standard remains a matter of personal practice.[197] If we are to believe that the presence of chronic inflammation predisposes to long-term complications and malignancy,[198] it may be a state of immunologic remission at the mucosal level that should be achieved in children with a lifetime of Crohn's disease ahead of them.

BODY COMPOSITION, ENERGY EXPENDITURE, AND PROTEIN METABOLISM

It has become clear that in both adults and children, active gut inflammation is associated with alterations in body composition. Although substrate metabolism during active Crohn's disease resembles that during starvation, this is more a consequence of malnutrition and may be easily reversed by treatment with exclusive enteral nutrition.[38,199] Body mass index (BMI), lean body mass, and fat mass are all decreased in children with IBD, and this may be related to poor calorie intake.[175] A higher BMI and lean body mass were both positively correlated with increased BMD, factors that again stress the importance of adequate nutrition in maximizing long-term BMD.[200]

Enteral nutrition provides a simple but effective treatment for children with Crohn's disease. Not only does it appear to influence disease activity directly, it also appears to have clear benefits on growth and nutrition.

Early evidence suggested that REE was increased in patients with inactive Crohn's disease.[201] It now appears, however, that if the REE is calculated per unit of lean body mass (LBM), it is the same in active Crohn's disease as it is in normal controls.[38] The REE/LBM ratio was found to be significantly lower in children with anorexia nervosa than in normal controls. When comparing these controls with malnourished noninflammatory disease with children with active Crohn's disease, the authors showed that the appropriate physiologic response to starvation is lost during active inflammation. Thus, this inappropriately elevated REE further contributes to weight loss. On treatment with elemental feed, their absolute REE did increase to above normal levels but per unit of LBM remained only within the normal range. This study also showed that an elemental diet was significantly better than steroids at accruing lean body tissue and was again better at achieving linear growth.

Despite the documented increase in energy intake by children on steroids compared with those on an elemental diet, the latter group have a significantly greater rise in their median height velocity standard deviation score after 4 weeks on an elemental diet.[157] Adequate calorie intake alone in the presence of steroid therapy (124% of Recommended Dietary Allowance) is thus unable to achieve optimal growth. The short-term growth suppressant effects of prednisolone probably override any advantage conferred by the improved calorie intake.[202] IGF-I levels appeared greater after steroid treatment than after enteral nutrition, yet a significant increase in IGF-I was only associated with greater height velocity after an elemental diet.[157]

The rate of protein turnover in six children with chronically active Crohn's disease receiving steroids was considered to be similar to that of normal adolescent controls,[175] although their nitrogen balance was found to increase fourfold during nutritional supplementation.[176] Another small study compared the effect of steroids ($n = 3$) and elemental feed ($n = 3$) after the first 7 days of treatment in acute Crohn's disease.[203] Labeled L-leucine studies showed an equal increase in protein turnover after 7 days of treatment, whereas in the steroid-treated group, this was at the expense of total-body protein stores. Clinical improvement was similar in each group. In a more recent study by Thomas and colleagues, rates of protein turnover were also elevated in active Crohn's disease.[204] Labeled L-leucine studies and mass spectrometry analysis showed an equal reduction in protein turnover to normal levels, both by steroids ($n = 4$) and by elemental feed ($n = 6$). This study only assessed protein turnover after several weeks of

TABLE 37-4 Mucosal mRNA Cytokine Values from Children with Active Crohn's Disease before and after Treatment with Exclusive Enteral Nutrition and from Normal Controls

	Terminal Ileum			*Colon*		
	Control	*Pretreatment*	*Post-treatment*	*Control*	*Pretreatment*	*Post-treatment*
IL-1β	15**	350	16*	0.54**	130	18*
IFN-γ	1**	8.6	1.1*	1.1**	3.5	1.2
IL-8	50	660	150	4.8**	1500	130*
IL-10	1.5	1.7	1.3	3.7**	1.9	1.2
TGF-β	16	4.2	34*	11	15	15

Adapted from Fell JM et al.[77]

Data showing messenger ribonucleic acid (RNA) transcripts (10^3)/μg total RNA from biopsies taken before and after treatment with CT3211 and normal controls.

*Significant change ($p < .05$) with treatment assessed by *t*-test; **significant difference ($p < .05$) between pretreatment (diseased) and control values assessed by Mann-Whitney *U* test.

IFN = interferon; IL = interleukin; mRNA = messenger ribonucleic acid; TGF = transforming growth factor.

treatment and only after effective recovery and nutritional restitution were almost complete.

Royall and colleagues published evidence in 30 adults with active Crohn's disease that proportionate increases in body fat, protein, and water occurred after 21 days of elemental nutrition.[205] In this study, a sustained remission was achieved only in patients who showed a gain in total-body nitrogen.

Further evidence that optimizing nutrition may contribute to a clinical remission arises from the study by Slonim and colleagues.[206] The combination of a protein-rich diet (> 2 g/day) together with subcutaneous growth hormone led to a significant reduction in CDAI within 4 months in a small group of adults with moderate to severe Crohn's disease. Increased uptake of amino acids and improved intestinal and muscle protein synthesis are mechanisms that are likely to be important in mediating this effect.[207,208] Direct effects of growth hormone on IGF-I are not felt to be as significant as no correlation was found between IGF-I levels and clinical response.

FUTURE DIRECTIONS

From the above discussion, it is abundantly clear that nutrition still has a major role to play in the management of children with IBD and in particular those with Crohn's disease. Although exclusive enteral nutrition is clearly effective in many children with active Crohn's disease, it remains difficult for some children and their families to complete prolonged courses. Work is continuing to assess whether long-term supplementation of a normal diet prolongs remission.

Palatable whole-protein formulas are being modified to include higher percentages of n-3 fatty acids, whereas the addition of probiotics to feeds is also already under way.

Work also continues on isolating the specific factors within formulas that may directly act on mucosal inflammation. Up-regulation of mucosal TGF-β may be a direct result of higher levels of TGF-β within a formula (Modulen IBD, Nestlé), whereas further characterization of the gut microflora in children with IBD may allow specific supplementation with specific prebiotics, substrates that selectively stimulate the growth of certain favorable probiotic species.

CONCLUSIONS

Despite the ever-increasing choice of therapies available to children with IBD, the role of nutrition remains central to their optimal management. The impact of bowel inflammation on growth and development cannot be underestimated. As final adult height is determined during the pubertal growth spurt, it is crucial to minimize the impact that both the disease and its therapies may have on a child's growth potential.

We strongly suggest that exclusive enteral nutrition remains the best primary therapy for the treatment of all children presenting with a new diagnosis of Crohn's disease, apart from those with severe perianal disease. Thereafter, the challenge is to maintain a lasting remission, particularly during puberty. This is likely to be best achieved with early use of immunosuppressants such as azathioprine or 6-mercaptopurine, hoping to minimize steroid use. Continued vigilance of undernutrition and appropriate use of dietary supplementation remain essential to an optimal outcome.

The consequences of developing a chronic inflammatory disease during childhood will be felt long after a child is handed over to our adult physician colleagues. Increased risks of osteoporotic fractures, high rates of surgery, and a reduced final height are only some of the areas in which nutritional therapy is vitally important. The ability of therapies to achieve healing of the gut mucosa is of utmost importance in children who have a lifetime ahead of them. Although dietary therapies do not yet play a significant therapeutic role in maintenance therapy for IBD, it is likely that evidence about potential disease-modifying dietary supplements will continue to appear. It is important that as more potent immunologic agents become available to treat these diseases, we do not forget the therapeutic role of nutrition in Crohn's disease, its absence of adverse effects, and its proven impact on growth and gut mucosa.

Although newer therapies may require less commitment from families and medical teams, their unknown long-term safety profile will make enteral nutrition an excellent choice for children with Crohn's disease for many years to come.

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CHAPTER 38

PEDIATRIC HIV INFECTION

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Nutritional problems of human immunodeficiency virus (HIV)-infected children are common, pervasive, and often frustrating to treat. Because of the strong link between immunity and nutrition, which are outlined in this and other chapters, clinicians caring for HIV-infected children need to attend to nutritional problems by trying to help children achieve normal growth. Scientific studies are emerging on the importance of nutrition in both predicting and improving clinical outcomes, such as hospitalization rates and survival. This chapter provides current background information on pediatric HIV infection and the associations between nutrition and HIV. Focus also turns to the emerging problem of the metabolic syndrome in HIV-infected children. Furthermore, the growth patterns of HIV-infected children, pathogenesis of nutritional disorders, and current diagnostic and therapeutic interventions are presented. It is hoped that this chapter both provides practical advice to clinicians caring for HIV-infected children and serves as a basis to stimulate much needed scientific research in this area.

PEDIATRIC AIDS EPIDEMIC

Despite the dramatic progress that has been made over the past decade regarding the detection, diagnosis, and treatment of HIV infection, it is a chronic disease that continues to carry high morbidity and mortality rates. The World Health Organization estimated that, by the end of 2001, about 40 million people worldwide were living with HIV/acquired immune deficiency syndrome (AIDS); 2.7 million of these were children.[1] In 2001, there were 800,000 newly infected children under the age of 15 years and 580,000 AIDS-related deaths in this age group. About 90% of children under 13 years of age with HIV infection in the United States have acquired it from their HIV-infected mother. Almost all new cases of HIV infection in children can be attributed to vertical transmission from the mother to infant because complete screening of blood products was initiated in 1985. Maternal risk factors include intravenous drug use, heterosexual contact, and previous transfusion or transplantation. Other known risk factors for pediatric HIV infection include hemophilia or being a recipient of some other blood product. Similar risk factors exist in Europe, except for the special circumstance in Romania, where most children acquired HIV through contaminated needles and syringes. Although mother–infant transmission has diminished substantially in the United States with increased use of pre- and perinatal antiretroviral therapy, as many as 30% of pregnant women in regions of sub-Saharan Africa are HIV infected, with limited access to such treatment. In addition, more than 70% of deaths in infants under 5 years of age are attributable to AIDS in this part of the world.[1] In developing countries, half of the HIV-infected individuals are women of childbearing age. Children in developing countries who have HIV infection are especially affected by the endemic problems of protracted diarrhea and severe malnutrition.

HIV, a ribonucleic acid (RNA) virus that belongs to the Lentivirinae family, was first isolated in 1983.[2] The virus has a particular tropism for the CD4 surface antigen of cells, and the binding of HIV to the CD4 receptor initiates the viral life cycle, which is mediated by the HIV-1 envelope glycoprotein (gp)120. The binding of gp120 to CD4 leads to events that cause fusion of the virus into the host membrane, with subsequent steps leading to replication of the virus within the host cell. The proviral DNA within the host cell may also remain latent for varying amounts of time until cellular activation occurs. Human T lymphocytes and monocytes or macrophages are the primary cells that are infected with HIV, although numerous other cell lines have been reported to be infected as well. The net biologic effect on the immune system of children with HIV infection is the progressive decline in CD4-positive T lymphocytes, leaving children susceptible to opportunistic and recurrent bacterial infections.

NUTRITION AND IMMUNITY

Malnutrition is the most common cause of immunodeficiency worldwide. Nutritional status and immunity have long been linked in many disease situations. Before HIV was described, *Pneumocystis carinii* pneumonia and Kaposi's sarcoma, known opportunistic diseases, were first described in otherwise healthy, but malnourished, children and adults in developing nations.[3,4] This association led investigators to conclude that nutrition alone can impact on the immunologic response of an individual. In malnourished children, there is a profound involution of lymphoid tissues, including thymic atrophy and diminished paracortical regions of lymph nodes.[5] In young infants and children, protein-calorie malnutrition increases the risk of death several-fold by increasing the susceptibility to infec-

tion.[6] In many countries, mortality rates increase from 0.5% in children whose weight-for-height percentage of standard is greater than 80% to a mortality rate of 18% in children whose weight-for-height percentage of standard is less than 60%.[7] In other diseases, such as cystic fibrosis and cancer, nutritional status has been linked closely to survival rates and morbidity. With leukemia and lymphoma, the incidence of infection with *Pneumocystis carinii* is higher in patients with protein-calorie malnutrition.[4]

Biochemically, protein-calorie malnutrition leads to changes in several aspects of the immune system that are similar to the immunologic changes in HIV infection. Cell-mediated immunity, microbial function of phagocytes, complement systems, secretory antibodies, and antibody affinity are consistently impaired in patients with significant malnutrition. Additionally, deficiencies of micronutrients, especially zinc and iron, as well as many others, may also have deleterious effects on the immune system. Other aspects of immunity that are altered by protein-calorie malnutrition include impaired chemotaxis of neutrophils, decreased lysozyme levels in serum and secretions, and interferon production in antibody response to T-dependent antigens. A child with protein-calorie malnutrition may also have impaired mucosal immunity with lowered concentrations of secretory immunoglobulin (Ig)A in the saliva, nasopharynx, and tears compared with well-nourished control children. Figure 38-1 illustrates the significant and close interaction between nutrition and immunity. This topic is discussed in greater detail in Chapter 20, "Malnutrition and Host Defenses."

Because many of the immunologic changes in malnutrition are similar to those found in children infected with HIV, malnutrition has been proposed to act as a cofactor of immune dysfunction by influencing both susceptibility to HIV infection and progression of the disease. It is logical to expect that augmenting the nutritional status of an HIV-infected child may improve the function of an already compromised immune system. Preliminary evidence to support this notion is presented later in this chapter.

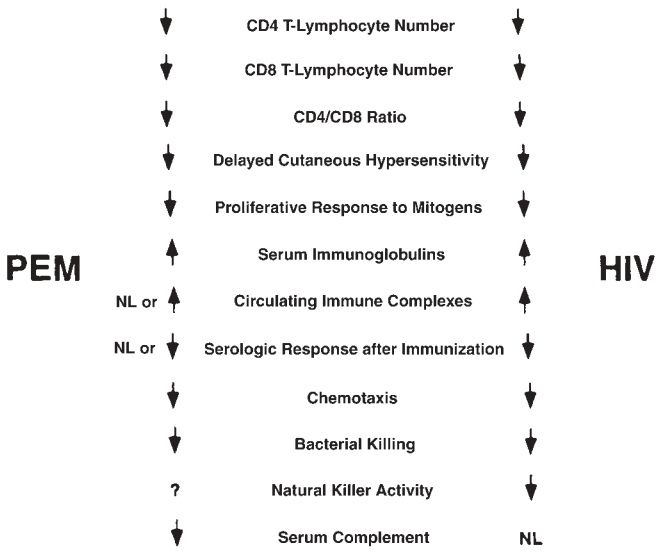

FIGURE 38-1 Diagrammatic representation of immunologic abnormalities associated with malnutrition and human immunodeficiency virus (HIV) infection. NL = normal; PEM = protein-energy malnutrition.

GROWTH AND BODY COMPOSITION OF HIV-INFECTED CHILDREN

Growth

Nutritional problems are common in infants and children with HIV infection, and the wasting syndrome is considered one of the major AIDS-defining illnesses.[8] As of 1998, HIV wasting rose from the fifth to the second most common AIDS-defining illness in children in the United States.[9] Most, if not all, children with HIV infection will experience nutritional abnormalities during the course of their illness. Even in the era of antiretroviral therapy, failure to thrive defined as weight for age z-score ≤ –2.0 SD is common in HIV-infected children in the United States and was found in 37% of perinatally infected children at 1 year of age.[10] In this study, failure to thrive was also associated with a significantly increased mortality rate by 36 months of age (36.3% versus 14.3% among HIV-infected children without failure to thrive). Weight loss and gastrointestinal symptoms are one of the most common presenting symptoms of HIV disease in developing countries. In a Tanzanian study, 200 children with severe malnutrition and controls who were matched for age, sex, and area of residence were screened for evidence of HIV infection.[11] Twenty-five percent of the malnourished group were HIV positive compared with 1.5% of the control group. These authors recommend routine screening for HIV infection in malnourished children in developing nations because there is a high likelihood that they will be HIV positive.

Acute malnutrition is manifested by more of a decline in weight than in height, with lower weight-for-height percentiles. Chronic nutritional deprivation will result in below-standard weight and height with near-normal weight for height. This is a growing child's adaptation to undernutrition. The following section summarizes recent studies that evaluate growth in HIV-infected children. In some HIV-infected children, abnormalities in height growth velocity precede weight changes and may reflect altered endocrine function, as is described in future sections.

In general, children with HIV infection have similar birth weights and are at no higher risk of prematurity than children who are not HIV infected but who are born to HIV-infected women,[12] although several studies found differences between groups at birth.[13–15] In a prospective study of infants born to HIV-infected women in the United States, as early as 6 months of age and up through age 5 years, HIV-infected infants had significantly lower weight-for-age and height-for-age z-scores than their HIV-exposed but uninfected counterparts.[10] Thus, growth abnormalities may begin postnatally and may develop even in asymptomatic children.

A natural history study of somatic growth in pediatric HIV infection is being conducted in the United States (Women and Infants Transmission Study [WITS]). An analysis of 282 infants born to HIV-infected women

revealed that, at birth, HIV-infected infants were 0.28 kg lighter and 1.64 cm shorter than uninfected infants, and these differences persisted after controlling for the effects of maternal drug and alcohol use.[16] HIV-infected children had a progressive decrement in weight, length, and body mass index (BMI) extending to 18 months of age. The authors also identified early and sustained decrements in head circumference. Preliminary data from 10 years of follow-up in this same study demonstrate considerable progressive growth decrements, with as much as an 8.9 kg weight and 8.0 cm height deficit among HIV-infected children at 9 years of age.[17]

In developing nations, other confounding factors exist, which could explain different outcomes relating to growth. In one study of 822 HIV-infected pregnant women from Tanzania, low birth weight was associated with maternal advanced-stage HIV, but malaria, any helmintic infection, and intestinal parasites were also strong predictors of low birth weight.[18] Infant HIV infection was not associated with low birth weight but was predictive of being small for gestational age. In a study from Malawi, 362 children born to HIV-infected women (92 infants HIV infected) and 686 infants born to noninfected women were evaluated at birth and followed for 2 years.[14] HIV-infected infants had significantly lower weight for age at birth and lower length for age by 5 months of age. Infants born to HIV-infected mothers who were not perinatally infected initally weighed less and were shorter than infants born to HIV-seronegative mothers, but this difference disappeared by 24 months. A prospective cohort study from Rawanda of 318 HIV-infected and 309 HIV-seronegative women was conducted to determine growth parameters in their offspring.[19] Birth weight was significantly lower among infants born to HIV-infected mothers compared with those born to HIV-seronegative mothers. Length, head circumference, and placental weight were also reduced between the two groups.

Additional studies in children with hemophilia have documented poor growth as a prognostic indicator to progression to AIDS. HIV-positive children with hemophilia who downwardly crossed 15 percentile points in height or weight for age on two repeated measurements were found to have a greater likelihood to progress to AIDS.[20]

Body Composition

Weight loss, or a decrease in growth velocity, is a simple marker to diagnose the wasting syndrome in children with HIV infection. However, using weight as the only marker of nutritional status can be misleading because weight can be confounded by symptoms such as vomiting and diarrhea. Also, hydration therapy may increase body weight while not truly reflecting an actual improvement in nutritional status. A more accurate measure of nutritional status is body cell mass, which refers to the nonadipose cellular mass and is roughly equivalent to the intracellular water volume.

Anthropometry and body composition studies can give clues to the potential etiology of a nutritional disorder. The body's first (and normal) response to starvation (inadequate food intake) is the preferential loss of body fat, which can be reflected in diminished triceps skinfold thickness measurements or other measurements of body fat. When fat stores are depleted, wasting of lean body mass occurs. In contrast, cachexia or wasting refers to the preferential and inappropriate loss of lean body mass over fat mass, with or without concomitant weight loss. Cachexia has been described previously in patients with cancer but more recently has been found in patients with HIV infection, including children. Cachexia may be mediated by chemical intermediates such as cytokines and is discussed in the section on pathogenesis.

Several studies using various methods to assess body composition have been performed in HIV-infected children. We reported body composition measurements of 89 children born to HIV-infected women, of whom 52 children were HIV infected. Lean body mass, as measured by arm muscle circumference, was significantly less in the HIV-infected group by 2 years of age. There were no differences in fat mass between the two groups of children.[12] In a cross-sectional study of HIV-infected children treated with nucleoside reverse transcriptase inhibitors, Fontana and colleagues compared bioelectrical impedance measurements of fat-free mass (FFM) in 86 HIV-infected children (mean age 6.9 years) and 113 healthy controls (mean age 7.7 years).[21] These investigators found that FFM was lower in HIV-infected children compared with controls; however, when FFM was evaluated as a percentage of total body weight, there was no difference between groups. Weight for age and FFM z-scores < –2.0 were associated with increased risk of death (relative risk 11.4 and 5.1, respectively), with weight for age serving as a stronger prognostic indicator than FFM. Arpadi and colleagues used dual-energy x-ray absorptiometry (DXA) and also found reduced FFM but normal fat stores among HIV-infected children compared with uninfected controls, regardless of whether growth failure was also present.[22] These findings indicate that poor growth and decreased FFM are a considerable problem for children living with HIV infection and that these parameters have a significant deleterious effect on survival.

The introduction of highly active or combination antiretroviral therapy (HAART) has revolutionized the management of HIV infection in adults and children. Much recent attention has focused on the potential impact of HAART on growth and body composition as well as immune function and survival. For example, as part of the Pediatric AIDS Clinical Trials Group 219 Study, the effects of the introduction of protease inhibitor (PI) therapy were assessed in 906 HIV-infected children between 3 months and 18 years of age.[23] In this study, initiation of PI treatment was associated with small but statistically significant increases in height and weight z-scores. In a prospective longitudinal study of 67 prepubertal children (mean age at entry 6.8 years) initiating PI therapy, PI treatment resulted in a twofold reduction in viral load and increased weight and weight-for-height z-scores.[24] These improvements and increases in lean body mass as measured by arm muscle circumference were significant even after controlling for exposure to all antiretrovirals, duration of HIV, immune

status, energy intake, and use of megace. In this study, the improvement in height was not statistically significant, and no significant changes in tricep skinfold were identified.

There is also evidence that improvement in growth parameters may be linked to immune response to antiretroviral therapy. Verweel and colleagues found that both weight and height improved after initiation of HAART but only in a subset of children who demonstrated viralogic response defined as 1.5 or greater log reduction in HIV RNA.[25] Furthermore, a Swiss study assessing a cohort of 44 prepubertal HIV-infected children found that children with stunting prior to initiation of PI therapy experienced statistically significant increases in height-for-age z-scores after 72 weeks of treatment.[26] In this study, there was a significant positive correlation between change in CD4 T-cell count and change in height z-score. These data represent preliminary evidence that effective viral suppression and immune reconstitution with HAART may substantially ameliorate the growth deficits in HIV-infected children. Longitudinal information is needed to determine the potential long-term benefits of antiretroviral therapy on growth and body composition.

PATHOGENESIS OF WASTING IN HIV-INFECTED CHILDREN

The pathogenesis of malnutrition, or the wasting syndrome, in pediatric HIV disease is currently unknown but is most likely multifactorial. A limited number of studies have determined the risk factors for malnutrition in HIV-infected patients, and even fewer have been performed in children. These risk factors include fever, diarrhea, acute infection, and anorexia in a population of predominantly homosexual men,[27] female gender and increasing age in a group of intravenous drug users,[28] and opportunistic infections, drug use, and psychosocial issues in a mixed population of HIV-infected patients.[29] Four potential mechanisms for weight loss include inadequate oral intake, gastrointestinal malabsorption, abnormal energy use, and psychosocial influences. Several factors may be operating simultaneously.

Energy Intake

A variety of potential factors may lead to abnormal intake, as outlined in Table 38-1. For example, inflammation and ulcers of the upper gastrointestinal tract can lead to anorexia owing to odynophagia, dysphagia, or abdominal pain that is associated with eating. In a series at Children's Hospital, Boston, 70% of upper gastrointestinal endoscopies in HIV-infected children revealed abnormal histologic findings.[30] These lesions may be attributable to acid-related injury or infectious agents such as *Candida albicans*, cytomegalovirus, or herpes simplex virus, all of which may cause inflammation and pain with swallowing or after eating. Furthermore, oral ulcers that are attributable to viral agents or idiopathic oral ulcers are common and may cause pain with eating and reduce oral intake.[31]

Pancreatic and biliary tract disease can also cause vomiting and abdominal pain in HIV-infected children, leading to poor oral intake. Pancreatic disease has been linked to medications (eg, nucleoside analogue reverse transcriptase inhibitors [NRTIs], PIs, sulfonamides) and opportunistic infections (eg, cytomegalovirus and mycobacterial disease).[32,33] Biliary tract disease with sclerosing cholangitis and papillary stenosis has been associated with *Cryptosporidium*, cytomegalovirus, and *Microsporidia* infection.[34,35] Primary anorexia, described in patients with cancer and other chronic disorders, may also contribute to inadequate oral intake. It is postulated that increased cytokine production (eg, tumor necrosis factor [TNF]-cachexin, interferon-γ, and interleukin [IL]-1 and -6) may be associated with anorexia. In animal models, administration of exogenous TNF has produced anorexia and cachexia.[36] TNF also causes delayed gastric emptying, which can increase anorexia as well.[37] Currently, the scientific data that implicate these cytokines as mediators of anorexia are controversial. HIV encephalopathy, which can be present in up to 34% of untreated children with HIV infection,[38] may result in the physical inability to consume enough calories to sustain growth. Oral administration of feedings under this condition may also be dangerous

TABLE 38-1 Causes of Malnutrition for HIV-1-Infected Children

Cause	*Mechanism*
Decreased nutrient intake	
Peptic disease	Pain
Opportunistic infections of upper gastrointestinal tract (*Candida*, CMV, HSV)	Pain, dysphagia
Pancreatic/hepatobiliary disease	Pain
Encephalopathy	Discoordinated swallow
Aphthous ulcers	Pain
Primary anorexia	Nausea, CNS, cytokines
Gastrointestinal malabsorption	
Mucosal disease	
Infectious	Bacterial, parasitic, viral
Inflammatory	HIV enteropathy, IBD
Disaccharidase deficiency	Infectious, inflammatory
Protein-losing enteropathy	Infectious, inflammatory
Fat malabsorption	Infectious, inflammatory
Hepatobiliary	
Sclerosing cholangitis	Infectious
Chronic pancreatitis	Infectious, drug-induced
Cirrhosis	HBV, HCV
Increased nutritional requirements or tissue catabolism	
Protein wasting, hypermetabolism, futile metabolic cycling	Fever, infections, sepsis Neoplasms (Kaposi's sarcoma, lymphoma) Medications Release of catabolic factors (cytokines, tumor necrosis factor)
Psychosocial factors	
Poverty	
Illness in biologic family members	
Limited access to health care	
Substance abuse	

CMV = cytomegalovirus; CNS = central nervous system; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; IBD = inflammatory bowel disease.

owing to the high risk of aspiration in neurologically compromised children. Finally, many medications that HIV-infected children are required to take may result in gastric irritation, vomiting, and nausea. These medications are listed in Table 38-2.

Despite the numerous potential situations that can result in low energy intake, few scientific data exist on children to support this. Oral intake during periods of acute illness has yet to be evaluated in HIV-infected children, although intake is very likely to be poor. We evaluated total energy intake in 26 children with early HIV disease and 16 noninfected children.[39] Total caloric intake and carbohydrate, protein, and fat intake were similar between groups, yet HIV-infected children had lower weight percentiles. These results suggest that mechanisms other than suboptimal oral intake (relative to the Recommended Daily Allowance [RDA]) exist, which cause altered growth and nutrition during stable periods of HIV infection. In an Italian study of 15 asymptomatic HIV-infected children and 18 symptomatic children with a mean age of 42 months, caloric intakes were compared with a control group of noninfected children.[40] In the symptomatically infected group of children, energy, calcium, phosphorus, and iron intakes were below 70% of the RDA more frequently than in the asymptomatic and control groups, although these differences were not statistically significant. Protein intakes were consistently high and above the RDA for most children across groups. There was no correlation between energy intake and nutritional status. Thus, with limited data, it appears that energy intake below the RDA is not common in HIV-infected children during stable periods of disease, and other mechanisms for poor nutrition must come into play.

More data on dietary intake exist in adults with HIV infection. Grunfeld and colleagues found that caloric intake was similar in HIV-positive patients and AIDS patients without opportunistic infections.[41] AIDS patients with secondary infections had a 36% lower energy intake coincident with a 5% weight loss. Resting energy expenditure (REE) in AIDS patients was greater than the other two groups. Thus, it appears that a combination of increased REE and inadequate oral intake in a group of patients with active secondary infections may be responsible for the significant weight loss over the study interval. Abrams and colleagues prospectively evaluated the relationship between dietary intake at baseline and the development of AIDS over a 6-year period in 296 HIV-positive men.[42] They found that with the exception of energy, zinc, thiamin, and vitamin E, reported nutrient intakes from food alone exceeded the RDA, and when supplements were included, all micronutrients exceeded the RDA, with the exception of zinc. Nutrient intake was positively associated with CD4 counts at baseline and inversely related to the risks of AIDS. Thus, supporting normal nutrient intake in patients with HIV infection may have a protective effect for progression to AIDS in adult patients.

Gastrointestinal Absorption

Adequate nutrient absorption is essential to maintain growth and nutrition in infants and children. HIV-infected

TABLE 38-2 Medications and Common Gastrointestinal Side Effects

Medication	*Action*	*Side Effects*
Abacavir	NRTI	Nausea, vomiting, abdominal pain, pancreatitis, abnormal liver function tests
Acyclovir	Antiviral	Nausea, abdominal pain, diarrhea, abnormal liver function tests
Amprenavir	Protease inhibitor	Abdominal pain, diarrhea
Azithromycin	Antibacterial	Nausea, vomiting, melena, jaundice
Ciprofloxacin	Antibacterial	Ileus, jaundice, bleeding, diarrhea, anorexia, oral ulcers, hepatitis, pancreatitis, vomiting, abdominal pain
Clarithromycin	Antibacterial	Nausea, diarrhea, abdominal pain, abnormal taste
Combivir (zidovudine/ lamivudine)	Combination	Nausea, vomiting, abdominal pain, abnormal liver function tests, pancreatitis
Dideoxycytidine	NRTI	Nausea, vomiting, abdominal pain
Dideoxyinosine	NRTI	Nausea, vomiting, abdominal pain, pancreatitis, abnormal liver function tests
Efavirenz	NRTI	Nausea, vomiting, abnormal liver tests
Erythromycin	Antibacterial	Nausea, vomiting, abdominal pain
Ganciclovir	Antiviral	Nausea, vomiting, diarrhea, anorexia, abnormal liver function tests
Indinavir	Protease inhibitor	Nausea, vomiting, abdominal pain, diarrhea, changes in taste, jaundice, abnormal liver function tests
Ketoconazole	Antifungal	Hepatotoxicity
Lamivudine	NRTI	Nausea, diarrhea, vomiting, abdominal pain, pancreatitis, abnormal liver function tests
Nelfinavir	Protease inhibitor	Nausea, diarrhea, fatigue, abnormal liver function tests
Nevirapine	NRTI	Stomatitis, nausea, abdominal pain, elevated γ-glutamyl transpeptidase
Pentamidine	Antiparasitic	Abdominal pain, bleeding, hepatitis, pancreatitis, nausea, vomiting
Rifampin	Antibacterial	Abdominal pain, nausea, vomiting, diarrhea, jaundice
Ritonavir	Protease inhibitor	Nausea, vomiting, diarrhea, abdominal pain, pancreatitis, abnormal liver function tests
Saquinavir	Protease inhibitor	Mouth ulcers, nausea, abdominal pain, diarrhea, pancreatitis, abnormal liver function tests
Stavudine	NRTI	Nausea, vomiting, abdominal pain, diarrhea, pancreatitis, abnormal liver function tests
Sulfonamides	Antibacterial	Hepatitis, pancreatitis, stomatitis, nausea, vomiting, abdominal pain
Trisavir (abacavir/ lamivudine/ zidovudine)	Combination	Nausea, vomiting, abdominal pain, pancreatitis, abnormal liver function
Zidovudine	NRTI	Nausea, vomiting, abdominal pain, abnormal liver function tests

NRTI = nucleoside analogue reverse transcriptase inhibitor.

patients are at risk of developing malabsorptive disorders, which can potentially impact on their growth and nutritional status. Possible reasons for gastrointestinal malabsorption in HIV-infected children include infections of the gastrointestinal tract that affect the intestinal architecture, malnutrition alone, or direct or indirect effects of HIV on the intestinal epithelial cell. Infections that are known to affect the small bowel and that may promote malabsorption of nutrients include *Cryptosporidium*, *Isospora belli*, *Microsporidia*, *Mycobacterium avium intracellulare* complex (MAC), *Giardia lamblia*, and rotavirus. These pathogens can injure the intestinal epithelial cell, where critical digestive enzymes are present to digest essential nutrients. Enteric infections may also decrease bowel transit time, thus shortening nutrient contact with the epithelial cell and causing malabsorption. Malnutrition alone can cause villous blunting and secondary malabsorption of nutrients, which would further impact on nutritional status. Malabsorption has also been linked to an "HIV enteropathy," in which the villi are blunted with a hypercellular lamina propria and absence of a detectable enteric pathogen.[43] The presence of HIV in enterocytes is controversial; some investigators have found it by in situ hybridization,[44] whereas others have found it only within the lamina propria, which is rich in lymphocytes and macrophages.[45] An in vitro study of enterocytes showed that HIV-1 exposure, regardless of cell entry, evoked massive disruption of microtubules and inhibited a major sodium/glucose transporter, suggesting a pathophysiologic mechanism for HIV enteropathy and malabsorption.[46] In addition, HIV may affect the maturation of enterocytes and the subsequent expression of digestive enzymes on the brush border.

Children with HIV are also susceptible to small bowel bacterial overgrowth, which can result in malabsorption. Bacterial overgrowth may be attributable to an "AIDS gastropathy," in which the stomach produces only small amounts of hydrogen chloride, allowing bacterial pathogens to escape the acid barrier of the stomach and colonize the duodenum, where they may live and grow, using essential nutrients.[47] Additionally, "iatrogenic" hypochlorhydria occurs with the administration of acid-blocking agents. In a recent study of HIV-infected adults, small bowel bacterial overgrowth was infrequently identified, regardless of the presence of diarrhea, and when found was not associated with hypochlorhydria.[48]

Evidence to support the presence of malabsorption in HIV-infected children comes from a limited number of pediatric studies.[49–53] Twenty-eight HIV-infected children from Children's Hospital, Boston, and Boston City Hospital were evaluated for gastrointestinal malabsorption.[49] Over 60% were found to have some degree of carbohydrate malabsorption by D-xylose testing or lactose hydrogen breath testing. Carbohydrate malabsorption was not associated with nutritional status or gastrointestinal symptoms. Lactose malabsorption was found in 40% of children who were tested while free of known enteric infection. Abnormal D-xylose absorption was associated with an active enteric infection. Yolken and colleagues documented lactose malabsorption as well, but in association with clinical symptoms and weight loss.[50] In an Italian study, intestinal function of 47 symptomatically infected children was compared with that of 50 noninfected children with diarrhea and 48 healthy children.[51] Intestinal absorption was measured using the steatocrit method to determine fat absorption, fecal concentration of α_1-antitrypsin as a measure of protein absorption, and D-xylose absorption. Fecal fat loss was detected in 30%, carbohydrate malabsorption in 32%, and protein loss in 17% of HIV-infected children. Investigators found that intestinal dysfunction was not associated with diarrhea, poor growth, enteric agents, or degree of immune dysfunction but was significantly different from that of healthy control children. In a similar series, Sentongo and colleagues identified fat malabsorption in 39% of 44 HIV-infected children, but no patient had exocrine pancreatic insufficiency, and there was no relationship between steatorrhea, growth, HIV viral load, or CD4 count.[52] Thus, although malabsorption is fairly common, it cannot account for all of the gastrointestinal symptoms or malnutrition in HIV-infected children.

Metabolism

Increased energy metabolism of HIV-infected children can contribute to malnutrition by increasing the child's caloric demands to maintain weight and sustain growth. Total daily energy expenditure is the sum of energy needed to maintain a child at rest, the energy needed for activities of daily living, and the thermic effect of eating. Measurements of REE through indirect calorimetry and total daily energy expenditure through techniques such as doubly labeled water studies and whole-room calorimetry will enable investigators to determine the metabolic rates of HIV-infected patients.

There are limited studies in the pediatric HIV population that delineate resting or total daily energy expenditure, although more studies have been performed in the adult HIV population. In a small study of nine HIV-infected children without recent opportunistic infections, REE was measured using indirect calorimetry.[54] There was a strong correlation between measured REE and predicted estimates of energy needs, and all subjects met the RDA for calories and protein based on dietary recall. Additional literature on children generally shows no differences in REE or total energy expenditure between children with growth failure and those with normal rates of growth.[54–57] However, these studies have been performed in clinically stable children; metabolism in sicker children is likely to be much higher. One study has determined whole-body protein turnover in children with HIV-1 and found that increased protein turnover is associated with low weight and height.[58] There was no correlation with other markers of intermediary metabolism.

In adults with HIV, an active opportunistic infection appears to cause significant increases in resting metabolic rates. Melchior and colleagues studied REE in 165 malnourished patients with HIV infection.[59] The mean REE was 11% higher in the HIV-infected patients with no secondary infections compared with the control group and was 34% higher in HIV-infected patients with an active

infection. An increased metabolic rate, coupled with the findings of diminished energy intake, could be responsible for the significant weight loss.[41]

In patients without active secondary infections, resting metabolic rates are also increased. Hommes and colleagues studied REE of a group of 18 HIV-infected men who were free of clinically active opportunistic infections for at least 2 months.[60] Patients with AIDS or AIDS-related complex (ARC) had 9% higher rates of REE when compared with 11 healthy volunteers. They found no differences between patients and controls in plasma concentrations of catecholamines, thyroid hormones, cortisol, or TNF, except for lower concentrations of norepinephrine in the study patients. In the absence of acute infections, increased REE may contribute to the weight loss seen in patients with AIDS or ARC. Furthermore, Slusarczyk and colleagues evaluated the REE of 53 HIV-infected male volunteers. REE was significantly different between Walter Reed stage 0 (less symptomatic) and Walter Reed stage 3 and 4 patients (more symptomatic) (1.11 kcal per minute versus 1.45 kcal per minute, respectively).[61] These findings emphasize the need to stratify patients according to disease severity because pooling patients of all stages may not have shown a difference among HIV-infected individuals.

Suttmann and colleagues correlated resting energy metabolic rates to weight loss in HIV-infected adults.[62] REE differed significantly from predicted values in 40% of the patients, with 7% of the patients showing marked increased resting expenditure and 13% of the patients with decreased metabolic rates. Increased resting expenditure was found during all clinical stages of HIV diseases and was not strictly associated with a degree of immune impairment, presence of diarrhea, Kaposi's sarcoma, or nutritional status or wasting. Twenty-seven patients were evaluated longitudinally, and 11 lost more than 5% of their initial body weight during the observation period. Weight-losing patients were normometabolic before but showed a significant increase in REE during the follow-up period, in which there was weight loss (an increase of 7% of predicted values). The degree of deviation from estimated REE was strongly associated with the degree of weight loss. Thus, in this study, increased REE is not always a constant feature of HIV infection and is not associated with clinical and laboratory parameters of immune deficiency but occurs during weight loss and may be a causative factor for weight loss.

In contrast, Kotler and colleagues studied five clinically stable patients with AIDS and HIV-negative control subjects.[63] They found that the AIDS patients were hypometabolic compared with the control subjects and concluded that short-term energy balance can be maintained in clinically stable patients with AIDS. Hypometabolism, in this circumstance, was an appropriate metabolic response to the combination of body cell mass depletion and nutrient malabsorption.

Thus, similar to other controversial topics in the HIV literature, discrepancies in metabolic outcomes are possibly attributable to the variability of disease expression in patients infected with HIV. This emphasizes the need for small studies of patients with similar entry characteristics or larger studies in which modifiers of the outcomes can be controlled properly.

Cytokines

Altered metabolic rates may be attributable, in part, to chemical messengers such as cytokines. This hypothesis is supported by experimental and animal studies. The cachectin hypothesis was first described by Beutler and Cerami, who noticed that patients with chronic infections have significant weight loss that is associated with hypertriglyceridemia and reduced clearance of triglycerides by lipoproteins.[64] They postulated that a decrease in triglyceride clearance could lead to a decrease in fat storage and wasting of lean body mass as a result of the inability to use fats as a reserve source for energy. In animal studies, supernatants from activated macrophages induced weight loss when given daily to rodents.[65] This factor in the supernatant was subsequently isolated and named cachetin; it was later discovered to be the cytokine TNF. Other cytokines, such as IL-1 and the interferons, have similar effects.

Subsequently, specific cytokines, such as TNF, IL-1, and IL-6, have been associated with infectious, inflammatory, and wasting disorders. They share remarkable similarities in their biologic properties. These cytokines appear to be among the body's key mediators of acute response to inflammation and infection, leading to the shunting of protein and energy sources away from the lean body compartments. Systemically, IL-1 exerts catabolic effects on liver, fat, and connective tissues. IL-1 induces hepatocyte synthesis of acute-phase proteins while depressing serum albumin synthesis by decreasing transcription of RNA coding for albumin. IL-1 also has the ability to reduce serum iron and zinc, which has implications for its role in nonspecific resistance to infection. In cancer patients, TNF has been implicated as a signal molecule that may induce severe weight loss and may be related, in part, to the profound systemic suppression of lipoprotein lipase with subsequent lipemia.[66]

Increased levels of TNF in AIDS patients have been reported,[67] although some studies suggest that there are no significant differences in TNF levels between patients with AIDS and appropriate control subjects.[68,69] However, active secondary infections may increase TNF levels in AIDS patients.

Cytokines, as described above, alter metabolic processes in non-HIV populations. In patients with HIV, cytokines can cause ineffective use of energy substrates. Hellerstein and colleagues studied hepatic lipogenesis in HIV-infected adult patients and correlated it with peripheral cytokine levels.[69] Both symptomatic HIV-infected patients with normal CD4 counts and HIV-infected patients with weight loss had elevated hepatic lipogenesis compared with noninfected controls. Hepatic lipogenesis correlated with interferon-α levels in the fasted state in the patients with HIV infection and weight loss. Other cytokines were not correlated with increased hepatic lipogenesis. In addition to increasing the hepatic synthesis of fatty acids, TNF also mobilizes free fatty acids by stimulat-

ing peripheral lipolysis. The net result, "futile cycling," the process by which fatty acids are shuttled from adipose tissue to liver and back to adipose tissue, uses energy ineffectively. The process results in increased metabolic rates, with greater caloric needs to maintain nutrition.

The net effect of cytokines for patients infected with HIV is nonproductive use of precious energy substrates. Approximately 28% of calories are lost if lipogenesis from carbohydrate precedes its oxidation. Roubenoff and colleagues found that loss of lean body mass was driven by catabolic cytokines and not by inadequate dietary intake or hypogonadism.[70] Other investigators have found similar associations, independent of viral load.[71] Limited studies in children showed increased IL-6 activity, as well as low insulin-like growth factor (IGF)-I and increased viral load, to be associated with growth impairment.[57] The net effect of elevated cytokine levels may contribute to the relative hypermetabolism seen in HIV-infected patients. Because depression of immune function secondary to malnutrition is potentially reversible, nutritional rehabilitation in HIV-infected children may significantly lower serum cytokine levels by positively improving immunologic function, decreasing opportunistic infection, and diminishing HIV replication. This, in turn, would decrease cytokine production. With lower TNF and IL-1 production, promotion of HIV replication would be decreased, and the systemic effects of these cytokines, such as the wasting and malabsorptive symptoms, would be reduced.

Endocrine Disturbances

Although not the main focus of this chapter, endocrine abnormalities may contribute to growth failure in HIV-infected studies. In a subset of children, a decrease in height growth velocity precedes changes in weight, with resulting increases in weight-for-height percentiles. The exact etiology of this growth pattern is unclear, yet it suggests problems with endocrine regulation of linear growth. A study examining IGF-I secretion of HIV-infected children showed that IGF-I secretion was diminished in both asymptomatic (45% of children) and symptomatic (86% of children) HIV-infected children and was associated with growth failure. Less clear association with thyroid function was found.[72]

Psychosocial Factors

Psychosocial factors are also important contributors to suboptimal nutrition of HIV-1-infected children. An unstable home environment and inadequate emotional and social support have been shown to be factors for growth problems in both HIV-1-infected and non-HIV-1-infected children by many mechanisms, including growth hormone (GH) deficiencies.[73–75] Children with HIV-1 infection are at risk for living with parents who are ill, who have limited access to social services and support, and who may have ongoing problems with drug and substance abuse.[76] Investigators have found maternal crack and cocaine use during pregnancy to be a predictor of growth and nutritional problems for the child.[10,16] This finding is not unique for HIV-1 as it has been reported in other non-HIV-1 cohorts.[77] Children born to drug-using women are often small, suggesting that drugs have a prenatal effect, but the postnatal home environment is likely to influence growth as well. Current studies have also found that home care providers can both positively or negatively influence the functional status of HIV-1-infected children.[73]

MICRONUTRIENTS

Micronutrients have been linked to immunomodulation, both in vivo and in vitro, and are an area of active investigation in HIV-infected patients. Extensive work with micronutrients has been performed in laboratory animals. Deficiencies of pyridoxine, folic acid, vitamin A, vitamin C, and vitamin E result in impaired cell-mediated immunity and reduced antibody responses. Vitamin B_6 deficiency results in decreased lymphocyte response to mitogens, yet a moderate increase in betacarotene intake may enhance immune responses. With zinc deficiency, there is lymphoid atrophy and decreased delayed cutaneous hypersensitivity responses. Likewise, zinc deficiency in animals can reduce the number of antibody-forming cells in the spleen and impair natural killer activity. Clinically, wound healing is impaired. Excessive zinc can depress neutrophil function and lymphocyte responses. Iron is important for bacterial growth as well as the function of neutrophils and lymphocytes. Deficiencies of iron may reduce bacterial multiplication but may also impair lymphocyte proliferation response to mitogens and antigens. Clinically, in patients with iron deficiency, lymphocyte response to tetanus toxoid and herpes simplex antigen is low. Overall, in animal models, it is clear that selected vitamin and micronutrient deficiencies impact on immune function in many ways.

Because of the close link between immunologic function and micronutrients, it is logical to expect that low micronutrient levels can affect susceptibility to infection. For HIV-infected children, whose immunologic function is already compromised, further alterations of immunologic function, through micronutrient deficiencies or excesses, may synergistically decrease resistance to infections. Current studies of micronutrients and HIV infection are outlined in the following section.

General Studies

There are increasing data available on the micronutrient status of children with HIV infection. Eley and colleagues evaluated 60 HIV-infected children in Cape Town, South Africa, and in this cohort, vitamin deficiencies were frequently identified: vitamin A (80%), retinol binding protein (85%), vitamin B_6 (37%), vitamin E (37%), zinc (20%), and copper (25%).[78] Sixty-two percent of children had two or more deficiencies, and deficiencies were more common and more severe in children older than 24 months. Only 5% of patients were found to have low vitamin B_{12} levels. In a large series of symptomatic HIV-infected children (n = 71) in Italy, 48% were iron deficient and 66% had anemia, and this was positively associated with markers of malabsorption.[79] Micronutrient deficiencies appear to be common and may be linked to immune function and disease progression.

In adults, Tang and colleagues showed a relationship between total vitamin A intake and progression to AIDS, but it was U-shaped; the lowest and highest quartiles of intake did poorly, whereas the two middle quartiles demonstrated a significantly slower progression to AIDS.[80] They also found that increased intake of zinc was significantly associated with an increased risk of progression to AIDS. In a final multinutrient model, vitamin A, niacin, and zinc remained significantly associated with progression to AIDS, whereas vitamin C was only marginally significant.

Vitamin A

In earlier work, Semba and colleagues studied the association between plasma vitamin A, immunologic status, and clinical outcome during HIV infection.[81] In a cohort of 179 subjects with intravenous drug use, 15% of HIV-positive patients had low plasma vitamin A levels, significantly different from the HIV-negative control patients. Vitamin A deficiency was associated with increased mortality in HIV-infected patients, with a relative risk of 6.3 (95% confidence interval [CI] 2.1 to 18.6). However, more recent data available from HIV-infected children in North America found vitamin A deficiency to be relatively uncommon, and vitamin A concentrations did not appear to be related to mortality in this population.[82]

Vitamin A deficiency and supplementation, however, may have a significant role in HIV disease transmission and progression in areas of the world where vitamin A deficiency is more prevalent. Vitamin A deficiency in pregnant HIV-positive women was associated with increased risk of vertical transmission.[83,84] In a trial of vitamin A supplementation in Tanzania, HIV-infected children experienced a 63% reduction in all-cause mortality with vitamin A supplementation compared with placebo.[85] In a longitudinal observational study of 194 HIV-infected children in Uganda, low plasma betacarotene levels, but not vitamin A levels, were predictive of increased mortality. This and other studies, however, show a relationship between low vitamin A levels and poor growth in HIV-infected children.[85,86] For example, in a placebo-controlled trial of vitamin A supplementation in Tanzania, including 50 HIV-infected children, vitamin A–treated children under 18 months of age experienced a 2.8 cm greater height increase compared with placebo.[87] One potential mechanism for this beneficial effect on growth may be improved gut permeability (ie, reduced permeability with vitamin A), which was shown with perinatal vitamin A supplementation in HIV-infected infants.[88]

B Vitamins and Folate

Baum and colleagues studied vitamin B_6 status in HIV-infected adults.[89] In this study, vitamin B_6 was significantly associated with decreased lymphocyte responsiveness to mitogens and reduced natural killer cell cytotoxicity. Vitamin B_6 was not related to CD4 cell number. Thus, vitamin B_6 is an important factor of immune function, and, as noted previously, vitamin B_6 deficiency was detected in 37% of HIV-infected children in one series.[78]

Dowling and colleagues studied vitamin B_{12} and folate in 35 HIV-infected men, of whom 16 were asymptomatic.[90] Serum vitamin B_{12} was normal or above normal in all patients, coincident with high vitamin B_{12} intake. Lower red blood cell folate was found in only 3 patients, but levels were lower overall in the more symptomatic group. Folate intake was low in 36 to 56% of patients.

Folic acid absorption was studied in 25 HIV-infected patients after an oral folic acid dose, with blood samples taken sequentially over 3 hours.[91] Absorption of folic acid was significantly impaired in patients, regardless of the stage of the disease. Thus, intestinal absorption of folate and other nutrients may be responsible for abnormal blood levels.

Antioxidants

Oxygen radicals are generated during normal metabolism, yet production may increase during infection, malnutrition, stress, or drug therapy. Patients with HIV infection are subject to all of these factors, which can increase oxygen free radicals. Catalase (an important hydrogen peroxide scavenger) was studied in adult patients with advanced HIV infection.[92] As HIV disease progressed from asymptomatic infection to AIDS, serum catalase activity increased sequentially, reflecting or compensating for antioxidant deficiencies in HIV-infected patients. Potent nutritional antioxidants include vitamin E and selenium.

Vitamin E may have independent effects on immunomodulation. Studies in laboratory and farm animals suggest that vitamin E doses in excess of the RDA increase the immune response and improve host resistance to microorganisms. In laboratory studies, vitamin E inhibited nuclear factor-κB activity by TNF (this normally induces HIV replication). Clinically, vitamin E supplementation is beneficial in reducing the incidence or severity of infectious diseases in elderly persons.[93]

Selenium is a potent antioxidant and is also an important cofactor for immune function in humans. Recently, in vivo studies have shown the importance of this element in protecting cells from HIV activation and the effects of TNF through increasing glutathione peroxidase activity.[94] In one cross-sectional study, HIV-infected children had low glutathione levels, which correlated with CD4 cell count.[95] As well, in a cohort of patients studied at Children's Hospital, Boston, 61% of the patients had a low serum selenium level.[96] Selenium levels significantly correlated with weight z-score, albumin levels, and CD4 counts, suggesting a strong relationship with nutrition and immunity. Dworkin and colleagues reported 12 adult patients with AIDS compared with 27 healthy controls and found that there was a significant difference in whole blood selenium and red blood cell selenium levels in those patients with AIDS.[97] They also found that myocardial biopsies in AIDS patients demonstrate significant selenium deficits.[98] These data may provide a link between a selenium deficiency in cardiomyopathy and AIDS.

Trace Metals

Serum copper and zinc have also been studied in HIV-infected patients. A study by Graham showed that serum copper levels were higher and zinc levels lower in HIV-infected adult patients who progressed to AIDS than

seropositive patients who did not progress.[99] In a logistic regression model, they found that higher serum copper levels (odds ratio [OR] 2.23 [95% CI 1.02–4.87]) and lower serum zinc levels (OR 0.3 [95% CI 0.14–0.66]) predicted progression to AIDS independently of baseline CD4 lymphocyte levels, age, and calorie-adjusted dietary intake of both of these nutrients. In an open treatment study of HIV-infected children with a CD4 count < 500/mm^3, supplemental zinc was administered for 1 month. Although 69% of the children had low zinc levels at baseline, supplementation did not have an effect on p24 antigen or CD4 count.[100] Zinc's role in metabolic function has been well studied. It is important in the stabilization and function of metabolic enzymes, including those involved in protein synthesis, catabolism, energy metabolism, and RNA and DNA synthesis. Regeneration of gut epithelium, stabilization of brush border enzymes, and improved immune function are all proposed mechanisms for zinc's beneficial effects in acute diarrhea. In a randomized, placebo-controlled study of non–HIV-infected infants and toddlers with acute diarrheal illnesses (n = 937) in India, zinc supplementation resulted in significant reductions in stool frequency and duration of illness.[101] Given the prevalence of zinc deficiency among HIV-infected children, it is possible that zinc supplementation may be of particular benefit in children with HIV and diarrheal illness, but this needs to be investigated further.

DIAGNOSTIC EVALUATION

Because malnutrition and wasting are common in most HIV-infected children, routine nutritional assessment should be performed every 3 months in every child who is at risk for acquiring HIV infection. Careful consideration of the pattern of growth will lead to an investigation of nutritional versus endocrine dysfunction. Subtle changes in growth and altered nutrient intake can be detected. The nutritional assessment should include measures of weight, height, head circumference, triceps skinfold thickness (to measure fat mass), and muscle circumference (to measure muscle mass). A detailed dietary history and recall should be ascertained regardless of the child's nutritional condition. Dietary advice or encouragement should be reinforced at each visit. Figure 38-2 outlines a clinical algorithm of diagnosis and management of HIV-infected children with nutritional abnormalities.

If a child shows evidence of malnutrition (Table 38-3), nutrient losses should be evaluated in addition to nutrient intake. Clinical symptoms should be determined with the focus on gastrointestinal problems, such as vomiting, abdominal pain, and diarrhea. A complete physical examination will provide clues. The child should be evaluated for oral thrush, abdominal pain, and gross or occult blood in the stool. Laboratory studies should include a hemogram, liver function studies, pancreatic enzyme levels, including a lipase level, and a complete evaluation for enteric pathogens. Studies such as an upper gastrointestinal contrast series, upper gastrointestinal endoscopy, and abdominal ultrasonography may provide a definitive diagnosis. If clinical symptoms warrant, a complete gastrointestinal absorption evaluation should be performed, including a lactose hydrogen breath test, D-xylose absorption study, and 72-hour fecal fat collection.

Serum micronutrients should be assessed in malnourished or wasted HIV-infected children. Vitamins A, E, and D should be measured, especially if there is liver, biliary tract, or pancreatic disease. Serum zinc and selenium should be measured and may be low; if so, they should be replaced to optimize immune function. As other micronutrients such as vitamin B_6, vitamin B_{12}, iron, and copper may be depressed, they should also be measured in malnourished children.

It may also be important to evaluate a child's energy needs. Studies such as indirect calorimetry (to measure resting metabolic rate) and doubly labeled water studies (to measure total daily expenditure) are useful tools. However, these tests are impractical in a clinical setting not equipped to perform them owing to their expense and time required to complete them. In a practical sense, the best estimation of energy needs for an HIV-infected child is the child's response to a diet enriched in calories, with accurate documentation of caloric intake and type of food.

NUTRITIONAL INTERVENTIONS

Oral Supplementation

Nutritional interventions should be instituted when the child fails to meet growth standards, as defined in Table 38-3. In general, a proactive approach to nutritional guidance is preferred when early nutritional interventions are more effective than during the later stages of HIV disease. Nutritional therapies should be instituted in parallel with treatment for other ongoing systemic or gastrointestinal diseases. Oral nutritional therapies, in most patients, should be tried initially. Formula caloric density should be increased by concentration or adding fat or carbohydrate. If the child is eating solids, adding a high-fat supplement, such as butter or margarine, may be helpful. Efforts should be made to increase formula volume as much as can be tolerated. Because a precise estimation of caloric needs is usually not available, the caloric goal, in general, should be targeted at 50% above the RDA for age and sex. Other nutritional requirements are shown in Table 38-4, although these requirements are considered minimal, and more may be required if the child has clinical and biochemical evidence of nutritional deficiencies. Formula composition should be prescribed according to the extent of nutrient malabsorption. If the child has clinical symptoms indicating a malabsorption of lactose (diarrhea, bloating, flatulence), then a lactose-free diet is indicated. Caution is advised, however, in prescribing a lactose-free diet if the child has no clinical symptoms of lactose malabsorption as limiting lactose may also restrict the foods that are the most enjoyable and richest in calories. In addition, an oral lactose supplement may be added in some cases of lactose intolerance. A protein hydrolysate formula should be considered if the child has evidence of gastrointestinal mucosal dysfunction with malabsorption of fats and proteins.

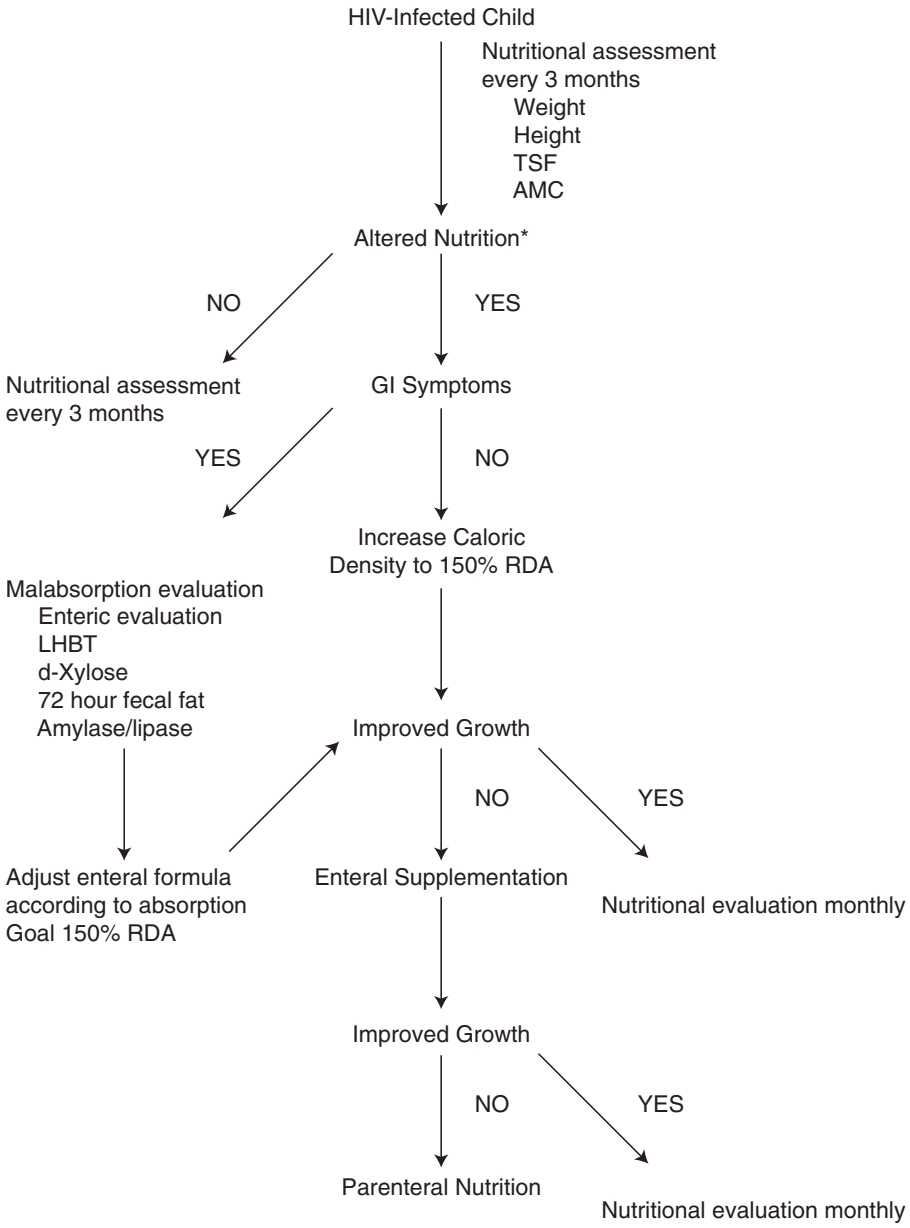

FIGURE 38-2 Algorithm for monitoring, diagnosing, and treating malnutrition associated with human immunodeficiency virus (HIV) disease in infants and children. AMC = arm muscle circumference; GI = gastrointestinal; LHBT = lactose hydrogen breath test; RDA = Recommended Dietary Allowance; TSF = triceps skinfold.

Breast milk is generally considered the best nutrition for infants worldwide because it contains factors that protect the infant against pathogens. Breast-feeding also fosters the mother–infant bond. Unfortunately, women with HIV infection can transmit the virus to their infant through breast milk; therefore, breast-feeding in this circumstance is strongly discouraged in countries where other safe feeding options exist.

Enteral Supplementation

If oral interventions fail because the child cannot consume adequate calories to sustain growth, enteral supplementation should be considered. Nasogastric tube feedings should be instituted first to document the child's ability to gain weight with supplemental enteral feedings. Nighttime feedings are most practical because they allow the child to eat normally throughout the day. Complications relating to nasogastric tube feedings include sinusitis and the technical inability of the caretaker to administer the feedings or place the tube. If delivery of feedings through a nasogastric tube improves growth, then placement of a more permanent device, such as a gastrostomy tube, should be considered. A gastrostomy tube provides easy access to the stomach with less physical and emotional trauma to the child.

Table 38-3 Clinical Indicators of Malnutrition in HIV-Infected Children

Weight growth velocity < 5% for more than 2 mo
Decrease in 1 major growth percentile for weight
Weight or weight-for-height percent standard < 90%
Weight for height < 5%
Loss of > 5% of lean body mass
Serum albumin < 3 g/dL

In addition, recent studies show that gastrostomy tube placement results in significant improvements in medication compliance and reductions in medication administration time in children with HIV infection.[102,103]

In a study of 23 HIV-infected children from Children's Hospital, Boston,[104] weight and weight-for-height z-scores increased with gastrostomy tube feedings. This increase in weight and weight for height was coincident with an increase in caloric intake. Fat stores, as measured by triceps skinfold thicknesses, increased in parallel with weight and weight for height, with no appreciable effect on lean body mass. Additionally, children who gained weight with gastrostomy tube feedings were hospitalized less in the 6 months after gastrostomy tube placement and had a 2.8-fold reduction in risk of dying. Children with higher age-adjusted CD4 T-lymphocyte counts and lower weight-for-height z-scores at the initiation of enteral supplementation were more likely to gain weight. In a more recent study, Guarino and colleagues evaluated the effects of enteral (n = 16) and parenteral (n = 46) nutritional therapy for HIV-infected children with malnutrition and evidence of diarrhea or malabsorption.[105] More than 80% of patients receiving enteral therapy gained > 5% of their baseline weight, and enteral therapy was associated with significant increases in CD4 cell count. In addition, enteral therapy improved gut absorption, with 75% of patients experiencing normalization in the xylose absorption test. Combined, these findings suggest that early nutritional intervention is indicated in children with HIV infection and may improve morbidity and survival.

Parenteral Nutrition

Parenteral nutrition should be reserved for HIV-infected children who continue to lose weight on an aggressive enteral program, who have severe recurrent or chronic pancreatic or biliary tract disease, or who have intractable diarrhea with weight loss. The placement of a central venous catheter can provide venous access that is often difficult to obtain in terminal stages. Central venous catheters present an additional risk for sepsis, and studies in adults and children with HIV infection present conflicting results regarding the risk of infection.[106,107]

Limited data are available on the benefits of total parenteral nutrition (TPN) in children with HIV infection. In the series reported by Guarino and colleagues, 46 HIV-infected children with malnutrition and malabsorption received a median of 157 days of TPN.[105] Although CD4 cell count, weight, and xylose absorption all improved significantly in the patients receiving enteral therapy (n = 16), these measures improved on TPN but not significantly. One possible explanation for the difference in findings between TPN and enteral nutritional support is that this was an observational study, and patients on TPN had more advanced disease, as indicated by a lower baseline CD4 count (154 cells/mm^3 for enteral patients versus 55 cells/mm^3 for TPN patients). In addition, 58.7% of TPN patients versus 18.8% of enteral patients died during the follow-up period, which may be related to increased risk of infection with central lines and TPN but may also reflect the practice of reserving TPN for late- and end-stage patients. Further study is needed to determine the appropriate role of TPN therapy in the setting of HIV infection in children.

Other Nutritional Therapies

Appetite Stimulants Megestrol acetate, a synthetic orally active progesterone, widely used to treat breast cancer, has shown promising results as an appetite stimulant in adults with HIV infection. The mechanism of weight gain with megestrol acetate is under investigation, but preliminary findings show that it has an effect both on behavior (ie, food intake) and metabolism by the induction of lipogenic enzymes and fat synthesis.[108] A prospective, randomized, double-blind, placebo-controlled trial of megestrol acetate in 271 HIV-infected adults found that 64.2% of patients who received 800 mg megace per day gained 5 pounds or more compared with 21.4% of those receiving placebo.[109] These patients also reported an improvement in overall well-being and had an increase in lean body mass, appetite, and caloric intake as well. Lean body mass increased, although total body water did not change, implying a significant increase in cellular body mass.

Oster and colleagues studied the effects of megestrol acetate, 800 mg daily, on body weight, composition, caloric intake, and mental outlook in patients with AIDS who had cachexia.[110] One hundred patients with AIDS who had lost 10% or more of their ideal body weight were

Table 38-4 Nutritional Requirements for HIV-Infected Children

Nutrient	*Requirements per Day**
Total calories	100–150% RDA for age and sex
Protein	100–150% RDA for age and sex
Vitamin A	400–1,000 µg retinol
Vitamin D	400 IU
Vitamin E	3–10 mg d-alpha-tocopherol
Vitamin K	5–80 µg
Vitamin C	30–60 mg
Thiamin	0.3–1.1 mg
Riboflavin	0.4–1.3 mg
Niacin	5–15 mg
Vitamin B_6	0.3–1.6 mg
Folate	25–180 µg
Vitamin B_{12}	0.3–2.0 µg
Iron	6–15 mg
Zinc	5–12 mg
Selenium	10–55 µg

*Requirements reflect the clinical nutritional state of the child; more may be needed if there is biochemical evidence of deficiency. Ranges reflect increasing needs for age and sex.

randomly assigned to placebo or megestrol acetate. Patients receiving megestrol acetate had greater caloric intake, resulting in weight gain of predominantly fat. Body water, lean body mass, and survival were not significantly different between the two groups. There are few reports on the use of megestrol acetate in children with HIV infection. Clarick and colleagues evaluated the effects of megestrol acetate in 19 HIV-infected children for a median of 7 months at doses between 4.0 and 8.5 mg/kg/day and found increased weight z-scores with continued therapy but no improvement in linear growth.[111] The authors also reported that poor weight gain and/or weight loss occurred after megestrol acetate was withdrawn. More recently, the same group noted adrenal suppression with corticotropin stimulation testing in 7 of 10 HIV-infected children treated with megestrol acetate compared with 0 of 10 HIV-infected children not on megestrol acetate.[112] Therefore, use of megestrol acetate may be beneficial for weight gain and improved appetite in HIV-infected children, but caution is warranted, particularly when discontinuing or withdrawing therapy.

Dronabinol (Δ^9-tetrahydrocannabinol) is another appetite stimulant that has been used in adult HIV-infected patients. It was approved for use in the United States in 1986 for treatment of chemotherapy-induced nausea and vomiting, although it was found to stimulate appetite as well. A randomized, placebo-controlled study of dronabinol was performed on 139 patients.[113] Appetite stimulation, measured by visual analog scale, was maintained or increased in patients receiving dronabinol. After at least 2 months of treatment with dronabinol, 38% of patients gained greater than or equal to 2 kg of weight. Altered mental status was the primary adverse effect for this medication. Currently, there are no dosing recommendations for children.

Growth Hormone GH is being used as a therapeutic agent to improve lean body mass and weight in HIV-infected patients. It improves nitrogen balance, is anabolic, improves serum protein levels, and promotes lipid mobilization and protein synthesis in burn and postoperative patients. Because it appears that fat oxidation is inappropriately suppressed, at the expense of glucose and amino acid oxidation, recombinant human GH (rhGH) is starting to be evaluated in both the adult and the pediatric HIV populations. Heijligenberg and colleagues examined 24-hour GH and IGF-I levels in eight asymptomatic HIV-infected men, eight clinically stable AIDS patients, and eight healthy controls.[114] No differences were demonstrated in 24-hour GH profiles or IGF-I levels among the three groups, suggesting that HIV disease per se does not affect the GH-IGF-I axis. In contrast, profound abnormalities in GH have been demonstrated among patients with AIDS wasting.

Mulligan and colleagues studied the anabolic effects of rhGH in patients with wasting in six HIV-positive men, with an average weight loss of 19%, and six healthy HIV-negative, weight-stable controls.[115] Weight increased promptly and progressively and urinary nitrogen excretion decreased during treatment with GH. REE increased, protein oxidation decreased, and lipid oxidation increased during treatment. There was increased glucose flux and moderate increases in fasting plasma triglyceride, glucose, and insulin levels. Thus, short-term human GH treatment increased protein anabolism and sparing, as well as lipid oxidation effects, which should increase body cell mass with chronic therapy.

Subsequently, Schambelan and colleagues conducted a longer-term, randomized, placebo-controlled study in 178 HIV-infected patients with the wasting syndrome.[116] Over 12 weeks, weight and lean body mass increased significantly in the rhGH-treated patients compared with the placebo-treated patients. In contrast, total body fat decreased significantly in rhGH- versus placebo-treated patients. Total body water increased by 6% and accounted for a substantial portion of the increase in FFM in GH-treated patients. Furthermore, side effects of arthralgias and myalgias, including carpal tunnel syndrome, were seen significantly more often in patients treated with GH compared with placebo (50% versus 35%). Numerous other therapies have been employed to initiate weight gain in patients with HIV infection. These include essential fatty acid supplementation (n-3 fatty acids), specific vitamin and antioxidant replacements, pancreatic enzymes, testosterone replacement, and cytokine inhibitors such as pentoxifylline and thalidomide. As well, studies are under way evaluating the effects of exercise and aerobic training in patients with HIV infection. Unfortunately, there are no therapies discovered to date that universally prevent or reverse nutritional derangements in HIV-infected patients.

Malnutrition has historically been the condition that has been most prevalent and targeted for treatment in children with HIV infection in developed countries. However, a syndrome of fat redistribution and lipid and glucose abnormalities, referred to as "lipodystrophy," has been identified among increasing numbers of HIV-infected patients receiving potent combination antiretroviral therapy. This syndrome, which is discussed below, has been recognized in children as well and may pose an important challenge in the nutritional and metabolic management of children living with HIV/AIDS in the future.

HIV-ASSOCIATED LIPODYSTROPHY

Shortly after the widespread introduction of HAART, a constellation of metabolic abnormalities and changes in body fat distribution were recognized among many HIV-infected patients (Table 38-5).[117–119] The loss of subcutaneous fat stores and increased adiposity of the abdomen and dorsocervical fat pad were reminiscent of congenital and acquired forms of lipodystrophy, and this term has been used in the HIV population. Although the exact cause of these metabolic and body composition changes has not been identified, there is increasing evidence that both protease inhibitors and NRTIs contribute directly to this lipodystrophy syndrome.[120–122]

In addition to significant and often disturbing changes in fat distribution, patients may develop hypertriglyc-

TABLE 38-5 Clinical and Biochemical Abnormalities Associated with the Lipodystrophy Syndrome in Children

Clinical Features	*Laboratory Features*
Increased abdominal (visceral) fat	Hyperlipidemia
Increased waist-to-hip ratio (not reliable in growing children)	Increased triglycerides
Buffalo hump	Increased total cholesterol
Fat atrophy	Increased low-density lipoprotein
Wasting of extremities	Decreased high-density lipoprotein
Wasting of buttocks	Insulin resistance
Loss or thinning of facial fat, prominence of nasolabial fold	Normal to increased serum glucose
No change to increased weight	Increased insulin
Fatigue and weakness	Increased C peptide
	Decreased glucose tolerance/insulin resistance

eridemia, insulin resistance, and diabetes. In a study of patients (n = 71) presenting with complaints of fat redistribution, Hadigan and colleagues found increased prevalence of hypertriglyceridemia (> 200 mg/dL) low high-density lipoprotein cholesterol (<35mg/dL), impaired glucose tolerance, and diabetes compared with age-, sex-, and BMI-matched control subjects from the Framingham Offspring Cohort.[119] Investigation is ongoing to determine precisely how antiretroviral medication(s) and other factors may contribute to lipodystrophy. In addition, preliminary studies show that the use of lipid-lowering therapies and insulin-sensitizing agents may help ameliorate the metabolic complications of lipodystrophy.[123–125] The long-term effects of insulin resistance, hyperlipidemia, and fat redistribution remain unknown, but there is considerable concern for increased cardiovascular disease risk in patients affected by HIV-associated lipodystrophy.

Several studies have been conducted to evaluate whether pediatric patients with HIV infection receiving HAART are also experiencing changes in body fat distribution or metabolic abnormalities. Arpadi and colleagues assessed body fat distribution in 28 prepubertal HIV-infected children with DXA scans and 29% had evidence of lipodystrophy (defined as fat atrophy and trunk fat accumulation).[126] The presence of lipodystrophy was positively associated with PI use (OR 7.0) and stavudine use (OR 9.0) in this population. In a similar cross-sectional study, Jaquet and colleagues identified lipodystrophy (defined as subcutaneous fat atrophy and/or truncal adiposity) in one-third of the HIV-infected children evaluated.[127] There was a trend toward a statistically significant increase in fasting insulin levels in those children with lipodystrophy but no association with PI use or exposure to other antiretroviral agents. Other studies comparing children exposed to PIs and PI-naive children show increased levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides with PI use.[128,129] Clearly, more research is needed to determine the effects of HAART on fat redistribution, lipids, and glucose homeostasis in children, particularly given the potential lifelong exposure to HAART, which may be required for HIV viral suppression. In addition to the potential increased risk of diabetes and cardiovascular disease, children may also experience as yet unappreciated abnormalities in pubertal development and bone health in relation to metabolic complications of HIV and lipodystrophy.

CONCLUSION

Great strides have been made over the past two decades regarding the detection, prevention, and virologic treatment of HIV in childhood, with the basic understanding of the interaction between nutritional status and HIV becoming better understood. The cause of nutritional problems in patients with HIV-1 infection is complex and likely multifactorial. It is clear, however, that malnutrition of HIV-infected children is among the most serious, chronic, and difficult to treat problems confronting clinicians caring for HIV-infected children, especially in developing countries. Clinicians should be aware of nutritional problems, and close surveillance on nutrition should be conducted on all children who are at risk for HIV infection. Early, aggressive nutritional interventions are indicated. As a treatment strategy, improving nutritional status of HIV-infected children may improve clinical outcome.

Although the incidence of malnutrition in developed countries has decreased with HAART therapy, other metabolic problems can arise. The long-term risks of HAART on HIV-1-infected children are unknown. Close surveillance for the emergence of insulin resistance, dyslipidemias, and premature cardiovascular disease will be important as children with perinatally acquired HIV-1 age into adulthood. Further investigations on the short- and long-term nutritional and metabolic effects of HAART therapy are needed. Investigators should continue to study the effects of oral hyopglycemic agents, lipid-lowering medications, and health-style changes on cardiovascular risk factors for HIV-infected children with lipodystrophy.

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CHAPTER 39

EXOCRINE PANCREATIC DISEASE INCLUDING CYSTIC FIBROSIS

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Exocrine pancreatic diseases (EPDs) associated with maldigestion and malabsorption of both macro- and micronutrients are common causes of acute and chronic malnutrition in tertiary pediatric referral populations. They are characterized clinically by excessive fecal losses of undigested fat and protein, with resultant oily stools and, in some, severe hypoproteinemia with edema. Descriptions of patients with "bacon fat" or "melted butter" stools are commonplace and serve to emphasize the excessive fat and energy losses, which can exceed 50% of the fat/energy ingested.[1] It is not surprising that with such losses, undiagnosed or untreated patients with these disorders present with variable degrees of and often severe undernutrition and require careful investigation and treatment. This chapter highlights the variety of disorders associated with EPDs in childhood, their pathophysiology, nutritional consequences, and an approach to their investigation and management from a nutritional perspective.

EXOCRINE PANCREATIC DISEASES IN CHILDHOOD

Following the original reports describing the pathology of cystic fibrosis (CF) of the pancreas,[2,3] a variety of inherited and acquired EPDs of childhood have been described, as per Table 39-1. Of the inherited disorders, CF is the most common, occurring in 1 in 2,500 to 1 in 4,000 live births,[4] with Shwachman-Diamond syndrome (SDS) estimated to be on the order of 1 in 10,000 to 1 in 100,000.[5–7] The other inherited disorders are rare, with only isolated anecdotal reports.[8–11] Of the acquired disorders, the incidence of tropical calcific pancreatitis and pancreatic disease owing to protein-energy malnutrition is essentially unknown, but one would suspect that they are among the most common EPDs in children worldwide.

Although many of the disorders are rare, elucidation of the underlying mechanism of the disorder or assessing the influence of an isolated enzyme/coenzyme deficiency on digestion, for example, has contributed to the understanding of normal physiology of the exocrine pancreas, the pathophysiology of pancreatic diseases, and the process of normal digestion. SDS, for instance, is associated with lipomatosis of the exocrine pancreas and acinar cell hypoplasia, with preservation of the ductal system. This "ductal model" of the exocrine pancreas has provided ductal fluid and electrolyte secretion data during pancreatic stimulation tests for comparison with similar data from CF patients.[12,13] The latter were known to have poor fluid and electrolyte secretion in response to secretin,[14] but it was unknown as to whether this was related to destruction of pancreatic tissue or to the underlying fluid and electrolyte secretion deficit in CF. Careful comparison of data from the CF and SDS control populations demonstrated a similar decline of fluid and electrolyte secretion with a decline in acinar function in both populations, indicating that pancreatic destruction did contribute to the impaired fluid and electrolyte secretion in CF.[12,13] However, the data also demonstrated that for any level of acinar function, the CF patients had significantly lower HCO_3^- and Cl^- secretion,[12,13] thus indicating that the underlying epithelial secretion deficit in CF was a major factor contributing to the impaired fluid and electrolyte secretion observed during pancreatic stimulation tests. The discovery of isolated colipase deficiency has also helped our understanding of normal fat digestion. In vitro, pure pancreatic lipase activity is completely inhibited in the presence of supramicellar concentrations of bile acids normally found in duodenal contents.[15,16] The heat-stable cofactor colipase, with a mol-

TABLE 39-1 Exocrine Pancreatic Disorders in Childhood

Inherited
Cystic fibrosis
Shwachman-Diamond syndrome
Pearson's pancreas/marrow syndrome
Johanson-Blizzard syndrome
Pancreatic agenesis
Hereditary pancreatitis
Isolated enzyme deficiencies
Trypsinogen
Lipase
Lipase/colipase
Enterokinase
Acquired
Malnutrition
Tropical calcific pancreatitis (possible genetic defect present)
Chronic pancreatitis

ecular weight of 10,000, however, relieves this inhibition,[17,18] and lipase is activated in a linear fashion with increasing concentrations of colipase activity. Absence of colipase impairs lipase activity and fat digestion, as subsequently demonstrated in vivo in patients with inherited colipase deficiency or in CF or SDS patients with relative colipase deficiency.[19,20]

MOLECULAR BASIS/PATHOPHYSIOLOGY OF ENDOCRINE PANCREATIC DISEASES (EPDs)

The molecular basis for many of the inherited diseases, for instance, CF and inherited pancreatitis, has been found over the last decade, and one would anticipate that similar data will be forthcoming with the other disorders, for example, SDS, in the near future. The following is a summary of the recent developments.

Cystic Fibrosis

The cystic fibrosis transmembrane conductance regulator gene (*CFTR*) was located on the long arm of chromosome 7 in 1989.[21,22] The gene product, the CFTR protein, was subsequently demonstrated to be a cyclic adenosine monophosphate (cAMP)-dependent chloride channel on the apical membrane of the epithelial cells.[23] There are now at least 1,000 *CFTR* mutations described in CF patients, and the majority would be regarded as rare or personal mutations. The most common, ΔF508, is found on 70% of CF chromosomes or 90% of the alleles of patients of mid- and northern European origin, with 50 to 55% being ΔF508 homozygotes, 35 to 40% ΔF508 compound heterozygotes, and 5 to 10% non-ΔF508 compound heterozygotes.[24] In southern European and other Mediterranean populations, ΔF508 is less common, occurring on 50% of CF chromosomes in white southern Europeans and only 30% of chromosomes of Ashkenazi Jewish patients.[25,26]

As per Table 39-2, *CFTR* mutations have been categorized into five classes according to defects in the biosynthesis and function of the mutated CFTR protein.[27]

In Classes I and II, the mutated CFTR protein fails to localize in the cell membrane, and in Class III, although located in the cell membrane, channel function is very impaired. In Classes IV and V, the CFTR protein locates appropriately in the cell membrane. However, in Class IV, conductance of Cl^- is reduced, and in Class V, although Cl^- conductance is normal, the splice mutations result in a reduction of the amount of CFTR protein produced, thus effectively reducing net Cl^- transport.

The above classification of *CFTR* mutations reflects not only the defects in biosynthesis, insertion into the cell membrane, and Cl^- conductance but also some of the phenotypic features of CF. Of specific importance is the correlation with pancreatic phenotype. The latter includes pancreatic-insufficient (PI) patients who have fat malabsorption and those who are pancreatic sufficient (PS) with sufficient endogenous enzyme production to produce normal fat absorption.[20] In any large CF population, 80 to 90% of patients are PI and 10 to 20% PS.[28] The PI patients usually have two of the Class I, II, or III mutations (so-called "severe" mutations, examples of which are ΔF508 homozygotes, ΔF508 compound heterozygotes with another severe non-ΔF508 mutation). In contrast, PS patients have at least one of the Class IV or V mutations (so-called "mild" mutations), noting that even if combined with a severe mutation, for example, ΔF508/R117H, the mild mutation R117H appears dominant and confers the milder disease.[29,30]

As indicated above, in vivo pancreatic secretion studies in CF have demonstrated that CF patients have impaired pancreatic HCO_3^-, Cl^-, and fluid secretion, and these changes are present irrespective of the degree of glandular destruction.[12,13] How mutations of *CFTR* influence these changes is not entirely clear. Previously, one model suggested that *CFTR* mutations impaired cAMP-stimulated acinar-ductal Cl^- secretion and luminal Cl^- concentration was low.[31] Low luminal Cl^-, in turn, did not drive the Cl^-/HCO_3^- exchanger; thus, ductal HCO_3^- secretion was also impaired. However, in normal duct cell models, secretin-driven HCO_3^- secretion occurs in the absence of luminal Cl^- and possibly occurs by a conductive pathway.[32] Moreover, others have shown that HCO_3^- accumulates in normal ductal cells via a basolateral cell membrane Na^+–$nHCO_3^-$ cotransporter, which is dependent on the electrogenic gradient owing to membrane depolarization caused by CFTR cAMP-dependent Cl^- secretion on the luminal apical cell membrane.[33] *CFTR* mutations interfere with Cl^- secretion, membrane depolarization, and thus HCO_3^- entry and secretion from the cell.

Although the mechanisms of impaired Cl^- and HCO_3^- pancreatic ductal secretion are the subject of intense investigation, the ultimate effect is inadequate alkalinization of pancreatic duct contents. In a CF mouse model, the latter has been shown to interfere with the normal endocytosis of zymogen granule membranes and the solubilization of zymogen granule–associated proteins, including glycoprotein 2.[34] This leads to dilatation of the lumen and accumulation and aggregation of glycoprotein 2 and is consistent with the known early pancreatic pathology in CF humans, that is, duct protein accumulation and obstruction, with inflammatory changes proximal to the obstruction and

TABLE 39-2 Classification of *CFTR* Mutations Reflecting Biosynthetic Defects and Function

Class I
Defective protein production
Frameshift and nonsense mutations
Unstable messenger ribonucleic acid
Class II
Defective *CFTR* processing; includes ΔF508 as most common mutation
Class III
Defective regulation of *CFTR*
Mutations can dramatically impair channel function, G551D
Class IV
Defective channel conduction, eg, R117H
Class V
Abnormal splicing of *CFTR*
Partial or complete reduction of channel function, eg, 2789+5G to A

subsequent acinar and small duct destruction and replacement by fibrofatty tissue.

Non-CF Disorders

The molecular pathogenesis of several of the non-CF pancreatic diseases has been investigated over the last decade, including SDS, Pearson's pancreatic marrow syndrome (PPMS), pancreatic agenesis, and hereditary pancreatitis. Preliminary work suggests that the gene for SDS is near the centromere on chromosome 7.[35] It is hoped that further work in this area will define the gene and its product and identify mutations specific for SDS. Correlation of specific mutations with the phenotypic features will be of significance, particularly if some mutations are associated with bone marrow malignancy. Mitochondrial DNA basepair deletions have been demonstrated in PPMS,[36] and a single case of pancreatic agenesis has been associated with a single-nucleotide deletion within codon 63 of the insulin promoter factor gene at 13q22.1.[37] Of equal interest, mutations in the cationic trypsinogen gene at chromosome 7q35 have been identified in the autosomal dominant disorder hereditary pancreatitis.[38] Continuing work elucidating the molecular basis for these disorders should also help to unravel the mechanisms of how the defects lead to the specific disease and also provide specific diagnostic tests for each of these disorders.

From a functional perspective, SDS, PPMS, Johanson-Blizzard syndrome (JBS), and pancreatic agenesis can all be associated with PI. Unlike CF, ductal function appears to be well preserved, but acinar cell hypoplasia is predominant. Both SDS and JBS patients can have severe lipomatosis of the pancreas, but PPMS patients appear to have extensive pancreatic fibrosis in association with their severe sideroblastic anemia.

CLINICAL MANIFESTATIONS

Although PI is common to all of the EPDs and is associated with macro- and micronutrient deficiencies, many of the disorders are multisystem diseases and have nutritional complications owing to nonpancreatic involvement, for instance lung, liver, and gut disease in cystic fibrosis; bone marrow disease in both SDS and PPMS; developmental delay in JBS, SDS, and PPMS; and diabetes mellitus in CF and pancreatic agenesis. The following text highlights those complications with nutritional implications for CF and non-CF disorders.

Cystic Fibrosis

The major manifestations of cystic fibrosis are outlined in Table 39-3. Although most are gastrointestinal/hepatic in origin, such complications, except for liver failure, portal hypertension, or surgery for meconium ileus, rarely are life threatening. In contrast, pulmonary disease accounts for over 90% of the mortality and is the major cause of morbidity and hospitalization in this disorder.

Pulmonary Disease CF lung disease is characterized by thick tenacious secretions obstructing the bronchial tree, recurrent suppuration, the development of bronchiectasis, severe lung fibrosis with cyst formation/emphysema, and, terminally, respiratory failure. The presentation and course of the pulmonary disease vary considerably among individual patients with CF, with some developing severe disease during their childhood years and others with relatively mild disease persisting into their adult years.[39] In the modern era, many factors contribute to this variability, including early diagnosis and institution of chest therapy with antibiotics, nutritional status, *Pseudomonas* lung colonization, the emergence of antibiotic-resistant infections, the cross-contamination of patients with infections, and the genetic variability of the disease. In regard to the latter, PS patients exhibit better preservation of lung function, maintaining an average near-normal lung function to age 30,[28] and have a median survival into the midfifties. On the other hand, PI patients suffer significant deterioration of lung function during their early adult years, and median survival is only into the thirties. The greater survival of the PS patients is likely related to their "mild" genotypes, and although the more severe disease in the PI group is at least

TABLE 39-3 Clinical Manifestations of Cystic Fibrosis

Pulmonary disease
Recurrent infections
Staphylococcus
Pseudomonas
Burkholderia
Fungal
Bronchiectasis
Lung fibrosis
Pneumothorax
Emphysema
Respiratory failure
Pancreatic disease
Pancreatic insufficiency
Pancreatic sufficiency ± pancreatitis
Gut disease
Gastroesophageal reflux
Esophagitis
Giardiasis
Celiac disease
Neonatal meconium ileus
Distal intestinal obstruction syndrome
Intussusception
Appendicitis
Appendiceal mucocele ± abscess
Fibrosing colonopathy
Crohn's disease
Fecal retention, megacolon
Rectal prolapse
Ileocecal adenocarcinoma
Biliary tract/liver disease
Microgallbladder
Nonfunctioning gallbladder
Obstructed cystic duct
Cholelithiasis
Common bile duct stenosis
Common bile duct stones
Hepatosteatosis
Focal biliary fibrosis
Multilobular biliary cirrhosis ± portal hypertension

partly contributed to by their "severe" genotype, the large variation in lung disease and progression at any one age in this group suggest that other factors, including environmental and nutritional, contribute to this variation.[40]

Lung disease per se can contribute to the development of malnutrition. Recurrent infections, antibiotic therapy, and severe pulmonary dysfunction are anorexigenic. Severe disease with recurrent coughing can also exacerbate gastroesophageal reflux with esophagitis and further impair appetite. These interdependent effects may not only prevent the patient from achieving recommended high energy intakes but may also reduce the energy intake below that recommended even for normal subjects.[41] Equally important, lung disease, lung infections, inflammatory mediators, and drugs (eg, β-agonists) can substantially increase energy expenditure in excess of 20% above normal energy expenditure in a large number of patients.[42–44] This energy "wasting" is a significant factor interfering with the maintenance of normal nutritional status in CF and becomes even more critical in patients with anorexia.

Gut and Liver Disease CF patients can experience a wide variety of gut and liver complications, as outlined in Table 39-3. Gastroesophageal reflux disease (GERD) with esophagitis occurs in at least 10% of the population.[45] Of importance, some patients will admit only to symptoms of water brash and heartburn on direct interrogation. Many will have anorexia and weight loss, and, in some, these may be the only presentation of their esophagitis. The presence of the typical symptoms or unexplained anorexia and weight loss should alert the physician to the possibility of GERD, and investigations, including contrast radiology and endoscopy, should be considered. Conservative therapy with proton pump inhibitors usually provides a considerable improvement in symptomatology, including appetite, and if not, surgical intervention with laparoscopic fundoplication could be necessary depending on the severity of lung disease.

Patients with distal intestinal obstruction syndrome (DIOS), gallstones, or common bile duct disease present with recurrent abdominal pain postprandially and may restrict their dietary intake to alleviate their pain. DIOS should be apparent clinically with a mass palpable usually in the right iliac fossa. Radiologic examination is mandatory to confirm the diagnosis, and abdominal ultrasonography is necessary to exclude complex disease, including associated intussusception or appendiceal disease. Lavage therapy with the polyethylene glycol–containing colonoscopy lavage solutions (eg, Golytely, USA; Colonlytely-Dendy, Victoria, Australia; Glycoprep, Pharmatel, Thornleigh, Australia) is required to wash out the impacted fecal masses. Failure of this therapy should initiate further investigation, including contrast radiography and/or colonoscopy, to exclude other diseases, including fibrosing colonopathy, Crohn's disease, and, in the adult patient, colonic/ileal malignancy. Patients with biliary tract disease and biliary colic will require abdominal ultrasonography to exclude cholelithiasis and biliary tract dilatation and hepatobiliary scintigraphy to screen for bile duct stenosis.[46,47] Persistent pain with associated weight loss and deterioration of liver function tests may necessitate further imaging with contrast cholangiography or magnetic resonance imaging cholangiography prior to possible surgical intervention.[46]

Some small intestinal diseases, including giardiasis and celiac disease, can contribute to the nutritional problems of CF patients as they can induce anorexia and exacerbate problems with diarrhea and malabsorption. In one study using a fecal antigen test, 30 of 107 (28%) CF patients tested positive for *Giardia*.[48] The positivity increased with age, with 44% of those over 20 testing positive for the antigen in contrast to the controls, of whom 11% under 5 years of age and none over 10 years were antigen positive. Single-stool microscopy confirmed the presence of *Giardia* cysts in 44 and 43% of the CF and control groups, respectively, proportions that are not dissimilar to those in comparison with small bowel biopsy results. Although giardiasis most commonly causes a watery diarrhea in non-CF patients, it can be associated with steatorrhea and also severe protein malabsorption and hypoproteinemia. Considering these findings and the suggested increased susceptibility of CF patients to acquire giardiasis in the above study, CF patients experiencing diarrheal symptoms outside of their normal bowel movement pattern should be investigated further and treated appropriately with metronidazole.

Celiac disease is an alternative diagnosis for patients with anorexia, persistent steatorrhea, or deterioration of bowel movement pattern despite compliance to adequate enzyme therapy. It has been documented in CF adults with a prevalence of 1 in 1,258 in a US survey[49] and may be even higher in European communities, where screening of non-CF populations suggests prevalence rates of > 1 in 100.[50] As yet, there are no studies confirming the reliability of antiendomysial antibody testing in CF populations, and small bowel biopsy remains the gold standard test for this disorder. Given the similarity of symptoms of CD with giardiasis, small bowel biopsy would be the ideal test to prove or exclude these complications in the absence of optimal noninvasive tests.

Since the early 1990s, a new entity, fibrosing colonopathy, has been described in CF patients.[51] Pathologically, there are extensive areas of noninflammatory fibrosis affecting the lamina propria, causing bowel wall thickening and long fusiform strictures in the ascending, transverse, and/or descending colon. Clinically, patients can present with intestinal obstruction, abdominal pain, anorexia, weight loss, and/or chylous ascites and may require surgical intervention to alleviate the obstruction.[52] Two case-control studies have attributed fibrosing colonopathy to the use of high-dose lipase preparations and the ingestion of enzyme dosage in excess of 20,000 U of lipase/kg/day or in excess of 6,000 U of lipase/kg/meal; thus, current recommendations encourage patients to restrict their total daily dose to < 10,000 U of lipase/kg of body weight.[53,54]

Pancreatic Disease As indicated in the introduction, there are two pancreatic phenotypes in CF, namely PI and PS, based on the presence of fat malabsorption (a fecal fat > 7% of fat intake) and normal fat absorption (fecal fat ≤ 7%

of fat intake). This terminology arose out of quantitative pancreatic stimulation test studies in children and young adults with CF or SDS, demonstrating that PI patients had less than 1 to 2% of normal pancreatic colipase/lipase secretion, respectively, and PS patients from 1% to within the control range (over 50% of average normal colipase/lipase secretion),[20] that is, PI patients had insufficient endogenous enzyme secretion to prevent fat malabsorption and PS patients had sufficient enzyme secretion to give normal fat absorption. Whereas in older childhood and adult populations, PI patients comprise 80 to 90% of the patients,[28] in newborn screened populations, 60 to 70% are PI and 30 to 40% PS.[55] The latter reflects preservation of exocrine acinar function in the younger population and deterioration of pancreatic function in some PS patients who ultimately become PI. This phenomenon accounts for the presentation of some PI patients in nonscreened populations during later childhood. Patients in this category (PS to PI) in general have "severe" pancreatic genotypes, but one should be aware of the occurrence of recurrent pancreatitis in those with "mild" genotypes and that recurrent pancreatitis could induce PI during their adolescence or adult years.[56]

Untreated patients with PI have average fecal fat losses of 40%, but they can exceed 50% of fat intake.[1] Nitrogen losses are also excessive, with some reaching 50% of nitrogen intake.[57] The wide range of fat malabsorption evident in PI patients is largely unaccounted for. Some of the variability (fecal fat from 10 to 25% of fat intake) is accounted for by the decline in residual enzyme/cofactor secretion, that is, from < 1 to < 0.5% of enzyme secretion.[20] However, the increase of fecal fat above the 25% level is enigmatic. It may relate to the variable output of nonpancreatic pregastric lipases,[20] duodenal bile salt concentrations,[58] or the interference of nonhydrolyzed phospholipids on triglyceride digestion.[59] Irrespective of this variation, the nutritional consequences of these losses, as outlined in Table 39-4, are evident in patients from nonscreened populations and include wasting, stunting, hypoproteinemia, and essential fatty acid (EFA) deficiency with a seborrheic dermatitis. Associated fat-soluble vitamin deficiencies may contribute to early morbidity.

In terms of management, it is essential to determine the pancreatic phenotype and thus the necessity or otherwise for oral pancreatic enzyme replacement therapy (OPERT). In this regard, the time-honored gold standard test is a 3- to 5-day fat balance study with measurement of weighed dietary fat intake and fecal fat output and expression of the latter as a percentage of the former. The test provides reliable and accurate data, as evident by comparison with pancreatic stimulation test data.[20] It allows longitudinal follow-up of individual patients in assessing and reassessing response to OPERT and for the presence of other intestinal disease that may exacerbate fat malabsorption. As such, it has been an ideal investigative tool, particularly in determining the efficacy of OPERT. Unfortunately, many laboratories and clinics do not undertake fat balance studies as handling fecal material is unesthetic, undesirable, and potentially hazardous.

Consequently, there has been a proliferation of tests, including serum measurements of pancreatic enzymes, for example, trypsinogen, the PABA (para-aminobenzoic acid) test, and ^{13}C triglyceride–labeled breath tests. Others have used spot fecal samples for measurements of pancreatic enzymes, including chymotrypsin and fecal elastase (FE-1). Sensitivity and specificity of ^{13}C-labeled breath tests for assessing PI and PS are high at over 90% but are noninformative regarding the degree of steatorrhea in PI patients or the degree of residual pancreatic function in PS patients. FE-1 has been touted as a simple test with ease of collection and performance on spot fecal samples.[60] However, until recently, the vast majority of the patients studied were PI CF patients or normal subjects, and little was known regarding other childhood pancreatic or intestinal disease.[61,62] Nevertheless, in non-CF adults with chronic pancreatitis, FE-1 was more sensitive and specific and had higher practicability and lower cost than the ^{13}C mixed-triglyceride breath test for assessing pancreatic function.[63] A recent publication has evaluated FE-1 in PI and PS of CF and non-CF origin and in patients with intestinal diseases alone in comparison with controls.[64] The test had a sensitivity of 98% and specificity of 93.6% to identify patients with steatorrhea owing to PI with a positive predictive value

TABLE 39-4 Nutritional Consequences of Pancreatic Insufficiency

Protein maldigestion and malabsorption	
Creatorrhea	
Hypoproteinemia	
Edema	
Fat maldigestion and malabsorption	
Steatorrhea	
Wasting	
Stunting	
Increased fecal bile acid losses	
Cholelithiasis	
Phospholipid maldigestion and absorption	
Impaired triglyceride hydrolysis	
Impaired bile acid reabsorption	
Essential fatty acid deficiency	
Seborrheic dermatitis	
Thrombocytopenia	
Poor wound healing	
Micronutrient malabsorption	
Vitamin A	
Raised intracranial pressure in infants	
Night blindness	
Corneal and conjunctival xerosis	
Bitot spots	
Vitamin D	
Rickets	
Osteomalacia	
Vitamin E	
Infants	Hemolysis
Older children	Loss of deep tendon reflexes
	Peripheral neuropathy
	Spinocerebellar degeneration and ataxia
	External ophthalmoplegia
Vitamin K	
Coagulopathy	
Salt depletion in cystic fibrosis patients	

of 89.9% and a negative predictive value of 99%. Sensitivity and specificity in CF patients in predicting PI were both 100%, but noteworthy among the PS non-CF group, 30% had low FE-1 (< 100 μg/g stool). The latter was similar to one of the large original adult studies in non-CF patients with chronic pancreatitis in which in a group classified as having moderate pancreatic disease (approximately less than 25% of normal enzyme secretion on pancreatic stimulation tests with normal fat absorption), over 50% had low FE-1 < 100 μg and would have been misclassified as PI on the basis of the FE-1 alone.[65] Clearly, however, the results in the CF population are encouraging but less so in the non-CF group with pancreatic disease. One should be aware that FE-1 has not provided information to date on the degree of residual function in PS patients and cannot be used as a specific guide as to the efficacy of enzyme therapy.

OPERT is required for patients with proven PI. There is no current evidence that OPERT is efficacious for PS patients who maintain normal digestion and absorption owing to their own endogenous enzyme production. OPERT has changed substantially over the last two decades. Prior to 1980, the delipidated porcine pancreatic powder was administered either directly as the powder mixed with food or in gelatin capsules. Efficacy in most patients was poor, reducing average fat excretion from 40 to 25 to 30% of fat intake and often with excessive doses capable of causing hyperuricemia. The lack of efficacy was shown in both non-CF and CF patients to be related to gastric acid pepsin destruction of enzymes, which could be alleviated by adjunctive therapy with gastric acid suppression. Subsequently, the microspheric preparations were developed and marketed. These products have an outer gelatin capsule containing multiple microspheres, which contain the enzyme powder. The microspheres have an outer pH-sensitive coating resistant to acid dissolution but soluble in an alkaline environment and thus should pass through the stomach and into the small intestine before they dissolve and release their enzyme contents. In studies of mainly older children and adolescents, that is, > 30 kg in body weight, increasing doses to a maximum of 25 to 30 standard 5,000 IU lipase-containing capsules improved steatorrhea to an average 12 to 15% of fat intake, with 40 to 50% of patients having a fecal fat < 10% of fat intake.[66–68] We have thus used a regimen of one capsule (5,000 IU) of lipase/kg of body weight/day to a maximum of 30 capsules/day and have demonstrated normal growth from early infancy to late childhood with this regimen.[55,69] Others adhere to the more complex regimen of providing an enzyme dose per gram of fat ingested. Whether this will be advantageous in the long term remains to be proven, but provided that the enzyme dose is kept below 10,000 U lipase/kg/day and preferably below 5,000 IU lipase/kg/day, then safety is reasonably ensured in terms of developing fibrosing colonopathy.

Other Pancreatic Diseases

The above discussion of pancreatic dysfunction is also relevant to the non-CF pancreatic diseases. Specific features of these diseases are described in Table 39-5. In addition to maldigestion and malabsorption of nutrients, recurrent infections and antibiotic therapy in SDS, severe sideroblastic anemia and transfusion therapy in PPMS, diabetes in pancreatic agenesis, and developmental delay in JBS may contribute to poor intake and exacerbate undernutrition in these patients. Long-term outcome in the non-CF disorders in the main is unknown given that most of these disorders have been recognized only in the last two to three decades. In SDS, however, there is a known propensity for these patients to develop bone marrow malignancies, such as acute myeloid leukemia, and, currently, research activity is under way to determine factors or markers that may predict this occurrence, including myelodysplasia and the presence of monosomy 7 and isochromosome 7q.[6] An interesting feature of SDS is that although most are PI at diagnosis in the first year of life, up to 50% or more will become PS at a later age.[70] Reasons for this improvement in pancreatic function are unknown, but it will be important to determine if it is mutation related and whether these patients with improving pancreatic function have less of a risk for developing bone marrow malignancy.

NUTRITION IN EXOCRINE PANCREATIC DISEASES

The introductory remarks regarding the various pancreatic diseases emphasize that many are multisystem diseases

TABLE 39-5 Non–Cystic Fibrosis Pancreatic Diseases

Shwachman-Diamond syndrome
Pancreatic acinar cell hypoplasia with lipomatosis
Bone marrow dysfunction
Neutropenia
Thrombocytopenia
Red cell hypoplasia
Myelodysplastic syndrome
Acute myeloid leukemia
Bone disease
Metaphyseal dysplasia
Shortened splayed ribs
Short stature
Miscellaneous
Developmental delay
Eczematous skin lesions
Hepatosteatosis
Renal tubular dysfunction
Pearson's syndrome
Pancreatic fibrosis with pancreatic insufficiency
Severe macrocytic anemia
Vacuolated cells and ringed sideroblasts in bone marrow aspirates
Developmental delay
Johanson-Blizzard syndrome
Pancreatic lipomatosis with pancreatic insufficiency
Aplasia or hypoplasia of alae nasi
Congenital deafness
Hypothyroidism
Short stature
Imperforate anus
Absence of permanent teeth
Pancreatic agenesis
Pancreatic insufficiency
Diabetes mellitus

that interfere with the nutritional status of the patients involved. To date, most of the clinical nutritional research has been directed at CF, and there are large gaps in our knowledge about the nutritional outcomes of the non-CF disorders, at least partly related to their rare occurrence. The following description is thus mostly concerned with the nutritional status of CF patients.

The first reports on growth and nutritional status in CF documented that a large proportion of patients were wasted and/or stunted,[71,72] and through the 1970s, growth failure was regarded as being inherent to the underlying disease process. However, a large cross-sectional study from the Toronto clinic (Royal Alexandra Hospital for Children) in 1980 demonstrated, as per Table 39-6, that over 40% of patients had achieved the 50th percentile for height and only 10% were at or below the 3rd percentile.[73] Males had achieved similar percentiles for weight, but females appeared to be disadvantaged, with 16% being below the third percentile over age 8 years. These data contrasted with other clinics, including our own clinic in Sydney, where 13% of males and 21% of females were stunted over age 8 years and 33% and 42% of males and females, respectively, were wasted.[74] Clearly, the Toronto clinic had demonstrated that they could achieve near-normal linear growth in their patient population; thus, growth failure could not be readily attributed to the underlying disease process. Independent observers suggested that the growth advantage achieved in the Toronto clinic was directly related to their dietary policy, that is, their clinic had adhered to a high-quantity normal-quality diet with at least 40% of the energy intake as long-chain triglyceride,[75,76] in contrast to the more universal policy in other clinics of using a low-fat diet to control malabsorption. Energy intakes on low-fat diets averaged 80% of the Recommended Dietary Intake (RDI) for energy compared with the 113% achieved on the higher-fat diet in Toronto.[41,76,77] Subsequently, others demonstrated improvement in growth parameters over the short term with reversal of the low-fat diet policy.[78] We have also observed an improvement in growth at our own clinic over a 10-year period following a change of dietary policy with a major increase in the fat content of the diet, with a marked improvement in both linear growth and weight, particularly in the female population, as seen in Table 39-6. These data provided further evidence supporting the concept that growth failure in CF was nutritionally related and could be reversed and improved with the consumption of a high-energy, normal-quality, fat-containing diet.

Significantly, in 1980, the Toronto clinic also reported median survival of their population to the early thirties, and this was at least 10 years in advance of survival reported by other Canadian and US clinics.[73] These data suggested that as the only difference between the Toronto and other clinics was their nutritional policy and outcome, then these could be major factors contributing to the difference in survival. Subsequently, a direct comparison between the Toronto clinic with a "high-fat" diet policy and the Boston clinic with a "low-fat" diet policy demonstrated a near 10-year survival advantage to the Toronto patients, although average spirometric lung function parameters at 20 years were virtually identical.[79] Most clinics have now reversed their dietary policy to emulate the Toronto clinic and have not only shown improvement in growth but also an improvement in median survival to the late thirties and early forties.

Longitudinal growth studies for most non-CF diseases are not available, except in SDS. The latter appear to maintain a normal linear growth velocity but usually at or below the 3rd percentile throughout childhood.[80] The linear growth percentile does not increase with the institution of OPERT, and this suggests that short stature in SDS is inherent to the disease and possibly related to the underlying bone complications.

TABLE 39-6 Comparison of Height and Weight Data between RAHC and the Toronto Clinic in 1984 and RAHC Data from 1994*

		RAHC		*Toronto*	
	Gender	*< 8 Yr*	*≥ 8 Yr*	*< 8 Yr*	*≥ 8 Yr*
RAHC vs Toronto in 1984					
Height					
≤ 3rd %ile	Male	9	13	16	6
	Female	6	21	8.5	12.5
≥ 50th %ile	Male	29	41	48	37
	Female	25	29	40	40
Weight					
≤ 3rd %ile	Male	21	33	5	8
	Female	29	42	5	16
≥ 50th %ile	Male	20	22	40	41
	Female	15	18	34	26
RAHC height and weight data in 1994					
Height					
≤ 3rd %ile	Male	0	13		
	Female	7	5		
≥ 50th %ile	Male	33	37		
	Female	43	41		
Weight					
≤ 3rd %ile	Male	0	9		
	Female	4	2		
≥ 50th %ile	Male	29	30		
	Female	32	36		

Adapted from Soutter VL et al.[74]
*Presented as a percentage of male and female patients in each age group.
RAHC = Royal Alexander Hospital for Children.

Nutritional Complications of EPD

The major nutritional complications of EPD are summarized in Table 39-4. These complications are common to all of the diseases except for salt depletion resulting from excessive sweat salt losses in warmer climates in CF patients. The origin of the nutritional complications/deficiencies relates to nutrient balance, that is, whether nutrient intake is adequate for maintenance of normal function and growth in the context of excessive nutrient losses owing to maldigestion and malabsorption or excessive use as observed with elevated energy expenditure in CF.

Macronutrients

Macronutrient intakes have been documented in several studies of CF patients using recall methods, food frequency questionnaires, and weighed diets.[41,75–78] Protein

intakes are usually well in excess of RDI, reaching in one study an average 200% RDI in a group of well-nourished patients and 170% in a malnourished group on relatively low-fat diets.[41] In contrast, as alluded to above, although those on normal-quality diets could achieve energy intakes on average in excess of 110% of recommended,[76] those on low-fat diets consistently averaged only 80 to 90% of their required energy.[41] The latter energy intake for malnourished patients leads to a decline in their nutritional status, with associated wasting and stunting of growth in the longer term. Recovery from the malnourished state is difficult for most as energy intakes may have to reach 150 to 200% of RDI for prolonged intervals for catch-up growth to occur, and usually invasive nutritional support is required to achieve these high energy intakes.[68]

As evident from Table 39-6, although most clinics now have liberalized the dietary fat content, there are still a significant number of CF patients who are wasted in their older years. Many of these patients experience anorexia, which is contributed to by a number of the complications of this disease, as outlined in Table 39-3. Lung, gut, and liver/biliary tract disease; recurrent infections; antibiotic therapy; psychosocial/behavior problems; and micronutrient deficiencies, including salt depletion, can all interfere with appetite, impairing dietary intake. Although lung disease and pulmonary infections manifest clinically, reflux and esophagitis, biliary tract disease, and micronutrient deficiencies may not be clinically obvious and will need to be excluded in the anorexic patient. Equally, patients without obvious physical complications may have psychosocial/behavioral problems and disordered eating behavior, either alone or in combination with physical problems, and thus will require careful investigation and management.[81,82] Equally in the other EPDs, recurrent infections, bone marrow disease with anemia and neutropenia, liver disease, and developmental delay can contribute to impaired nutrient intake.

Macronutrient maldigestion and malabsorption are classic characteristics of PI, leading, as indicated in the introduction, to substantial fat and protein losses from the gut. However, the marketing of microspheric/microtablet forms of OPERT has markedly decreased stool fat and protein losses to, on average, below 15% of nutrient intakes. Thus, in the current era of OPERT, lipase doses of up to 5,000 IU/kg/day should prevent major nutrient gut losses. Notwithstanding these comments, there has been a perceived difficulty in many centers to the use of either powdered preparations or microspheric OPERT in infancy. As a result, the use of medium-chain triglyceride (MCT) semielemental formulas has been advocated in these centers for CF infants as, purportedly, fat absorption was markedly improved with MCT without enzyme therapy.[83,84] However, in both studies, fecal fat was estimated by the Van de Kamer method, which does not measure MCT, so the fecal fats were underestimated. When, in fact, the appropriate technique for measuring fecal MCT was used, it was clearly demonstrated that enzymes were required for MCT digestion, that is, the use of an MCT formula did not obviate the need for OPERT.[85]

Increased energy expenditure also contributes to the negative energy balance in patients with CF. Feigel and Shapiro first demonstrated a doubling of oxygen consumption in cultured fibroblasts from CF patients compared with controls,[86] a finding confirmed by others when studying CF nasal epithelium.[87] Several studies subsequently reported varying elevation of resting (REE) or total energy expenditure (TEE) in CF subjects and suggested that the elevation was related directly to the combination of malnutrition and lung disease.[42–44,88] However, Shepherd and colleagues contended that the increase was intrinsic to the underlying disease as TEE in CF infants seemingly with minimal lung disease was increased when compared with controls.[88] Two studies later disputed these findings.[89,90] Fried and colleagues, in a group of male CF adolescents/young adults with normal lung function, were unable to demonstrate significant differences in REE between two groups with PI and another with PS, and average values were only minimally above (104%) normal predicted values.[89] Furthermore, in a retrospective analysis, they showed a curvilinear relationship between REE and forced expiratory volume (FEV_1), so that as FEV_1 decreased below 75% predicted, REE increased exponentially.[89,91] These findings were also supported by a study of newly diagnosed CF infants, in whom there was no difference in energy expenditure between controls and various genotypic groups of CF infants.[90] However, in the study of Fried and colleagues, there were only nine patients in each of the ΔF508 compound heterozygote PI and PS groups, and the latter demonstrated a near 20% reduction in REE when expressed per fat-free mass, despite having lower average lung function than the PI group.[89] Furthermore, in the CF infant study, the standard deviation among the groups of CF infants varied from 30 to 70% of the average values compared with only 21% in the control group. Values for the PS patients were also not provided; thus, it was difficult to determine whether the CF results were lowered to the normal range by the PS patients' results.

Other studies have disputed these findings. O'Rawe and colleagues demonstrated in three genotypic groups (ΔF508/ΔF508, ΔF508/other, and non-ΔF508/non-ΔF508) average REEs of 121%, 109%, and 104%, respectively.[92] Seemingly, this disproved the above as multiregression analysis did not show a relationship with pulmonary dysfunction. However, average FEV_1 percent predicted was low in the ΔF508/ΔF508 group (56%) and also in the ΔF508/other group (63%), and these data therefore appeared confirmatory of the effect of lung dysfunction elevating REE. In a more recent study of 104 CF patients with both males and females with near-normal lung function (FEV_1 percent predicted 87% and 83% for males and females, respectively) and 131 age-matched controls, REE was highly significantly elevated in CF females, and the average REE in PI patients adjusted for fat-free mass was 110% of the PS value, despite similar pulmonary function.[93] The female disadvantage had been recognized by other investigators.[94] Of importance, these recent studies, although not negating that a large proportion of the increase in REE in CF is contributed to by deteriorating

lung function, do emphasize the significant increase in females and those with the PI phenotype and the necessity for a larger energy intake than normal, even at an early age, in these groups of patients. Further investigation of the gender difference is warranted considering previous reports of a poorer prognosis for CF females.[73]

Essential Fatty Acid Metabolism

EFA deficiency (EFAD) has been well described in patients with CF.[95,96] Clinical deficiency with seborrheic dermatitis, poor wound healing, thrombocytopenia, anemia, and increased propensity for infections may be present in PI infants prior to treatment of PI but is far less evident in older PI patients receiving a normal diet and appropriate OPERT.[97] Older PI patients, however, have subclinical/biochemical deficiencies of blood and tissue EFA levels, particularly showing decreases of linoleic acid and increased palmitoleic, oleic, and eicosatrienoic acids. Although some have suggested that EFAD is a primary abnormality and unrelated to malabsorption,[98] others have suggested that EFAD is evident only in patients with < 5% of normal exocrine pancreatic function and, furthermore, can be improved by optimizing OPERT and dietary intake.[99]

There has been considerable recent interest in EFA metabolism in a CF knockout mouse model without functional *CFTR*.[34] These animals demonstrate an elevated arachidonic acid (AA)-to-docosahexaenoic acid (DHA) ratio in tissue that normally expresses *CFTR*, for example, lungs, pancreas, and small intestine, compared with wild-type controls. Of significance, early dilatation of pancreatic ductules in the CF mouse can be normalized with supplemental DHA and normalization of the tissue AA-to-DHA ratio. In CF humans, the average AA-to-DHA ratio in nasal epithelium and monocytes from PI patients is two to three times that observed in controls, and the same phenomenon was observed in six PS patients, although, in the latter, there was considerable overlap with control data.[100] Further work is currently under way. Priorities include determining the optimal dose and method of delivery and toxicity/safety margins for humans given the high doses required in the knockout mouse. In addition, given that the mouse model has no functional CFTR, one is left to assume that the effect of DHA on improving the pancreatic pathology is by up-regulating alternate chloride and fluid secretion. This aspect also requires further investigation. Until these studies are completed, one would have to caution against routine DHA supplementation of human CF patients.

Micronutrients

Micronutrient deficiencies have been described in EPD, particularly in patients with CF. These have included fat-soluble vitamin deficiencies, vitamin B_{12} deficiency, trace metal deficiencies, and salt depletion.

Fat-Soluble Vitamins Fat-soluble vitamin deficiencies A, D, E, and K are well documented in CF PI patients.[101–110] Most descriptions of deficiencies have occurred in patients prior to diagnosis and commencement of OPERT and in an era where OPERT was suboptimal, that is, prior to microspheric therapy. Clinical evidence of deficiency is unusual in patients on optimal diets and OPERT, although it has been described in noncompliant patients and those with evidence of liver disease. Clinic policies vary considerably regarding vitamin supplementation, although the latter would appear unnecessary in PS patients and PI patients who normalize their fat absorption on OPERT and maintain normal serum vitamin levels and coagulation profiles. Omission of fat-soluble vitamin supplementation in PS patients is certainly reasonable, and, in fact, declining levels in this group are a useful strategy for monitoring pancreatic function and should alert the physician to the development of PI and instigate further investigations.

Vitamin A Infants with vitamin A deficiency may present with a bulging fontanelle owing to benign intracranial hypertension.[101] Older patients present with night blindness, xerophthalmia, corneal xerosis, and ulceration with Bitot spots. Although night blindness is usually associated with very low serum vitamin A levels (< 0.5 μmol/L), subtle impairment of dark adaptation tests was associated with serum levels from 0.2 to 1.4 μmol/L, which overlapped the range in those with normal adaptation of 0.5 to 2.1 μmol/L.

Vitamin D Frank clinical rickets and osteomalacia are unusual phenomena in CF populations,[103] but subclinical/biochemical rickets with low serum 25-hydroxycholecalciferol levels are common in northern hemisphere patients.[104,105] Low 25-hydroxyvitamin D levels are very unusual in patients in Australia, presumably related to year-round exposure to sunlight.

Vitamin E Vitamin E deficiency has been best described in non-CF patients with either persistent cholestasis or in the rare disorder abetalipoproteinemia. Early signs include loss of deep tendon reflexes and impaired position and vibration sensations. Untreated deficiency may be associated with the development of ataxia, tremors, dysarthria, proximal muscle weakness, and external ophthalmoplegia, and these more severe symptoms may have a variable response to vitamin E repletion therapy. In infancy, CF patients may present with a hemolytic anemia and may have concomitant hypoproteinemia and poor weight gain.[111] In screened populations, nearly 40% of infants have low serum α-tocopherol levels, and in some 10%, low levels may persist despite seemingly optimal oral replacement.[112] In older patients and through adolescence, clinical symptomatology and low serum vitamin E levels are unusual, particularly in PI patients with normal absorption on OPERT or PS patients. Regular monitoring of levels with supplementation to maintain levels > 7 to 8 μg/mL would appear appropriate.

Vitamin K Vitamin K deficiency is associated with a coagulopathy and hemorrhagic manifestations. It has been described in CF infants prior to diagnosis and in patients with persistent cholestasis. Monitoring and maintenance of

normal coagulation profiles, particularly in patients with persistent steatorrhea, are appropriate.

Water-Soluble Vitamins Water-soluble vitamins are well absorbed by CF patients. The exception is vitamin B_{12}. Normally, the vitamin B_{12}–intrinsic factor complex is bound to R proteins, and prior to binding to the specific terminal ileal receptors, the R proteins need to be separated from the vitamin B_{12}–intrinsic factor complex. This process requires pancreatic proteases; thus, there is a theoretic possibility that untreated PI CF patients can develop vitamin B_{12} deficiency. This is unlikely to occur in patients receiving optimal OPERT. On the contrary, terminal ileal resection, as could occur in infants with complex meconium ileus, could seriously impair vitamin B_{12} absorption, and such infants may require prolonged parenteral supplementation.

Trace Metals Trace metal deficiencies, particularly zinc and selenium, have been described in CF populations but usually in association with protein-energy malnutrition. Selenium deficiency associated with a cardiomyopathy in non-CF populations is likely a geographic phenomenon as it was not evident in a US CF study but was present in a Scottish study.[113,114]

Salt Depletion Salt depletion owing to excessive sweat salt losses occurs not infrequently in patients residing in or visiting warm to hot climates. Depending on age, activity, and ambient temperature, salt losses can exceed 10 g/day. Whereas the older patient has access to salt, younger patients, particularly infants, are at risk from salt depletion if not receiving appropriate oral salt supplements. Symptoms are nonspecific and include lethargy, anorexia, nausea, and vomiting, but they may rapidly escalate and produce frank signs of dehydration, poor perfusion, and collapse. Gut symptoms with nausea, vomiting, and abdominal distention may predominate as a result of hypokalemia and the ensuing gut dysmotility with paralytic ileus. Patients presenting in this manner may be misdiagnosed as having mechanical intestinal obstruction and may not receive appropriate salt replacement until circulatory collapse ensues. Classically, on measuring serum electrolytes, patients have hyponatremia and hypochloremia but also evidence of hyperaldosteronism with hypokalemia and a metabolic alkalosis with associated tetany. Intravenous salt replacement is usually required to treat symptomatic patients. In patients with evidence of poor perfusion and dehydration, intravenous therapy with a bolus dose of normal saline 10 to 20 mL/kg should be given immediately and replacement therapy continued over the next 4 to 5 hours with normal saline, depending on the patient's response. Potassium can be replaced following establishment of urine flow and monitored by measurement of serum electrolytes. Patients less severely compromised may respond to oral electrolyte solutions or simple oral salt replacement, but if nausea and vomiting prevail, intravenous replacement will be required.

Nutritional Assessment

Nutritional assessment is an essential element of the management of CF patients both at diagnosis and on a regular basis thereafter. Normal growth usually indicates patient well-being, but, in contrast, impaired growth signifies activation or exacerbation of lung disease or the onset of gut complications, which require investigation and management.

At diagnosis, all patients require examination with height and weight, head circumference measurements, assessment of muscle and subcutaneous fat wasting, and examination for macro- and micronutrient deficiencies, including edema. Baseline biochemical parameters should include fat-soluble vitamin levels, coagulation profile, hemogram, serum albumin, and, if available, serum EFA levels. Pancreatic status should be assessed preferably with a 3- to 5-day fat balance study but, if unavailable, one of the other tests as indicated previously. Beyond infancy, a fecal fat in excess of 7% indicates PI and conversely ≤ 7% PS and the necessity or not, respectively, for OPERT. In infants < 6 months of age, a fecal fat > 10% of fat intake or, if breastfed > 2 g/day indicates PI and the necessity to start OPERT.

In follow-up, accurate growth measurements are the simplest and most important clinical data to obtain to assess patient well-being from a nutritional point of view. Patients should be questioned in regard to their appetite, the occurrence of heartburn, water brash, abdominal pain, and constipation, that is, in an attempt to elicit gastrointestinal complications. Abdominal examination should be undertaken to look for hepatomegaly and splenomegaly and the presence of fecal masses in the right lower quadrant. Older patients can be asked about night blindness, and in younger infants, the fontanelle should be examined to assess for vitamin A deficiency. Deep tendon reflexes should be elicited to determine early-onset vitamin E deficiency and the ribs and long bones examined for evidence of rickets. Biochemically, patients should have, at least on an annual basis, a hemogram, coagulation profile, serum electrolytes, albumin, liver function tests, fat-soluble vitamin levels, and a blood glucose performed.

More elaborate nutritional studies, including indirect calorimetry and body composition studies, are performed at some clinics but usually in the context of a clinical research project. The possible exception is the routine measurement of bone mineral density with dual-energy x-ray absorptiometry (DXA) because of the reported high incidence of osteoporosis and osteopenia in older children and adolescents with CF.[115]

Repeat assessments of pancreatic function are required in PS patients who have developed symptomatology suggestive of steatorrhea or in PI patients who are not responding to their OPERT. The latter can be reliably tested only with formal fat balance studies, and if fat malabsorption is in excess of 20% of fat intake on a standard OPERT regimen, the patient may require adjunctive gastric acid suppression with histamine (H_2) receptor antagonists or proton pump inhibitors.

Nutritional Management

Nutritional guidelines for the management of EPD are outlined in Table 39-7, noting that salt supplementation

is required only for CF patients and that PS patients irrespective of the underlying disorder can adhere to a normal diet. The aim of these nutritional guidelines is to ensure that PI patients achieve normal linear growth and weight gain. Diets for children in Western countries ensure a high protein intake well in excess of the recommended. Energy requirements, however, will vary from patient to patient depending on the degree of residual malabsorption, response to OPERT, and the variable increase of energy expenditure.

As indicated above, OPERT doses equivalent to 5,000 lipase U/kg/day achieve average fat losses of 12 to 15% of fat intake in fat balance studies. Most patients will achieve values < 20%, and nearly half of the patients normalize their fat excretion below 10% of fat intake. Approximately 10% of patients have suboptimal responses to their OPERT and maintain fat excretions in excess of 20% of fat intake. They should be further investigated to exclude small intestinal disease (celiac disease and giardiasis) and also biliary tract complications. In the absence of these complications, the use of adjunctive gastric acid suppression therapy with proton pump inhibitors or H_2 receptor antagonists may improve fat excretion by elevating upper intestinal pH and thus ensuring dissolution of the microspheres and release of enzyme at a pH more optimal for their activity.[67] Many clinics permit patients to self-modulate OPERT doses according to their clinical symptoms. However, in this group with suboptimal response to OPERT, a "dose-creeping effect" is seen, with often large doses of enzymes in excess of 20,000 lipase IU/kg/day and in some instances over 50,000 lipase IU/kg/day being considered. These patients have an increased risk of developing fibrosing colonopathy, and this practice should be discouraged.

Energy intake should also be modified depending on the variability of energy expenditure. CF patients, for instance, those with chronic lung disease or those experiencing acute exacerbations of their lung disease, can demonstrate REE in excess of 150% of predicted. Failure to meet these requirements leads to weight loss and, if persistent, to growth failure. Thus, although recommendations for average energy intake of 115 to 120% of RDI are not unreasonable between exacerbations of pulmonary disease, a degree of flexibility in terms of dietary advice is required.

The recommendations for micronutrient supplements also have to be considered in regard to the presence and degree of malabsorption. PS patients usually maintain normal serum vitamin levels and coagulation profiles without supplementation. Similarly, a large proportion of PI patients who are compliant to OPERT have normal fat absorption and do not demonstrate vitamin deficiencies based on monitoring of serum vitamin levels; thus, vitamin supplementation is of questionable value in this group. We would recommend at least annual monitoring rather than encumber the patients with yet another medication. The recommendation for salt supplementation applies specifically to those children residing in warm to hot climates or those in more temperate climates who undertake strenuous exercise.

TABLE 39-7 Nutrient Requirements in Pancreatic Insufficiency including Cystic Fibrosis

Nutrient	*Requirement*
Protein	> 120% of RDI
Energy	Variable, depending on disease status, but in PI patient should average near 120% RDI with 40% as LCT and 3–5% as EFA
Vitamins	
A	5,000 IU/d* 1–3 yr of age 10,000 IU > 3 yr of age
D	400–800 IU/d†
E	200–400 IU/d*
K	5 mg twice weekly*
Salt intake‡	
Age	
0–6 mo	0.5 g/d
6–12 mo	1 g/d
1–5 yr	2 g/d
> 5 yr	3–5 g/d

Adapted from Gracey M et al.[116]
*If serum levels and coagulation profile are normal, patients may not need supplement.
†Not required if exposed to sunlight throughout the year.
‡Double salt dose in hot weather or during strenuous exercise.
Can use vitamins A, D, E, and K (Scandipharm) or vitamins A, B, D, E, and K (Technipro): 4–10 yr, 1 cap daily; > 10 yr, 2 caps daily; 0–1 yr, 1 mL daily; 1–3 yr, 2 mL daily; or Micelle A & E, 1–2 mL daily or Aquasol E (Rover Pharmaceutical, PA) 1 ml daily.
EFA = essential fatty acid; LCT = long-chain triglyceride; PI = pancreatic insufficient; RDI = Recommended Dietary Intake.

Special Circumstances ***Infant Nutrition.*** In the pre-microspheric OPERT era, OPERT was presented to infants in a powdered form, usually mixed with food. Many infants developed mouth ulcers, impairing nutrient intake; thus, alternative regimens were formulated. Considering also that human milk and soy formulas had been associated with the development of hypoproteinemia, predigested MCT-containing semielemental formulas were introduced into the management of CF infants.[83,84] As they, purportedly, improved fat absorption, this obviated the need for OPERT and avoided the oral complications seen with powdered OPERT. However, long-term growth rates were suboptimal, suggesting that as energy intakes were appropriate, there were ongoing unrecognized problems with malabsorption.[116] Others indicated that the earlier studies had not used the modified technique for measuring MCT in stools and thus had underestimated the degree of malabsorption.[85] Furthermore, they demonstrated that, using the correct technique, average fecal fat on Pregestimil alone was 26% of fat intake and improved to < 9% with the concomitant use of OPERT.[85] These results questioned the routine use of semielemental formulas, given their high cost, but comparative studies with human milk or standard cow's milk formulas were unavailable, and the feeding of semielemental formulas became standard practice in CF clinics.[117]

Breast-feeding was, in fact, not recommended because of its lower protein content and the frequent occurrence of hypoproteinemia at presentation in PI patients in unscreened populations. In the early 1980s, several centers commenced neonatal screening for CF, and, as a result, PI patients were diagnosed and commenced on OPERT at an

early age. A re-evaluation of breast-feeding in this population demonstrated that breast-fed PI infants could maintain normal average growth to age 2 years, which was at least comparable to those given humanized cow's milk formulas and clearly better than those on predigested formulas who had suboptimal standardized weight scores.[69,117] Breast-feeding is thus entirely appropriate in the context of neonatal screening, in which there is early recognition and treatment of PI, but has yet to be evaluated in a non-screened population in which older PI infants may be severely malnourished and hypoproteinemic at diagnosis.

***Invasive* Nutrition.** Most patients with CF adhering to a high-quantity energy intake diet with normal quality in terms of fat content achieve normal growth rates throughout childhood and adolescence.[73] Nevertheless, as per Table 39-6, a substantial proportion of patients are both underweight and stunted, even in the modern era. Many anecdotal studies have demonstrated that nocturnal tube feeding of this group of patients can improve weight gain and linear growth and can even restore growth to the previous normal growth channels.[118,119] Some of the short-term studies not only improved growth but also demonstrated improvement in spirometric lung function and a decline in pulmonary infections. However, these studies were uncontrolled with small numbers; thus, the beneficial effects on lung disease could not be determined.

Subsequently, three large studies over at least 12 months were conducted at three different centers.[120–122] They demonstrated improvement in growth, and whereas one demonstrated a mild improvement in FEV_1 percent predicted in the treatment group, the other two suggested that the expected decline in lung function was prevented in the treatment group. However, the number of patients in each study was small, that is, 10 to 20 per treatment or control cell; thus, the effect of improving growth on pulmonary function in malnourished subjects remains contentious. Recommendations regarding the type of formula used (elemental, polymeric), the feeding technique (nasogastric, gastrostomy, jejunostomy), duration of use, etc, vary from clinic to clinic. We have used a nocturnal feeding regimen with a polymeric formula, Ensure Powder (Abbott), which, on reconsitution, has a fat content of 35.5 g/L. We have advised patients to use an enzyme dose providing approximately 1,000 lipase U per gram of fat, so if receiving a liter of the formula, they would take $7 \times 5{,}000$ IU capsules, with half the dose given prior to sleep and the other half on awakening.

Nocturnal feeding regimens are demanding on the patients and their families, and the psychological/emotional impact of this therapy is not well documented. Although some cope extraordinarily well and are highly compliant, in others, the burden of the therapy is overwhelming and unsuccessful. Given that improvement of lung function with these regimens is questionable and without information on whether they improve survival, one has to be cautious about recommending this type of therapy. Families need to have education and thorough discussions regarding the commitments needed to ensure success of the therapy and a psychological evaluation to assess their ability to cope with this extra treatment burden. It may well be that this type of therapy in the future will be restricted to compliant patients and potential lung or liver transplantation recipients.

In view of the difficulties frequently encountered with "invasive" nutrition regimens, there has been considerable interest generated by three recent studies on the use of megestrol acetate as an appetite stimulant in CF patients.[123–126] The drug acts directly via the hypothalamus to stimulate appetite and has been used in other anorexigenic/cachetic illness.[127] The most recent study, a double-blind, placebo-controlled study, demonstrated a substantial improvement in average weight gain in the treatment versus control group (5.3 kg versus 1.5 kg, respectively) over 6 months.[125] This is an encouraging result, but the study numbers were small (10 versus 7, respectively), and there is still some uncertainty about long-term adverse events, including adrenal suppression and the occurrence of diabetes mellitus, although they did not occur in this study. Bone mineral density was also said to be stable over the 6 months, but only 7 patients had DXA evaluation of their bone mineral density. Although one can be cautiously optimistic about these reports, clearly, further long-term studies are required to evaluate the potential for adverse events and to determine which patients are likely to benefit from such therapy. One would hope that it could be avoided in the 90 to 95% of patients who, in general, maintain normal growth, but it may well have application in the 5% of patients who do not respond to routine regimens.

CONCLUSION

Many of the EPDs, including CF, are multisystem disorders and require a team approach for delivery of optimal care. Personnel with nutritional expertise are required for monitoring the patient's nutritional status and growth and for educating the patients and their families regarding optimizing dietary intake and OPERT. Patients consuming high energy intakes by avoiding low-fat diets can achieve normal growth and with appropriate vitamin intake can avoid most micronutrient deficiencies. It is essential in addition to monitoring growth and micronutritional status to ensure appropriate but not excessive OPERT ingestion to avoid treatment-related disease such as fibrosing colonopathy. Some patients, despite optimal advice and care, experience growth and nutritional problems and may be candidates for invasive nutrition if they clearly fail to demonstrate a response to specific oral supplementation regimens.

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CHAPTER 40

ACUTE AND CHRONIC LIVER DISEASE

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The liver has a central role in energy metabolism, nutritional homeostasis, and absorption of nutrients. Severe liver disease, whether acute or chronic, leads to multiorgan failure, which can have significant effects on growth and development in the long term. The pathophysiology of malnutrition in liver disease is complex and multifactorial and has extensive implications (Table 40-1). It is most severe in infants with chronic cholestatic liver disease, who are particularly vulnerable to the effects of malnutrition because of their high energy and growth requirements.[1] This chapter reviews the pathophysiology of malnutrition in pediatric liver disease and current treatment strategies, including liver transplantation.

PATHOPHYSIOLOGY OF MALNUTRITION IN LIVER DISEASE

Prevalence of Malnutrition

Malnutrition is common in children with chronic liver disease. Estimates vary from 50 to 80% in studies from North America and Europe.[2–5] In general, children who present with acute liver disease such as viral hepatitis or fulminant hepatitis are not malnourished at presentation but can become so as a result of their illness.[6]

Reduced Energy Intake

Anorexia is a common symptom in children with either acute or chronic liver disease. They often take in less than the recommended requirements or less than is appropriate for their energy requirements because of increased energy expenditure.[7] The consequent reduction in enteral intake can lead to considerable loss of body stores or lean body mass, which alters body composition.

In children with chronic liver disease, the complications of portal hypertension, such as ascites and hepatosplenomegaly, can lead to malabsorption of nutrients. The treatment of ascites, which includes fluid restriction, the prescription of unpalatable feeds, or both, can exacerbate anorexia and reduce energy intake further.[3]

Carbohydrate Metabolism

Under normal circumstances, the liver receives portal vein blood rich in absorbed glucose, which can be stored in the liver as glycogen or circulated to extrahepatic tissues, especially muscle, where lactate, pyruvate, and alanine are generated by glycolysis.[8,9] In children with liver disease, this substrate supply and use can be abnormal. The loss of glycogen stores in chronic liver disease leads to fasting hypoglycemia and an inability to meet energy demands. In addition, any significant hepatocyte loss, especially in acute liver failure,[10] has an immediate effect on glucose metabolism, leading to hypoglycemia.

In cirrhotic adults, the pancreas secretes increased amounts of insulin, which is not metabolized, either because of portosystemic shunting around the liver or because of reduced degradation owing to hepatic dysfunction.[11] Although there is increased circulation of insulin, glucose uptake in the peripheral tissues, especially muscles, is reduced as a result of insulin resistance. Adult studies suggest that this could be attributable to impaired glycogen synthesis in the muscle, either because of abnor-

TABLE 40-1 Pathophysiology of Malnutrition in Liver Disease

Reduced calorie intake
Anorexia
Fat malabsorption
Use of bile salt resins
Portal hypertension
Unpalatable feeds
Inappropriate substrate use
Abnormal nitrogen metabolism
Reduction in glycogen stores
Negative protein balance
Increased metabolic needs
Energy expenditure
Calorie requirements
Hormonal dysregulation
Growth hormone/IGF-I
Insulin resistance

IGF = insulin-like factor.

mal insulin receptor numbers or affinity.[12,13] These data have not been confirmed in children, but it is possible that similar mechanisms occur, although few children (apart from those with cystic fibrosis) develop overt diabetes mellitus, unlike adults.[12]

Protein Metabolism

Amino acids are absorbed by the intestine directly into the portal vein and transferred to the liver, where they are synthesized into protein or used for energy. The liver is responsible for approximately 10% of plasma protein synthesis; thus, amino acids are constantly recycled.[9,14] Nonessential amino acids are oxidized in both liver and muscle. The seven aromatic essential amino acids (AAAs; arginine, histidine, lysine, methionine, phenylalanine, tryptophan, and threonine) are metabolized in the liver, whereas the three branched-chain essential amino acids (BCAAs; leucine, isoleucine, and valine) are metabolized predominantly in muscle and pass unaltered through the liver to the periphery, where their uptake is regulated by insulin.[15] The liver is also responsible for detoxification of nitrogenous wastes via the urea cycle, leading to the production of ammonia—hence the rise of plasma ammonia in both acute and chronic liver failure.[16]

Reduced hepatic and muscle glycogen stores lead to early recruitment of fat and increased dependence on amino acids as an alternative fuel.[17] Abnormal protein use by the liver leads to a rise in AAAs and a reduction in the BCAAs, which are metabolized in muscle in both children and adults.[18–20] An abnormal ratio of BCAAs to AAAs correlates with histologic damage and encephalopathy in adults[21] and children.[19]

Studies in adults demonstrating abnormalities in BCAA metabolism using studies of BCAA fluxes and protein turnover have given conflicting results. It is possible that the hyperinsulinemia detected in cirrhosis could cause the decreased BCAA levels by increasing BCAA uptake in muscle or adipose tissue. Alternatively, it is possible that there is an increase in liver transamination of BCAAs in addition to abnormal protein turnover.[22] Three recent adult studies demonstrated that protein synthesis can be increased or decreased depending on clinical condition and that muscle wasting is attributable to a relative increase in protein breakdown.[23–25] Those patients who had more efficient protein retention were less malnourished.

A study of protein metabolism in infants with liver disease, which used a whole-body leucine turnover model, demonstrated that muscle protein degradation and protein oxidation were increased, possibly as a result of a reduction in carbohydrate metabolism and the use of protein as an energy supply.[26] In contrast to normal children, muscle protein degradation continued in these children even when they were fed, suggesting that this could be a factor in the muscle loss common in infants with chronic liver disease.

In addition to protein synthesis and degradation, the liver is the site of synthesis of all of the coagulation factors except factor VIII, von Willebrand's factor, which is synthesized by vascular endothelial cells.[27,28] Thus, coagulopathy is an early sign of significant acute or chronic liver failure.

In chronic liver disease, these metabolic changes result in muscle wasting, hyperammonemia, hypoalbuminemia, hypoglycemia, hypolipidemia, and reduced circulating triglyceride levels secondary to the increased fat oxidation. Hypoalbuminemia is associated with a reduction in plasma oncotic pressure, exacerbating the development of ascites and peripheral edema. In acute liver failure, the main effects of deranged protein metabolism are hyperammonemia and abnormal coagulation.

Fat Metabolism

Most dietary fat is in the form of long-chain triglycerides (LCT) and is an excellent energy source.[29] The first step in fat digestion is emulsification in the stomach, followed by hydrolysis of triglycerides by pancreatic lipase in the intestinal lumen and then micellar solubilization of di- and monoglycerides by bile acids, which are then transported into the enterocytes. Once in the enterocytes, fatty acids are re-esterified and chylomicrons are formed and removed via the lymphatics through the portal system to the liver and other tissues.[29]

In contrast, medium-chain triglycerides (MCTs) do not depend on micellar solubilization for absorption and can be transferred directly from the enterocytes to the portal circulation without re-esterification.[29,30] In the liver, free fatty acids are metabolized into triglycerides or oxidized for energy. The very-low-density lipoproteins (VLDL) and high-density lipoproteins (HDL) are synthesized in the liver, as is cholesterol, which is the precursor for many hormones, vitamins, and bile acids.

In all forms of chronic liver disease, there is reduction in the synthesis and secretion of bile salts, although this is more severe in cholestatic diseases such as biliary atresia. Up to 50% of LCTs, fat-soluble vitamins, and essential polyunsaturated fatty acids (PUFAs) might not be absorbed because of reduced biliary secretion and reduction in intraluminal bile concentration.[31–33] In contrast, 95% of water-soluble lipids, such as MCTs, which do not depend on bile solubility, are absorbed even in cholestatic infants[34] and form the basis for nutritional replacement.[35]

Fat malabsorption can also be affected by portal hypertension, which leads to congested gastric and intestinal mucosa, and by small bowel overgrowth in the Roux-en-Y blind loop created by a Kasai portoenterostomy. In addition, therapy such as cholestyramine to reduce pruritus can exacerbate steatorrhea because it binds bile salts, decreasing micellar solubilization.

Pancreatic function is usually normal except in children with Alagille syndrome, in which pancreatic lipase can be reduced.[34,36]

Long-Chain Polyunsaturated Fatty Acids

Long-chain polyunsaturated fatty acids (LCPs) such as arachidonic acid and docosahexaenoic acid (DHA) are essential nutrients in infancy. LCPs, in particular DHA, play a major role in the development of visual acuity and mental development in the first year of life, particularly in preterm infants.[37–40] The main source of LCPs is maternal,

in the last trimester of pregnancy and through breast-feeding, because breast milk is a rich source of LCPs, containing both arachidonic acid and DHA in a combination of phospholipid and triglyceride forms.

Studies in adults have demonstrated that LCP deficiency can develop either from malabsorption of long-chain fat and essential fatty acids or from reduced synthesis or function of the Δ-6-desaturase enzyme required for the de novo synthesis of very-long-chain (20–22) carbon PUFAs from their essential fatty acid 18-carbon dietary precursors.[41,42]

Children with cholestatic liver disease have normal LCP and DHA levels at birth but can become deficient within 8 to 12 weeks,[43] either from malabsorption of LCTs, from prescription of formula feeds rich in MCTs, or as a result of inadequate liver desaturase enzyme activity.[41,44,45]

Fat-Soluble Vitamin Deficiency

Chronic liver disease affects vitamin absorption, metabolism, and storage. Reduction in bile salt secretion leads to malabsorption of the fat-soluble vitamins A, D, E, and K. Fat-soluble vitamin deficiency can develop within 6 to 12 weeks of birth, depending on body stores and availability of vitamin supplementation. Vitamin A deficiency can also develop secondary to reduction in protein synthesis or depletion of hepatic stores. Vitamin D deficiency can occur either from fat malabsorption or from reduction in hepatic 25-hydroxylation. Vitamin K deficiency arises partly from fat malabsorption and partly from a reduction in intake, particularly in breast-fed infants.

Because the liver has a central role in lipoprotein metabolism and cholesterol synthesis, hypercholesterolemia and hypertriglyceridemia are common in chronic liver disease. There can be increased synthesis of cholesterol esters as a result of loss of hepatic lecithin cholesterol acyltransferase, which can alter lipoprotein fractions. In cholestatic liver disease such as Alagille syndrome, unusual lipoproteins, such as lipoprotein X, are produced with cutaneous xanthomata and hemolysis from alterations in red cell and platelet membranes.[46]

In terminal liver disease, however, the reduction in cholesterol synthesis leads to hypocholesterolemia, which is a poor prognostic sign.[47]

Growth Hormone/Insulin-Like Growth Factor Axis

Growth failure in chronic liver disease can be exacerbated by an impaired growth hormone/insulin-like growth factor (IGF-I) axis[48,49] because IGF-I and its major circulating binding protein, IGF-BP3, are synthesized in the liver. It seems that IGF-I is nutritionally regulated[50] because there is animal evidence that nutrients influence synthesis and action of IGF-I and its binding proteins at many levels, including defects in pre- and post-translational expression. Thus, protein malnutrition not only decreases the IGF-I production rate but can also increase serum clearance and degradation. Evaluation of growth hormone, growth hormone binding proteins, and IGF-I in children with protein-energy malnutrition, before and after nutritional rehabilitation, has confirmed the role of malnutrition in these hormones.[51]

Children with chronic liver disease have low plasma levels of IGF-I despite elevated levels of growth hormone, which could be a result of diminished hepatic synthesis or malnutrition or related to end-organ insensitivity to IGF-I.[52,53]

Increased Energy Expenditure

Adult studies have produced conflicting data on energy expenditure, but the situation is different in a growing child. A number of studies have indicated an increase in energy requirements of up to 140% in children with chronic liver disease.[54,55] Mechanisms implicated include portosystemic shunting and ascites, abnormal intermediate metabolism, and the energy demands of specific complications, such as sepsis and variceal hemorrhage. Children with acute liver failure also have excess energy expenditure and requirements because of multiorgan failure, but this has not been specifically studied.

Trace Elements and Metals

Biochemical deficiencies of water-soluble vitamins such as thiamin and pyridoxine can occur and lead to nutritional cardiomyopathy and peripheral neuropathy.[56] Trace metal deficiencies include iron deficiency secondary to gastrointestinal bleeding or diminished intake and zinc and selenium deficiencies caused by reduced enteral intake, malabsorption, or increased losses.

Consequences of Malnutrition

Many different nutrient deficiencies occur in children with chronic liver disease (Table 40-2), and malnutrition per se can increase liver dysfunction because of the energy required for synthesis, storage, and detoxification. Children with progressive cholestasis, such as those with biliary atresia or Alagille syndrome, develop significant fat malabsorption, which leads to steatorrhea, fat-soluble vitamin deficiency, essential fatty acid deficiency, loss of fat stores, and a reduction in growth (Table 40-2 and Table 40-3). Essential fatty acid deficiency can present with a skin rash, whereas DHA deficiency is associated with abnormalities in visual function, as demonstrated by electroretinograms in cholestatic infants.[43]

Fat-soluble vitamin deficiency is more common and can be detected biochemically before clinical symptoms, which are obvious only with severe deficiencies, appear. Clinical signs and symptoms of vitamin A deficiency are rare but include night blindness, xerophthalmia, and keratomalacia.[57] Vitamin D deficiency leads to hypocalcemia, hypophosphatemia, rickets, and pathologic fractures, particularly in infants who are rarely exposed to sunlight or who have inherited metabolic liver disease and a renal tubular disorder. Deficiency of vitamin E leads to hemolysis, peripheral neuropathy, and occasionally visual loss.[58,59] Vitamin K deficiency can present as hemorrhagic disease of the newborn, particularly in breast-fed babies who are given insufficient vitamin K at birth.[60] It leads to coagulopathy, which is exacerbated by decreased synthesis of liver-dependent clotting factors. In vitamin K deficiency secondary to fat malabsorption, parenteral vitamin K will

TABLE 40-2 Clinical Manifestations of Malnutrition in Liver Disease

Nutritional Deficit	*Clinical Manifestation*
Protein-energy malnutrition	Stunting, muscle wasting, motor developmental delay
Fat malabsorption	Steatorrhea, loss of fat stores
Essential fatty acid deficiency	Peeling skin rash
Vitamin A deficiency	Conjunctival and corneal drying, night blindness
Vitamin E deficiency	Peripheral neuropathy, ophthalmoplegia, ataxia, hemolysis
Vitamin D deficiency reduced bone density	Osteopenia, rickets, fractures,
Vitamin K deficiency	Bruising, epistaxis, coagulopathy
Zinc deficiency	Acrodermatitis, anorexia, poor growth
Hypercholesterolemia	Xanthomata
Immunosuppression secondary to reduced cell-mediated immunity	Systemic infections

improve the coagulation profile, whereas it will be ineffective in parenchymal liver disease.[61]

Metabolic bone disease with reduced bone density is usually observed in end-stage liver disease.[62] Although malabsorption of vitamin D is a factor, the etiology is more complex as normal levels of vitamin D do not prevent bone demineralization.[62] Children with liver disease have a higher incidence of dental caries and enamel hypoplastic defects, which could be related to nutritional deficiency or to bone disease. They also have discolored teeth as a result of hyperbilirubinemia.[63]

Trace element and mineral deficiencies include iron deficiency with anemia and zinc deficiency, which leads to acrodermatitis, immunodeficiency, and altered protein metabolism; both zinc and selenium deficiency can exacerbate growth failure and poor protein synthesis.[2]

In the course of chronic liver failure, fat malnutrition develops first, as demonstrated by loss of fat stores. Protein malnutrition is a late development and is associated with a reduction in muscle bulk, stunting, and significant motor developmental delay. In time, children with significant malnutrition will have impaired growth and psychosocial development[64,65]; thus, malnutrition is not only an important indication for liver transplantation but also one of the most important prognostic factors for survival post liver transplantation.[64–66]

TABLE 40-3 Anthropometric Definitions in Children with Liver Disease

Acute malnutrition	Decreased weight for height Decreased triceps skinfold or midarm muscle area
Chronic malnutrition	Decreased height for age
Severe malnutrition	< 2 SDS below the mean < 3rd percentile

SDS = standard deviation scores (z-scores), 0 = 50th percentile.

Nutritional Assessment

Accurate nutritional assessment is essential to the management of children with acute or chronic liver disease. It is important to start with a comprehensive clinical history, feeding history, and careful physical examination. Serial anthropometric examination is critical and can identify early malnutrition. Standard weight and height ratios are of little value in children with liver disease because of misinterpretation caused by fluid overload, ascites, and visceromegaly. Many researchers, using sophisticated methods such as whole-body potassium and dual-energy x-ray absorptiometry (DXA) scanning, have demonstrated that body weight underestimated the incidence of malnutrition by 50% in both adults and children,[3,12] and for this reason, simple methods of measuring body composition, such as body impedance analysis, are not reliable in children with liver disease.[67,68]

Thus, the assessment of malnutrition should be performed using a number of parameters, such as triceps or subscapular skinfolds, midarm circumference, and arm muscle measurements (midarm muscle area).[1,69] Triceps skinfold and midarm circumference are useful indicators of body fat and protein and serial recordings demonstrate early loss of fat stores before weight and height changes become obvious.[1,69] Although linear growth is a sensitive parameter, it is a late sign of growth failure in infancy; stunting (or negative height velocity) might not be apparent until 1 year of age (Table 40-3).[70]

Growth data are best expressed as standard deviation scores (or z-scores) related to the median value for the child's age and sex in which the z-score of 0 = 50th percentile. This is particularly useful for comparisons between centers and for evaluation of new feeds.

Biochemical evaluation of vitamin deficiency is a useful adjunct to nutritional assessment. Plasma vitamin A levels can be measured but might not reflect hepatic stores.[71] Plasma betacarotene, or the ratio of plasma retinol to retinol binding protein, can be helpful.[71] Vitamin E deficiency is monitored by serum vitamin E levels or the ratio of vitamin E to total lipids. Vitamin D deficiency is evaluated by measuring serum levels of calcium, phosphate, and alkaline phosphatase, whereas the diagnosis of rickets is confirmed by radiographic examination of the wrist or knee. In some centers, it is possible to measure 25-hydroxyvitamin D levels. Vitamin K deficiency is identified by measuring coagulation times and monitoring the response to parenteral vitamin K.

Acute malnutrition is evidenced by loss of weight compared to height and loss of fat stores, whereas chronic malnutrition is documented by stunting and reduction in the height-for-age index (Table 40-3).

Indications for Nutritional Therapy

The aim of nutritional therapy is to prevent or treat malnutrition by providing adequate calories for energy and sufficient nitrogen for protein synthesis, to restore plasma amino acid imbalance, to prevent vitamin and trace element deficiency, and to achieve normal growth and activity. The need for nutritional support is often underestimated, par-

ticularly in infants with liver disease, who might have an increased appetite in the first few months of life.

Children who are at particular risk for developing malnutrition include the following:

- Children under 2 years of age who have severe cholestasis (serum bilirubin > 70 mmol/L [4 mg/dL])
- Those with progressive liver disease such as biliary atresia or severe familial intrahepatic cholestasis
- Those with end-stage liver failure awaiting liver transplantation
- Children with recurrent hepatic complications such as ascites and bleeding varices

Strategies for Nutritional Support

Increased Energy Intake Because the resting energy requirements of infants and children with liver disease are increased,[54] it is important to increase the energy intake to 140 to 200% of estimated average requirements. In cholestatic infants, this can be achieved by using concentrated formulas (the formula is concentrated by 13 to 15%, which increases the number of kilocalories from 67 to 80 per 100 mL) or by supplementing milk feedings with extra carbohydrate and fat to produce a feed with an energy density of 4.18 kj/mL (1 kcal/mL or more). As such a feed can have a high osmolality (500 to 800 mmol/L), it should be introduced gradually to establish intestinal tolerance (Table 40-4). Caloric supplementation added to drinks can be effective for older children. If there is no response to an increase in energy intake alone, nocturnal enteral feeding by nasogastric tube might be required (Figure 40-1).

Medium-Chain Triglycerides Because fat is an important calorie source, with an energy value of 8 to 9 kcal/g, it is a major source of energy for infants. Because absorption is deranged in liver disease, the fat content of the diet needs careful consideration. Low-fat diets are no longer considered appropriate, but an increase in the MCT content will reduce steatorrhea.[32,35,44] Hydrolyzed-protein infant formulas, such as Pregestimil (Mead Johnson), which contain 50% MCTs, will maximize fat absorption and improve steatorrhea,[44,72] but formulas with more than 80% MCTs can lead to essential fatty acid deficiency.[44] Although MCTs are a useful energy source, there is no evidence that growth improves with formulas with a high MTC content,[73,74] so it is necessary to increase the total fat intake with both LCTs and MCTs. This will increase the overall amount of fat absorbed and improve growth despite increasing steatorrhea.[35] In practice, this means supplementing feeds with approximately 50% MCTs with essential fatty acids. In older children, MCT oil can be added to meals and should be balanced by fats with high LCP content.

Long-Chain Polyunsaturated Fatty Acids The malabsorption of long-chain fats in chronic liver disease means that it is important to ensure adequate intake of LCPs. The minimal intake of linoleic acid recommended for infants is 1 to 2% of energy in a ratio of linoleic to linolenic acid of 5:15.1.[39]

TABLE 40-4 Formulas for Children with Liver Disease*

Formula	*kcal/Kj*	*Protein (g)*	*Fat (% MCT)*	*Sodium (mmol)*	*Essential Fatty Acids (omega-6: omega-3)*
Pregestimil†	68/285	1.9	55	1.4	16.5:1
Peptijunior‡	67/280	1.8	50	0.9	64:1
Caprilon§	66/276	1.5	75	0.8	7.5:1
Generaid Plus§	75/314	1.9	35	0.5	56:1
MCT Pepdite§	68/285	2	75	1.5	6.9:1
Modular feed§	70–200/ 293–837	Flexible	0–100	0-1.5	None

*Per 100 mL.
†Mead Johnson.
‡Cow and Gate.
§Scientific Hospital supplies.
MCT = medium-chain triglyceride.

The LCPs, or PUFAs, can be supplemented by the addition of soybean or rapeseed oil, whereas LCP supplementation is provided in dietary products such as egg yolk (which is rich in arachidonic acid) or fish oil (which is rich in DHA). Alternatively, infants can be given conventional LCP-supplemented formulas, which are commercially available.[75]

Structured Lipids Recently, chemically defined structured lipids have been developed to increase absorption of both medium- and long-chain and essential fatty acids.[76] These lipids combine pure MCTs with LCTs, resulting in a triglyceride that contains combinations of short-, medium-, and long-chain fatty acids on a single glycerol backbone, which should be absorbed like MCTs. To date, clinical studies in adults have evaluated structured lipids in postoperative patients receiving parenteral nutrition and demonstrated that they were safe and effective when compared to LCP emulsion.[77,78] Although clinical studies of these modified lipids in children are currently in the preliminary stages,[79] studies in rats have demonstrated improved fat absorption and reversal of essential fatty acid deficiency in vitro in caco-2 cells.[80,81] If successful, there might be considerable benefit for cholestatic infants.

Carbohydate Carbohydrate is a major source of energy and is particularly useful for increasing calorie intake. It can be given as a monomer, short-chain polymer, or starch, but complex carbohydrates such as maltodextrin or glucose polymer restrict the osmolality of the feed while maintaining a high energy density of more than 1 kcal/mL. This allows fluid restriction if necessary while providing up to 20 g/k/day of carbohydrate. In infants, glucose polymers are best added to milk feeds, whereas in older children, they can be provided as supplemental drinks.

Protein

Historical advice, which restricted protein in advanced end-stage liver disease, is now considered inappropriate in both children and adults.[82,83] Children with end-stage liver disease require minimal protein intake of approximately 2 to

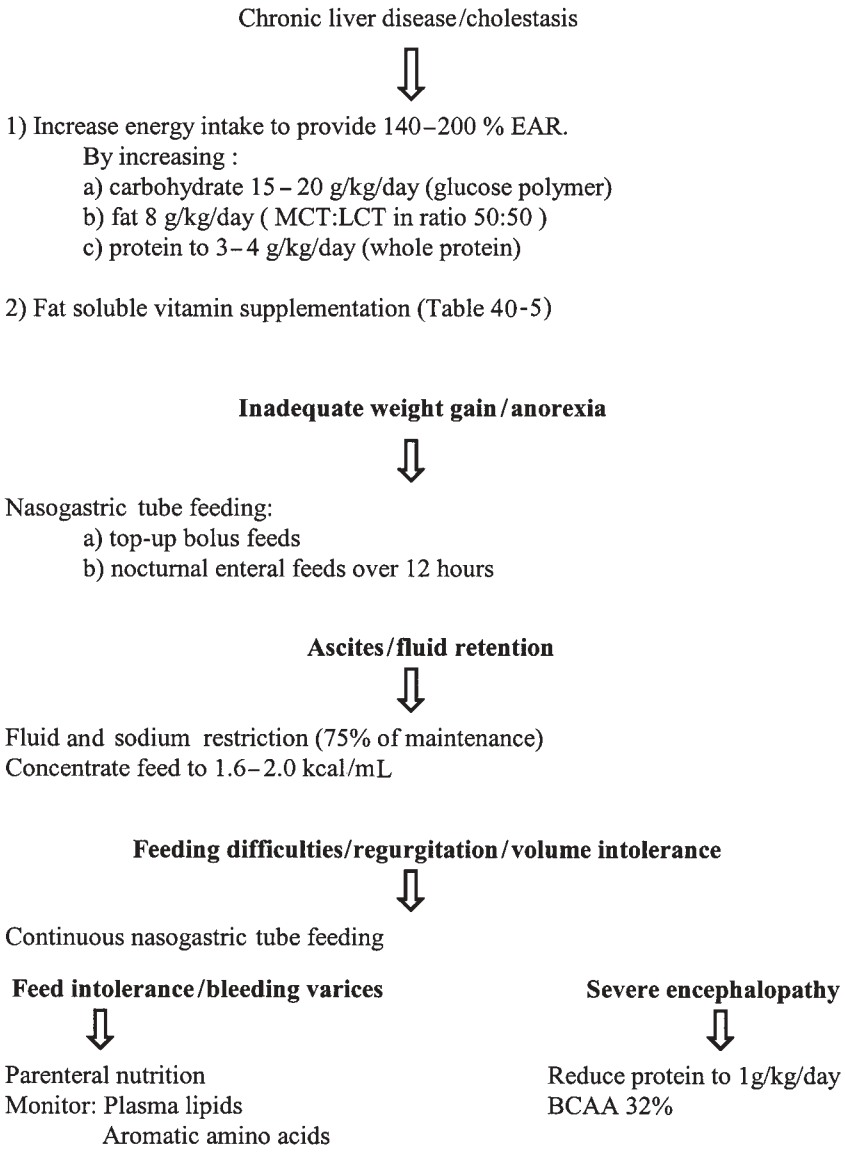

FIGURE 40-1 Nutritional support for chronic liver disease. BCAA = branched-chain amino acid; EAR = estimated average requirement; LCT = long-chain triglyceride; MCT = medium-chain triglyceride.

3 g/kg/day but will tolerate up to 4 g/kg/day without developing encephalopathy or a significant increase in plasma amino abnormalities.[84] Severe protein restriction (less than 2 g/kg/day) might be required for acute, severe encephalopathy but should be avoided in the long term as it can lead to endogenous muscle protein consumption.[54] There is no necessity to use semielemental diets or protein hydrolysates because there is no evidence of protein malabsorption.

In view of the abnormal arachidonic acid-to-BCAA ratio, there has been considerable interest in the use of a modified amino acid formulation designed to improve this imbalance. Numerous studies in adults have not demonstrated a clear benefit for BCAA nutritional supplementation, despite the evidence that BCAAs did improve nitrogen retention and protein synthesis; their effect on patient outcome was not proven.[85]

There is both animal and clinical evidence that suggests that BCAA-enriched formulas could have significant nutritional benefit in children. BCAAs increased weight gain, protein and muscle mass, body composition, and bone mineral density in an animal model of biliary obstruction.[86] A study that compared a feed containing 32% BCAAs with a standard feed demonstrated improved lean body mass in children awaiting liver transplantation but no improvement in amino acid levels.[87] In another study in infants with liver disease, the effect of a modified amino acid feed containing 50% BCAAs was compared with an isonitrogenous formula containing 22% BCAAs by measuring whole-body protein turnover.[55] The BCAA-supplemented feed improved protein retention when compared with the standard formula by suppressing endogenous protein catabolism and normalizing the plasma amino acid profile. Formulas rich in BCAAs, complete with MCTs and vitamin and mineral supplements, have been developed for use in infants, and oral supplements rich in BCAAs are available for older children, but both are particularly unpalatable.

Attempts to use BCAA supplementation to treat hepatic encephalopathy in adults could be of value in those patients with advanced encephalopathy,[88] but similar studies have not been performed in children.

Vitamin and Mineral Supplementation

Both water- and fat-soluble vitamins should be supplemented in children with chronic liver disease. Supplementation should be based on plasma levels of selenium, zinc, calcium, and magnesium. Iron supplementation might be required in children with chronic blood loss.

Fat-soluble vitamins are required in all children with prolonged or cholestatic liver disease (Table 40-5). Most children will be maintained adequately on oral fat-soluble vitamin administration, but monthly intramuscular administration is occasionally required for children with severe cholestasis.

Mode of Delivery

Nutritional supplementation should be provided enterally for as long as possible because it has a number of advantages over parenteral feeding. Not only is it cheaper and more physiologic, but it maintains gastrointestinal tract immunity, reduces bacterial overgrowth, and maintains the integrity of the gut barrier to microorganisms.[89,90] It is also essential to maintain normal feeding behavior. Few children with end-stage liver disease will be able to tolerate the increased calorie intake necessary to prevent or reverse malnutrition orally; thus, nasogastric tube feeding is indicated for children who have no nutritional response to an increase in calorie intake or who become anorexic.

Despite anxiety about using nasogastric feeding in children with esophageal varices, there is no evidence that the use of modern soft Silastic nasogastric tubes is harmful. Nocturnal feeding is the method of choice because it allows calorie supplementation while maintaining normal oral feeding during the day. For infants with severe liver disease, nocturnal feeding can be beneficial because it will prevent fasting hypoglycemia and reduce protein catabolism. Continuous enteral infusion might be required in children with severe malabsorption or feed intolerance. Intensive enteral nasogastric feeding has effectively reversed malnutrition in infants and children with liver disease and can transform the child's affect and increase voluntary intake.[35,84,91] Under normal circumstances, it should be possible to provide nocturnal or continuous nasogastric feeding at home with appropriate support from a nutritional care team including a dietitian, a liaison nurse, and clinicians.

Gastrostomy tube placements might be preferable in older children but should be avoided in children with severe portal hypertension because of the development of stomal varices. In children with stable compensated liver disease (eg, cystic fibrosis), percutaneous endoscopic gastrostomy might be beneficial.

Growth Hormone Therapy

In view of the disruption of the growth hormone/IGF-I axis, it is tempting to prescribe growth hormone therapy for children with significant growth failure, but this has not proven beneficial in two studies of its use in children with end-stage liver disease.[92,93]

Parenteral Nutrition

In view of the well-recognized hepatobiliary complications that occur in premature infants with short-gut syndrome or intestinal failure, parenteral nutrition has been used cautiously in children with liver disease. Particular concern has focused on whether the potentially toxic components of parenteral nutrition could be exacerbated in children with established chronic liver disease or cholestasis. There is no evidence that amino acids, carbohydrates, or lipid emulsions are any more toxic in children with established liver disease, although amino acid levels and plasma lipids need careful monitoring.

Although aluminum toxicity is well recognized in parenteral nutrition and can lead to bone disease, there is no evidence that it is implicated in parenteral nutrition liver disease or that it exacerbates the metabolic bone disease associated with chronic liver disease.[94,95] In contrast,

TABLE 40-5 Assessment and Management of Nutritional Deficiency in Pediatric Liver Disease

Deficit	*Investigation*	*Management*
Energy	Calorie intake, energy expenditure, anthropometry (body cell mass [TBK], DXA)	Increase calorie intake, achieve 130–150% EAR, nocturnal enteral nutrition, continuous enteral nutrition
Protein	Plasma proteins (albumin), BCAA/AAA ratio, protein stores (muscle mass, TBN)	Provide adequate protein, (3–4 g/kg/d), BCAA-enriched protein (32%), albumin infusion (if serum albumin < 25 g/L)
Fat	Triceps skinfolds, body composition, EFA deficiency, plasma lipid profile	Improve fat absorption (MCT:LCT, 50:50), provide saturated fats high in EFA, ? supplement DHA
Fat-soluble vitamins	Plasma 25-OH-D (skeletal X-rays, DXA), prothrombin time ([< 138 c] INR = 1), plasma vitamin E and A	Light exposure, vitamin D-1-α (50 ng/kg), vitamin K (2.5–5 mg/d), vitamin E (50–400 IU/day as TPGS), vitamin A (5,000–10,000 IU/d)
Water-soluble vitamins	Specific levels, blood count	Supplement as requested
Minerals	Specific levels, cardiac evaluation	Supplement as requested

AAA = aromatic amino acids; BCAA = branched chain amino acids; DHA = docosahexaenoic acid; DXA = dual-energy x-ray absorptiometry; EAR = estimated average requirement; EFA = essential fatty acids; INR = international normalized ratio; LCT = long-chain fatty acids; MCT = medium-chain fatty acids; TBK = total body potassium; TBN = total body nitrogen; TPGS = tocopherol polyethylene glycol-1000 succinate.

chromium toxicity has been reported in animals on parenteral nutrition. Although both serum and urine chromium levels are higher in children on long-term parenteral nutrition, there is no correlation with liver disease.[96]

Manganese toxicity in children on long-term parenteral nutrition has recently been reported, however.[97–99] Although 79% of children on long-term parenteral nutrition had whole-blood manganese concentrations above the reference range, children with impaired liver function had the highest manganese levels. There was a significant correlation between whole-blood manganese levels, aspartate amino transferase ($r = .63$, $p = < .001$), and total plasma bilirubin ($r = .64$, $p = < .001$). Eleven children had both high manganese levels and cholestasis; four of these died. In the seven survivors, whole-blood manganese declined when the supplements were reduced or withdrawn. Although manganese is toxic to both brain and liver, it is not clear whether the high manganese levels led to cholestasis or were secondary to it because manganese is excreted in the bile. Nevertheless, it is likely that manganese toxicity exacerbates cholestasis in children with established liver disease; thus, monitoring of manganese levels is particularly important in this group.[100]

In general, the use of parenteral nutrition in children with established liver disease is for short-term purposes only; thus, they are unlikely to develop biliary sludge and gallstones from the prescription of parenteral nutrition alone,[101,102] although prescription of ursodeoxycholic acid (15 to 20 mg/kg) might be of value.[103]

Parenteral nutrition should be considered in children with chronic liver disease only if they cannot be enterally fed because of feed intolerance or secondary to complications such as recurrent variceal bleeding or abdominal sepsis. As stated above, there is no evidence that short-term parenteral nutrition is associated with hepatobiliary dysfunction or an increase in cholestasis; it can improve nutritional status in the short term. Standard amino acid and lipid solutions are well tolerated in stable patients, and lipids can be particularly beneficial in achieving adequate calorie intake. If encephalopathy develops, the amino acid content of the feed can be reduced to 1 to 2 g/kg/day; lipid administration requires careful monitoring in children with severe liver dysfunction, hepatic encephalopathy, or sepsis.

Although MCT emulsions have been suggested for adults with advanced liver failure, intravenous MCTs should be used with caution in children because incomplete oxidation can occur, producing metabolic acidosis.[104] Parenteral structural lipid emulsions have not yet been evaluated in children.

The use of parenteral nutrition is particularly important for children with acute fulminant hepatitis who are awaiting liver transplantation because they are hypercatabolic. Standard formulas should be used, although the volume needs to be restricted to 75% of maintenance and the concentration should be increased to maintain glucose levels (> 4 mmol/L). There is no need to reduce protein content, particularly if the patient is electively ventilated. As indicated above, intravenous use of BCAAs for the treatment of hepatic encephalopathy or coma has not been evaluated in children, although they can be of value in adults.

Behavioral Feeding Problems

Behavioral feeding problems are common in this group of children, particularly in infants who have had long-term nasogastric feeding. Feeding problems are compounded by the use of unpalatable feeds, medications, and excess parental anxiety about feeding and growth.

Strategies to prevent behavior problems include daytime feeding to provide oral stimulation and encouraging children to experiment with flavors and textures appropriate to their age. The success of these techniques is dependent on a multidisciplinary approach involving a clinician, nurse specialist, dietitian, clinical psychologist, speech therapist, and play therapist.[35]

SPECIFIC DISEASE STATES

Acute Liver Disease

Most children with acute viral or autoimmune hepatitis require no nutritional supplementation. Fulminant hepatic failure requires careful management of protein to prevent hepatic encephalopathy and to reduce excess protein catabolism. Protein should be restricted only for short periods of time to treat severe encephalopathy (see above). Fluid volume can be reduced to prevent or treat cerebral edema; it is critical to maintain adequate glucose levels by infusing 6 to 8 mg/kg/minute of glucose to prevent hypoglycemia. Enteral nutrition should be continued as long as the child is conscious and in the early stages of elective ventilation. Once the requirement for liver transplantation becomes obvious, parenteral nutrition should be started to provide sufficient calories to prevent additional protein catabolism (see above).

Chronic Liver Disease

The majority of children with chronic liver disease will have cholestasis, either from biliary atresia, Alagille syndrome, or familial intrahepatic cholestasis and should be managed as indicated above. Children who are not jaundiced require similar support, although their requirement for fat-soluble vitamin supplementation will be less.

Problems can arise with children who have ascites and fluid retention; fluid restriction might be required. In these circumstances, modular feeds, which allow individual prescription of protein, sodium, and water and to which complex carbohydrate polymers, fats, vitamins, and mineral are added to produce a highly energy-dense feed, can be of value.

Inborn Errors of Metabolism

A number of inborn errors of metabolism rely on dietary modification as part of therapy. These include galactosemia, hereditary fructose intolerance, and tyrosinemia type I.

Galactosemia is an autosomal recessive disorder in which there is a reduction in the enzyme activity of galactose-1-phosphate uridyl transferase, which prevents the conversion of galactose to glucose. Dietary treatment

includes removing all products containing galactose (ie, milk and milk products).[105]

Hereditary fructose intolerance is an autosomal recessive disorder caused by a deficiency or absence of the enzyme aldolase B, which leads to cirrhosis and renal tubular disorders. Dietary management consists of elimination of fructose, sucrose, and sorbitol from the diet; this must be maintained for life. This means that all fruit and fruit juices are eliminated from the diet and only certain vegetables are permitted. Commercial products such as breads and cereals can also contain small amounts of sucrose, as can medications and toothpaste.[106]

Tyrosinemia type I is an autosomal recessive disorder caused by a defect in the enzyme fumarylacetoacetase, which leads to hypertrophic cardiomyopathy, cirrhosis, and renal tubular acidosis. For many years, dietary treatment was the only method of therapy and included restriction of phenylalanine, tyrosine, and methionine. Although restriction of these amino acids was effective in normalizing plasma amino acids, it did not prevent the progression of liver failure or the development of metabolic crises. The development of NTBC (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexenedione) in association with dietary treatment has altered the natural history and outcome of the disease.[107]

Glycogen Storage Disease

The hepatic glycogen storage disorders are a group of autosomal recessive inherited disorders that lead to defects in the metabolism of glycogen. Liver and skeletal muscle are usually affected but heart, kidney, bones, and brain can also be involved. The presentation and biochemical features depend on the precise enzyme deficiency. Nevertheless, the treatment is dietary: to provide a continuous supply of exogenous glucose, either intravenously or enterally, to maintain normal glucose, and to suppress counterregulatory responses. In infants this is best achieved by frequent daytime feedings or continuous nocturnal enteral glucose feeding. In older children, the oral feeding of uncooked cornstarch (1 to 2 g/kg every 4 hours), which is hydrolyzed in the gut to release glucose slowly, can reduce the need for frequent daytime feedings or continuous nocturnal feeding.[106] Glycogen storage disease type III requires similar treatment but with a higher protein intake (3 g/kg). In most instances, dietary management is successful and can prevent the long-term complications of these diseases.

Preparation for Liver Transplantation

Liver transplantation is indicated for both acute and chronic liver failure. Nutritional support is of particular importance for children with chronic liver failure because malnutrition is a significant risk factor for mortality and morbidity related to liver transplantation.[64,66,67]

Chin and colleagues prospectively studied 26 children pre- and post-transplantation. They identified a significant difference in the 2-year actual survival for children with standard deviation scores (SDS) for weight of greater than –1 (57%) compared with those with scores less than –1 (95%) at the time of transplantation.[67] Similar data were obtained from Moukarzel and colleagues using height SDS. Children who were less stunted (height SDS < –1) had less morbidity and mortality (91% 1-year survival) compared with those who were more stunted (height SDS > –1), who had a 1-year survival rate of 75%.[64] These data have recently been confirmed in a study that evaluated a number of risk factors, including malnutrition, in infants undergoing liver transplantation.[66]

Children awaiting liver transplantation require intensive nutritional support, depending on the etiology of their liver failure, as documented above, but the main principle is to provide a sufficient energy intake (Table 40-6).

Effect of Liver Transplantation on Nutritional Status

Many recent studies have documented the nutritional rehabilitation achieved by successful liver transplantation.[5,67,70,108]

Following liver transplantation, surviving children experience a rapid return to normal midarm muscle area and midarm fat within 3 to 6 months.[70,108] Initial weight gain can be rapid because of the effects of corticosteroids on appetite and salt and water retention, but most children return to a normal weight once corticosteroids are reduced or discontinued. Linear growth is often delayed by 6 to 24 months, depending on the rate of hepatic complications and the withdrawal or reduction of corticosteroids.[109–111]

Preoperative nutritional status has a strong influence on post-transplantation growth. Children who were less stunted at transplantation grew slowly initially but finally achieved normal growth velocity, whereas older children who were more stunted (height SDS > –2) grew more quickly initially post-transplantation but did not achieve normal height.[112,113] There are no differences in catch-up growth between the sexes or with pretransplantation disease, apart from Alagille syndrome, which is associated with growth failure before and after transplantation in 50% of patients.[114,115]

Although successful liver transplantation reverses most aspects of malnutrition, it can be some months or years before bone density returns to normal. Persistent osteoporosis and bone fractures have been described at 3 to 6 months following transplantation[116] and were exacerbated

TABLE 40-6 Nutritional Support in Children Before and After Liver Transplantation

Requirement	*Preoperative*	*Postoperative*
Carbohydrate (g/kg/day)	Glucose polymer 15–20	Glucose polymer 6–8
Protein (g/kg/d)	Low-salt protein 3–4	Whole protein 2.5–3
Fat (g/kg/d)	50–70% medium-chain triglyceride 8	Long-chain triglyceride 5–6
Energy intake (estimated average requirement)	130–150%	120%

by the effects of corticosteroid therapy. Clinical studies to evaluate the use of bisphosphonates in the treatment of metabolic bone disease before and after transplantation are under evaluation.

Effect of Growth Hormone and IGF-I

As indicated earlier, both growth hormone and IGF-I are necessary for normal growth, and it has been shown that plasma IGF-I levels are low in children with chronic liver disease, despite elevated serum growth hormone. Although post-transplantation IGF-I and IGF-BP3 rise significantly and IGF levels return to normal, abnormalities in the IGF-binding proteins BP1, BP2, and BP3 remain for some months.[49]

Prevention of Growth Failure After Transplantation

The nutritional strategy for the prevention of growth failure before and after liver transplantation begins with intensive nutritional support preoperatively. Children who are malnourished before transplantation should be maintained with parenteral nutrition perioperatively until normal nutrition is resumed, whereas children with normal nutritional status should start enteral feeding with a rapid buildup of calorie intake 3 to 5 days following transplantation.

It is important to ensure sufficient energy intake (at least 120% of estimated average requirement) following the operation. This can be provided as a modular feed or supplemental nocturnal enteral nasogastric formula feedings in infants who refuse oral feeding and as diet in older children with calorie supplements. The energy intake should include 2.5 to 3 g protein/day and glucose polymer (6 to 8 g/kg/day), but fat can now be provided entirely as long-chain fat (5 to 6 g/kg/day) unless cholestasis secondary to chronic rejection is a complication (Table 40-6).[117]

Glucocorticoids, used to prevent organ rejection, interfere with growth hormone excretion. As growth hormone, IGF-I, IGF-BP1, IGF-BP2, and IGF-BP3 remain abnormal following transplantation, it is rational to consider whether growth hormone therapy might be helpful. Recombinant human growth hormone has been evaluated in eight growth-retarded children following liver transplantation.[118] The median growth rate increased from 3.2 to 7.1 cm/year ($p = .025$) and height SDSs increased from –2.9 to –3.1 ($p = .036$) during the first year of growth hormone treatment. Both IGF-I and insulin IGF-BP3 levels increased significantly during treatment. There was no effect on graft function, and no child developed rejection or any other complication, but growth velocity was not maintained beyond the first year.

CONCLUSION

The essential role of the liver in energy and growth has particular relevance for infants and children with end-stage liver failure. Considerable progress has been made in understanding the pathophysiology of malnutrition in liver disease, and this has improved our ability to support these children. Nutritional rehabilitation has been achieved by intensive nutritional support, and mortality following liver transplantation has been reduced. Its success depends on a multidisciplinary approach based on early intervention and prevention of malnutrition.

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CHAPTER 41.1

CANCER PREVENTION

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There is increasing evidence supporting the concept that nutritional factors play a major role in the pathogenesis of several forms of cancer. Doll and Peto have estimated that, overall, about one-third of cancer cases are related to nutritional factors.[1]

Many of these studies, however, deal with cancers that generally do not occur in childhood, such as cancers of the breast, colon, prostate, and lung.[2–4] Our efforts in children need to be targeted at establishing at an early age those healthful dietary and lifestyle patterns that will form the basis for long-term reduction of risk of these cancers, as well as the risk of heart disease, diabetes, and other chronic diseases.

Chief among the concerns of prevention of adult cancer is the ominous rise of obesity in childhood.[5] Many more children are obese and even massively obese than in previous years,[6] especially in lower socioeconomic groups in the United States. Type II diabetes, previously and appropriately called adult-onset diabetes, is increasingly being diagnosed in adolescents, particularly in obese adolescents.[6] Childhood obesity is well recognized as leading to adult obesity, which, in turn, increases the prevalence and accelerates the course of several forms of cancer.

Nevertheless, there appear to be nutritional factors that might be specifically involved in the development of cancer during childhood and adolescence. Immune deficits could be important in cancer proliferation, and specific dietary factors, such as zinc,[7] clearly regulate immune competence. Hormonal secretion, particularly of insulin-like growth factor[8] and insulin,[9] is influenced by dietary factors, which, in turn, influence immune function. The colonization of the gut has been proposed as another factor specifically involved in the development of immune response in childhood[10] that could influence risk of cancer later in life. Nutritional and metabolic factors influence the child under treatment for cancer and the risk of second malignancy.[11]

A body of knowledge thus suggests that diet and nutrition in childhood set the stage for adult cancer as well as influence the prevalence of cancer in childhood itself. The pathogenesis of cancer is complex, but it might be useful to assess the current status of the scientific basis for making cancer prevention recommendations for children, as well as identifying the gaps in knowledge that need to be addressed by future research.

Let us begin by examining some of the specific nutritional factors that might relate to cancer etiology in children.

BREAST-FEEDING

There has been interest for many years in the possible association between breast-feeding and reduction in risk of subsequent maternal breast cancer. For example, Chinese women who breast-fed their children for 9 or more years had less than 40% of the risk for breast cancer than did mothers of infants breast-fed for 3 or fewer years.[12] Although long-term breast-feeding is common in China, it is hardly practiced at all in Western societies, but other findings show that breast-feeding for 6 or more months is associated with significant risk reduction of breast cancer compared with no breast-feeding.

More recently, there are suggestions that maternal breast-feeding might also have a protective effect on development of cancer in children. In one report, those women who reported having had any degree of breast-feeding as infants had 0.7 risk of developing breast cancer as adults. The reduction in risk was similar in premenopausal and postmenopausal women.[13] In a case-control study undertaken in the United States by Davis and colleagues, a negative correlation was observed between the duration of breast-feeding and the incidence of a variety of malignancies in the children.[14] For those who had been bottle-fed exclusively or breast-fed for periods shorter than 6 months, there was nearly a doubling of overall cancer risk compared with the rate in children who had been breast-fed for longer than 6 months. The protective effect of breast-feeding was strongest for lymphoma: children who were not breast-fed at all or breast-fed for less than 6 months had more than five times the risk of lymphoma than those who had been breast-fed for 6 or more months. These results are dramatic but, in our opinion, still preliminary because of the small number of cases involved.

Similarly, in a case-control study of children aged 2 to 14 years from the United Arab Emirates, breast-feeding for 6 months or less was associated with significantly increased risk for acute lymphocytic leukemia (OR = 2.5), Hodgkin's lymphoma (OR = 3.8), and non-Hodgkin's lym-

phoma (OR = 4.1) compared with that of children breast-fed longer than 6 months.[15]

A comprehensive study intended to identify risk factors for acute childhood leukemia found that breast-feeding for any period reduced the risk of childhood leukemia by about one-fifth.[16] The reduction in risk was comparable for acute lymphoblastic leukemia and acute myeloid leukemia and appeared to be greater for both types with more prolonged breast-feeding.

Parker, in summarizing the results of recent reports, concluded that the evidence in its entirety is in support of a significant protective effect of breast-feeding on childhood leukemia and lymphoma.[17] Based on the effects described so far, Parker estimated that as many as one-fourth of the cases of childhood leukemia and lymphoma could be prevented if all infants were breast-fed. This benefit is in addition to other well-established effects of breast-feeding, including improving immunologic function, resisting infection, and reducing obesity and the prevalence of subsequent chronic diseases as adults.

SEXUAL ACTIVITY

One of the health risks of early adolescent sexual activity that has not received adequate attention is an increase in the prevalence of cervical cancer. Although health professionals tend to think of this cancer as being restricted to adult women, in fact, it is being found increasingly in adolescents.[18] The age at which invasive cervical cancer is first diagnosed has been decreasing in Western countries[19] and has been correlated with the age of first sexual intercourse.[20] Certain methods of contraception, such as condoms and diaphragms, which form barriers, tend to reduce the risk of cervical cancer somewhat. The infrequent use of these methods by adolescents further compounds the risk of unprotected sexual activity. Adolescence is a critical time because the cervical epithelium is undergoing rapid evolution and is particularly sensitive to carcinogens.[19,21]

The worrisome rise in cervical cancer offers the opportunity for nutritional intervention at a time when it could potentially be highly effective. The most appropriate nutritional regimen for the prevention of early cervical cancer, however, is not clearly established at present. It is likely to include cessation of smoking and alcohol use, as well as folate and zinc supplementation. Further research is needed on the natural history of cervical cancer in young women because it is not known with certainty what percentage of cases will remain localized and what percentage will become invasive, and whether nutritional factors regulate invasiveness.

PESTICIDES AND OTHER ENVIRONMENTAL CARCINOGENS

The role of pesticides as possible causes of cancer in childhood has attracted recent interest. Children can be exposed to pesticides not only in foods that they consume but also in the environment of household gardens and farms. A recent report found an association between neuroblastoma in young children above the age of 1 year and an environment with high concentrations of pesticides in the garden.[22] It is conceivable that pesticides compromise immune function and limit immune surveillance.[23] Other pesticides have estrogen-like activity and could possibly disrupt normal development by inducing higher than normal concentrations of hormonal stimuli that regulate neural cell development.[24]

In any event, the entire subject of potential risks of pesticides serves as a lightning rod for controversy. At present, these findings are intriguing but can be viewed only as preliminary, requiring further extension and confirmation before they can serve as guidelines for public health recommendations. Obviously, unnecessary exposure of children to pesticides should be avoided, but their significance as a major cause of childhood malignancy is still unclear.

There is no doubt that there are a large number of toxic substances in the environment that potentially could be causes of childhood cancer. These substances can be grouped into several categories:

- products of nitrosation, including betel nut and nitrites
- natural carcinogens, such as mycotoxins, pyrrolizidines, and safrole
- products of pyrolysis and smoking of food to yield carcinogenic hydrocarbons
- certain specific food additives, including flavors, azo dyes, pollutants, and contaminants[25]

These agents generally have a long latent period so that exposure during early infancy and childhood conceivably could be carcinogenic during the period of late childhood or in adult life.[25] More information is urgently needed on the factors that govern bioavailability, absorption, excretion, and metabolism of these potential carcinogens and on possible nutritional means of prevention.

Recent reports have proposed that some cases of childhood leukemia and neuroblastoma could be attributable at least in part to the role of external pollution. Infante-Rivard and colleagues have alerted the scientific community to the possible association of contaminated drinking water, with its contents of trihalomethanes, metals, and nitrates, with increased prevalence of acute lymphoblastic leukemia.[26] This is an intriguing suggestion that needs further extension and confirmation. One critic of the study felt that it could explain at most only a small fraction of the total number of cases.[25] Daniels and colleagues reported an association between exposure to pesticides and incidence of neuroblastoma.[22] This preliminary finding is also provocative but needs further support.

The results of studies of pesticides are disquieting because they raise the prospect that these environmental agents could lead, over the long run, to cancer development. Herbicide and pesticide use is widely practiced in the United States, and it is likely that for any given dose of these agents, children might be more vulnerable than are adults.[27,28]

A disturbing report indicated that baby bottle nipples and children's pacifiers contain appreciable concentrations

of nitrosamines and their precursors.[29] Under conditions of normal use, as much as one-third of the nitrosamines in the nipples were taken up by the formula within a few hours. This study, if confirmed and extended, urges intense scrutiny of such baby products on an international basis because they could cause serious hazards that are avoidable.

CHILDREN'S DIETS

As noted above, children are becoming more and more obese; this is generally attributable to a combination of reduced physical activity and larger portion sizes of readily available high-calorie food. Efforts to link childhood cancers with weight gain or with specific dietary items, however, have generally proven elusive. It is of interest, therefore, that more than 20 years ago, an association between rhabdomyosarcoma in childhood and consumption of organ meats was described with a relative risk (RR) of 3.7.[30] A small number of cases were involved, but the association was quite strong. It would have been helpful if the duration of adherence to this diet had been specified. To our knowledge, this intriguing relationship still requires confirmation with respect to rhabdomyosarcoma. If verified, it would be one of the first examples of a cancer in childhood that is influenced by some of the same factors linked to cancer in adults.

Several studies have examined the possible association between brain tumors and cured or organ meat consumption by mothers during pregnancy. It seems fair to conclude that increased maternal consumption of cured meats has been observed in some studies of infant brain tumors, but the associations are by no means definitive, and they have not been observed in every report.[31] There seems to be no clear relationship between consumption of cured or organ meats by children and the development of any cancer, except as noted above.

MALNUTRITION AND CANCER IMMUNITY

Causal relationships among malnutrition, immune deficiency, and susceptibility to cancer development have been suspected for more than three decades. Malnutrition is increasingly recognized as a frequent cause of immune deficiency (see also Chapter 20, "Malnutrition and Host Defense").[32–34] Although the relationship between malnutrition and impaired host defense against infections is supported by many studies and observations, establishing analogous relationships for immune response against cancer has proven complex.

Tumors compete for the same nutrient supply as the host, and dietary composition affects tumor growth.[35,36] Spontaneous tumors are immunologically "self," and classic antibody responses are rarely detectable and perhaps might be only weakly recognizable by the host immune system. Furthermore, evidence that caloric restriction reduces cancer risk in the cancer-prone animal might be interpreted to mean that nutrient intake generally supports cancer growth.[37,38] The discussion presented here will show that nutrients have differential effects on tumor growth and host immune response. Caloric restriction in animal models does not translate easily to human tumor risk, although these investigations could reveal key interactions relevant to obesity. Furthermore, new data reveal the potential effectiveness of human immune response to tumors.[39–42] On balance, emerging data suggest that nutrients are regulators of immune response and as such are also critical host modifiers for risk of cancer development.

Malnutrition and Host Response to Cancer

Malnutrition is frequently an important complication of malignancy despite normal nutrient provision, and poor nutrient status appears to confer risk of reduced response to cancer treatment.[43,44] This can present as progressive wasting in many types of cancer and is currently recognized as a critical factor in morbidity and mortality.[45,46] Loss of skeletal muscle protein and depletion of body lipid stores are notable in the cachectic patient. Furthermore, adipose tissue is depleted as well, in association with nitrogen loss. Metabolic change is associated with alterations in circulating hormone concentrations, including insulin, glucagon, and glucocorticoids.[47] Effects on metabolism are examined in Chapter 41.2, "Cancer Treatment."

Cancer-associated anorexia and cachexia are characterized by a persistent inflammatory immune response and a catabolic hormonal environment marked by increased circulating levels of tumor necrosis factor α (TNF-α), also known as cachexin.[48,49] Other cytokines, including interleukin(IL)-1, IL-6, interferon-γ, and factors such as leukemia inhibitory factor and ciliary neurotrophic factor, are also mediators of the cachectic process.[50–52] Some investigators have proposed that anorexia could involve persistent stimulation of anorexigenic neuropeptides, such as corticotropin-releasing factor, acting to inhibit the neuropeptide Y orexigenic network.[51] Other studies have focused on the possible role of leptin, the proinflammatory and cytokine-like hormone that acts as a negative feedback signal in the control of food intake and body weight but also affects immune response. However, current studies indicate that increased levels of proinflammatory cytokines, including IL-1, IL-6, TNF-α, and interferon-γ, do not correlate with increased levels of leptin. Although some individual patients show significantly increased levels, no direct correlations have emerged.[53,54] Thus, the basic causes of anorexia in cancer patients remain unclear.[55]

Cachexia, which is often independent of anorexia, is closely associated with an increased and deregulated inflammatory response and appears to reflect the stress of host defense and evolving immune deregulation in response to the presence of the tumor.[43,46–48] Nutritional support and appetite stimulation are largely ineffective in restoring lean body mass in the cancer patient, although weight gain and quality of life can be improved.[48,56] In contrast, reducing the proinflammatory response, specifically with fish oil supplying eicosapentanoic acid through dietary means, appears promising in reversing the catabolic environment.[38,57] Perhaps equally importantly, directed nutrient support could be capable of enhancing immune response toward the tumor and therefore could potentially exert a protective effect against metastasis.

Deficient Immune Response and Cancer Risk

Deficient immune response is often observed in studies of cancer patients when thymus-derived, T-lymphocyte proliferation to mitogens is assessed in vitro.[58–60] However, spontaneous T-cell activation and increased circulating levels of cytokines such as interferon-γ are also observed,[58] suggesting a link between increased inflammatory cytokine production and reduced response to another stimulus. Heimdal and colleagues recently showed that decreased response to nonspecific mitogen and increased spontaneous T-cell activation are associated with poor prognosis in head and neck cancer.[59] Current studies also report that an increased inflammatory response characterized by high circulating levels of IL-2 receptors is linked to poorer response to immunotherapeutic use of IL-2 in the cancer patient.[60]

These studies suggest causal links among deregulation of the cytokine network, effects on the neuroendocrine response, and host response to cancer. As discussed below, the pattern of cytokine response the host produces in response to tumor could be prognostic. Thus, re-establishment of nutrient balance might be used to modify host response and decrease risk of inadequate treatment response.

The concept that tumor antigens could ever be significantly immunogenic in the cancer-bearing host, despite being of self-origin, is gaining credence as investigations reveal existence of tumor-reactive cells using novel recombinant protein strategies.[40] Related studies have shown that type and strength of host response to tumor vaccine are specifically related to cancer survival and are also independent of response to other, unrelated antigens or to nonspecific activators.[39] Furthermore, emerging studies are showing that the type of immune response that patients develop toward autologous tumor is related to outcome.

For example, in the case of experimental murine lymphoma, host immune response that is predominated by production of T helper type 2 (Th2) cytokines has been shown to be fatal.[61] Extensive investigation into why response to tumor antigens is frequently ineffective has shown that tumors induce immune dysfunction in the host through a variety of mechanisms, including blockade of monocyte antitumor defense. For example, tumors produce cytokines, growth factors, and other molecules, including IL-4, IL-6, IL-10, tumor growth factor β1 (TGF β1), prostaglandin E_2 (PGE_2), and monocyte colony-stimulating factor (M-CSF), that have differential effects on immune cells in different blood compartments, leading to suppression of monocyte-mediated host defense.[62] These tumor mechanisms operate through impact on the cytokine response, and this response is critically modulated by nutrients (see Chapter 20, "Malnutrition and Host Defense").

Until comparatively recently, evidence that immune deficiency alone is a risk factor for cancer was sketchy because primary immune deficiency was underdiagnosed and few follow-up studies were completed or reported. With continued study, the relationship between impaired immune response and cancer has been clearly shown. Immune deficiency arising from primary genetic causes or in the context of immune system infection is a significant and direct cause of increased susceptibility to cancer. Malignancies, particularly B cell lymphoma, often develop in patients with common varied immunodeficiency or hypogammaglobulinemia.[63,64] Human immunodeficiency virus (HIV) infection, which produces profound immune deficiency, is frequently associated with cancer even in the context of effective antiretroviral therapy. Increased incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma has been consistently observed in epidemiologic studies of HIV-infected adults, in whom appearance of these tumors is diagnostic for acquired immune deficiency syndrome (AIDS). Now that children congenitally infected with HIV are living longer with better treatment, they are developing these malignancies with a frequency that is similar to that reported for adults.[65,66]

Nutrients as Modifiers of Host Response

Worldwide variation in diet is thought to account for perhaps one-third of the environmental differences in cancer incidence.[67] However, the exact causal relationships have been difficult to establish. Intake of fruits and vegetables and increased fiber consumption are clearly protective against certain cancers,[68–71] and some current supplementation studies indicate benefit.[72,73] Variable and conflicting results have also been reported,[74,75] suggesting difficulties in obtaining clear results with single interventions when underlying variables among participants, such as smoking—currently on the rise in adolescents—can confound the observations.

Nutrients can have different effects in pediatric cancer patients because presentation is often acute and occurs over a wide range of ages and developmental stages that need to be considered in terms of both effects on growth and possible interactions with the immune system. Severe weight loss is a notable cause of morbidity in children with cancer.[76] As discussed in Chapter 41.2, "Cancer Treatment," the basis of weight loss in children with cancer is incompletely understood but includes increased protein turnover and loss of the normal compensatory mechanisms that occur in starvation.[77,78]

Whereas children with failure to thrive often have decreased immune response, especially reduced reactivity on skin testing, there is no clear association with spontaneous tumor development. Children with Bloom syndrome have genetic susceptibility to almost all cancers and also have marked growth deficiency. In a recent study, Keller and colleagues reported that all children with Bloom syndrome are stunted throughout life. In addition, more than half of children with Bloom syndrome are significantly wasted until 8 years of age. Yet this difference was unrelated either to early death or to malignancy when wasted children with Bloom syndrome were compared with children with Bloom syndrome who were not wasted.[79]

Among children, the predominant malignancies are hematopoietic, and some studies of untreated children have reported no anthropometric changes even when high-risk disease was considered.[80] However, more subtle changes could prove important in stratifying children who would benefit from early intervention.[81] For example, recent studies show that chronic zinc and magnesium

deficiency are differentially prevalent among children with lymphoblastic leukemia and lymphoma.[82] Both zinc and magnesium deficiencies have profound effects on immune response. Thus, the importance of evaluating children with cancer for potential nutritional support is increasingly recognized and could reduce risk of inadequate response to therapy by increasing immune response, as well as by supporting tolerance of therapy and improving quality of life.[77,81,83]

Risk that chemotherapy will lead to febrile neutropenia, precipitating an inflammatory syndrome and weight loss, is well recognized as a major concern in pediatrics.[84,85] Importantly, bone marrow recovery is often uneven, and reconstitution of immune response can lag behind, leaving the weakened host vulnerable to infection. Cytokines are involved in the etiology of sepsis and are more predictive than acute-phase proteins, such as C-reactive protein,[86] because these are markers of a process in which loss of immune function is central. Future studies might include the impact of dietary elements such as glucans, which appear to exert growth factor effects in supporting hematopoiesis and immune response in the cancer patient.[87]

Tumor phenotype is affected by environmental nutrients.[35,36] Growing tumors require more nutrients, and nutrient modulation can strongly affect metastatic activity.[88] In general, antioxidant nutrient supplementation and protein depletion appear to reduce tumor growth.[89,90] Furthermore, a large body of data over many decades strongly supports the protective effect of caloric restriction in reducing tumor growth in animal models of solid tumors.[37] Caloric restriction could also have a benefit in obese persons with risk of colon cancer, as measured by effects on rectal cell proliferation.[91] One epidemiologic study on adult height and risk of breast cancer found that adolescent caloric restriction during World War II leading to reduced final height was associated with reduced risk of breast cancer.[92] Relationships to specific foods eaten or not eaten, however, was outside the scope of the study.

In contrast, the Netherlands Cohort Study, which performed a similar examination, found no correlation between energy restriction owing to food deprivation during the adolescent growth spurt and decreased incidence of breast cancer.[93] Whereas anorexia nervosa can be associated with reduced risk of cancer in women, another relevant study also noted the suggestion of a possible increase in men.[94] Studies using the cancer-prone p53-deficient mouse convincingly show that caloric restriction reduces insulin-like growth factor I and leptin levels, reduces cell proliferation, including thymocytes, and increases latency of spontaneous tumor appearance while decreasing tumor progression.[38,95]

On the other hand, deficiencies of micronutrients, such as zinc, can increase cell proliferation and enhance tumor incidence experimentally.[96] The value of caloric restriction, which is based on increasing the caloric expenditure-to-intake ratio possibly through adrenal hypertrophy,[97] might be less relevant in growing children and even potentially dangerous, especially when compared with more moderate approaches that include increasing exercise as a safe means of reducing risk.[98] In light of new data suggesting fundamental gender-related differences in immune response and other studies linking neuroendocrine and immune response in a range of stress-producing circumstances, such as trauma and severe nutrient deprivation, the effects of caloric restriction on the immune system need to be studied in greater detail.[99–101]

Taken as a whole, these studies have introduced a note of caution regarding the possible risk of indiscriminate nutrient supplementation in cancer. However, as epidemiologic and experimental studies have suggested the benefit of such dietary constituents as fiber in cancer prevention, alternative dietary approaches have emerged for the cancer patient. Although most are nutritionally adequate for adults, no anticancer diet has been shown to cure cancer, and there is concern that such diets might not be adequate for children.[102] As discussed below, the balance of studies to date suggest that support of the mucosal immune system in the cancer patient is beneficial and often critical. Therefore, despite theoretic concerns that nutrients provided to stimulate host immunity might in fact feed the tumor, evaluation and treatment of malnutrition in the pediatric cancer patient are recommended as a means of reducing risk of poor outcome.[76,77,83]

NUTRIENT SUPPORT OF MUCOSAL IMMUNE RESPONSE

Products of digestion have been linked with cancer risk. For example, increased calcium from milk consumption in adolescence, which can lower levels of 1,25-dihydroxyvitamin D, has been linked to susceptibility to testicular cancer in men but has shown a protective effect for breast cancer among women.[103,104] The mechanisms of these effects likely involve changes at several levels and precede tumor development by months or years. Furthermore, levels of nutrients known for chemoprotective effects, such as betacarotene, zinc, and selenium, studied in children at the time of cancer presentation do not appear to correlate with outcome.[105] Understanding the interaction among nutrients, the gastrointestinal immune system, and the emerging role of the normal or commensal microflora could illuminate some of the critical relationships.

Immunonutrition

Concerns that total parenteral nutrition (TPN) can enhance tumor growth in the cancer patient have been allayed by growing experience, such as a recent report that TPN was beneficial in treatment of malnourished patients undergoing high-dose IL-2 therapy for metastatic cancer.[106] TPN has also proven useful in support of catch-up growth in the child with cancer[107] and could support restoration of innate immune function.[108] However, nutrient metabolism provides an essential stimulus for the induction, differentiation, and maintenance of the mucosal immune system.[109,110] Prolonged illness, reduced dietary intake, and lack of enteral feeding directly affect this. Lack of enteral dietary intake impairs mucosal IgA and secretory component production, the number of IgA-containing cells, and the level of IgG, as shown in recent studies.[111,112]

The enteral route of nutritional intake promotes mucosal growth.[113] Loss of this stimulation is associated with immune suppression, as shown by the negative effects of parenteral nutrition. Glutamine, arginine, certain combinations of omega-3 polyunsaturated fatty acids, and dietary nucleotides are necessary for recovery of mucosal immune function.[114] Experimental and human studies have shown that glutamine supplementation of the tumor-bearing host attenuated loss of protein caused by glutamine depletion of host tissues and had a protective effect on immune and gut-barrier function.[115] The benefit of other nutrient combinations is not as clear.

A recent meta-analysis evaluated response to key nutrient enteral supplementation in gastrointestinal surgery and found reduction in infections.[116] However, this benefit was not as clear for cancer patients given early enteral feeding after surgery for upper gastrointestinal malignancy.[117] Supply of normally nonessential amino acids, specifically arginine and glutamine, promotes cellular proliferation in the gut, T-cell production, and the development of host defense against infection.[118] The central impact of glutamine administration on immune function appears to be mediated through initiation of a Th2-type cytokine response with increased IL-4 production and mucosal IgA level,[119] which has been shown to improve both gut-associated lymphoid tissue (GALT) and respiratory tract immunity.

Commensal Microbes and Probiotics

As discussed above, nutrients stimulate and act as substrates for the development of mucosal immunity. In addition, emerging studies have shown that lactic acid bacteria traditionally used in the production of food can play a key role in support of a healthy gastrointestinal tract. Mucosal immune response is largely developed after birth in response to microbial interactions. Microflora mold the architecture and physiology of the mucosa through activation of immune response, and this interaction continues to influence immune response throughout life.[120,121] Emerging studies suggest that the specific composition of microflora is highly varied in different cultures.[122] Normal flora do not directly harm the normal host and also contain certain commensals that produce nutrients, absorbable peptides, and vitamins that benefit the host.[123,124]

The potential significance of this lifelong interaction could be studied only comparatively recently, with the advent of genetic typing. These studies show that the well-characterized beneficent commensals, such as lactobacilli, form a small and rather fragile part of the overall flora.[122] Commensal bacteria are mainly obligate anaerobes, whereas key pathogenic bacteria are facultative anaerobes and replicate faster in the presence of oxygen. Thus, lactobacilli and bifidobacteria, which are normal gut commensals, survive and replicate in the presence of oxygen but not as effectively as *Escherichia coli* does.

Metchnikoff was the first to propose that lactic acid bacteria could have a favorable effect on health,[125] but the concept of probiotic bacteria as living microbes introduced to improve intestinal microbial balance is recent.[126] Probiotic bacteria can be administered to stabilize the gut mucosal barrier[127] and have been found effective against bacterial and viral diarrhea in infants,[128] perhaps against antibiotic-associated diarrhea[129] and even against the effects of *Clostridium difficile*.

Experimental studies have shown that probiotic lactobacilli can replace microflora that produce carcinogens and tumor promoters, neutralize carcinogens, and produce antitumor factors through direct actions in the gastrointestinal tract.[130,131] Furthermore, related studies indicate that consumption of certain fructans, such as oligofructose and insulin, which have been observed to selectively increase the growth of intestinal probiotic bacteria such as bifidobacteria, exerts a beneficial prebiotic effect, leading to reduced colon cancer risk.[132] Essential characteristics for probiotic efficacy include resistance to acid and bile and ability to colonize and adhere to the colonic mucosa.[133] Moreover, current studies suggest that probiotic lactobacilli can promote immune response and serve as immunoadjuvants and that lactobacilli can be used to increase weak systemic immune response, even in the HIV-positive host.[10,120,134]

Recent studies show that lactic acid bacteria synergize with the immunomodulatory effects of alkylglycerols.[135] Mechanisms of action could include competition for specific ecologic niches, immunologic stimulation of the mucosal barrier, and induction of specific cytokine patterns.[128,136,137] Indirect evidence suggests that some probiotic bacteria could protect against risk of cancer.[138] In the colon, probiotics or prebiotics could have detoxifying effects on genotoxins.[139] Ingestion of prebiotics affects the spectrum of fermentation products, leading to high concentrations of short-chain fatty acids. Gut flora have been shown to induce chemopreventive glutathione transferase activity.[139] These changes could provide a balance to the potentially pathologic consequences of normal persistent microbial colonization of the gut.[140]

Although studies in humans are preliminary, there are suggestions that lactic acid bacteria could have a balancing effect on immune function in addition to antimicrobial effects. For example, probiotic bacteria appear to improve conditions related to food allergies and to down-regulate a proinflammatory response to milk in hypersensitive subjects while up-regulating the same response in healthy, unaffected persons.[141,142] Consumption of lactobacillus-fermented dairy products could elicit antitumor effects. These effects are possibly attributed to the inhibition of mutagenic activity and a decrease in activities of several enzymes implicated in the generation of carcinogens, mutagens, or tumor-promoting agents.[143] Future studies are needed to show how these interactions will affect lifetime risk of cancer and whether the child with cancer can benefit from probiotics.

Future Directions

The challenge of understanding the nutritional factors that might be involved in the pathogenesis of cancers in adults is difficult enough, but in childhood it is even more difficult. The prevalence patterns of cancer are different, the time periods of exposure to carcinogens or to relevant dietary fac-

tors are shorter, and there is a significant lack of appropriate biomarkers. Furthermore, fewer studies have been carried out among children, and those cancers most extensively explored with respect to diet in adults, namely lung, colon, breast, and prostate, very rarely occur in childhood.

Thus, it is apparent that very little information is currently available on the dietary and nutritional factors that promote cancer in infancy and childhood. In particular, the possible effects of maternal dietary and metabolic influences during pregnancy and lactation require clarification. To elucidate these possible relationships and to describe the underlying mechanisms involved precisely, our research must become more interdisciplinary. It is vital to link basic science with clinical investigation. We should be investigating gene–nutrient interactions using the latest techniques in molecular biology and molecular nutrition, such as DNA microarray, in order to provide recommendations for cancer prevention in childhood. It is essential that we gain an understanding of the relationships among dietary constituents, risks of carcinogens, and genetic polymorphisms.

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CHAPTER 41.2

CANCER TREATMENT

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The need for nutrition support in children with cancer is dictated by how the combined impact of the tumor, the chosen therapy, and their complications affect host metabolism. The prevalence of weight loss and malnutrition at the time of cancer diagnosis is low in children compared with that in adult cancer patients.[1,2] This may be partly attributable to the higher incidence of leukemia in children, in which energy expenditure is not affected and tumor metabolic burden is small, and to the lower incidence of solid tumors in children compared with adults. Few pediatric malignancies affect the digestive system directly, and tumors that secrete metabolically active peptides are rare in children. Loss of appetite is more likely to be owing to therapy and the psychological effects of cancer diagnosis and treatment. However, reduced food intake can be related to cancer cachexia in children, and children are more susceptible to cancer-related undernutrition.[3,4]

Increased energy requirements have been reported in some, but not all, studies of adult patients with cancer. This has not been found to be the case in the single pediatric study to date.[5] The authors of this study reported that leukemia patients were not different in energy expenditure at diagnosis or during the first 2 weeks of therapy from age- and sex-matched controls. Energy needs of individual children who are undergoing therapy would be affected by decreased energy intake, infection, surgical stress, and cancer cachexia.[6]

TUMOR CACHEXIA: IMPACT OF CANCER ON TISSUE METABOLISM

In the first edition of this text, Dr. Kien described cancer cachexia as "a malnourished state characterized by weakness, anorexia, and altered body composition."[7] In this state, the body's response to starvation is altered, with loss of the ability to conserve nitrogen during food deprivation. Normal adaptation to starvation results in decreased protein synthesis, protein catabolism, and protein turnover, but in cancer cachexia, the rate of each of these processes is increased. Hepatic gluconeogenesis and protein synthesis increase at the expense of somatic protein, yet serum albumin may be low owing to increases in body water. Lipid stores are depleted and serum lipid is elevated, suggesting a loss of feedback control over peripheral triglyceride breakdown.[8] Glucose requirements appear to be increased, hepatic gluconeogenesis increases, and insulin resistance has also been documented.[9] Characteristically, cachexia is irreversible with the simple provision of adequate energy and protein. Cachexia, then, is similar to the hypermetabolism of sepsis, which is described below.

Of the various theories that have been proposed to explain cachexia, most evidence suggests that circulating cytokines cause these metabolic alterations.[10] Septic hypermetabolism, which is the systemic response to severe illness, and cancer cachexia are associated with a similar group of cytokine mediators. Lymphocyte-derived proteins (ie, cytokine, lymphokine, or interleukin [IL]) are released as a nonspecific response to tissue injury or immune insult, with resulting local and systemic effects. Lymphokine release can lead to a cascade of further lymphocyte response with release of other active peptides. Various cytokines are being studied, both as potential mediators of cancer cachexia and to provide potential therapeutic approaches to reversal of the cachectic metabolic derangement.[11] Several of these are discussed here briefly.

Tumor necrosis factor (TNF; cachectin) was identified as a peptide produced by macrophages in response to bacterial lipopolysaccharide and as a serum factor responsible for antitumor activity.[12] In animal studies, injection of TNF reproduced symptoms of cancer cachexia,[13] whereas anti-TNF antibodies reversed these effects.[14] Measurable quantities of TNF have been found in some, but not all, sera of cachectic cancer patients.[15] TNF is thought to act primarily locally rather than systemically.[16] Parenterally administered TNF probably causes cachexia by direct action on the brain.[17] The action of TNF is mediated in concert with the action of other cytokines (see below). Studies are in progress investigating the use of anti-TNF antibody as an adjunct to nutrition support in cachectic patients.[18]

IL-1 is also produced by macrophages in response to endotoxin. Its actions are similar to those of TNF, and the effects of the two cytokines are synergistic.[19] IL-1 has not been detected in the serum of either animals or humans with cancer[20]; however, systemic administration of IL-1 induces changes in hepatic protein synthesis that are similar to the changes observed in cachexia.[21] When IL-1 and TNF are administered to animals, they become hyperglycemic as gluconeogenesis and glucose turnover are increased.[22] IL-1-mediated inhibition of lipoprotein lipase results in hypertriglyceridemia,[23] similar to TNF. IL-1 induces production of TNF that, along with other cytokines, mediates some of IL-1's actions.[24] Antibodies to IL-1 are also being studied as adjunctive therapy for cancer cachexia.[14]

IL-6 and interferon-γ (IFN-γ) are cytokines that are part of a pathway induced by TNF or IL-1.[25] IL-6 is secreted by fibroblasts and macrophages stimulated with TNF, IL-1, and endotoxin.[14] As a mediator of the acute-phase response, circulating levels of IL-6 are associated with poor prognosis in sepsis.[26] Serum IL-6 concentrations have been shown to increase with increasing tumor burden in animals and with TNF treatment in cancer patients.[27] IFN-γ is produced by activated T lymphocytes, stimulates macrophages, and has antiviral properties. Anti–IFN-γ antibody was given to tumor-bearing animals, with resultant improved appetite and reduction in weight loss.[28] IFN-γ, like TNF, inhibits lipoprotein lipase activity.[29]

Because all of these active peptides have antitumor as well as antihost effects (ie, cachexia), the research goal is to discover how antitumor activity can be preserved at the same time that metabolism can be modulated by manipulating these effectors.[14,28] At this point in time, cachectic, like hypermetabolic, patients can be supported, but without the expectation that nutrition support can reverse the metabolic derangement (see below).

TUMOR THERAPY: IMPACT OF TREATMENT ON NORMAL METABOLISM

Surgery causes additional metabolic and nutritional stress in patients with malignancy. Meta-analyses of studies evaluating the efficacy of perioperative nutrition support have concluded that in normally nourished patients, nutritional support has no impact on surgical recovery and subsequent tolerance for intensive chemotherapy or radiation therapy.[30] Patients who are expected to have prolonged postoperative recovery of intestinal function benefit from parenteral support.[31] Also, for patients who are malnourished before surgery, perioperative nutrition support improves surgical outcome. A more recent study has shown that enteral therapy modulates cytokine responses after surgery. These responses were actually more exaggerated when parenteral nutrition (PN) was used.[32]

Chemotherapy often disrupts oral intake but can also result in dysfunction of the gastrointestinal tract, liver, or pancreas. Antimetabolites, alkylating agents, and inhibitors of nucleotide synthesis can cause oral or esophageal ulceration, anorexia, nausea, vomiting, and enteritis with malabsorption and consequent diarrhea. Asparaginase and streptozocin can disrupt pancreatic islet cell function and result in diabetes. Excess weight gain can result from increases in energy intake secondary to glucocorticoid treatment.[33] Antimetabolites can result in liver dysfunction. The latter is more likely to occur during infectious episodes. Although the physical effects of chemotherapy are generally short term and self-limited, there may be persistent changes in taste sensation and food preferences or the development of a psychological aversion to feeding. Conversely, preexisting malnutrition may alter the effectiveness of chemotherapeutic agents as well.[34]

Radiation therapy can have both acute and chronic effects. Acutely, radiation to the head and neck can cause mucositis, anorexia, nausea, vomiting, dysphagia, dysgeusia, and diminished salivation.[35] Irradiation of the chest can damage the esophagus. Stomach and or bowel irradiation will cause nausea, vomiting, and diarrhea. Chronically, stricture formation can occur in the small or large intestine. Other pathologic consequences that have been reported include villous atrophy, lymphangiectasia, ulceration and inflammation, perforation, fistulization, and vasculitis.

Hematopoietic cell transplantation (HCT) has previously represented the extreme end of the spectrum of chemotherapy and radiation effects. However, developments in HCT in the last several years have resulted in a much wider range of the intensity of supportive care that is needed by HCT recipients. Much of this widening of the spectrum of supportive care is attributable to developments in the use of hematopoietic growth factors. Cytokine therapy has had a major impact in autologous transplantation and is being used to reduce complications of allogeneic transplantation as well.[36,37] Colony-stimulating factors are used to stimulate hematopoietic stem cell graft function, decreasing the period of time in which HCT recipients are neutropenic and susceptible to infection.[38] The debilitation of infection is often a limitation to a recipient's ability to maintain or resume adequate oral nourishment. Autologous transplantation has been impacted by the use of cytokines such that both autologous marrow and peripheral blood stem cell transplantation can now be done in the outpatient setting, particularly for nonhematologic malignancies.[39,40] Recipients are admitted to the hospital for any complications, which can include nutritional depletion. Recipients who are hospitalized for autologous transplantation are also not routinely started on PN. Criteria at the University of Minnesota for initiating PN in adult patients include the following: (1) the patient is taking in < 50% caloric requirements orally for at least 5 days and has weight losses of 5% of baseline weight, (2) the patient is at < 95% of ideal body weight, and (3) the patient's clinical condition has deteriorated. These criteria are used for both autologous and allogeneic recipients, and PN is not generally initiated until cytoreduction has been completed.

Conventional HCT still involves lethal chemotherapy and/or radiation therapy to achieve adequate cytoreduction for the patient to be able to engraft the donor stem cells (allogeneic HCT) or to reduce the tumor burden and rescue the patient with his own stem cells (autologous HCT).[41,42] This may follow closely an intensive induction course of chemotherapy or months of maintenance chemotherapy to ensure that the patient's disease is in remission at the time of preparation for HCT. Cytoreductive therapy causes painful mucositis in the oral pharynx and esophagus. Taste sensation is altered; both hypogeusia and dysgeusia are reported.[43] Normal growth and repair of intestinal mucosa are disrupted. Histologic changes attributable to cytoreductive conditioning therapy have been reported to persist as long as 21 days after transplantation.[44]

The loss of functioning intestinal epithelium results in malabsorption and reversal of salt and water absorption. The result is typically an interval of watery diarrhea in the first week following chemotherapy and/or radio-

therapy.[45] Stool sodium transiently increases to 50 to 80 mEq/L. There is usually enough mucosal disruption to cause a transient rise in exudative protein loss into the feces,[46,47] with concomitant loss of zinc, and failure to absorb minerals and vitamins.[48] In addition, the debilitated condition of the gastrointestinal tract at this time predisposes these patients to viral, bacterial, and fungal infestation of the bowel, leading to further mucosal damage and malabsorption and providing a portal of entry for systemic infection.

The benefits of maintaining nutritional intake during bone marrow transplantation (BMT) were established over 15 years ago.[49] In the randomized, controlled study done at the University of Minnesota, there was a clear long-term survival advantage for BMT recipients who received prophylactic nutrition support in the form of PN compared with control recipients who were fed ad libitum with intravenous supplementation of minerals and vitamins until nutritional depletion was documented. This effect was even stronger when the 104 allogeneic patients were compared separately from the 32 autologous patients (Figure 41.2-1). Improved survival may have been attributable to a nutritional effect on graft function, as was suggested by murine studies.[50] In this study, the control group was fed orally until four of six standard nutritional assessment measures fell below the 10th percentile values. Sixty-one percent of control patients met these criteria for nutritional depletion at a median of day 21 post-transplantation. These patients had significantly longer hospitalizations than the PN patients, whereas the other 39% of control patients who were able to maintain adequate oral nutrition had significantly shorter hospitalizations than PN patients. In another study published in the same year, intensive dietary counseling with use of both nasogastric feedings and intravenous protein supplementation, nutritional support was maintained without a prolonged course of PN in a majority (~ 75%) of patients without adverse effects on graft function.[51] In both of these studies, patients generally met the criteria for initiation of PN after several weeks of profound neutropenia, often with infection. Therefore, reducing the period of time following cytoreduction during which recipients are neutropenic with the use of colony-stimulating factor has reduced the requirement to use PN for all patients throughout the course of HCT. The resolution of mucositis and the ability of HCT recipients to resume oral intake frequently coincides with the appearance of circulating neutrophils. Although nutrition support remains an essential aspect of supportive care, the range of nutrition support options is now as varied as the settings for HCT. Nutrition support recommendations are now based on the nutrition status of the individual patient, and PN is no longer indicated for all HCT recipients.[52]

In addition to nitrogen losses occurring as a result of enteritis, patients can excrete tremendous amounts of nitrogen in urine during and immediately after cytoreductive therapy. Nitrogen losses have been documented in a number of studies.[53,54] This occurs whether or not patients are receiving nutrition support and is reflected in decreased visceral protein status by the second week post-transplantation.[55] It is often necessary to increase protein intake up to 3 to 3.5 g/kg in some children to achieve zero nitrogen balance in the face of nitrogen losses by the third week post-transplantation. It appears that, in therapy this intense, there is a certain obligate nitrogen loss owing to tissue damage and altered metabolism directly attributable to the catabolic effect of chemotherapy and radiation and compounded by relative immobilization and infection. The massive increased waste nitrogen must be processed by the liver via the urea cycle, which increases the energy demands of the liver and consequently of the whole patient.

Hypermetabolism and multiorgan failure syndrome are parts of a clinical spectrum initiated by a severe defect in tissue perfusion or oxygenation.[56] Hypermetabolism may result from sepsis, multiple trauma,[57,58] acute pancreatitis,[56]

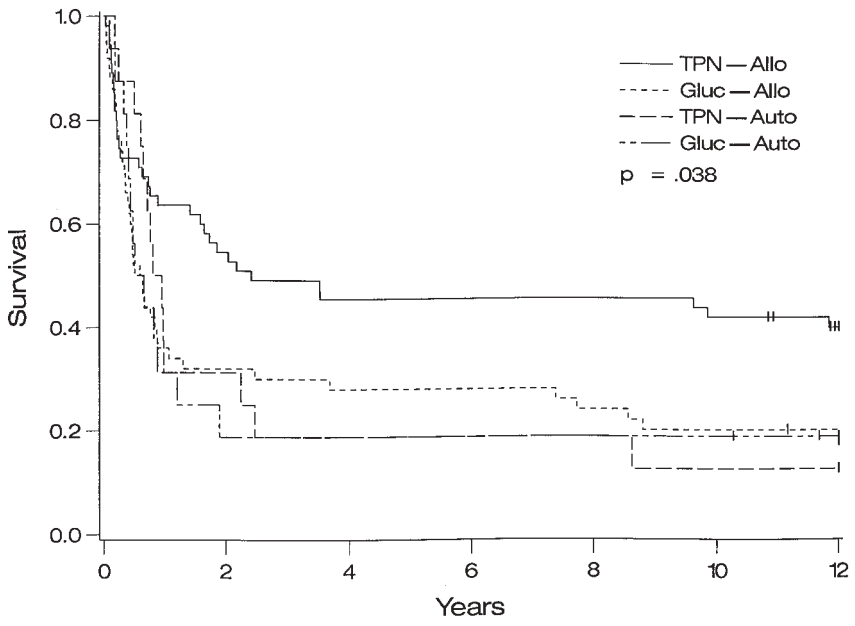

FIGURE 41.2-1 Results of the randomized, controlled study done at the University of Minnesota comparing survival in bone marrow transplantation recipients who received prophylactic nutrition support in the form of parenteral nutrition compared with control recipients who were fed ad libitum with intravenous supplementation of minerals and vitamins until nutritional depletion was documented. Allo = allogenic bone marrow transplantation; Auto = autologous bone marrow transplantation; Gluc = glucose infusion until nutritional depletion; TPN = prophylactic total parenteral nutrition. Courtesy of Anne Goldman, PhD.

or other catabolic events (such as severe graft-versus-host disease [GVHD] in HCT patients). Sepsis is the most common stress associated with hypermetabolism in cancer patients, and the risk is increased by the use of PN.[59] The mediators of hypermetabolism are thought to be the same or similar active cytokine peptides as the mediators of cachexia.[60] The hypermetabolic state may resolve over 7 to 10 days or may persist, with progressive kidney and liver dysfunction. These final stages constitute multiorgan failure syndrome, which has a mortality rate in excess of 50%.[56]

Similar to cachexia, hypermetabolism is characterized by the loss of body protein, in distinction to simple starvation, in which lean body mass is preserved. Protein catabolism is accounted for, in part, by use of amino acids from skeletal muscle in areas of wound healing or in acute-phase response protein synthesis. However, in the hypermetabolic state, amino acids are also used for gluconeogenesis, and branched-chain amino acids may be oxidized outside the liver for energy. The net result is a dramatic shift to negative nitrogen balance and azotemia, with hyperglycemia.[56,61,62]

POSTSURVIVAL ISSUES: IMPACT OF LATE EFFECTS OF CHILDHOOD CANCER AND ITS TREATMENT ON NUTRITION

There has been significant progress in the treatment of childhood cancer, with an estimated survival for these patients now of 80%. This means a yearly increase in the survival population of approximately 6,000 children. As this number has grown and aged, many long-term complications of the therapy they received have become apparent. Complications of radiotherapy or chemotherapy may be recognized years after treatment. Persistent toxicity may be appreciated only when it manifests as failure to thrive, poor growth, or failure of normal sexual development.[63] Table 41.2-1 lists some specific consequences of childhood cancer therapy that may lead to problems with growth or nutrition. In addition, we cover more fully two of the more common problems, excess fat mass and obesity associated with treatment of leukemia and impairment of normal bone formation, which occurs after many forms of cancer therapy.

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. Its treatment, although largely successful, is commonly associated with reduction in growth, reduction in lean body mass, and increased fat mass.[3] About 40% of children treated for ALL exhibit obesity in the late recovery period.[64,65] This childhood and adolescent adiposity frequently results in obesity in the adult, with the attendant risks of cardiovascular disease and type 2 diabetes.

Studies of preobese ALL patients have shown reduced total energy expenditure, related to reduced physical activity.[66] Cranial irradiation is a major risk factor for obesity,[65,67] although nonirradiated patients also have an increased risk of obesity of about 20%. Although cranial irradiated patients do not eat more than nonirradiated patients, their activity is less. In part, this may be the result of complications involving the musculoskeletal system, which lead to pain and fractures. The resting metabolic rate was significantly reduced in the irradiated group compared with the nonirradiated group. They are also at increased risk of hypothalamic abnormalities.[65]

No study has systematically attempted to intervene in this condition. It would be expected that a thorough endocrinologic evaluation would be a necessary first step in the management of this problem. Increased activity,

TABLE 41.2-1 Effects of Childhood Cancer Treatment on Growth and Nutrition

Late Effect	*Likely Causes*	*Useful Adjunctive Studies*	*Other Information*
Short stature	Cranial radiation (dose dependent), high-dose prednisone and methotrexate, spinal radiation	Growth hormone testing, thyroid function studies, tests of gonadal dysfunction	In some studies, only pulsatile growth hormone was affected
Obesity	Etiology unclear; may be related to adrenocorticosteroid therapy	Thyroid function studies, imaging of hypothalamus	
Weight loss	Multifactorial		
Dental abnormalities (delayed or arrested tooth development, malocclusion, or caries)	Cranial radiation	Evaluation by dentist or oral surgeon	May manifest as reduced intake
Chronic enteritis or intestinal fibrosis or stricture	Radiation of gastrointestinal tract	Barium studies of small bowel and/or colon, evaluation for malabsorption, quantitative assessment of macro- and micronutrients	Stomach and small intestine are more radiosensitive than colon and rectum
Hepatic fibrosis/cirrhosis	High-dose hepatic radiation, methotrexate	Liver enzymes; coagulation studies; vitamin A, E, and D levels; liver biopsy	
Second malignancy	Multifactorial	Oncologic evaluation	May manifest as weight loss
Psychosocial problems	Multifactorial	Psychological assessment	Anxiety or depression may manifest as weight loss

Adapted from information in Dreyer ZE et al. [63]

which will need to be carefully supervised by a physical therapist, will likely be a cornerstone of therapy.

Similar obesity has not been seen after HCT, even when irradiation is involved. The European Bone Marrow Transplantation Late-Effects Working Party has shown that irradiation, whether total-body irradiation, thoracoabdominal irradiation, or cranial irradiation, is associated with diminished height. Nutritional status in general, however, is good 5 years after an HCT.[68]

Reduced bone mineral density (BMD) in survivors seems to be a short-term problem if properly managed. If longitudinally monitored, BMD is often diminished at the start of cancer therapy and may further decline during the treatment period.[69] There are several factors involved in this decline, among them poor vitamin D status and poor calcium intake during chemotherapy,[70] hypomagnesemia associated with hypermagnesuria resulting from steroids and/or aminoglycosides,[71] and reduced activity.[65]

However, long-term studies of these patients largely suggest that BMD improves after the completion of chemotherapy. Henderson and colleagues found that, 1 year after the end of chemotherapy, BMD z-score was –0.37 ± 0.27 in the lumbar spine, with a similar finding in the proximal femur.[69] The large study of Kadan-Lottick and colleagues of survivors of ALL demonstrated normal whole-body areal BMD z-scores. This was true despite the fact that 28% of this population had at least one fracture after the diagnosis of ALL. It should be noted that, despite the overall good results, 11% of individuals had osteopenia. BMD improved after completion of chemotherapy.[72] In a study of Danish survivors of childhood cancer, the median length of follow-up was 10.7 years from diagnosis, yet the median BMD z-score was low, –0.5 (areal density, whole-body scan).[67] Thus, although great recovery is possible, we must be alert to identify the survivor with remaining osteopenia.

Therapeutic intervention must focus on the osteopenic long-term survivor. It will be important to identify risk factors that lead to osteopenia and determine if mineral supplementation and/or weight-bearing exercise can reduce this late complication of cancer therapy in children.

PRACTICAL INFORMATION FOR NOURISHING PATIENTS DURING THERAPY

Indications and Treatment Choices

Although controversies still exist concerning the role of nutritional support in cancer therapy, malnutrition remains a strong indication for intensive nutritional support therapy.[73] Support is indicated for all malnourished children whether at diagnosis, during induction and/or maintenance therapy, or in terminal care. Nutrition support therapy is also indicated when there will be a period of time lasting over 5 days when patients are unable to eat owing to recovery from surgery or in the case of a previously documented inability to eat during chemotherapy. A 2- to 3-week period of severe mucositis is well documented to occur in a majority of patients following HCT.

General goals of nutrition support are to reduce morbidity and minimize complications. Four of the ways in which optimal nutrition support may potentially serve these goals are (1) to provide bowel rest during intensive therapy with severe gastrointestinal side effects, (2) to decrease transfusion dependence by decreasing the amount of time in which patients are cytopenic,[74] (3) to decrease incidence of infection by improving return of immune competence, and (4) to increase the patient's sense of well-being. To achieve these ends, therapy needs to be individualized because in individual patients, optimal support will differ: some patients will require PN, others will require supplementary PN or supplementary peripheral PN, and still others will be able to achieve optimal intake and absorption with chemically defined enteral diets or supplements.[75]

Enteral Feedings

Increasingly, it is clear that enteral feedings provide the most physiologic method of nourishing the patient with cancer, with, in general, fewer and less severe complications and the least cost.[76] The gut should be the "default" method of feeding, with PN used in patients unable to be nourished enterally.

In the surgical patient, oral feeding should be attempted as soon as bowel function returns. Although gastric motility may be abnormal for a prolonged interval, small bowel motility may improve rapidly, allowing the use of nasojejunal feedings until a patient is ready to resume oral intake. In patients receiving intensive chemotherapy and radiation or BMT, oral intake can resume when mucositis subsides and narcotic therapy is reduced. Continuing parenteral amino acid is often necessary, even in a patient consuming adequate calories, because protein-containing foods are often refused. A dietitian trained in cancer management is essential to counsel patients regarding appropriate food choices and encourage patients to keep retrying foods.[77]

Contraindications to enteral feeding include bowel obstruction, severe enteritis, and severe malnutrition at diagnosis.[76,78] Impediments (but not necessarily contraindications) to enteral feedings include nausea and vomiting, severe mucositis, oral aversion, and intestinal motility disorder. New information regarding the treatment of nausea and mucositis may improve oral intake in children with cancer, and more centers are using nasogastric feedings when the intestine is the appropriate route, but the child cannot ingest enough. Some patients leave the hospital on PN or nasogastric feedings, and children are often resistant to oral intake until in familiar surroundings. If there is no organic cause of prolonged refusal of enteral intake, food aversion is suspected, and behavioral modification therapy can be sought.

The choice of enteral feeding is wide. Oral feedings should be tailored to fit the child's tastes, which may not be the same as before therapy began. For example, taste sensation is altered after HCT, with a decreased threshold for sweet and salt that may last for more than a year.[43] A variety of tumor types lead to dysgeusia, with a heightened sense of taste for bitter and reduced capacity to sense sweet.[79] Although these studies were performed in adult

cancers, clinical experience suggests similar alterations of taste sensation in children with cancer. Feedings delivered through a tube can be either elemental or nonelemental. Elemental formulas are more expensive and should be used when there is severe enteritis or evidence of malabsorption.

It has been the practice at many institutions for neutropenic patients to be fed restricted diets to limit their exposure to microorganisms.[80] It is clear that certain foods pose an increased risk for the neutropenic patient (as well as, in some cases, for the normal patient). Poorly cooked meat is a risk for these patients, as may be aged or fermented products, such as aged cheeses. Raw fruits and vegetables may also have large numbers of microorganisms present. Unfortunately, it is unclear to what degree these restrictions are effective in reducing infections in neutropenic patients. Most infections are hospital acquired, rather than food borne.[81] The severity of the restrictions further limits choices for patients. Although many centers continue to use some restrictions for neutropenic patients, some are allowing raw fruits and vegetables if they are well washed.

Nutritional support guidelines generally cover strategies for patients undergoing chemotherapy or HCT. It is important to realize that patients who complete therapy undergo a recovery period when catch-up growth and rehabilitation occur. During this phase, patients continue to need guidance with regard to food choices and graduated exercise programs. Patients who have advanced cancer can also benefit from nutrition support counseling to allow them to be as active as possible prior to death.[82] There is virtually no information on nutrition support management in children who are survivors of cancer in these situations.

Managing Mucositis, Vomiting, and Anorexia

Mucositis, vomiting, and/or anorexia associated with cancer and cancer therapy can limit oral intake in many patients. A full discussion of these complications is beyond the scope of this text, but some general comments and appropriate references are provided. The information provided, with few exceptions, derives from the adult cancer literature. Few studies directly address these complications in children, although it might be expected that children might have different degrees of complications and require different treatments, given the difference in therapy and underlying tumors.

Mucositis is a common, debilitating complication in which mucosa in the gastrointestinal tract, lost as a result of cancer therapy, are replaced very slowly because of injury to the basal tissue layers. Ulceration and superinfection may occur. Mucositis limits oral intake. Therapy for mucositis is limited, but some options are effective.[83,84] The basic principles are to relieve pain, provide nutrition and hydration, and treat any superinfection. All patients should have routine mouth cleansing with a saline solution. Pain management often requires narcotic therapy, which may reduce gastrointestinal motility and further impair oral intake. Oral glutamine is controversial; one study demonstrated a reduction in oropharyngeal mucositis in HCT with glutamine,[85] whereas another study in patients with gastrointestinal cancer showed no effect.[86] Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor stimulate increased growth of mucosal cells in the oropharynx, reducing the length and severity of mucositis. Other, novel therapies are being investigated and may further improve the prospects for oral intake in children with cancer.[83,84]

Nausea and vomiting are also common during cancer therapy. The severity of this side effect depends on the agent used, the dose administered, and the route of administration. Host factors may also be important.[87] Treatment of the child with nausea begins with identification of any infectious or metabolic causes of nausea and vomiting (eg, uremia, oral thrush, or electrolyte disturbances). Radiation therapy to the abdomen and GVHD may lead to partial bowel obstruction, exacerbated by narcotic agents. However, chemotherapy itself is at the root of most nausea and vomiting in children with cancer.[88]

In chemotherapy-induced emesis, cytotoxic agents stimulate the release of serotonin in the gastrointestinal tract. The serotonin binds to 5-hydroxytryptamine$_3$ receptors in the intestine, stimulating the vagus nerve to transmit signals to the chemoreceptor trigger zone in the brain. Cells in this zone then stimulate the vomiting center, which responds with gastroparesis and retching.[87] Although there are many agents that are useful in different stages of chemotherapy-induced nausea and vomiting, metoclopramide and the serotonin receptor antagonists (ondansatron, granisetron, and dolasetron) are most effective as they directly impact the underlying physiology of the problem. In children especially, diphenhydramine may be required to reduce side effects of metoclopramide.[87,89]

In adults, anabolic agents are recommended in some situations for patients with cancer cachexia (for a recent review, see Langer and colleagues[90]). Similar studies in children are limited, and it is not recommended that these agents be used in children except in very specific circumstances. Megestrol acetate, an orexigenic agent (appetite stimulant), has been studied in children and is also the agent most commonly used in adults. In children with human immunodeficiency virus, megestrol acetate promotes weight gain. Adrenal function may also be suppressed, at times requiring corticosteroids to relieve symptoms.[91] Weight gain is generally composed of fat and water, with little change in lean body mass[90]; however, it may improve quality of life in children with advanced, untreatable cancer and severe failure to thrive. Other agents, including anti-TNF-α medications (melatonin and thalidomide) and anabolic agents (growth hormone, oxandrolone), are under investigation in adults.[90]

Nasogastric Feedings and Gastrostomies

Concerns have long been expressed about the safety and efficacy of nasogastric feedings in children undergoing chemotherapy. Among the concerns are bleeding, vomiting with the necessary tube replacement, sinusitis from sinus os occlusion, and poor parental and patient acceptance of nasogastric tubes. In the last decade, as the benefits of enteral feeding have become apparent, nasogastric feedings have been attempted in both HCT and cancer patients.

Pietsch and colleagues fed 17 children with high-risk cancer or HCT by nasogastric tube for a total period of 216 days.[92] The children were not randomly assigned to tube feedings. Although 6 children vomited out their tubes, they were replaced without incident. No child experienced tube-related sinusitis or bleeding. The conclusion is that nasogastric feedings should be further explored in children with cancer, including those at high risk.

In children with solid tumors, administration of nasogastric feedings in those patients with clear evidence of malnutrition at the onset of or during chemotherapy reduced the incidence of nonleukopenic infections.[93] This study also emphasized the need for aggressive management of vomiting to promote enteral nutrition and weight gain. Formulas with higher energy density are more effective in promoting weight gain and improving body composition than are standard formulas, probably because smaller volumes are required for adequate calorie intake.[93]

Both aggressive enteral feeding programs and nasogastric feedings have been used in children undergoing HCT, with generally positive results.[51, 94,95] Although more children fail to complete nasogastric protocols in HCT than in cancer chemotherapy, it is not clear if this is owing to the more severe complications of HCT or the result of differences in the practices of the institutions performing the studies. There is a need for studies to assess whether polymeric or monomeric formulas are most appropriate in HCT patients.

In summary, enteral feeding via a nasogastric feeding tube is appropriate for many children undergoing HCT or chemotherapy. The paucity of controlled trials of specific feeding protocols limits the recommendations, but a prudent course can be suggested with the current information. The criteria proposed by den Broeder and colleagues for initiating nasogastric feedings may serve as guidelines until more specific criteria are established through clinical research. Specifically, consider nasogastric tube feedings when the child has malnutrition at diagnosis, when weight decreases more than 5% compared with weight at diagnosis, or when the child's oral intake is < 80% of the child's total estimated energy requirement.[93] High-energy, polymeric formulas are more likely to achieve the desired weight gain.

The studies thus far suggest that most children with cancer or HCT will tolerate nasogastric feeding tubes for the time necessary to improve and maintain a reasonable level of nutrition. Patients unable to tolerate nasogastric feedings or who will require supplemental feedings for a prolonged time (generally > 3 months) may be candidates for a feeding gastrostomy. Several studies have shown that gastrostomies are safe and effective in children with cancer.[96–98] They can generally be placed under general anesthesia percutaneously during endoscopy. Children with significant mucositis may require radiographic placement to avoid pulling the gastrostomy tube through the eroded esophagus.[99]

Complications included incisional pain, leakage of gastric juices, and local infection, usually during periods of neutropenia, and may occur in about 40% of patients.[96,99] Serious complications, including peritonitis, occur in < 10% of patients.[99] Complications can be reduced with good wound care, avoiding attempts at traction removal until chemotherapy is complete or engraftment has occurred after HCT and, in the HCT patient, scheduling placement of the tube 3 weeks before cytoreduction begins.[96,100] In some centers, neutrophil counts less than 500 and platelet counts less than 50,000 are considered relative contraindications to gastrostomy tube placement.[99]

Parenteral Therapy

When patients are unable to ingest adequate nutrients owing to surgery, radiation, chemotherapy, or combinations of these, such as HCT, PN is indicated. For adequately nourished patients, a graded approach is recommended; such a regimen is used in HCT patients. PN is initiated for HCT patients when the oral intake is less than 50% of the basal energy expenditure (BEE) calculated using the Harris-Benedict equations plus 10% for growth. Initially, 120 to 130% BEE is prescribed, and approximately 33% of total calories are given as lipid daily. Lipid-based PN has been shown to be associated with a lower incidence of lethal acute GVHD when compared with carbohydrate-based PN.[101] Protein is given at the Recommended Daily Allowance (RDA), 2 g/kg in children. Because this is the period during which tissue damage is occurring, resulting in an increased endogenous nitrogen burden, exogenous nitrogen is prescribed only for maintenance of lean body mass. This maintenance formula is similar to that prescribed for patients receiving chemotherapy or for post-surgical patients who are unlikely to eat for at least 5 days. Electrolytes, minerals, vitamins, and trace elements are added to the PN according to the RDA and individual needs. Multivitamin mix and standard trace element solutions containing chromium, zinc, copper, manganese, and selenium are added.[102]

At the time of engraftment, or about 21 days post-transplantation, the energy intake is decreased to 100 to 110% BEE, and protein intake is increased to compensate for negative nitrogen balance, hypoproteinemia, and tissue repair as the marrow graft begins to function and mucositis resolves. This recommendation anticipates the additional protein required for tissue repair and regrowth but decreases the amount of energy the patient uses to dispose of a high-caloric intake.

Managing Hypermetabolism

The metabolic changes of hypermetabolism cannot be corrected with either glucose infusions or insulin. The goals of nutrition support in the hypermetabolic patient are to avoid starvation and to maintain acceptable levels of electrolytes, glucose, and blood urea nitrogen (BUN). Protein is administered at increased levels, up to 1.5 to 2.0 g/kg/day in adults and up to 2.0 to 2.5 g/kg/day in children, to compensate for urinary nitrogen loss, unless uremia supervenes. Glucose administration should not exceed 5.0 g/kg/day, and fat intake should not exceed 30% of calories. This therapy will not achieve positive caloric balance in hypermetabolism, nor will it prevent loss of lean body mass. It will, however, support the ongoing inflammation-associated protein synthesis and may improve nitrogen balance, which has been associated with increased survival.[56,61,62]

Complications requiring adjustments of nutritional management include azotemia, which requires decreasing protein intake or dialysis to permit increased protein support. Patients with respiratory difficulty may benefit from decreasing their carbon dioxide production by reducing the glucose infusion rate. Indirect calorimetry can indicate if caloric intake is too high. Excess energy intake does not preserve lean body mass or restore the patient to health more quickly but promotes hyperglycemia, lipogenesis, hypertriglyceridemia, and hepatic steatosis. Fluid overload in the stressed patient is an indication to concentrate PN, decreasing free water and correcting hyponatremia. Electrolyte supplementation can be given separately from the PN, avoiding the need for frequent PN reformulation. Recommended allowances of trace elements and vitamins may not be adequate in the severely stressed patient, particularly for zinc, copper, and vitamin K. Patients with renal or hepatic dysfunction may require further modification of the PN, and serum trace element monitoring can anticipate chromium toxicity or excessive manganese and copper supplementation.[57,61]

Monitoring Nutrition Support

To individualize therapy, certain nutritional/metabolic parameters need to be monitored. It is somewhat arbitrary to distinguish between a monitoring schema to follow nutrition therapy and one to follow the overall medical status of the patient. Certain laboratory studies are indicated to anticipate and correct potential metabolic problems that can be caused by PN or metabolic problems of other causes that can be treated with the PN solution. From a collection of studies, a consensus can be derived (Table 41.2-2).

Weight is followed primarily to judge hydration status, which is also reflected by electrolytes, BUN, creatinine, and albumin. Changes in glucose tolerance can signal infectious as well as metabolic complications. The association between hyperglycemia and *Candida* sepsis was initially described some years ago.[103] Liver function abnormalities may result from PN, or liver dysfunction from other causes may require modification of the PN formula (see below).

Parenteral and enteral protein and caloric intake are recorded daily to allow for reduction of parenteral intake as enteral intake increases. Measurement of electrolytes, major minerals, and zinc is needed to adjust a patient's PN formula. Ascribing abnormalities in serum albumin to protein nutrition does not seem to be reliable in this setting.[101] Serum albumin is helpful in assessment of fluid status and as a guide to albumin replacement therapy for maintenance of intravascular volume. Transferrin seems more reflective of amino acid intake for visceral protein synthesis.[49] We have found that prealbumin levels reflect caloric, rather than protein, intake and should not be used to adjust protein intake. Although nitrogen balance is helpful, attempting to maintain positive balance is unrealistic and could result in an increased demand on the liver to process ammonia. Measurement of resting energy expenditure and respiratory quotient can assist in individualizing therapy and anticipating complications.[104] The quantity and appropriate mix of energy-producing substrate can be optimized with these data.[53]

Complications of Nutrition Support

There are risks for complications in both parenteral and enteral nutrition support, and these are covered in detail in other chapters in this text. Some of the more common problems encountered in cancer patients are reviewed briefly.

Catheter-Related Complications Central venous access catheters remain a major source of complications in cancer patients, especially those with neutropenia. The incidence of central line sepsis is high, despite the use of strict aseptic technique for blood draws, infusions, and tubing changes, as well as daily site cleaning and dressing changes. Christensen and colleagues have reported the infection risk associated with PN in 310 pediatric patients with cancer.[59] These patients had central venous access devices (CVADs) in place for the delivery of chemotherapy and supportive care. Overall, the infection rate was 0.06 infections/100 days. During the period of PN administration, the rate increased to 0.5 infections/100 days. After adjustment for diagnosis and CVAD type, the risk of infection was 2.4-fold greater in patients given PN (95% confidence interval 1.5 to 3.9; $p < .001$). In a prospective study of 143 Hickman catheter placements in 111 BMT recipients, 44% of the patients had positive blood cultures during the lifetime of the catheter.[105] Of these infections, 40 of 63 were coagulase-negative *Staphylococcus*, suggestive of primary line sepsis rather than catheter contamination from a blood-borne enteric source. The majority of these infections are treated with antibiotics and not catheter removal.[106] In the prospective study, mechanical obstruction occurred in 38% of the catheters; half of these episodes required no intervention, whereas the others responded to heparin or urokinase or required catheter replacement.

Hepatic Enzyme Elevations PN is associated with hepatic dysfunction, although, in general, patients with cancer or BMT are rarely treated with PN long enough to develop cirrhosis or clinically significant hepatic failure. The causes are still being elucidated and appear to be complex.[107,108] In many cases, cholestasis associated with PN may cause confusion when the clinician is considering the differential diagnosis of cholestasis in the patient with cancer. Stopping the PN is not appropriate unless enteral alimentation can be used as malnutrition also has adverse consequences for the liver.

Initially, there is an elevation of transaminases occurring approximately 1 to 2 weeks after the start of PN infusion. Elevated serum bilirubin and canalicular enzymes (alkaline

TABLE 41.2-2 Nutrition Support Monitoring Studies

Daily: weight, urine glucose, calorie/protein intake, and, for first 3 days, electrolytes, blood urea nitrogen (BUN), glucose, and creatinine
Biweekly: glucose, BUN, creatinine, electrolytes, calcium, magnesium, phosphorus, hepatic transaminases, 5′-nucleotidase, bilirubin, and alkaline phosphatase
Weekly: triglyceride, albumin, transferrin, nitrogen balance, BUN, and zinc

phosphatase, 5′-nucleotidase) may occur 2 to 3 weeks into therapy. Histopathologic changes in the liver include steatosis, glycogenosis, intrahepatic cholestasis, and sometimes a nonspecific portal infiltrate. Most abnormalities resolve on discontinuation of PN, cycling, or adjustment of the nonprotein calone–to-nitrogen ratio (NPC:N), and there is little or no functional disability of the liver.

With long-term PN therapy, functional abnormalities may develop. Steatonecrosis and fibrosis can occur and may progress to cirrhosis with complications of hepatic dysfunction and portal hypertension. The time course for development of this lesion is variable; some studies have shown fibrosis with as few as 6 months of PN. Finally, acalculous cholecystitis or gallstone formation can occur during the administration of PN.[109]

Steps may be taken to reduce the likelihood of PN-associated hepatic dysfunction. Some suggested therapies that may modify liver enzyme or bilirubin increases include the following:

1. Appropriate therapy for any other causes of liver dysfunction such as sepsis, hepatitis, hepatotoxic medications, veno-occlusive disease, or GVHD
2. Administration of PN over 12 to 18 hours rather than 24 hours[110,111]
3. Initiation of small enteral feeds[112]
4. Empiric reduction of the total calorie intake by 10 to 15% to reduce the NPC:N[112]
5. Treatment with ursodeoxycholic acid, 15 to 20 mg/kg/day orally divided into three or four doses to decrease cholestasis
6. In older children and adults, a trial of metronidazole to decrease intestinal bacteria and thus decrease endotoxin formation

Treatment modalities being examined include modified enteral feedings with medium-chain triglycerides and/or marine oils rich in omega-3 fatty acids, administration of antioxidants (vitamin C, vitamin E, or *N*-acetylcysteine), reduction in intravenous lipid calories, and administration of cholecystokinin.[108] Carefully controlled clinical trials will be necessary to demonstrate that any of these novel therapies improves PN-associated liver disease.

Complications Associated with Enteral Feedings The most common problem associated with enteral feedings in the child with cancer is determining when the feedings are being tolerated. Commonly, abdominal pain, diarrhea, or nausea will lead to the feedings being stopped or temporarily held. To prevent failure of an enteral feeding regimen, it is essential that a well-thought-out protocol be established with clear guidelines for when feeds may be held. Such a protocol can be found in a recent article by Spain and colleagues.[113]

NOVEL THERAPIES

The trend in nutrition support research is toward specific nutrient modifications during critical illness to promote immune function or healing or to reduce infectious complications ("immunonutrition").[114,115] It is prudent to view early studies with a degree of skepticism; many therapies show promise in small trials but ultimately prove to be of no benefit to the patient in large-scale studies. In particular, in cancer, the modification of the immune system may improve the well-being of the host but may or may not be detrimental to the eradication of the cancer itself.

Most immune-modifying nutritional therapies include some combination of arginine, glutamine, nucleotides, and polyunsaturated fatty acids. Although some of these products are being tested parenterally, it is more common to see enteral products with some of these substrates.[115] In principle, each of these components affects some aspect of the immune defense syndrome: improving the intestinal mucosal barrier, improving the cellular defense function, or modifying the systemic inflammatory response.[115] Meta-analysis of randomized, controlled clinical trials of enteral supplementation with some of these nutrients in adults with gastrointestinal cancer suggests that this therapy may reduce infectious complications and hospital stay.[116] Further clinical research will determine whether this modality is of use in the treatment of children with cancer. Two of these components, glutamine and marine oils, have been specifically studied in patients with cancer or HCT and are reviewed here.

Glutamine plays a crucial role in nitrogen transport, is an important scavenger of ammonia, and is required for nucleotide synthesis. Intestinal mucosa, because of its high turnover rate, uses large amounts of glutamine. In the enterocyte, metabolism of glutamine produces α-ketoglutarate, which enters the tricarboxylic acid cycle, and ammonia, citrulline, alanine, and proline. Alanine is used by the liver for gluconeogenesis, whereas citrulline is used in the kidneys to synthesize arginine and in the liver as a component of the urea cycle. Critical illness is associated with depletion of plasma glutamine levels, with impaired maintenance of intestinal structural integrity. In these situations, glutamine is an essential amino acid. Glutamine depletion has been shown to lead to loss of the intestinal mucosal integrity, resulting in increased bacterial translocation and increased episodes of sepsis owing to enteric organisms. It is likely that glutamine is conditionally essential in catabolic states.[117,118]

Glutamine supplementation of PN was studied in allogeneic HCT patients in a double-blind, randomized trial. The PN was identical in calorie and nitrogen content; one group received standard amino acids and the other group received glutamine, 0.57 g/kg/day, with standard amino acid solution to the same total nitrogen content as the control group. The group receiving glutamine demonstrated improved nitrogen balance and decreased morbidity compared with the control group. The number of bacterial infections and the length of hospital stay were less in the glutamine group.[119] Subsequent studies of adults with cancer and/or HCT have suggested that this amino acid may improve nitrogen balance and reduce infections and length of hospital stay.[119] The use of glutamine as a nutritional supplement in children with cancer is limited to case reports.[120]

Omega-3 polyunsaturated fatty acids are enriched in marine oils. They include eicosapentaenoic and docosa-

hexaenoic acids. Administration of omega-3 polyunsaturated fatty acids appears to modify inflammation by altering the fatty acid composition of the cell membrane. They displace omega-6 polyunsaturated fatty acids. This alteration in membrane fatty acid composition alters membrane fluidity and the production of lipid-derived mediators of inflammation. In particular, displacement of omega-6 polyunsaturated fatty acids reduces production of arachidonic acid series of derivatives.[115]

Supplementation of enteral nutrition with marine oils has been suggested to prevent and treat cancer cachexia in adults with cancer. Small controlled clinical trials have demonstrated improvement in nutritional status and reduced evidence of inflammation with use of fish oil–enriched nutritional supplements.[121,122] Further research is necessary to determine if the potential benefits of marine oils will be achieved in children with cancer.[115]

COMPLEMENTARY AND ALTERNATIVE NUTRITIONAL THERAPIES

Complementary therapies are those not supported by evidence-based clinical studies used in conjunction with standard medical care. Alternative therapies are those not supported by evidence-based clinical studies used in place of standard medical care. Both classes of therapies are used frequently by patients with cancer. In one study, half of all pediatric cancer patients had used complementary/alternative therapies at some point during their illness.[123]

Nutritional therapies are very attractive to many patients. First, studies support a relationship between diet and cancer development. Second, food and, by extension, dietary supplements, vitamins, and micronutrients are viewed as "natural" and, thus, safe. Finally, the industry that produces complementary/alternative nutritional regimens and supplements is a multibillion dollar industry without regulation but with a clear incentive to promote their products regardless of the degree of evidence for effectiveness. Compared with chemotherapy and radiation therapy, food appears much less harmful. However, many of the complementary/alternative nutritional regimens and supplements are directly harmful or, by displacing standard medical therapy, indirectly harmful.

Classes of therapies commonly encountered include complete dietary modification, for example, macrobiotic diets, raw vegetable diets, or juice diets. Currently available evidence does not support the claims made for the extreme dietary modifications in the cure of cancer, and rigid adherence may result in poor weight maintenance and reduced growth in children.[82,124] Other therapies include megavitamin therapy and antioxidant or trace element supplementation. Concerns with regard to these therapies include the potential toxicities of some treatments and the question of whether the tumor or the normal tissue is more affected by these treatments. Again, no therapy has been shown to be effective in cancer treatment using evidence-based criteria.[82,124] There are a plethora of therapies using various herbs and botanicals, some in conjunction with other nutritional regimens.

Considerable study of nutritional therapies is ongoing; however, most of the research investigates the impact of these treatments on adult-type cancers. Few studies are addressing pediatric-type, nonepithelial cancers. Generalizing from studies of adult cancer to those of children is fraught with problems.[124]

It is essential that physicians managing children with cancer become knowledgeable about complementary/alternative therapies. Patients and parents should be questioned regarding the use of these therapies. Patients and their families are frequently looking for some aspect of care to control; diet seems a harmless choice. Particularly because diet during and after cancer therapy is often ignored by conventional medical therapy, there is little to dissuade them, unless their physician becomes involved in these decisions. Establishing a nonjudgmental but candidly informative discussion of complementary/alternative therapies offers the physician a chance to educate parents about their choices. Physicians and families can access information about complementary/alternative nutritional therapies at the Web site of the Office of Complementary and Alternative Medicine of the National Institutes of Health (<http://www.cancer.gov/occam>), where there are several links to reliable information.

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CHAPTER 42

DIABETES MELLITUS

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Recommendations for medical nutrition therapy of diabetes mellitus have repeatedly changed since the advent of insulin therapy in 1922. Nevertheless, meal planning remains a cornerstone of the management of all types of diabetes mellitus, and nutrition education is an essential component of a comprehensive program of diabetes education for patients and their families.[1] This chapter briefly reviews the history of medical nutrition therapy, the scientific basis on which the general principles are founded, and recent investigations that implicate dietary factors in the etiology of immune-mediated or type 1a diabetes mellitus. This is followed by a discussion of the goals of treatment, the principles of meal planning, and formulation of an individualized meal plan in light of current evidence and recommendations promulgated by the Food and Nutrition Committee of the American Diabetes Association (ADA) in 2002.[2]

PREVALENCE, DEFINITION, AND CLINICAL DESCRIPTION OF DIABETES MELLITUS

Diabetes mellitus is not a single entity but a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[3] Most cases of diabetes fall into two broad etiologic categories. Type 1 diabetes is the most common form in children and adolescents and is caused by an absolute deficiency of insulin secretion. Type 2 diabetes is the most common form of diabetes worldwide, comprising 80 to 90% of the overall diabetic population, and is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.[4–7] Type 2 usually has its onset in middle life, often in association with obesity and hypertension. Until recently, immune-mediated or type 1a diabetes was the only type of diabetes prevalent among children in the United States, and 1 to 2% of children had type 2 or other rare forms of diabetes. However, the prevalence of type 2 diabetes in youth has increased at an alarming rate,[8–12] and recent reports indicate that 8 to 45% of children with newly diagnosed diabetes have nonimmune-mediated diabetes.[13] The variation in the percentages reported appears to depend on race/ethnicity and sampling strategy. Most of these children have type 2 diabetes, but other types are being increasingly identified. For example, maturity-onset diabetes of youth (MODY) is occasionally seen in adolescents.[14,15]

The prevalence of diabetes in the United States is about 1.7 cases per 1,000 people less than 20 years of age and the annual incidence of new cases of type 1 diabetes in people younger than 20 years is approximately 18 per 100,000. The peak incidence is at 10 to 12 years in girls and 12 to 14 years of age in boys. The empirical risk of developing diabetes before 20 years of age is about 0.5%.[16] It is estimated that about 150,000 children and teenagers in the United States have type 1 diabetes.

Type 1a diabetes occurs in genetically predisposed individuals as a consequence of immune-mediated destruction of the insulin-secreting beta cells of the pancreatic islet.[17,18] The onset of clinically overt diabetes represents a late stage in the process of chronic progressive beta cell destruction and occurs when the majority of beta cells have been destroyed. The disease typically presents with rapid onset of polyuria, polydipsia, and weight loss. The cardinal features are attributable to an absolute deficiency of insulin, which leads to hyperglycemia (the result of decreased uptake and use of glucose by liver, muscle, and adipose tissue and uncontrolled hepatic gluconeogenesis), unregulated release of free fatty acids from adipose tissue, and increased ketogenesis.

Patients with type 1 or insulin-dependent diabetes mellitus (IDDM), as the name implies, depend on exogenous insulin to survive. Normally, insulin is secreted in an oscillatory fashion at a low basal rate on which are superimposed periodic increases in insulin secretion in response to ingestion of food. In contrast, when insulin is injected subcutaneously, it is absorbed from the injection site in a more or less predictable fashion that depends on the type and combination of insulins used. Each type of insulin has a characteristic time of onset, time and duration of peak effect, and total duration of action. Consequently, meals and snacks have to be timed to match the pharmacokinetics of insulin. Short-acting insulin delivered via continuous subcutaneous insulin infusion (insulin pump therapy) significantly reduces the variation in absorption.[19]

Children with idiopathic or nonimmune-mediated type 1 diabetes may be difficult to distinguish from those with immune-mediated diabetes. Most patients with idiopathic type 1 diabetes are African American and have atypical diabetes mellitus ("type 1.5" or "Flatbush" diabetes). They, typically, have a positive family history of early-onset diabetes in several relatives in multiple generations. Although insulin may not be required for survival after the acute

metabolic deterioration has resolved, blood glucose control usually is poor without insulin therapy, and ketoacidosis may recur.

MODY is a form of diabetes that includes several disorders caused by monogenic defects in beta cell function inherited in an autosomal dominant pattern.[15] The clinical spectrum of MODY is broad, ranging from asymptomatic hyperglycemia to a severe acute presentation. MODY occurs in all racial and ethnic groups. The genetic abnormalities are thought to be rare, and molecular diagnostic testing, currently available only in research laboratories, is required for specific classification. Until such testing is widely available, children with MODY should be classified as having the type of diabetes that best fits their clinical picture.

Individuals with nonimmune-mediated diabetes may have clinical presentations indistinguishable from those of patients with immune-mediated type 1 diabetes. This is relevant because as the number of children with type 2 diabetes increases, it becomes increasingly important to classify their diabetes correctly to institute appropriate therapy.

Acute, life-threatening consequences of diabetes are hyperglycemia with ketoacidosis or the hyperosmolar nonketotic syndrome. Long-term complications of chronic hyperglycemia include retinopathy with potential loss of vision, nephropathy leading to renal failure, and peripheral and autonomic neuropathy with associated risk of foot ulcers and limb amputation and gastrointestinal, genitourinary, and cardiovascular symptoms. Glycation of tissue proteins and other macromolecules and excess production of polyol compounds from glucose are among the mechanisms thought to produce tissue damage from chronic hyperglycemia.

The initial classification is usually based on the clinical picture at presentation. Children with immune-mediated type 1 diabetes are typically not overweight, have a short duration of symptoms, and frequently have ketosis, and 30 to 40% present with ketoacidosis. As the childhood population in the United States becomes increasingly overweight, the percentage of children with immune-mediated type 1 diabetes who are coincidentally overweight, if not obese, is increasing. After metabolic stabilization, they may have an initial period of diminished insulin requirement (the honeymoon period), after which they require daily insulin replacement for survival and are always at risk for ketoacidosis. In contrast, approximately 95% of children with type 2 diabetes are either overweight or obese at the time of diagnosis and typically present with glucosuria, absent or mild polyuria and polydipsia, and little or no weight loss. Up to 33% have ketonuria at diagnosis, and 5 to 25% of patients classified as having type 2 diabetes present with ketoacidosis. Children with type 2 diabetes are usually older than 10 years of age and are in middle to late puberty; 45 to 80% of patients have at least one parent with diabetes, and 74 to 100% have a first- or second-degree relative with type 2 diabetes. Children and adolescents of African American, Hispanic, Asian, and American Indian descent are disproportionately represented.

HISTORY OF MEDICAL NUTRITION THERAPY FOR TYPE 1 DIABETES MELLITUS

Until the advent of insulin therapy in 1922, the only available treatment was diet and exercise. Meal plans severely restricted the total intake of energy and were low in carbohydrate and high in fat.[20] Nutrition recommendations were often based on dogma and a limited understanding of the metabolic derangements. Today, medical nutrition therapy, largely based on scientific evidence, continues to be a major component of the management of diabetes. After the introduction of insulin, nutrition recommendations changed but generally involved restriction of carbohydrate to a maximum of 40% of total energy because this was thought to reduce the severity of hyperglycemia.[21,22] By early in the twentieth century, several studies had already shown that a high-carbohydrate meal plan, provided that it was restricted in total energy, had beneficial metabolic effects.[23–25] Change was slow, and despite evidence to the contrary, patients continued to be indoctrinated in the use of a low-carbohydrate, high-fat meal plan until 1971, when the Committee on Food and Nutrition of the ADA formally recommended liberalizing the consumption of carbohydrate.[26] Sucrose had, traditionally, not been permitted in the meal plans of people with diabetes mellitus. However, considerable scientific evidence, accumulated over the past two decades, has shown that sucrose as part of the meal plan does not impair blood glucose control in people with either type 1 or type 2 diabetes (vide infra).

Increasingly widespread use of intensive insulin therapy (either multiple daily injections, so-called basal-bolus therapy, or continuous subcutaneous insulin infusion via an insulin pump), in combination with carbohydrate counting, allows patients with type 1 diabetes to live more normal lifestyles and have more dietary flexibility while maintaining near-normal blood glucose levels.

DIETARY FACTORS IN THE PATHOGENESIS OF TYPE 1A DIABETES MELLITUS

The role of diet, particularly cow's milk protein, in the pathogenesis of human type 1a diabetes is controversial.[27] Changes in food, particularly its protein content, influence the onset of diabetes in rodent models of autoimmune diabetes. These observations have been invoked as evidence that complex natural ingredients in standard human and rodent diets may be involved in the autoimmune-mediated destruction of beta cells.

Antibodies reactive against a peptide sequence contained within bovine serum albumin (BSA) occur in humans, biobreeding (BB) rats, and nonobese diabetic (NOD) mice, which cross-react with an islet antigen designated p69. Together with suggestive epidemiologic data, these observations have given rise to the controversial theory that dietary cow's milk may contribute to the pathogenesis of type 1a diabetes in susceptible individuals.[28] Removal of bovine proteins from the diet prevents diabetes in NOD mice.[29] Some investigators have shown that diets

containing cow's milk are diabetogenic in the BB rat; others have not confirmed the finding.[30] Diet clearly has a major diabetogenic effect in BB rats[31,32] and NOD mice[32]; however, the exact chemical identity of the food diabetogen(s) is still not clear.

The nature of the interaction among genetic, environmental, and immunologic factors in the etiology of type 1a diabetes remains poorly understood. The genetic predisposition to diabetes is associated with specific DQ and DR alleles in the human leukocyte antigen (HLA) region of chromosome 6, but the observation of less than 50% concordance for type 1 diabetes in identical twins indicates that environmental factors are also involved. The earliest report of an association between breast-feeding and protection from IDDM appeared in 1984.[33] A meta-analysis concluded that children with diabetes are 60% more likely to have had an early exposure to cow's milk than nondiabetic children.[34] When exposure to whole cow's milk was examined in children at high and low risk for IDDM, as defined by genetic markers in the HLA region, a gene–environment interaction was demonstrated. Exposure to cow's milk before 3 months of age and having the high-risk genotype was associated with an 11-fold increased risk of IDDM compared with subjects who possess no risk factors.[35] In Finland, 100% of newly diagnosed diabetic children have elevated serum levels of antibodies to BSA compared with less than 4% of control children.[36] These findings have not, however, been replicated.

The locus transcribing ICA69, a beta cell surface protein of the human pancreas, shows two short regions with nucleotide sequences similar to that of BSA but not human albumin.[37] These two antigenic determinants (ICA69 and BSA) could play a role in the induction of cow's milk–induced beta cell autoimmunity based on a theory of pathogenesis that involves molecular mimicry.[36] Alternatively, the similarity of these two antigens may simply be a case of cross-reactivity between anti-ICA69 antibodies and anti-BSA antibodies and have no role in the etiology of type 1 diabetes.

Increased levels of antibodies to cow's milk protein and β-lactoglobulin have been observed in newly diagnosed diabetic children.[38–40] The significance of the elevated levels of β-lactoglobulin antibodies is unclear. If molecular mimicry between ICA69 and BSA is involved in the etiology of type 1 diabetes, one would expect BSA antibodies to be elevated rather than the other antibodies to cow's milk proteins. Other exposures in the infant diet have not been as extensively evaluated as cow's milk–based formulas. Exposure to solid foods by 3 months of age was associated with a 2.5-fold increased risk of type 1 diabetes.[35] In Sweden, children with diabetes consumed larger quantities of protein and nitrosamines before diagnosis than did age-matched control children.[41]

Although equivocal and inconclusive, considerable epidemiologic evidence and experimental data from studies in genetically susceptible animals suggest that dietary exposures in infancy may be associated with an increased risk of type 1 diabetes. Early introduction of cow's milk in infants may contribute to the development of childhood diabetes.[42,43] A large-scale trial of dietary cow's milk protein restriction in infants at risk of type 1 diabetes is currently under way in Finland.[44]

GOALS OF MEDICAL NUTRITION THERAPY

The goals of medical nutrition therapy of children and adolescents are as follows:

1. To provide adequate energy to ensure normal growth and physical development
2. To integrate insulin regimens into usual eating and physical activity habits
3. For youth with type 2 diabetes, to facilitate changes in eating and physical activity habits that reduce insulin resistance and improve metabolic status and gradually achieve a more desirable weight for height
4. For individuals being treated with insulin or insulin secretagogues (type 2 diabetes), to provide self-management education for treatment and prevention of hypoglycemia, acute illness, and exercise-related blood glucose perturbations
5. To attain and maintain optimal metabolic outcomes, including near-normal blood glucose levels without excessive hypoglycemia, a lipid and lipoprotein profile that reduces the risk for macrovascular disease, and blood pressure levels that reduce the risk for micro- and macrovascular disease
6. To prevent and treat the chronic complications of diabetes and modify nutrient intake and lifestyle as appropriate for prevention and treatment of obesity, dyslipidemia, cardiovascular disease, hypertension, and nephropathy
7. To improve general health through healthful food choices and physical activity
8. To address individual nutritional needs taking into consideration personal and cultural preferences and lifestyle while respecting the individual's wishes and willingness to change

The Diabetes Control and Complications Trial (DCCT) confirmed that long-term maintenance of blood glucose levels near to normal delays or prevents the microvascular complications of type 1 diabetes.[45] This study also demonstrated that intensive management of type 1 diabetes is associated with a threefold increase in severe hypoglycemia and a tendency to gain weight. Obesity (greater than 120% of ideal body weight or body mass index [BMI] > 95th percentile) was more common in intensively treated patients.[46] Weight gain in intensively treated patients with type 1 diabetes has been primarily attributed to the elimination of glucosuria (70% of the weight gain) and a 5% reduction in daily energy expenditure (30% of the weight gain).[47] Recurrent symptomatic hypoglycemia requiring oral sources of carbohydrate to restore euglycemia also contributes to the tendency to gain weight in some intensively treated patients.

Our ability to help patients achieve these objectives is still limited by the imperfection of insulin replacement,

which does not precisely mimic normal physiology, the lack of methods to continuously monitor blood glucose concentrations, and the risk of severe hypoglycemia when glucose levels are near to normal but insulin delivery is not regulated by a closed-loop feedback system.[48]

The child with diabetes and his or her family have to assume primary responsibility for routine daily management, and the role of the health care professional is that of educator, advisor, and motivator. Even modest objectives are not achievable in all patients because psychosocial and economic factors make it impossible for some children and their families to perform daily all of the tasks that comprise a comprehensive treatment program.[49,50] The goals of therapy can, however, be accomplished in most patients most of the time by individualized meal planning, flexible insulin regimens and algorithms, self-blood glucose monitoring, and education of older children and adolescents that promotes independent decision-making.

GENERAL PRINCIPLES

There is little or no research on the nutrient requirements of children and adolescents with diabetes. Therefore, nutrient recommendations are based on the requirements of healthy children and adolescents.[51] The nutritional needs of children with diabetes do not differ from those of healthy children. They do not require special foods, nor do they need different amounts of vitamins or minerals.[52] The total intake of energy must be sufficient to balance the daily expenditure of energy and to satisfy the requirement for normal growth. This allowance has to be adjusted periodically to achieve an ideal body weight and to maintain a normal rate of physical growth and maturation. For patients with type 2 diabetes, most of whom are obese, the objective of medical nutrition therapy is to lose weight and then maintain a desirable weight without compromising linear growth and to achieve target blood glucose and hemoglobin A_{1c} (HbA_{1c}) goals.[13]

In contrast to healthy children, in whom insulin secretion is precisely regulated by the ingestion of food, children with type 1 diabetes must match their food consumption to the anticipated time of action of the specific insulin that is being used. For example, because intermediate-acting insulin is continuously released from the subcutaneous injection site into the circulation, hypoglycemia may occur between meals. Consequently, most patients whose insulin regimens include twice-daily intermediate-acting insulin have a snack between meals and at bedtime to prevent hypoglycemia.

It is essential that the patient and his or her family understand the importance of consistency with respect to both timing of meals and snacks and their content of carbohydrate, fat, and protein. How to adjust the meal plan for periods of either planned or spontaneous physical activity and unexpected illness must be addressed as part of a comprehensive program of nutrition education and counseling.

FORMULATION OF THE MEAL PLAN

Newly diagnosed children usually present with weight loss. Therefore, formulating the meal plan begins with estimating energy requirements to restore and then maintain an appropriate body weight and allow for normal growth and development. Energy requirements vary with age, height, weight, and sex, as well as with physical activity, season of the year, and stage of puberty. A child's actual food intake, estimated from a 24-hour or 3-day diet history, should be used as the primary indicator of daily energy needs. If the child's actual food intake cannot be satisfactorily determined, the nutrition prescription can be based on a formula for estimating energy and protein allowances. One method commonly used to estimate energy requirements is based on age and can be used as a crude approximation for children up to 12 years of age: basal daily needs for all children = 1,000 kcal; add to the basal needs 125 kcal × age in years for boys and 100 kcal × age in years for girls. Add up to 20% more kilocalories for very active children. Appendix 2 contains a guide to Recommended Daily Allowances (RDAs) for protein and energy for children and adolescents.[51] Because the energy needs of children continuously change, food intake should be re-evaluated at 3- to 6-month intervals, depending on the age of the child.[53,54]

Medical nutrition therapy begins with an assessment by a registered dietitian, which takes heed of the ethnic, religious, and economic factors that pertain to the individual patient and his or her family. The meal plan must take into account the child's school schedule, early or late lunches, gym classes, and after-school physical activity. Children's activities often differ on weekdays compared with weekends and holidays, and appropriate allowance must be made for these differences.

Children's daily eating patterns generally include three meals and two or three snacks, depending on the length of time between meals, age of the child, and level of physical activity. Although their daily energy intake is relatively constant over time, young children adjust their energy intake at successive meals.[55,56] The highly variable food consumption from meal to meal typical of young children is especially challenging when the child has type 1 diabetes. This normal pattern must be taken into consideration when meal planning advice is given to the parents of young children with type 1 diabetes. Administration of rapid-acting (lispro) insulin after the meal, which has been shown to achieve postprandial blood glucose targets, has provided a solution to this problem.[57,58] The purpose of snacks is to prevent hypoglycemia and hunger between meals. Patients who use intensified insulin regimens (multiple daily doses of rapid-acting insulin or an insulin pump) use pre- and postprandial blood glucose monitoring and individualized insulin-to-carbohydrate ratios (eg, 1 U per 15 g carbohydrate) to choose insulin doses to match carbohydrate intake.

The dietitian has the important task of evaluating the patient's and family's understanding of basic principles of nutrition and teaching them to apply this knowledge to the formulation of an individualized meal plan. The aim is to lay a foundation for lifelong healthful eating habits for the child and family. Even the most intensive regimens of insulin administration are not successful without careful attention to meal planning.[59] Nutrition education, like all

aspects of diabetes education, has to be an ongoing process with periodic review and revision of the meal plan and assessment of the child's and parents' levels of comprehension, ability to solve problems, and adherence to the nutrition goals. Teaching should be followed by systematic assessment of the patients' ability to perform in an environment that approximates as closely as possible the behaviors expected in the natural environment.[60]

Energy

The nutrition prescription must be sufficient to ensure normal growth and physical development. For overweight and obese children and adolescents with type 2 diabetes, energy is reduced to arrest weight gain while supporting normal linear growth and physical development. Even modest weight reduction increases sensitivity of tissues to insulin and improves fasting and postprandial plasma glucose levels.[61,62]

The child's appetite must be considered when determining energy requirements and the nutrition prescription. Because energy requirements change with age, physical activity, and growth rate, an evaluation of height, weight, and energy intake is recommended every 3 to 6 months.[63] Good metabolic control is essential for normal growth and development.[64] At each visit, the clinician should meticulously plot the child's growth data and screen for symptoms and signs of inadequate insulin delivery, hypo- or hyperthyroidism, celiac disease, and adrenal insufficiency when the child is not tracking along his/her height, weight, and BMI percentiles.

Once the nutrition prescription has been determined, the proportion of macronutrients can be modified, as necessary, according to blood glucose and plasma lipid goals and requirements for growth and development. Older children and teens can be taught to adjust the dose of insulin to match their carbohydrate intake, and most do well with this approach as it enhances their independence, helps them fit in with their peers, and develops a trusting and caring relationship with the health care team. Withholding food from a child because the blood glucose level is high, as an alternative to adjusting the dose of insulin, is strongly discouraged.

Carbohydrate

The ADA recommends that 60 to 70% of total energy be distributed between carbohydrate and monounsaturated fat.[65] Dietary dogma in diabetes has been to avoid simple sugars and replace them with complex carbohydrates. This belief was based on the assumption that simple sugars are more rapidly digested and absorbed than starches and would, therefore, aggravate hyperglycemia to a greater degree. During the past two decades, however, the blood glucose responses to various carbohydrate-containing foods have been extensively investigated, and there is little scientific evidence to support this assumption. Numerous factors influence the glycemic response to food, including the amount of carbohydrate,[66] the type of sugar (glucose, fructose, sucrose, lactose),[67] the nature of the starch (amylose, amylopectin, resistant starch),[68] cooking and food processing (degree of starch gelatinization, particle size, cellular form),[69] and food structure,[70] as well as other food components (fat and natural substances that slow digestion: lectins, phytates, tannins, fiber, and starch-protein and starch-lipid combinations).[71,72] The glycemic response to a particular carbohydrate food depends on whether it is eaten alone or as part of a mixed meal.[73] Fasting and preprandial blood glucose concentrations,[74–77] the severity of glucose intolerance,[78] and the second meal effect[79] are other factors that can affect the glycemic response to foods.

The glycemic index (GI), proposed in 1981 as an alternative system for classifying carbohydrate-containing food, measures the glycemic response (an indicator of the rate at which the blood glucose level rises and how it is sustained over time) after ingestion of carbohydrate. GI is defined as the incremental area under the plasma glucose response curve after consumption of a standard amount of carbohydrate from a test food relative to that of a control food, either white bread or glucose.[80] The glycemic and hormonal responses to a large number of ingested carbohydrates have been systematically examined and their GIs defined.[80–86] As a result of these studies, the validity of the dogma that ingestion of simple sugars causes a rapid and pronounced rise in blood glucose, whereas complex carbohydrates produce only modest increments in blood glucose concentration, began to be disputed,[87] and it is now clear that there is a wide spectrum of biologic responses to different complex and simple carbohydrates, with so much overlap that they cannot be simply classified into two distinct groups. Even a single food produces a substantially different glycemic response when it is prepared in different ways. For example, a pureed apple causes a greater increment in blood glucose than does an apple eaten whole.[88] Similarly, ground rice or rice flour causes a greater glycemic and insulinemic response than does whole cooked rice,[84] and cooking increases the glycemic response to starch.[89] Blood glucose levels after ingesting wheat flour in the form of pasta are lower than after an equal amount of wheat flour in bread.[90] Thus, the form of a carbohydrate-containing food, in addition to its chemical composition, influences its glycemic effect. The effect of food form alters the rate of digestion and absorption and, therefore, affects postprandial glycemia. Fruits and milk cause a lower glycemic response than most starches, and sucrose causes a glycemic response similar to that of bread, rice, and potatoes. In general, most refined starchy foods eaten in the United States have a high GI, whereas nonstarchy vegetables, fruits, and legumes tend to have a low GI.

The usefulness of low GI diets in individuals with type 1 diabetes continues to be controversial.[91] Three short-duration (3 to 6 weeks) studies of the effect of low GI foods on glycosylated proteins in patients with type 1 diabetes showed a 12 to 27% decrement in fructosamine in those who decreased their dietary GI by 12 to 26%.[92–94] Insulin requirements have been reported to be lower on a low GI diet, [93] but other studies have not observed this effect.[94–96] In a cross-sectional study of 2,810 people with type 1 diabetes, the GI calculated from 3-day food records was examined for its relation to HbA_{1c} and serum lipid concentrations.[97] HbA_{1c} levels were lower in the lowest GI quartile

compared with the highest quartile. Of the serum lipids, only high-density lipoprotein (HDL) cholesterol was independently related to the GI. The effects on lipids after low - compared with high-GI diets appeared to be minimal.

There is a strong relationship between the premeal insulin dosage and the postprandial response to the carbohydrate content of the meal.[98–101] In individuals using intensive insulin therapy, the total amount of carbohydrate in the meal does not influence the glycemic response if the premeal insulin is adjusted for the carbohydrate content of the meal. The premeal insulin dosage required is not affected by the GI, fiber, fat, or caloric content of the meal, nor do wide variations in the carbohydrate content of meals modify the basal (long-acting) insulin requirement. The concept of total carbohydrate intake determining the premeal insulin dosage is further supported by data from the DCCT. Individuals who adjusted their premeal insulin dosages based on the carbohydrate content of their meals had 0.5% lower HbA_{1c} levels than those who do not adjust premeal insulin doses.[59] Day-to-day consistency in the amount and source of carbohydrate has been associated with lower HbA_{1c} levels in individuals who receive fixed doses of short-acting (or rapid-acting) and intermediate-acting insulin.[102]

Low GI diets significantly improve metabolic control in adults with type 2 diabetes but have not been studied in children and adolescents with type 2 diabetes.[103–106] Although it is clear that carbohydrates cause differing glycemic responses, the literature demonstrates only modest long-term beneficial effects of low GI diets on glycemia and lipid concentrations. The recently published recommendations of the ADA, citing methodologic issues with some of the studies, concluded that there is insufficient evidence of substantial long-term benefit to recommend use of GI in the management of diabetes.[2] The total amount of carbohydrate consumed should be emphasized rather than its source.[2]

Fiber

Fiber refers to the portion of a plant that is not digestible in the human small intestine. It was thought to have no nutritive value, and in the past century, the quantity of fiber in the American diet has declined. During the last two decades, however, considerable attention has been focused on the various plant fibers because of their influence on gastrointestinal physiology. It is now known that fiber markedly influences the digestion, absorption, and metabolism of many nutrients.[107–110] Cellulose, lignins, and certain hemicelluloses, the fibers present in vegetables and grains, are usually insoluble in water. Many fruits and certain legumes are rich in water-soluble fibers such as pectins, guar, and storage polysaccharides. When carbohydrate is ingested together with soluble fiber, the resulting increase in blood glucose concentration is less than when carbohydrate is ingested alone.[111] Normally, a large test meal containing carbohydrate, protein, and fat causes significantly less postprandial glycemia when the meal is supplemented with guar.[112] The attenuated increment in blood glucose concentration that occurs when guar is added to ingested carbohydrate is attributable to delayed rather than incomplete absorption of carbohydrate.[113]

Short-term studies using large amounts of fiber (> 30 g/day) in small numbers of suboptimally controlled type 1 diabetic subjects suggested a positive effect of fiber on glycemia.[114–117] However, in subjects using intensive insulin therapy, 56 g of fiber had no beneficial effect on glycemic control.[95] Subjects receiving two or more injections per day and with baseline HbA_{1c} levels of 7 to 10% were randomized to either a high-fiber (50 g/day) low-GI diet or a low-fiber (15 g/day) high-GI diet for 24 weeks. The high-fiber diet significantly decreased mean daily blood glucose concentrations, number of hypoglycemic events, and, in the subgroup of patients compliant with diet, HbA_{1c} levels but had no beneficial effect on cholesterol, HDL cholesterol, or triglyceride concentrations.[118] Conversely, a cross-sectional analysis of dietary fiber in type 1 diabetes patients enrolled in EURODIAB IDDM showed that a higher intake of fiber was independently associated with higher levels of HDL cholesterol in both men and women and lower low-density lipoprotein cholesterol levels in men but not in women.[119] No substantial differences were observed between soluble and insoluble fiber intakes.

These observations suggest that inclusion of plant fiber in the diet may benefit patients with diabetes by diminishing postprandial hyperglycemia. Furthermore, certain soluble plant fibers significantly reduce serum cholesterol concentrations and decrease fasting serum triglyceride levels in diabetics with hypertriglyceridemia.[109] The mechanism responsible for the effects on cholesterol and triglycerides is not known.

Fiber intake for people with diabetes should be the same as for the general population. For adults, daily consumption of a diet containing 20 to 35 g dietary fiber from a wide variety of food sources is recommended. This goal can be readily achieved by increasing the consumption of minimally processed foods, such as grains, legumes, fruits, and vegetables.[120] Dietary fiber guidelines for children with diabetes are the same as for nondiabetic children. Updated Adequate Intakes (AI) for children and adolescents are as follows[121]:

AI for Children	
1–3 years	19g/day of Total Fiber
4–8 years	25 g/day of Total Fiber
AI for Boys	
9–13 years	31 g/day of Total Fiber
14–18 years	38/day of Total Fiber
AI for Girls	
9–13 yers	26g/day of Total Fiber
14–18 years	26 g/day of Total Fiber

In summary, it appears that the glycemic load of meals and snacks is more important than the source or type of carbohydrate. The glycemic load is defined as the weighted average of the GI of individual foods multiplied by the percentage of the dietary energy as carbohydrate and has been

proposed as a method to characterize the impact of foods and dietary patterns with different macronutrient composition on glycemic response. For example, a carrot has a high GI but a low glycemic load, whereas a potato has both a high GI and a high glycemic load. Individuals using intensive insulin therapy should adjust their premeal insulin dosages based on the carbohydrate content of their meals. Individuals receiving fixed daily insulin dosages should try to be consistent in their day-to-day carbohydrate intake. The use of low-GI foods may reduce postprandial hyperglycemia and may have long-term benefit on HbA_{1c} levels.

Protein

The optimal protein intake for individuals with diabetes has not been determined. Protein requirements are not increased when diabetes is well controlled with insulin; therefore, children with diabetes should follow the RDA guidelines suggested for children without diabetes. The physiologic requirement is determined by the amount of protein necessary to sustain normal growth. This requirement is based on ideal weight for height and varies with age, being highest in infancy and early childhood. The protein requirement (per kilogram body weight) of infants, children, and adolescents is higher than that of adults. Protein intakes range from 12 to 20% (0.9 to 2.2 g/kg body weight/day) of total daily caloric intake. Any ingested protein that exceeds the body's requirement for new protein synthesis enters the carbon pool and is converted into either glucose or fat. It is recommended that protein should constitute 15 to 20% of the total daily intake of energy, the same as for nondiabetic children and adolescents.

Dietary protein should be derived from both animal and vegetable sources; however, the source of protein is not especially important as long as all of the essential amino acids are provided in adequate amounts. To lower the consumption of saturated fat, less protein should be derived from red meat, whole milk, and high-fat dairy foods than is customary in the United States. With the onset of nephropathy, lower intakes of protein should be considered. A protein intake similar to the adult RDA (0.8 g/kg body weight/day), ~ 10% of daily calories, is sufficiently restrictive and is recommended for individuals with evidence of nephropathy. With protein intake of 0.6 g/kg/day, evidence of protein undernutrition has been reported.[122]

Fat

The prevalence of macrovascular disease is markedly increased in persons with diabetes mellitus.[123] Its major clinical consequences are atherosclerosis of the coronary, cerebral, and lower-extremity large arteries. In Westernized populations, atherosclerotic vascular disease is the major cause of mortality and morbidity in patients with diabetes. About 75% of patients with diabetes in Europe and North America die of coronary heart disease. This terrible toll is not inevitable. In other parts of the world, diabetic patients who escape atherosclerosis have low serum cholesterol levels and live on diets that are usually high in starch and have a low content of saturated fat. Cognizance of these facts compels us to focus attention on the amount and type of fat consumed by persons with diabetes in North America. A survey of Joslin Clinic patients with type 1 diabetes for 15 to 20 years, conducted between 1986 and 1988, showed that fat accounted for 36 to 40% of total calorie consumption.[124]

There is a clear relationship between hyperlipidemia and increased cardiovascular morbidity in type 2 diabetes, whereas in type 1 diabetes, microvascular disease is the more urgent problem. Although microvascular disease does not appear to be related to abnormalities of lipid metabolism, patients with type 1 diabetes eventually also develop atherosclerosis and its sequelae.

Excessive saturated fat, cholesterol, and total energy lead to increased blood levels of cholesterol and triglycerides. Because hyperlipidemia is a major determinant of atherosclerosis,[125] the meal plan should be modified to mitigate this risk factor. The recommended percentage of energy from fat depends on goals for body weight and plasma glucose and lipid concentrations. Children and adolescents with well-controlled type 1 diabetes are not at high risk for developing lipid abnormalities but should be screened and monitored according to guidelines issued by the National Cholesterol Education Program (NCEP) and by the American Academy of Pediatrics.[126,127] For children and adolescents who are growing and developing normally and have normal plasma lipid levels, recommendations are that less than 10% of energy comes from saturated fat, the daily intake of cholesterol should be less than 300 mg, and consumption of transunsaturated fatty acids should be minimized. Total fat should be reduced in the obese child in an effort to reduce total energy consumption. The consumption of saturated fat can be reduced by eating less red meat, whole milk, and high-fat dairy foods; eating more poultry, fish, and vegetable proteins; and drinking more low-fat milk.

The NCEP Step II diet guidelines should be implemented in the patient with elevated LDL cholesterol (> 100 mg/dL).[128] The guidelines recommend that total fat represent no more than 30% of total calories, less than 7% of calories is from saturated fat, and dietary cholesterol is 200 mg/day.

Sodium

The average consumption of salt in populations correlates well with the prevalence of hypertension,[129] and a high intake of sodium causes high blood pressure in susceptible individuals. Most processed foods contain considerably more sodium than similar foods prepared from raw ingredients. Sodium is present in the form of sodium chloride; it may also be present as sodium glutamate, added to enhance flavor, or as sodium nitrite included as a preservative. The leaders in sodium content are take-out or "fast foods," which account for an ever-increasing proportion of the US diet. It has been estimated that 70% of the sodium in the US diet is derived from prepared foods.

Sodium consumption in persons with diabetes should be the same as for the general population, between 2,400 mg[130] and 3,000 mg daily.[131] A reduction in salt

intake lowers blood pressure in both normotensive and hypertensive individuals. In nondiabetic adults, a reduction in salt consumption lowers systolic blood pressure by 4 to 5 mm Hg[132,133]; therefore, for diabetic patients with hypertension (in children and adolescents defined as the average of three separate systolic and/or diastolic blood pressures > 95th percentile for age, sex, and height), a reduction in salt intake to 2,400 mg daily is recommended. Note, however, that sodium restriction has not been tested in the diabetic population in controlled clinical trials.[134] To achieve these goals, patients should be taught to reduce their use of table salt and decrease their consumption of convenience foods.

Sweeteners

Sweetness is an established property of the Western diet.[135] The average per capita consumption of sugars in the United States is estimated to be 94 g per day, accounting for 22% of energy intake.[136] If the intake of sucrose has to be restricted as part of treatment, most patients demand an alternative source of sweetness if they are to adhere to their meal plans. Two varieties of sweeteners are available: nutritive and non-nutritive.[137]

Nutritive Sweeteners These include sucrose, fructose, sorbitol, xylitol, and corn sweeteners such as corn syrup, fruit juice or fruit juice concentrate, honey, molasses, dextrose, and maltose.

Sucrose Several studies have shown that sucrose as part of the meal plan does not adversely affect blood glucose control in individuals with type 1 or type 2 diabetes.[86,138–145] Therefore, sucrose and sucrose-containing foods may be substituted for other carbohydrates but may not simply be added to the meal plan. When making such substitutions, consideration must be given to the nutrient content of sucrose-containing foods, as well as the presence of other nutrients frequently ingested with sucrose, such as fat. Data are conflicting, and additional research will be necessary to determine whether dietary sucrose adversely affects serum lipids in people with diabetes.

The most recent ADA recommendations emphasize that priority should be given to the total amount of carbohydrate consumed rather than the source of the carbohydrate.[2] In clinical practice, therefore, the guiding principle should be "a carbohydrate is a carbohydrate." For example, a six-cookie serving of Nilla Wafers by Nabisco that contains 15 g of carbohydrate and 5 g of fat is approximately equivalent to one Eggo waffle. A serving of jelly beans containing 15 g of carbohydrate is equivalent to 4 oz of orange juice and may be used interchangeably. Each meal must be evaluated as a whole because the fiber, fat, and protein content, as well as the method of food preparation (as noted above), influences the glycemic response to the carbohydrate content of the meal.

Fructose Fructose is a constituent of sucrose and is present as the free monosaccharide in many fruits, vegetables, and honey. It accounts for ~ 9% of the average energy intake in the United States. About one-third of dietary fructose comes from fruits, vegetables, and other natural sources in the diet and about two-thirds come from food and beverages to which fructose has been added.[146] Fructose is similar in taste to sucrose but is 1.2 to 1.8 times sweeter. It is absorbed more slowly from the intestinal tract than glucose, sucrose, or maltose and is converted to glucose and glycogen in the liver.[147,148] Several studies have shown reduced postprandial plasma glucose levels when isocaloric amounts of fructose replaced sucrose or starch in the diets of people with diabetes.[86,139,149,150] Fructose has also been used in children in amounts up to 0.5 g/kg/day.[151] The potential benefit is tempered by the concern that fructose may have adverse effects on serum lipids, especially LDL cholesterol.[150] Consumption of large amounts of fructose (15 to 20% of daily energy intake [90th percentile of usual intake]) has been shown to increase fasting total and LDL cholesterol in subjects with diabetes[150] and fasting total and LDL cholesterol and triglycerides in nondiabetic subjects.[152] Therefore, people with dyslipidemia should not consume large amounts of fructose. There is no reason to avoid fruits, vegetables, and honey, in which fructose occurs naturally. Because of concern about the potential adverse effect of large amounts of fructose on serum lipids, fructose as a sweetening agent in the diet of people with diabetes may have no overall advantage over other nutritive sweeteners.

***Sugar Alcohols* (*Polyols*)** Sugar alcohols are classified as hydrogenated monosaccharides. These include sorbitol, mannitol, xylitol, hydrogenated disaccharides (eg, isomalt, maltitol, lactitol) and mixtures of hydrogenated mono-, di-, and oligosaccharides (eg, hydrogenated starch hydrolysates).[153]

Sorbitol is about half as sweet as sucrose. It is slowly and only partially absorbed from the gut and then metabolized in the liver by sorbitol dehydrogenase to fructose. Sorbitol has been assigned an energy value of 2.6 kcal/g; however, its precise caloric value is uncertain.[2] Its slow absorption causes blood glucose levels to rise less rapidly than after sucrose and other carbohydrates. When the daily intake exceeds 30 to 50 g, sorbitol can cause flatulence, intestinal cramps, and osmotic diarrhea.[154] The available evidence suggests that isocaloric substitution of sorbitol in the diet does not alter metabolic control.

Xylitol, a pentahydric alcohol, is as sweet as sucrose and is widely distributed in fruits and vegetables. The ingestion of xylitol in a single dose of 30 to 40 g causes diarrhea,[155] thus limiting its usefulness as an isocaloric carbohydrate substitute. It is metabolized to glucose, pyruvate, and lactate, mainly by the liver and, to a lesser extent, by the kidneys. Xylitol is slowly converted to glucose. There is scant information available on the effect of long-term oral administration on blood glucose control of diabetes. Many so-called dietetic foods marketed for people with diabetes contain sorbitol or xylitol instead of sucrose. In general, the sugar alcohols offer no nutritional advantage over other nutritive sweeteners and are usually more expensive.

Resistant starch (nondigestible oligosaccharides and the starch amylose) is not digested and, therefore, is not absorbed as glucose in the small intestine. It is, however,

almost completely fermented in the colon and produces about 2 kcal/g of energy. It is estimated that resistant starch and unabsorbed starch represents ~ 2 to 5% of the total starch ingested in the average Western diet.[156] Legumes are the major source of resistant starch (2 to 3 g per 100 g cooked legumes). Uncooked cornstarch contains about 6 g resistant starch per 100 g dry weight.[157] Single meal studies have found that meals high in resistant starch caused some reduction in postprandial glucose and insulin responses compared with meals with equivalent amounts of digestible starch. Uncooked cornstarch as part of the bedtime snack has resulted in less hypoglycemia at 2 am in children and at 3 am in intensively treated type 1 diabetic adults.[158–160]

Other Nutritive Sweeteners These include corn sweeteners such as corn syrup, fruit juice or fruit juice concentrate, honey, molasses, dextrose, and maltose. These sweeteners have the same calorie value as sucrose, and there is no evidence that they have any advantage over sucrose in terms of causing a less pronounced increase in blood glucose concentrations. All nutritive sweeteners contribute calories and, like sucrose and fructose, must be accounted for in meal planning.

Non-nutritive Sweeteners (High-Intensity Sugar Alternatives, Low-Calorie or Alternative Sweeteners) Saccharin, aspartame, acesulfame potassium (K), and sucralose are approved for use by the Food and Drug Administration (FDA) in the United States.

Saccharin was discovered in 1897 and, until the advent of aspartame, was the most commonly used artificial sweetener. It leaves a slightly bitter, metallic aftertaste. Administration of large amounts of saccharin to rats is associated with an increased occurrence of bladder tumors, which raised concerns about its carcinogenic potential and safety for use in human beings, but it is no longer on the FDA list of cancer-causing chemicals.[161]

Aspartame has been available since the early 1980s. It is a dipeptide consisting of phenylalanine and aspartic acid and is 200 times sweeter than sugar.[162] At one-tenth of a calorie, it has the sweetness of a teaspoon of sugar. It rapidly gained widespread popularity as an alternative to saccharin. The FDA determines an acceptable daily intake (ADI) for all food additives, including non-nutritive sweeteners. The ADI is defined as the amount of a food that can be safely consumed on a daily basis over a person's lifetime without any adverse effects. Actual intake is much less than the ADI. The ADI for aspartame is 50 mg/kg/day. The range of actual consumption at the 90th percentile is 2 to 3 mg/kg body weight, well below the ADI.

Acesulfame K is a white, colorless, crystalline sweetener approximately 200 times sweeter than sucrose. It is a derivative of acetoacetic acid and has a structure similar to that of saccharin.[163] It was approved for use by the FDA in 1988 and is marketed in the United States under the brand name Sunette when used as an ingredient of foods and as Sweet One when sold as a tabletop sweetener. It is stable both in liquids and during baking and cooking.

Sucralose is the newest product approved by the FDA. It was approved for use in 1998 under the brand name Splenda. It is made from sucrose through a process in which three hydrogen-oxygen groups are replaced with chlorine atoms. Sucralose is 600 times sweeter than sucrose. It is very stable and can be used for baking and cooking and has no effect on glucose homeostasis in diabetic subjects.[164,165]

TYPE 2 OR NON–INSULIN-DEPENDENT DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

Type 2 diabetes used to be virtually exclusively seen in adults. Changes in energy intake and expenditure have resulted in an epidemic of obesity in children and adolescents in the United States,[166] which has been temporally associated with an alarming increase in the prevalence of type 2 diabetes in children and adolescents, especially in minority populations, in the past decade. Almost 95% of patients are either overweight or frankly obese.[13,167]

Even in the absence of glucose intolerance, simple obesity is associated with impaired insulin action and with a reduced number of insulin receptors on target tissues.[61,62,168] In children, body composition is also a major determinant of insulin sensitivity. Adiposity accounts for 55% of the variance in insulin sensitivity in white children.[169] An inverse relationship between increasing adiposity and insulin sensitivity has also been demonstrated in black children. As BMI and percent adiposity increase, insulin sensitivity decreases and serum insulin levels increase.[170]

In adults, weight reduction alone causes increased sensitivity to insulin and improves fasting and postprandial hyperglycemia.[61,62] Similarly, plasma glucose levels decrease in type 2 diabetes following moderate calorie reduction.[171,172] Accordingly, lifestyle changes that lead to weight loss should be the cornerstone of therapy in all patients with type 2 diabetes.

Medical nutrition therapy for these patients emphasizes healthful eating to support optimal growth and weight management. Simple recommendations such as the elimination of sugar-containing sodas and juices and decreasing consumption of calorie-dense "fast foods" can improve blood glucose levels.

Children with type 2 diabetes should receive comprehensive self-management education similar to that for patients with type 1 diabetes. The entire family should be referred to a dietitian with knowledge and experience in nutritional management of children with diabetes. Nutrition recommendations should be culturally appropriate and sensitive to family resources and involve the entire family. Family members should be encouraged to adopt healthful eating habits and receive guidance on behavior modification strategies to change their lifestyles and decrease consumption of high-energy high-fat foods and incorporate daily aerobic physical activity into their lives.[173] To increase children's physical activity, the amount of time devoted to sedentary activities such as viewing television, playing video games, and sitting in front of a computer must be strictly limited.[174,175]

Treatment aims to normalize fasting and postprandial blood glucose and HbA_{1c} values and to identify and control any associated comorbidities such as hypertension and hyperlipidemia.[176] The ultimate goal of treatment is to reduce the risk of the acute and chronic complications associated with diabetes. The early age of onset of type 2 diabetes in children can reasonably be expected to increase the risk of microvascular complications, which are directly related to the duration of diabetes and hyperglycemia.

EDUCATION OF THE PATIENT AND FAMILY

It is hardly possible to overstate the importance of educating patients and their families in the basic principles of nutrition and in their application to the formulation of an individualized meal plan. The aim is to lay the foundation for lifelong healthful eating habits. A registered dietitian, experienced in the nutritional needs of the growing child and the behavioral issues that impact on adolescent diets, should be an integral member of the diabetes treatment team and is primarily responsible for teaching children and their families the principles of medical nutrition therapy and their application in the development of an individualized meal plan. Nutrition education must be an ongoing process, with periodic review of the meal plan and assessment of the child's and parents' level of comprehension. A single instructional session is inadequate. The patient with newly diagnosed diabetes and his or her parents should meet with a dietitian several times during the first few days after diagnosis. Within a few weeks of the child resuming his or her usual schedule, the patient and family should review the meal plan with a dietitian, who should also be available to patients and their families for telephone consultation. Because children's energy needs change with growth and variations in physical activity, food intake should be reassessed every 3 to 6 months in young children.[54] In older individuals, continuing education reinforces the principles of nutrition, and consultation with a dietitian is recommended at least annually. If the patient's glycemic control is poor, if growth is failing, if weight gain is excessive, or if other problems arise, the dietitian should be reconsulted to review the meal plan and to make appropriate dietary recommendations. The use of imaginative teaching methods and materials, applied on an individual basis, will engage the attention and cooperation of children and parents more effectively than abstract concepts of nutritional principles and detailed diet sheets that list the composition of individual foodstuffs.

THE MEAL PLAN

The meal plan must be simple, practical, and easy to modify and must offer foods that are interesting, tasty, and inexpensive. In the diabetes program at Children's Hospital Boston, meal planning is based on a combination of carbohydrate counting and the traditional exchange system, individualized to meet the ethnic, religious, and economic circumstances of each family. The exchange list system for meal planning is the most widely used substitution system. It was originally developed in 1950 by a joint committee of the ADA, the American Dietetic Association, and the Diabetes-Arthritis Program of the US Public Health Service and most recently was updated in 2003.[177] The system is based on six exchange lists: milk, fruit, vegetable, starch, meat, and fat. Each list indicates the appropriate size or volume of each food exchange. Thus, by prescribing the meal plan in terms of numbers of exchanges for each meal, consistency of total calories and of the proportions of nutrients can be maintained while allowing the patient a wide choice of foods. Accurate measurement of portion sizes has to be learned, and weighing and measuring foods help to achieve familiarity with the sizes of food portions specified in the exchange list. Weighing food is an educational exercise to train the eye and need not be continued indefinitely. However, if blood glucose control appears inexplicably to deteriorate, it is useful to resume weighing and measuring food portions to ensure that amounts are not excessive. Even the exchange system is not intended to be used in isolation; rather, it is intended to be one component of a nutritional program directed by a trained dietitian.

An example of how this system is applied to an individual patient is illustrated below. An 11-year-old girl's height is 144 cm (50th percentile on the Centers for Disease Control and Prevention's growth chart) and weight is 37.4 kg (50th percentile). Her daily energy requirement based on the RDA to support growth in the 50th percentile is 1,756 kcal. An appropriate distribution of macronutrients could be 50% of the total calories from carbohydrate, 20% as protein, and 30% as fat:

	Kcal	*G*
50% carbohydrate	884	221
20% protein	368	92
30% fat	531	59
Total kcal	1,783	

Table 42-1 shows how this patient's daily food allowance is distributed among the six food groups.

CARBOHYDRATE COUNTING

Carbohydrate counting is a meal planning method in which the grams of carbohydrate or number of carbohydrate servings eaten at each meal and snack are counted. Carbohydrate is the main nutrient in starches, fruits, milk, and sugar-containing foods and has the greatest effect on the blood glucose level. Therefore, it is the most important macronutrient to control to maintain optimal glycemic control. Using the exchange lists, one starch choice is considered to be equivalent to either one fruit choice or to one milk choice, and each contains approximately 15 g of carbohydrate and is equal to one "carbohydrate choice." A typical breakfast of two starch exchanges, one fruit exchange, and one milk exchange is equal to 60 g of carbohydrate or four carbohydrate choices. The "Nutrition Facts" on food labels list the portion size and the total amount of carbohydrate measured in grams per serving. Foods not included in

TABLE 42-1 Distribution of Daily Food Allowance among Six Food Groups

Group	*Exchanges*	*Carbohydrate*	*Protein*	*Fat*
Starch	8	120	24	
Fruit	4	60		
Milk	3 low fat (1%)	36	24	9
Vegetables	1	5	2	
Meat	6 medium fat		42	30
Fat	4			20
Grams		221	92	59
Calories (%)		884 (49.6)	368 (20.6)	531 (29.8)

the exchange lists may be incorporated into a meal plan. The serving size of sucrose-sweetened foods is typically smaller and less nutrient dense than foods with a lower sugar content. Moderation is important for optimal nutrition and satiety. For example, 3/4 cup of Frosted Flakes or 1 1/2 cups of regular Cheerios have approximately 30 g of carbohydrate. Accordingly, 3/4 cup of Frosted Flakes or 1 1/2 cups of Cheerios with 1 small banana and 1 cup of milk are both examples of a 60 g carbohydrate breakfast.

Carbohydrate counting allows flexibility in food choices and minimizes "cheating" as all foods can be included in the meal plan. See Table 42-2 for a sample menu incorporating both the exchange servings and grams of carbohydrate for the child described in the text.

Adherence

Adherence to a meal plan is one of the behaviors patients must maintain for optimal management of type 1 diabetes and strongly correlates with blood glucose control in children less than 16 years old.[178] For many patients, this is the most difficult aspect of diabetes management.[179–182] Patients frequently do not adhere to their prescribed meal plan,[49,50,183,184] and parents often have difficulty helping their young child to follow a meal plan.[182] Schmidt and colleagues, for example, found that subjects added or deleted approximately one of four prescribed food exchanges daily.[184] Furthermore, many children (and their parents) do not possess the knowledge and skill required for good dietary adherence regardless of motivation.[60,185] Approximately 60% of Finnish adolescents reported at least a satisfactory level of adherence to their meal plans.[186] In the United States, a self-report survey of 144 adolescents who attended a tertiary care diabetes program showed that 15% took extra insulin to cover inappropriate food intake, 73% ate inappropriate foods, and 50% missed meals and snacks.[187]

Management of diabetes is difficult for children and adolescents, and as children progress through adolescence and into young adulthood, satisfactory adherence to therapy and optimal glycemic control become increasingly difficult to achieve and maintain.[188] To achieve better diabetes outcomes, families must remain actively involved in their youngster's diabetes management, regardless of the child's age, even as the primary responsibility for diabetes care shifts from parent to adolescent.[189–191]

Health care professionals involved in the care of children with diabetes should not be discouraged from helping their patients to overcome the barriers to adherence so that they will be able to enjoy the benefits of good diabetes control.[45,192] Empirical research shows that adherence to the meal plan can be improved by psychosocial factors such as promoting a positive attitude toward the illness and its treatment as well as supportive relationships with their family, peers, and health care team.[186] Frequent follow-up and ongoing education to individualize the meal plan and set attainable goals are necessary to teach the patient and his/her family how to match insulin to exercise and food.[193,194] Self-monitoring of blood glucose and carbohydrate counting provide patients with a greater degree of dietary flexibility and enable adolescents to take a more active and informed role in their diabetes nutritional management.[191,195,196]

SUMMARY

Nutrition recommendations for treatment of diabetes have repeatedly changed since the preinsulin era, in which a starvation diet with negligible carbohydrate and 70% of calories from fat was the recommended treatment. Today, there is no one "diabetic diet." The recommended diet can be defined only as a meal plan based on a nutrition assessment and mutually accepted treatment goals and desired outcomes. Nutrition therapy should be

TABLE 42-2 Sample Menu Based on the Daily Food Allowance*

Foods	*Exchanges*	*Carbohydrate (g)*
Breakfast		
3/4 cup cornflakes	2 starches	30
+ 1 slice toast		
1 small banana	1 fruit	15
1/2 cup 1% fat milk	1/2 low-fat milk	6
1 tsp margarine	1 fat	
Snack		
1 granola bar	1 starch	15
Lunch		
2 slices bread	2 starches	30
1 slice turkey, 1 slice cheese	2 meat	
Lettuce + tomato	"free vegetable"	
1 tsp mayonnaise	1 fat	
1 cup 1% fat milk	1 low-fat milk	12
1 small apple	1 fruit	15
Snack		
17 grapes	1 fruit	15
3 cups low-fat popcorn	1 starch	15
Supper		
1/2 cup mashed potatoes	1 starch	15
3 oz chicken	3 meat	
1/2 cup broccoli	1 vegetable	5
1 small orange	1 fruit	15
2 tsp margarine	2 fat	
1 cup 1% low-fat milk	1 low-fat milk	12
Snack		
3 graham cracker squares	1 starch	15
1 ounce string cheese	1 meat	0
1/2 cup 1% fat milk	1/2 low-fat milk	6

*For child described in the text.

individualized and consideration given to usual eating habits and other lifestyle factors. Monitoring clinical and metabolic parameters including blood glucose, glycosylated hemoglobin, lipids, blood pressure, and body weight, as well as quality of life, is crucial to ensure successful outcomes. Modern diabetes management, combining frequent self-monitoring of blood glucose with multiple-dose insulin regimens, or insulin pump therapy, and mastery of carbohydrate counting, has made it possible for children and adolescents with diabetes to have considerable dietary flexibility while maintaining near-normal glycemic control.[197]

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CHAPTER 43

ACUTE DIARRHEA

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Diarrheal diseases are a major cause of pediatric morbidity and mortality worldwide, with 1.5 billion episodes and 1.5 million deaths of children under age 5 years estimated to occur annually.[1,2] If these statistics appear daunting, they should be compared with data from 1992, when 3 million annual deaths were estimated,[3] and 1982, when 5 million deaths were estimated.[4] The story underlying these statistics is the remarkable success of worldwide campaigns to treat acute diarrhea with oral rehydration therapy (ORT). The development of ORT is among the most successful collaborations ever between basic and applied biomedical research and one of the most significant applications of nutritional therapy to the management of acute disease. Interestingly, it is also a case of reverse technology transfer,[5] in which work originally carried out for benefit of those in countries with less developed economies has changed the standard of practice, even in the most developed setting.

It is, however, clear that the full benefits of the nutritional therapy of acute diarrhea have not been realized. Shortcomings in treatment are significant because, even in countries with established market economies, diarrheal diseases account for a substantial portion of pediatric hospital admissions and remain a significant cause of morbidity.[6] It may be argued that the full implementation of ORT for treatment of acute diarrhea in countries with developed market economies has lagged behind its use in less developed countries, perhaps because of ingrained use of intravenous therapy or the reduced appeal of a technologically simple solution.[7] In addition, it has been difficult to establish continued feeding during diarrheal episodes as normative therapy, in spite of a wealth of in vitro and in vivo data supporting the role of continued nutrition in improving measurements of gastrointestinal function, as well as anthropometric, biochemical, and clinical outcomes.[8,9]

This chapter reviews the historical background and scientific basis of ORT and provides a framework for assessing and treating the dehydrated patient or the patient at risk for dehydration. The discussion focuses on common clinical scenarios and traditional practices, especially with regard to feeding. The limitations of ORT are discussed, as well as areas of ongoing research.

HISTORICAL BACKGROUND

Early attempts at treating dehydration resulting from diarrhea were first described in the medical literature in the 1830s during epidemics of *Vibrio cholerae* infections.[10,11] It was not until 100 years later that the use of intravenous fluids became widespread. Accurate chemical analysis of diarrheal stools eventually permitted the formulation of physiologically appropriate replacement solutions, leading to the successful treatment of cholera with intravenous fluids by the 1940s.[12] Further research into intestinal electrolyte transport led to the development of oral solutions for rehydration.[13,14] In 1971, these were put to the test in the field with the large-scale treatment of refugees from the Bangladesh war of independence.[15] The remarkable success of oral solutions hastened the development of the World Health Organization (WHO) guidelines for ORT and production of standard packets of oral rehydration salts. It may be argued that the initial application of ORT to cholera epidemics in the developing world hindered the acceptance of this therapy as a mainstay in the United States and Europe. With time, however, ORT has become accepted as the standard of care for clinically efficacious and cost-effective management of acute diarrhea,[16,17] although it remains underused in settings in which parenteral rehydration has been the established practice.[18–21]

PHYSIOLOGIC BASIS FOR THE USE OF ORAL REHYDRATION SOLUTIONS

Fluid must be absorbed and reabsorbed for survival. Under the best of circumstances, the adult intestinal epithelium must handle 6,500 mL fluid per day, the combination of oral intake, salivary, gastric, pancreatic, biliary, and upper intestinal secretions. This is typically reduced to 1,500 mL by the distal ileum and is further reduced in the colon to stool output less than 250 mL/day.[22] Were it not for this ability for net absorption, there would be no balance of fluid to replace insensible losses and that necessary for renal filtration. During disease, the volume of intestinal fluid output is remarkably increased, overwhelming reabsorptive capacity, leading to diarrhea.

Applied clinical research, first carried out among cholera patients, showed that diarrhea in cholera is not the result of a failure of intestinal reabsorption but a state of extreme output in which reabsorptive mechanisms remain intact.[23] Not only *V. cholerae* but many strains of *Escherichia coli*, *Shigella, Salmonella*, and other pathogenic bacteria have been shown to produce toxins that bind to

enterocyte receptors, causing chloride-mediated secretion stimulated by second messengers, such as cyclic adenosine monophosphate, cyclic guanosine monophosphate, and calcium.[24,25] Even those infectious agents typically classified as causing osmotic diarrhea may, in some cases, also increase enterocyte secretion. *Rotavirus*, for instance, damages the villous brush border, causing osmotic diarrhea, but also produces an enterotoxin that causes a Ca^{++}-mediated secretory diarrhea.[26,27]

Basic scientific studies of intestinal solute transport mechanisms were also crucial in outlining the processes by which solute absorption is maintained. Water passively follows the osmotic gradient generated by the transcellular transport of electrolytes and nutrients. Although three principal mechanisms of sodium absorption have been described,[22] that essential to the efficacy of oral rehydration solutions (ORSs) was shown to result from the stoichiometric cotransport of sodium and glucose molecules at the intestinal brush border.[28] Figure 43-1 provides a schematic of the cotransport process. Cotransport across the luminal membrane is facilitated by the protein SGLT1. Once in the enterocyte, the transport of glucose into the blood is facilitated by GLUT 2 in the basolateral membrane. The Na^+-K^+ adenosine triphosphatase provides the gradient that drives the process. Clinical studies have demonstrated that this mechanism remains intact even in patients with severe diarrhea.[23]

In 1975, the WHO and the United Nations Children's Fund (UNICEF) agreed to promote a single solution (WHO-ORS) containing (in mmol/L) sodium 90, potassium 20, chloride 80, base 30, and glucose 111 (2%). This composition was selected to allow a single solution to be used among diverse populations in different countries. Although this solution performed well over 25 years, subsequent clinical research, documented in numerous controlled trials and summarized in a recent meta-analysis,[29] has favored the adoption of a lower-osmolarity standard solution. Based on these findings, UNICEF and WHO organized an expert consultation on oral rehydration that recommended a reduced-osmolarity solution.[30] In May 2002, WHO announced a new ORS formulation consistent with these recommendations, with sodium concentration 75 mEq/L, glucose 75 mmol/L, and total osmolarity 245 mosm/L.[31] See Table 43-1 for a comparison of the two solutions.

HOME MANAGEMENT OF ACUTE DIARRHEA

The simplicity of treatment based on ORSs makes possible the management of uncomplicated cases of diarrhea at home. As long as caretakers are properly instructed with regard to the need for clinical assessment when children appear significantly ill or appear to be failing treatment, then it is appropriate to begin therapy at home. Early intervention may reduce complications such as dehydration and poor nutrition. In developed, as in developing, settings, early administration of ORS may lead to fewer office or emergency room visits,[32] hospitalizations, or deaths.

In fact, it has always been the case that mothers and other caretakers begin treatment of diarrhea at home.[33] The advent of ORT allows a therapy that is more effective and less harmful than many traditional home therapies. All families should be encouraged to have a supply of ORS in the home at all times, much in the same way that acetaminophen and adhesive bandages are viewed as staples of the medicine chest. As soon as diarrhea begins, one of the commercially available products can be started at home. Although it is possible to produce a homemade solution with appropriate concentrations of glucose and sodium, possibilities for serious error abound, so that standard commercial oral rehydration preparations should be recommended where they are readily available and not prohibitively expensive. Regardless of the fluid used, an age-appropriate diet should be given as well.[9] The most crucial aspect underlying home management of diarrhea is the need to give increased volumes of fluid as well as to maintain adequate caloric intake. Infants should be offered more frequent feeds at the breast or bottle, and children should also be given more fluids.

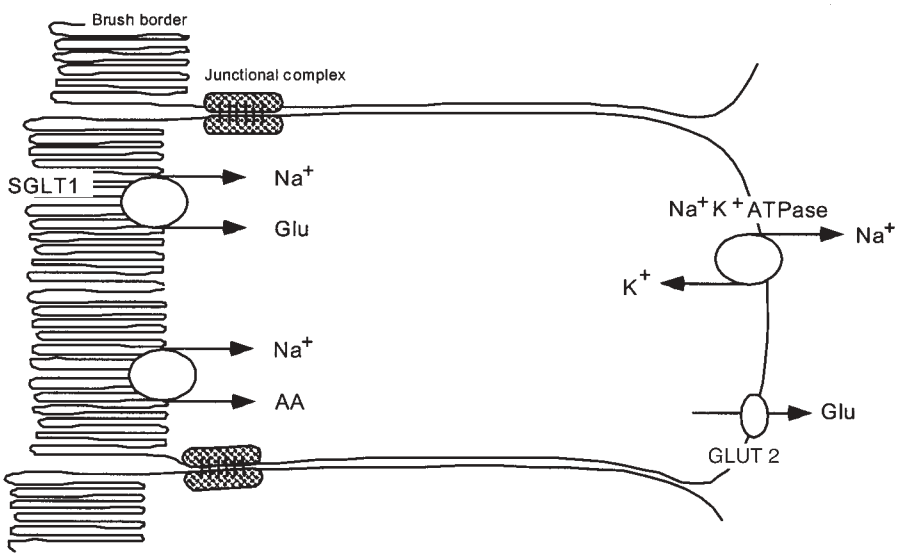

FIGURE 43-1 Solute-coupled sodium absorption. ATPase = adenosine triphosphatase.

TABLE 43-1 Comparison of 1975 and 2002 WHO-ORS

	Glucose (mmol/L)	*Na (mmol/L)*	*K (mmol/L)*	*Cl (mmol/L)*	*Citrate (mmol/L)*	*Osmolarity (mOsm/L)*
WHO-ORS (2002)	75	75	20	65	10	245
WHO-ORS (1975)	111	90	20	80	10	311

ORS = oral rehydration solution; WHO = World Health Organization.

Caretakers should be educated to recognize signs of illness or treatment failure that necessitate medical intervention. Infants with acute diarrhea are more prone to become dehydrated than are older children because they have a higher body surface-to-volume ratio, a higher metabolic rate, and relatively smaller fluid reserves and depend on others for fluid. For this reason, parents should seek medical care promptly for infants with diarrhea even before the first signs of dehydration are evident. Indications for prompt medical evaluation are summarized in Table 43-2. No guidelines have established a specific age under which evaluation is mandated, but, in general, infants should be evaluated by a health professional when there is risk of dehydration; in general, the smaller the child, the lower the threshold for hands-on evaluation. When fever is present, infants and children should be evaluated according to current guidelines. Naturally, underlying conditions, including history of prematurity, metabolic disorders, immune compromise, and recent recovery from surgical interventions, may prompt early evaluation, as may concurrent illness, even a concurrent respiratory infection. Children with dysentery (visible blood or mucus in stool) should be brought in for medical evaluation.

In developed settings, the decision as to whether to bring a child to an office or emergency room setting for evaluation is generally made after consultation with a physician or other health care provider over the telephone. Questions should focus on those factors putting a child at risk for dehydration. Whenever possible, quantification is helpful. The clinician should request a thermometer reading of temperature rather than an impression of fever and should determine how many hours or days the child has been ill, the number of episodes of diarrhea or vomiting, and the apparent volume of output. It should be noted that parents and other caretakers may fail, during a telephone call, to mention underlying conditions without prompting, so some questions regarding past medical history are essential.

Naturally, parents or other caretakers cannot be assumed to have skills of assessment comparable to a clinician, but their report of any of the easily recognized signs of dehydration may indicate the need for immediate evaluation. Reports of changing mental status are particularly concerning. When the child's condition is in doubt, there should be a low threshold for recommending office or acute care evaluation. The hands-on visit provides an opportunity for physical assessment, including vital signs, more detailed history, and better family instruction.

CLINICAL ASSESSMENT

Diarrhea may be characterized by the passage of three or more loose, watery stools per day. The volume of fluid lost through the stools can vary from 5 mL/kg/day (near normal) to 200 mL/kg or more.[34] Dehydration (loss of body water) and electrolyte losses follow untreated diarrhea and cause the primary morbidity of acute gastroenteritis. Loose stools may be among the presenting signs of nongastrointestinal illnesses, including meningitis, bacterial sepsis, pneumonia, otitis media, and urinary tract infection. Vomiting alone can be the first symptom of metabolic disorders, congestive heart failure, toxic ingestions, or trauma. To rule out other serious illnesses, a detailed history and physical examination should not be neglected in the diagnosis of acute gastroenteritis.

History taking should include questions about the onset, frequency, quantity, and character (including the presence of bile, blood, mucous) of vomiting and diarrhea. Recent oral intake, including food, fluids, and breastfeeding, as well as urine output, should be carefully noted and previous weight recorded, if known. Associated symptoms, including fever or changes in mental status, should be noted. Past medical history should include questions regarding underlying significant medical problems, history of other recent infections, and human immunodeficiency virus (HIV) status, if known. Relevant social history may include the number and nature of caretakers, which may affect instructions regarding follow-up care.

As part of the complete physical examination, an accurate body weight must be obtained, along with temperature, heart rate, respiratory rate, and blood pressure. When premorbid weight is not known but a previous growth curve is available, an estimate of fluid loss may be obtained by subtracting current weight from expected weight based on previous weight-for-age percentile.[35] The quality of this estimate will vary, depending on the number and variability of prior data points. The general condition of the patient

TABLE 43-2 Indications for Medical Evaluation

Young age, with low threshold for evaluating all children under 10 kg and lowest threshold for those under 6 mo
History of prematurity, underlying chronic medical conditions, or concurrent illness
Fever ≥ 38°C for infants under 3 mo, ≥ 39°C ages 3 to 36 mo
Visible blood in the stools
High output, including large-volume diarrhea and persistent vomiting
Caretaker's report of signs consistent with dehydration, including sunken eyes, decreased tears, dry mucous membranes
Changes in mental status including irritability, apathy, and lethargy
Poor apparent response to ORT already given or inability to administer ORT

ORT = oral rehydration therapy.

should be assessed, with special concern given to infants and children who appear listless, apathetic, or less reactive. The appearance of the eyes should be noted, including the degree to which they are sunken and the presence or absence of tears. The condition of the lips, mouth, and tongue will yield important clues as to the degree of dehydration, even if the patient has recently taken fluid. Deep respirations may be suggestive of metabolic acidosis. Faint or absent bowel sounds may suggest ileus. Extremities should not be neglected as general perfusion and capillary refill help the assessment of dehydration, as does examination of skin turgor. Visual examination of the stool can confirm abnormal consistency and determine the presence of blood or mucus.

The clinical signs and symptoms of dehydration are outlined in Table 43-3. Although it may be helpful in some instances, assessment of the anterior fontanel is absent from Table 43-3 because numerous studies have shown that it may be an unreliable or misleading sign. In infants and children, a fall in blood pressure is a late sign that heralds shock and may correspond to fluid deficits greater than 10%. Increases in heart rate and slowed peripheral perfusion may be more sensitive indicators of moderate dehydration, although both may be difficult to interpret as both may vary with the degree of fever. Decreased urine output is a sensitive but nonspecific sign.[35] Urine output may be difficult to measure in infants with diarrhea, although increased urine specific gravity may indicate dehydration when urinalysis is indicated.

Some guidelines, including 1992 Centers for Disease Control and Prevention (CDC)[36] and 1996 American Academy of Pediatrics (AAP) guidelines,[16] divide patients into subgroups for mild (3 to 5% fluid deficit), moderate (6 to 9% fluid deficit), or severe dehydration (> 10% shock or near shock). Other classification schemes, including 1995 WHO and 2001 European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines,[37] divide patients into those showing no signs of dehydration (< 5%), some signs of dehydration (5 to 10%), and severe dehydration (> 10%). Studies that have looked carefully at the correlation of clinical signs of dehydration with post-treatment weight gain suggest that the first signs of dehydration may not be evident until 3 to 4% dehydration, with more numerous clinical signs evident at 5% dehydration and those signs indicating severe dehydration not evident until fluid loss of 9 to 10%.[35,38] Because of this threshold effect, it may be difficult to distinguish between mild and moderate dehydration based on clinical signs alone. For this reason, Table 43-3 groups together patients with mild to moderate dehydration and notes that these signs may be seen over a relatively wide range of fluid loss, from 3 to 9%. The magnitude of ongoing losses and the patient's oral intake will determine the success of ORT as much as current status. The goal of assessment is not to determine the patient's hydration status once and for all but to provide a starting point for treatment and conservatively determine which patients may be safely sent home for therapy, which should remain for observation during therapy, and which should receive more intensive therapy immediately.

Supplementary laboratory studies in the assessment of the patient with acute diarrhea are usually unnecessary, including serum electrolytes.[34,39] Stool cultures are indicated in the case of dysentery but are generally not indicated in acute, watery diarrhea in the immunocompetent patient. Laboratory studies should not, however, be neglected where they may give important clues as to underlying or alternative causes of illness. For instance, urine cultures should not be neglected where there is reason to be concerned for urinary tract infection, and blood cultures and white blood cell count with differential are indicated where the clinical presentation suggests possible sepsis.

THERAPY OF ACUTE GASTROENTERITIS BASED ON DEGREE OF DEHYDRATION

Table 43-4 outlines the "Seven Pillars of Good Treatment of Acute Gastroenteritis," adapted from ESPGHAN guidelines,[37] and Table 43-5 provides a summary of specific

TABLE 43-3 Signs of Dehydration

	Minimal or No Dehydration	*Mild to Moderate Dehydration*	*Severe Dehydration*
Mental status	Well, alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious, floppy
Thirst	Drinks normally, may refuse	Thirsty, eager to drink	Drinks poorly, unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal, fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skin fold	Instant recoil	< 2 s	> 2 s
Capillary refill	Normal	Prolonged	Prolonged, minimal
Extremities	Warm	Cool	Cold, mottled, cyanotic
Urine output	Normal to decreased	Decreased	Minimal
Loss body weight	< 3%	3–9%	> 9%

Adapted from Duggan C et al[36] and World Health Organization.[34]

treatment recommendations synthesized from CDC, WHO, AAP, and ESPGHAN guidelines.[16,34,36,37] Although the first pillar, the use of ORS, should seem self-evident, one recent national survey of physicians in emergency care facilities in the United States showed that many would treat mild dehydration with intravenous therapy and half would always or almost always use intravenous therapy for a moderately (5 to 10%) dehydrated child under age 2.[21] Treatment should include two phases: rehydration and maintenance. In the rehydration phase, the fluid deficit is replaced quickly, over 3 to 4 hours, and clinical hydration is attained. In the maintenance phase, maintenance calories and fluids are given. Rapid realimentation should follow rapid rehydration, with a goal of rapid return to an age-appropriate unrestricted diet, including solids. Gut rest is not indicated. If anything, diet should be increased as soon as tolerated to make up for lost caloric intake during the acute illness. Lactose restriction is generally not necessary, nor are changes in formula usually indicated. Full-strength formula is generally tolerated and allows more rapid return to full caloric intake. Breast-feeding should be continued at all times, even during the initial rehydration phases. In both phases, fluid losses from vomiting and diarrhea are replaced in an ongoing manner. No unnecessary medications should be used, and laboratory studies should be limited to those necessary to guide management.

TABLE 43-4 Treatment of Acute Gastroenteritis

The "Seven Pillars of Good Treatment"	
I.	Use of ORS for rehydration
II.	Fast oral rehydration, over 3–4 h
III.	Rapid realimentation with age-appropriate unrestricted diet
IV.	Formula continuity: use of diluted formula is unjustified; special formula is usually not necessary
V.	Continuation of breast-feeding at all times
VI.	Additional ORS for ongoing losses
VII.	No unnecessary laboratory tests or medications

Adapted from Sandhu BK.[37]
ORS = oral rehydration solution.

MINIMAL DEHYDRATION

For those patients with minimal or no dehydration, treatment is aimed at replacing ongoing losses. Children with diarrhea must have increased fluid intake to make up for losses and to cover maintenance needs. In principle, 1 mL of fluid should be given for each gram output. In hospital settings, soiled diapers can be weighed (without urine) and the estimated dry weight of the diaper can be subtracted. When losses are not easily measured, a reasonable rule of thumb is that one may give 10 mL/kg additional fluid allotted for each watery stool or 2 mL/kg for each episode of emesis. Nutrition should not be restricted. Instructions regarding dietary therapy are given below.

MILD TO MODERATE DEHYDRATION

Children who are found on assessment to have mild to moderate dehydration should have their estimated fluid deficit rapidly replaced, with additional fluid given for ongoing losses. Current guidelines recommend giving 50 to 100 mL ORS per kilogram over 2 to 4 hours to replace estimated fluid deficit, with additional ORS given to replace ongoing losses. WHO guidelines recommend a maximum rate of 20 mL/kg/hour,[34] but the rate may be individualized. Using a teaspoon, syringe, or medicine dropper, small volumes of fluid (eg, one teaspoon) should be offered at first, with the amount gradually increased as tolerated. If a child appears to want more than the estimated amount of ORS solution, more can be offered. Although it is safe to give ORS very rapidly, vomiting may be increased with larger boluses. Frequent small-bolus feedings will generally be tolerated. Nasogastric (NG) feeding allows continuous administration of ORS at a slow, steady rate. Clinical experience supports the use of NG feedings even in vomiting patients. Rehydration via NG tube may be particularly useful in an emergency department setting where rapid correction of hydration may prevent unnecessary hospitalization. Although rapid intra-

TABLE 43-5 Summary of Treatment Plans

Degree of Dehydration	*Rehydration Therapy*	*Replacement of Losses*	*Nutrition*
Minimal or no dehydration	N/A	1 mL ORS for each g lost to vomiting or diarrhea or 10 mL/kg for each diarrheal stool, 2 mL/kg for each episode emesis	Continue breast-feeding; resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance*
Mild to moderate dehydration	ORS 50–100 mL/kg over 3 to 4 h	Same as above	Same as above
Severe dehydration	LR or NS in 20 mL/kg IV boluses until perfusion and mental status improve. Then give 100 mL/kg ORS over 4 h or 100 mL/kg D5 1/2 NS IV over 8 h	Same as above; if unable to drink, give via nasogastric tube or give IV D5 1/4 NS with 20 mmol/L KCl/L	Begin oral or enteral feedings after initial hydration as soon as acidosis corrected

Adapted from current guidelines (see text).[16,34,36,37]
*Overly restricted diets should be avoided during acute diarrhea. Breast-fed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat may be given breast milk or formula via nasogastric tube. Full-lactose formulas are generally well tolerated. If lactose malabsorption appears clinically significant, lactose-free formulas may be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended.
IV = intravenous; LR = lactated Ringer's; N/A = not available; NS = normal saline; ORS = oral rehydration solution.

venous hydration may also prevent unnecessary hospital admissions, one recent study showed that rapid NG rehydration was well tolerated, more cost-effective, and associated with fewer complications.[39]

OUTPATIENT OBSERVATION

Because a certain percentage of children with mild to moderate dehydration will fail to improve with ORT, it is prudent to observe dehydrated children until signs of dehydration subside. Similarly, children who do not show clinical signs of dehydration but who demonstrate unusually high output may be held for observation. Hydration status should be reassessed on a regular basis, with more frequent monitoring given to those patients whose status is more tenuous. This may be carried out in an emergency room, office, or other outpatient setting. Once dehydration is corrected, if ORT appears to be going well and if the child's caretakers demonstrate comprehension of home rehydration techniques, understand indications for returning for further evaluation, and have the means to do so, then further management may be carried out at home. Even among those whose illness appears uncomplicated on initial assessment, a small percentage may fail ORT, so that some plan for reassessment must be in place. Caretakers should be encouraged to return to medical attention should they have any concerns, if they are not sure that rehydration is proceeding well, or, naturally, should new or worsening symptoms develop.

MANAGEMENT IN THE HOSPITAL

Indications for management of the child in the hospital include (1) inability of caretakers to manage ORT at home; (2) significant difficulties administering ORT, including vomiting, ORS refusal, or inadequate intake; (3) concern for possible comorbidity, complicating course; (4) failure of treatment, including worsening diarrhea or dehydration in spite of ORT; (5) severe (> 9%) dehydration; (6) social or logistical issues that may prevent return evaluation if necessary; (7) or any factors, for example, very young age, unusual irritability or drowsiness, progressive course of symptoms, or uncertainty of diagnosis, that may indicate close observation.

SEVERE DEHYDRATION

Severe dehydration constitutes a medical emergency. Intravenous rehydration should begin immediately. Twenty milliliters per kilogram boluses of lactated Ringer's (LR) solution, normal saline, or a similar solution should be given until pulse, perfusion, and mental status return to normal. This may require two intravenous lines or even alternative access sites (eg, intraosseous infusion, venous cutdown). The patient should be closely observed during this period and vital signs monitored on a regular basis. Where available, serum electrolytes, bicarbonate, blood urea nitrogen, creatinine, and serum glucose should be obtained, although it is safe to commence rehydration therapy without these results as normal saline or LR infusion is the appropriate first step in either hyponatremic or hypernatremic dehydration. Hypotonic solutions should not be used for acute parenteral rehydration.[40]

The severely dehydrated patient may require several boluses, which may be carried out in short succession. Practically speaking, overly rapid rehydration is unlikely to occur as long as weight-based boluses are given with close observation. Errors occur most commonly in settings in which adult dosing is given to infants (eg, "500 cc normal saline intravenous bolus × ii" would provide 200 mL/kg for the average 2 to 3 month old). Edema of the eyelids and extremities may indicate overhydration. Diuretics should not be given. Once the edema has subsided, the patient may be reassessed for continued therapy. With very frail or malnourished infants, it may be prudent to proceed with 10 mL/kg boluses because of their poorer ability to increase cardiac output and because it may be especially difficult to distinguish dehydration from sepsis in these patients. The smaller boluses will also facilitate closer evaluation. Please see Chapter 53, "Protein-Energy Malnutrition." In general, frequent reassessment of hydration status should be performed to follow the adequacy of replacement therapy. Failure to respond to fluid bolus should raise the suspicion of alternative or concurrent diagnoses, including, as mentioned, septic shock, as well as metabolic, cardiac, or neurologic disorders.

As soon as the patient's level of consciousness returns to normal, therapy can often be changed to the oral route, with the patient taking by mouth the remaining estimated deficit. An NG tube may be helpful for patients too weak to drink adequately but with normal mental status. Although no studies have specifically documented increased aspiration risk with NG tube use in obtunded patients, intravenous therapy is ordinarily favored in these patients. If further intravenous therapy is necessary after initial resuscitation, ESPGHAN guidelines call for the use of 5% dextrose, 0.45% saline over 8 hours to replace calculated deficit, followed by 5% dextrose, 0.18% saline solution (with 20 mmol/L potassium once urine output is documented) for ongoing losses and maintenance.[37] Although it is reasonable to leave intravenous access in place in these patients should it be needed, early reintroduction of ORS is safer. The use of intravenous catheters is associated with frequent minor complications, including extravasation of intravenous fluid, and rare significant complications, including the inadvertent administration of inappropriate fluid, such as those containing excessive potassium. In addition, early ORS will likely encourage earlier resumption of feeding, and some recent data suggest that resolution of acidosis may be more rapid with ORS compared with intravenous fluid.[39]

DIETARY THERAPY

Recommendations for maintenance dietary therapy depend on the age and diet history of the patient. Breastfed infants should continue nursing on demand. Those on formula should continue their usual formula immediately

on rehydration in amounts sufficient to satisfy energy and nutrient requirements. Lactose-free or lactose-reduced formulas are usually not necessary. A meta-analysis of clinical trials shows no advantage of lactose-free formulas over lactose-containing formulas for most infants, although some infants with malnutrition or severe dehydration recover more quickly when given lactose-free formula.[41] Patients with true lactose intolerance will have exacerbation of diarrhea when a lactose-containing formula is introduced. The presence of low pH (< 6.0) or reducing substances (> 0.5%) in the stool in the absence of clinical symptoms is not diagnostic of lactose intolerance. Although medical practice has often favored beginning feeds with diluted (eg, half- or quarter-strength) formula, there is insufficient evidence to justify this practice; in general, full caloric intake should be restored as soon as possible.

Soy formulas containing soy fiber have been widely marketed to physicians, as well as directly to consumers, in the United States as Isomil DF. Brown and colleagues showed that added soy fiber reduced liquid stools without changing overall stool output.[42] This "cosmetic" effect might have some benefits with regard to diminishing diaper rash and encouraging early resumption of normal diet but is probably not sufficient to merit its use as a standard of care. A more recent trial by Burks and colleagues showed a reduction in the duration of antibiotic-associated diarrhea in older infants and toddlers fed soy formula with added soy fiber.[43]

Children receiving semisolid or solid foods should continue to receive their usual diet during diarrhea. Foods high in simple sugars should be avoided as the osmotic load may worsen diarrhea. For this reason, large amounts of juice, gelatin desserts, and other highly sugared liquids should be avoided. Some guidelines have recommended avoiding fatty foods, but it is difficult to maintain adequate calories without some fat, and fat may, in fact, reduce intestinal motility. The practice of withholding food for 24 hours is inappropriate. Early feeding may decrease changes in intestinal permeability brought about by infection,[44] reduces illness duration, and improves nutritional outcomes.[8,9] Highly specific diets, such as the BRAT (bananas, rice, applesauce, and toast) diet, have been commonly recommended. Although, interestingly, one recent study has shown some benefit from green bananas and pectin in persistent diarrhea,[45] the BRAT diet is unnecessarily restrictive and, like juice-centered diets, may provide suboptimal nutrition for the patient's nourishment and recovering gut.

Many children have multiple episodes of diarrhea in a single season, so that diarrhea may contribute to poor nutrition, which may, in turn, worsen the course of subsequent episodes.[46] For this reason, ESPGHAN guidelines call for increased nutrition in the 2 weeks following an episode of diarrhea.[37] WHO guidelines recommend caloric supplements following episodes of diarrhea, such as added cereal in milk, oil in cereal, and foods with high nutrient density.[34] In general, current guidelines call for age-appropriate unrestricted diets, including complex carbohydrates, meats, yogurt, fruits, and vegetables. Children should maintain caloric intake during acute episodes as best possible and should subsequently receive additional nutrition to make up for any shortfalls arising during the illness.

LIMITATIONS OF ORT

Although ORT is recommended for all age groups and for diarrhea of any etiology, some restrictions to its use do exist. In children presenting in shock, the administration of oral solutions may be contraindicated as airway protective reflexes may be impaired. Likewise, patients with abdominal ileus should not be given oral fluids until bowel sounds are audible. It should be remembered that intestinal intussusception may present with diarrhea, including bloody diarrhea. Radiographic and surgical evaluations are warranted when the diagnosis is in question.

Stool output in excess of 10 mL/kg/hour has been associated with a lower rate of success of oral rehydration[47]; however, no patient should be denied ORT simply because of a high purging rate because most patients will respond well if given adequate replacement fluid.

A small proportion of infants with acute diarrhea experience carbohydrate malabsorption, with a dramatic increase in stool output following the administration of ORS. The presence of stool-reducing substances alone is not sufficient to make the diagnosis because this is a common finding in patients with diarrhea and does not in itself predict failure of oral therapy. Patients with true glucose malabsorption will also show an immediate reduction in stool output when ORS is replaced with intravenous therapy. The incidence of clinically significant glucose malabsorption during acute diarrhea is probably less than 1%, although rates as high as 8% have been reported in selected populations.[48]

Many patients with acute diarrhea have concomitant vomiting. Most, however, can be successfully rehydrated with oral fluids if small volumes of ORS (5 mL) are given every 5 minutes, with a gradual increase in the amount consumed. Administration via a spoon or syringe with close supervision helps guarantee a gradual progression in the amount taken. Often, correction of acidosis and dehydration lessens the frequency of vomiting. Continuous slow NG infusion of ORS via a feeding tube may be helpful. Even if some emesis occurs after NG administration of fluid, treatment may not be adversely affected.[39] The physician may characteristically meet some resistance in implementing NG rehydration in the vomiting child. Education of the hospital staff may be helpful as the NG tube may not only help the initial rehydration but may also speed tolerance of refeeding, leading to improved patient disposition and quicker discharge.

HYPERNATREMIC DEHYDRATION

Patients with hypernatremic dehydration respond well to ORT. Those with severe dehydration should first receive intravenous hydration, as outlined above. Subsequent hydration may be achieved with ORS.[49] As with normonatremic dehydration, ORS should be given both to replace the calculated deficit and for ongoing losses. ORS is safer

than intravenous therapy because it is less likely to lead to a precipitous decline in serum sodium, which may increase intracranial pressure.[37] ESPGHAN guidelines recommend (slow) intravenous rehydration only should ORT fail, replacing the calculated deficit with 5% dextrose/0.45% saline over 8 hours, followed by repeat plasma sodium. If the patient is still hypernatremic, this may be repeated, followed by maintenance with 5% dextrose/0.18% saline.

PHARMACOLOGIC THERAPY

Antibiotics

Because viral agents are the predominant cause of acute diarrhea, the routine use of antimicrobial agents for the treatment of diarrhea wastes resources and may lead to increased microbial resistance. Especially in the hospital setting, bacterial causes of diarrhea are unusual. A survey of several years of stool cultures submitted to the microbiology laboratory at Children's Hospital in Boston, Massachusetts, revealed such infrequent occurrence of bacterial infections that the practice of sending stool cultures in patients who develop diarrhea while hospitalized has been abandoned. Hospitalized patients and patients with a history of recent antibiotic use are, however, at risk for infections with *Clostridium difficile*. Infections with *C. difficile* documented by toxin assay should be treated with metronidazole 30 mg/kg divided three times daily given orally. Oral vancomycin is also effective but should be reserved as a second-line agent, given its expense and concerns over the possible emergence of vancomycin-resistant *Enterococcus*.

Even when a bacterial cause is suspected, antibiotic therapy is generally not indicated in most children because most cases of acute diarrhea are self-limited and not shortened by antibiotics. In addition, antibiotics may cause harm. There is evidence that antibiotic use may increase the risk of hemolytic uremic syndrome from *E. coli* infections.[50] There remains some concern that treatment of *Salmonella enteritis* may increase the risk of the carrier state, although patients under 3 months old or with bacteremia should be treated.[51] Exceptions to these rules involve the special needs of individual patients, for instance, immune-compromised hosts, or patients with underlying disorders, such as those with sickle cell disease, who should be treated for *Yersinia enterocolitica*.[52]

Nonantibiotic Drug Therapies

The use of nonspecific antidiarrheal agents such as adsorbents (eg, kaolin-pectin), antimotility agents (eg, loperamide), antisecretory drugs, or toxin binders (eg, cholestyramine) is a common practice. Few data are available to support their efficacy. The side effects of these drugs are well known, in particular among the antimotility agents, including opiate-induced ileus, drowsiness, and nausea owing to atropine effects and binding of nutrients and other drugs. One report from Pakistan detailed 18 cases of severe abdominal distention in association with use of loperamide, including at least 6 deaths.[53] Bismuth subsalicylate has shown some efficacy in traveler's diarrhea and other causes of acute gastroenteritis in children,[54] and although the side effects are less than antimotility agents, some theoretic concerns over the potential toxicity of salicylate remain. In any event, reliance on antidiarrheal agents shifts the therapeutic focus away from appropriate fluid, electrolyte, and nutritional therapy and adds unnecessarily to the economic cost of the illness.

It should be noted that none of the drugs mentioned above specifically address the underlying causes of diarrhea, specifically increased secretion by intestinal crypt cells. Racecadotril, an enkephalinase inhibitor, preserves the antisecretory activity of enkephalins, first discovered in 1975. It does not slow intestinal transit or promote bacterial overgrowth.[55] Its use has shown promise in two controlled clinical trials in children, significantly reducing acute watery diarrhea compared to placebo.[56,57] As long as it use does not distract from ORT and education regarding home management of diarrhea and cost is reasonable, racecadotril may prove to be a useful adjunct to the treatment of watery diarrhea.

Similarly, the use of antiemetics may be warranted in some cases. Although the use of phenothiazines may interfere with oral rehydration by causing sleepiness, two recent randomized, double-blind, placebo-controlled pediatric trials have shown ondansetron, either by oral[58] or intravenous[59] route, to be effective in decreasing vomiting and limiting hospital admission. The cost is not trivial, and nausea is frequently self-limited, but where admission or even the need for outpatient intravenous therapy is avoided, this intervention may be cost-effective.

FUNCTIONAL FOODS

Functional foods may be defined as those that have an effect on physiologic processes separate from their established nutritional function.[60] Probiotics, live microorganisms found in fermented foods, intended to promote intestinal health, are the classic functional food. The modern interest in probiotics may date from Metchnikoff's hypothesis that fermented milk products were responsible for the longevity of Bulgarian peasants.[61] Although a number of recent reviews[62] and journal supplements[63] have more broadly evaluated their use, numerous recent studies have looked specifically at their use in reducing the severity or duration of diarrheal illnesses in children, especially those caused by *Rotavirus*[64] or associated with antibiotic use.[65] Generally, these have included various species of lactobacilli or bifidobacteria, or the nonpathogenic yeast *Saccharomyces boulardii*. The mechanism of action may include competition with pathogenic bacteria, either for receptor sites or intraluminal nutrients, production of antibiotic substances, and enhancement of host immune defenses.[66,67] One recently published meta-analysis concludes that *Lactobacillus* spp are both safe and effective as treatment for children with infectious diarrhea.[68] One recent comprehensive review concluded that there is evidence for the efficacy of a wide variety of probiotics in acute gastroenteritis, especially *Rotavirus*.[69] A recommendation also emerges from a recent meta-analysis of probi-

otic use in antibiotic-associated diarrhea.[70] Because these products are generally not regulated, there is potential for great variability among products, so that it may be difficult for the prescribing physician to make an informed recommendation. But the relatively low cost and safety of probiotics may make recommendation of specific products worthwhile, especially where doing so may improve compliance with ORT.

Prebiotics differ from probiotics in that they are nutrients, rather than organisms, used to preferentially stimulate the growth of health-promoting intestinal flora.[71] Presumably, their use could be synergistic with probiotics. The oligosaccharides found in breast milk have been called the prototypic prebiotic in that they foster the growth of lactobacilli and bifidobacteria in the colon of breast-fed neonates.[72] The prebiotic effects of inulin and fructose oligosaccharides have been studied primarily in vitro and in animal model studies.[73] Specific recommendations should await well-controlled human trials, but in the meantime, it should be noted that dietary fiber may serve as a prebiotic as well as a modifier of intestinal motility agent. Current guidelines recommend fiber-containing fruits and vegetables as part of the diet of children recovering from acute gastroenteritis.

SUPPLEMENTAL ZINC ADMINISTRATION

Many reports have linked diarrhea and abnormal zinc status,[74] including increased stool zinc loss,[75] negative zinc balance,[76] and reduced tissue levels of zinc.[77] It has long been observed that diarrhea may occur with severe zinc deficiency, as in acrodermatitis enteropathica, but the broader clinical question is whether more incremental deficiencies of zinc may play a role in childhood diarrhea and whether supplementation may be of benefit, either for improved outcomes in acute or chronic diarrhea or as prophylaxis against diarrheal disease.

A large number of studies have addressed these questions. One early study showed reduced duration of acute diarrhea in patients with low rectal zinc levels.[77] In Bangladesh, zinc supplements also improved markers of intestinal permeability in children with diarrhea.[78] In India, zinc supplementation was associated with a decrease in both the mean number of watery stools per day and the number of days with watery diarrhea.[79] More recently, prophylactic zinc supplementation in India was associated with substantially reduced incidence of severe and prolonged diarrhea, two of the most important determinants of malnutrition and diarrhea-related mortality.[80] In Nepal, this effect was shown to be independent of concomitant vitamin A administration, with very few side effects noted in a substantial number of patients, apart from a slight increase in emesis.[81] In Peru, zinc administration was also associated with a reduction in duration of persistent diarrhea.[82] In two different pooled analyses of randomized, controlled trials in developing countries, the Zinc Investigators' Collaborative Group reviewed evidence that zinc supplementation is beneficial for treatment of acute and persistent diarrhea[83] and as a prophylactic supplement for decreasing incidence of diarrheal disease and pneumonia. Among infants and young children who received supplemental zinc for 5 or 7 days per week for 12 to 54 weeks, the pooled odds ratio for diarrhea incidence was 0.82 (95% confidence interval [CI] 0.72 to 0.93) and that for pneumonia incidence was 0.59 (95% CI 0.41 to 0.83).[84] Further research is needed to identify the mechanism of action and to determine optimal schemes for delivery of zinc to the neediest populations. It remains to be seen whether zinc supplements are useful in more developed settings.

OTHER CLINICAL SCENARIOS

Acute Bloody Diarrhea (Dysentery)

Dysentery is defined as acute bloody diarrhea caused by invasive microbial infection. This does not include occult blood (detected by guaiac card only), streaks of blood on the surface of formed stool, or melena. The reader is referred to WHO guidelines, which discuss the evaluation and management of dysentery at length.[34,85,86] AAP, CDC, and ESPGHAN guidelines[16,36,37] do not specifically address dysentery. The treatment of dehydration in dysentery follows the same principles as the treatment of acute watery diarrhea. The child with bloody diarrhea is at higher risk for complications, including sepsis and other systemic disease, so that the threshold for admission to the hospital for close observation is lower. Stool cultures are indicated in the setting of acute bloody diarrhea and are helpful for guiding therapy. Food should not be withheld in dysentery any more than in other cases of diarrhea. Because patients with dysentery may have significant anorexia, they should be coaxed to eat.[86] More frequent, smaller meals may be better tolerated. Children convalescing from dysentery should be given extra food to help them regain nutrition lost during the acute illness.

Cholera

Cholera differs from other causes of acute diarrhea in that (1) it may occur in large epidemics involving adults and children; (2) it produces voluminous diarrhea, which may lead to shock and death by dehydration in a very short period; and (3) certain antibiotics may shorten the course.[34] Management of cholera may be carried out using the methods for assessment of dehydration and treatment plans outlined above and summarized in Tables 43-3, 43-4, and 43-5. The health worker must be prepared to deliver prodigious quantities of fluid, either by ORS or intravenously, to overcome ongoing losses. These losses should be quantified so that treatment may be updated and modified under continuous close observation. Unlike diarrhea from other causes, where cereal-based ORSs are equivalent to standard ORSs, there may be some advantages in using rice-based ORS in treating cholera.[87] Traditional wisdom held that sodium concentrations of ORS used in treating cholera should be higher than those for other causes of diarrhea (based on measured stool sodium losses), but a CHOICE study group trial showed no clinical difference between those treated with the lower-osmolarity solution compared with a stan-

dard solution, apart from some increased incidence of asymptomatic hyponatremia.[88]

Persistent Diarrhea

Persistent diarrhea may be defined as diarrhea of acute onset that lasts more than 14 days. The approach to the patient with persistent diarrhea should include assessing and treating diarrhea, as in the acute presentations. In the developing world, bacterial infections are risk factors for persistent diarrhea and therefore warrant aggressive therapy. Education regarding sanitation and hygiene may reduce rates of reinfection. Attention to nutrition is crucial, with restoration of nutritious diet, including adequate calories, a key element of therapy. WHO guidelines recommend at least two Recommended Dietary Allowances (RDAs) of folate, vitamin A, iron, zinc, magnesium, and copper,[34] although, as discussed above, zinc supplementation may be the most important of those mentioned and should be continued for prophylaxis against additional episodes after appropriate therapy is complete.[84]

In the developed world, persistent diarrhea is often the result of restricted diets, either low in fat, which modulates intestinal motility, low in fiber, which may promote balanced intestinal flora, and/or high in high-osmolarity carbohydrate drinks. Dietary modification should be attempted before undertaking an extensive diagnostic evaluation.

Diarrhea with Severe Malnutrition

Assessment of the malnourished child is difficult because many of the signs outlined in Table 43-1 may be unreliable. Skin turgor may appear poor owing to the absence of subcutaneous fat. Eyes may be sunken from loss of periorbital fat. Irritability or apathy from malnutrition may complicate the assessment of mental status. When possible, malnourished children with diarrhea should be referred to a hospital. A severely malnourished child with signs of dehydration without a history of increased stool output should be treated for septic shock.[34] Because of the increased risk of bacteremia in severely malnourished children, and, in fact, in a broad range of children with diarrhea in a less developed setting,[89] the use of empiric antibiotics is not unreasonable where blood cultures cannot be obtained, although the literature regarding choice of antibiotics, doses, and duration is sparse.

Because intravenous therapy may cause overhydration and heart failure in the severely malnourished child, except for treatment of shock, slow oral rehydration is the treatment of choice. An NG tube may be used for children who drink poorly. Rehydration should begin with 10 mL/kg over 2 hours. This rate may be adjusted based on the child's thirst or ongoing stool losses. Increasing edema may be evidence of overhydration.

Full-strength WHO-ORS contains too much sodium and inadequate potassium for the severely malnourished child. WHO guidelines recommend modified solutions, as outlined in Table 43-6. Feeding should begin as soon as possible once hydration has been achieved and should continue every 2 to 3 hours day and night. Malnourished children often exhibit anorexia and require coaxing to eat.

CHOICE OF ORS

Table 43-7 outlines the composition of several commonly available ORSs, as well as other beverages frequently used for inappropriate rehydration. In July 2002, WHO and UNICEF recommended a significant change in ORS composition, including a reduction in sodium and glucose to maintain a 1:1 molar ratio but to decrease total osmolarity to 245 mOsm/L. The change was prompted by clinical trials showing that this solution resulted in less use of supplemental intravenous fluid therapy as well as lower stool output and less vomiting compared with the previous WHO standard ORS.[29,90] Although the differences in measured stool output resulting from different ORS formulations may be modest, reduction in intravenous fluid use is a substantial economic and health benefit of the new solution. The composition of the new solution is also more in line with solutions more commonly used in industrialized countries. Studies are still needed to confirm the safety of this new solution in areas of the world where cholera is an important cause of diarrhea.

NEW SOLUTIONS

Numerous improved ORSs have been attempted. These have generally included additional substrates for sodium cotransport (such as the amino acids glycine, alanine, and, glutamine)[91,92] or, as reviewed by Fontaine and col-

TABLE 43-6 ORS for the Severely Malnourished Child

Simple ORS for the Severely Malnourished Child	*More Effective ORS for the Severely Malnourished Child*
Dilute 1 L WHO-ORS to make 2 L	Dilute 1 L WHO-ORS to make 2 L
Add 45 mL KCl solution from stock solution containing 100 g KCl/L	Add the following salts:
Add and dissolve 50 g sucrose	3.6 g KCl
	1.3 g K citrate
Children given this solution should also receive	1.2 g MgCl
	130 mg Zn acetate
2 mL 50% MgSO4 solution (4 mEq Mg/mL) IM once and zinc chloride solution (10 g/L) 1 mL/kg/d until diarrhea stops	22 mg CuSO4
	0.44 mg NaSeO4
	0.20 mg KI
	Add and dissolve 50 g sucrose

Adapted from World Health Organization (WHO).[34]
IM = intramuscularly; ORS = oral rehydration solution.

TABLE 43-7 Composition of Commercial Oral Rehydration Solutions as well as Commonly Consumed Beverages

Solution	*CHO (g/L)*	*Na (mmol/L)*	*K (mmol/L)*	*Cl (mmol/L)*	*Base (mmol/L)*	*Osmolarity*
WHO-ORS (2002)	13.5	75	20	65	10	245
WHO-ORS (1975)	20	90	20	80	10	311
ESPGHAN ORS	16	60	20	60	10	240
Enfalyte*	30	50	25	45	34	200
Pedialyte†	25	45	20	35	30	250
Rehydralyte†	25	75	20	65	30	305
Apple juice‡	120	0.4	44	45	—	730
Coca Cola§	112	1.6	—	—	13.4	650
Gatorade‖	46	23.5	2.5	17	3	330
Chicken broth‡	8	260	0.5	260	—	450
Tea‡	4	—	6	—	—	6

*Mead-Johnson Laboratories, Princeton, NJ.
†Ross Laboratories, Columbus, OH (data for Flavored and Freezer Pop Pedialyte are identical).
‡US Department of Agriculture.
§Coca-Cola Corporation, Atlanta, GA (figures do not include electrolytes, which may be present in local water used for bottling; base = phosphate).
‖The Gatorade Company, Chicago, IL.
CHO = carbohydrate; ESPGHAN = European Society of Paediatric Gastroenterology, Hepatology and Nutrition; ORS = oral rehydration solution; WHO = World Health Organization.

leagues,[87] substituting complex carbohydrates for the glucose (rice- and other cereal-based ORSs) to reduce osmolarity while preserving glucose-sodium cotransport. Given trials to date, the amino acid preparations do not appear to be more effective than traditional ORSs and are more costly. Rice-based ORS may be recommended where training is adequate and home preparation is preferable and appears to be particularly effective in treating diarrhea from cholera.[87,93] Nevertheless, given the simplicity and safety of ORS packets in developing countries and commercially available ORSs in developed countries, these remain the first choice for most clinicians.

Other potential additives to ORS include substances capable of liberating short-chain fatty acids. These include amylase-resistant starch derived from corn[94] and partially hydrolyzed guar gum.[95] The presumed mechanism of action is the enlistment of increased colonic sodium uptake coupled to short-chain fatty acid transport. Other possible future ORS composition changes include the addition of probiotics, prebiotics, and zinc.

BARRIERS TO ORT

Barriers to the use of ORS and continued nutrition during diarrheal disease include, among patients, cultural practices[33] and lack of information[96] and, among physicians, preference for intravenous hydration, even where evidence suggests improved results from oral rehydration.[19,21,97] At the other extreme from the development of the ultimate ORS, it remains distressingly common for patients, even at times under physician supervision, to attempt rehydration with solutions bearing no resemblance to physiologically based ORS. Table 43-7 includes a number of fluids commonly used in treating diarrhea, which do not contain physiologically sound concentrations of carbohydrates and electrolytes. An informal survey of numerous hospital Web sites reveals outdated recommendations for the treatment of diarrhea that include nonstandard fluids. A recent case report of one child whose care was compromised by following advice obtained from a prominent hospital's Internet site highlights the continued gap between knowledge and practice and the ongoing need to disseminate accurate information regarding oral rehydration.[98]

CONCLUSION

The treatment of acute diarrhea has for many years been shown to rely on the simple but overwhelmingly effective therapy of oral rehydration. More recently, the important coprinciple in case management of early refeeding of children immediately on rehydration has also gained wider acceptance. The combination of oral rehydration and early nutritional support promises to safely and effectively guide a patient through a bout of diarrhea. If the principles of therapy outlined above are accepted by all levels of the medical community, and if education of parents includes beginning ORT at home, numerous deaths and unnecessary hospitalizations can be avoided. Meanwhile, we await further technological breakthroughs (eg, improved vaccines, superior rehydration solutions) to better combat one of the most important public health problems today.

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CHAPTER 44

CHRONIC DIARRHEA AND INTESTINAL TRANSPLANTATION

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Chronic diarrhea with prolonged mucosal injury, by inducing an imbalance between the infant's energy requirements and the dietary protein and caloric supply, is a source of protein-energy malnutrition (PEM). In addition, in children suffering from sepsis, malnutrition may occur quite rapidly, setting up a vicious cycle, with worsening of the PEM. In underdeveloped countries, it is calculated that 40 to 60% of infant diarrheal deaths are attributable to persistent diarrhea in combination with malnutrition.[1,2] Treatment of digestive disease and nutritional rehabilitation have to be achieved together. Each time the gastrointestinal (GI) tract can be used for refeeding, it should be used. However, in some situations, in which the GI tract is insufficient to cover the protein and energy requirements, parenteral nutrition (PN) is required to correct PEM. This nutritional support is efficient but at risk of metabolic complications directly related to the homeostatic changes secondary to severe malnutrition and known as the "refeeding syndrome."[3] This chapter examines the main consequences of PEM and the means whereby appropriate nutrition may be provided according to its advantages and risks for malnourished pediatric patients suffering from severe protracted diarrhea treated in hospital. According to the course of both digestive disease and nutritional rehabilitation, long-term nutritional support may be required.

CHANGES INDUCED BY MALNUTRITION

Interrelated factors are involved in children suffering from severe malnutrition: abnormal body fluid, electrolytes, and mineral balance; energy and protein deficiency; abnormal GI function; and depression of the immune system. An understanding of these factors should help to prevent or limit the consequences of PEM, as well as refeeding syndrome–related complications.

Abnormalities of Body Fluids, Electrolytes, and Minerals

Severe PEM, whatever its cause and whichever edema is present, is associated with water and sodium overload. Total-body water, whether measured by isotope dilution or tissue analysis, is generally greater in malnourished subjects, particularly in the presence of edema. Increases of some 20 to 25% have been reported,[4] with total-body water levels reaching 89% of body weight in some cases, whereas water accounts for only 60 to 67% of body weight in normal children. Some of the excess water is found in the intracellular space, but most is found extracellularly.[5] Sodium and water accumulation is probably owing to dysfunction of the enzyme Na^+-K^+-adenosine triphosphatase (ATPase).[6] Extracellular water accumulates, for the most part, in the interstitial spaces as the result of hypoalbuminemia and a fall in plasma osmotic pressure; intravascular volumes may be reduced by nearly 50% because of decreased plasma and red cell volumes. The ensuing reduction in renal plasma flow, hyperaldosteronism, and increased levels of antidiuretic hormone prolong and aggravate fluid retention.[5] The hemodynamic consequences of this abnormal distribution of extracellular fluid are an elevation of pulmonary and systemic vascular resistance, a fall in ventricular pressure, and a prolongation of circulation time, which explains the hypotension and bradycardia with risk of hypovolemic shock. Providing too much sodium and water to malnourished children is unsafe, leading to a risk of heart failure.[7] Oral rehydration solution with a high sodium content must be used very carefully in severely malnourished children.[8] Such children also have a low total-body potassium content, as evidenced by whole-body counting of ^{40}K radioactivity.[5] Total-body potassium is reduced, in certain cases by as much as 50%, attaining levels of 25 to 30 mmol/kg (normal 45 to 50) mmol/kg).[4] The depletion is both intra- and extracellular and is related to a reduction in total-body protein as well as to a true potassium deficiency. Both factors should be taken into account during recovery, particularly the cellular inflow of potassium during glucose infusion and the incorporation of potassium during protein synthesis. Low potassium stores increase mortality, especially from cardiac arrest,[9] cause sodium retention, and contribute to the persistence of edema.[10]

Severe malnutrition is associated with multiple deficiencies, of which magnesium and zinc have a special link to diarrhea. Phosphorus is always decreased in children with PEM. A fall in its urinary excretion with hypercalciuria and hypophosphatemia signals phosphorus depletion, which may become apparent only when anabolic metabolism begins.[11] Magnesium is reduced by 20 to 30% in mus-

cle[5]; plasma magnesium levels, however, are variable. Magnesium deficiency is associated with low potassium retention because children fail to retain potassium as long as their magnesium deficiency remains uncorrected. This may be related to a dysfunction of the enzyme Na^+-K^+-ATPase, which may aggravate the potassium deficiency.[6] Simultaneous correction of both deficiencies is required in the management of severely malnourished children. Zinc deficiency is often associated, especially in children suffering from protracted diarrhea.[12] Zinc supplementation decreases the risk of persistent diarrhea and seems warranted during rehydration of severely malnourished infants.[8,13] Iron deficiency frequently occurs and is partly responsible for alterations in immune defense mechanisms. It also has an anti-infection role by inhibiting bacterial growth. Deficiencies of copper, chromium, and selenium are usual, especially when there are abundant GI losses. Because of their importance in protein synthesis, glucose use, hematopoiesis, and polyunsaturated fatty acid metabolism, it is essential that deficits be corrected. The levels of most vitamins are usually lower, as indicated by reduced plasma and leukocyte levels and by their urinary excretion. Because of the many metabolic processes that vitamins govern, it is important to correct deficiency not only of fat-soluble vitamins but also of ascorbic acid and most of the B vitamins, especially at the onset of anabolism. Requirements should be adjusted to protein intake and, particularly, to energy needs.

The kwashiorkor syndrome, one of the most important forms of PEM, is very rare in developed countries. It is characterized by gross edema, skin and hair changes, neurologic abnormalities, and fatty liver. The kwashiorkor syndrome classically has been equated with pure protein deficiency in the face of adequate intakes of energy and other nutrients. Although conceptually useful, this view is probably simplistic. More recent data suggest that oxidative stress contributes to the cell damage occurring in various organs of children with kwashiorkor.[14,15] Their antioxidant status is more severely impaired than in any other form of PEM, and levels of highly unsaturated polyunsaturated fatty acids in plasma phospholipids and erythrocyte phosphatidylcholine are significantly reduced.[16] Plasma concentrations of the lipid peroxidation products as well as the urinary excretion of leukotriene E_4 have been found to be enhanced.[17] This may contribute to the formation of edema via increased capillary permeability. Provision of early antioxidants seems to be the logical approach in the therapy of this rare syndrome.[18,19]

Energy and Protein Deficiency

Glycogen stores are reduced by 50%, whereas blood glucose levels are maintained by increased hepatic glucose-6-phosphatase activity and particularly by increased gluconeogenesis, which depends on cortisol and growth hormone secretion and uses glycerol, glucogenic amino acids, lactate, pyruvate, and alanine. Reduction of glucose oxidation also contributes to the adaptation.

In case of additional stress, the abnormalities in response to a carbohydrate load reflect the metabolic disturbance. This may be owing to a reduction in insulin synthesis and secretion, but, in many cases, blood levels of insulin are high, indicating "peripheral insulin resistance."[20] This resistance is the result of several factors, such as chromium and potassium depletion and increased secretions of growth hormone, cortisol, catecholamines, and free fatty acids.

A marked decrease in adipose tissue—indeed, its almost complete disappearance—is usually observed.[20] Plasma triglyceride, cholesterol, phospholipid, and linoleic acid concentrations fall; very-low-density lipoproteins (VLDLs) are undetectable; and low-density lipoprotein (LDL) levels are reduced. In contrast, most of these values increase under the stress of an acute infection.[21] On the other hand, an increase in liver triglycerides may account for 40% of the hepatic volume,[20] and several factors may be responsible for this overload, namely deficiencies of VLDL, more specifically a decrease in VLDL apoprotein synthesis, and a lack of lysine, carnitine, choline, and essential fatty acids (EFAs).[20] As a result, liver function and the clearance and synthesis of triglycerides are critically impaired. Moreover, peripheral triglyceride use is reduced, owing, in particular, to decreased lipoprotein lipase activity; the use of intravenous fat emulsions at the early phase of renutrition is thus inappropriate.

As already noted, impaired function of the enzyme Na^+-K^+-ATPase partly accounts for sodium and water retention, as well as potassium, phosphorus, and magnesium depletion, which may be corrected by administering glucose. Adaptation to energy deficiency is characterized by a relative reduction in oxygen consumption and energy expenditure; the changes in basal metabolic rate are difficult to interpret but may fall.[5] Rates of cellular division and protein synthesis also may account for this decreased energy expenditure. Growth hormone plasma levels are elevated, whereas insulin-like growth factor I is low.[22] If the energy intake does not supply these minimum requirements, then the endogenous stores—free fatty acids, amino acids, and ketone bodies—are used immediately. Any infections, surgical stress, or GI losses accelerate the process. With a lack of energy stores, thermoregulation is impaired, and hypothermia is a constant threat that can be fatal.

In pediatric patients suffering severe malnutrition, total-body protein decreases by 20 to 30% and muscle protein by 50%. The rates of albumin synthesis and breakdown fall by 50%, and total reserve is reduced by 50%, especially in the extravascular pool, because the albumin is shifted into the plasma.[5] Despite this adaptive process, hypoalbuminemia is one of the most reliable indices of malnutrition. Transferrin, ceruloplasmin, and retinol binding protein are lowered to varying degrees, as are fibrinogen and other coagulation proteins, such as factors II, VII, X, and V. Because of the short half-lives of these proteins, the rapid variations in their plasma levels serve as indicators of nutritional status.[23]

The plasma concentration of essential amino acids decreases by 50%, which explains the fall in the essential-to-nonessential amino acid ratio. The decrease in plasma concentration is greatest for the branched-chain amino acids; valine levels may be decreased eightfold.[5] High cor-

tisol and growth hormone levels and a fall in insulin have been cited as possible causes of this phenomenon, as well as an increase in their muscle catabolism. Adaptation to low nitrogen intake includes reuse of 90 to 95% of amino acids (normal 75%) and decreased urea production, with a fall in its excretion in the urine, so conserving nitrogen. Ammonia excretion, however, increases because of potassium depletion and the acidosis that is induced by protein and fatty acid catabolism.[5] Muscle protein reserves are used to maintain the plasma and liver amino acid pool and to ensure the production of alanine as a glycogenic liver substrate by transamination of branched-chain amino acids and the use of liver amino acids for protein synthesis rather than urea production. Liver protein synthesis is thus spared in comparison with that of muscle protein. In case of aggression such as trauma, burns, or, especially, severe sepsis, muscle catabolism is particularly increased, worsening the negative nitrogen balance.

Gastrointestinal Dysfunction

Dysfunction of the GI tract during childhood PEM, especially from severe protracted diarrhea, includes varying degrees of morphologic and functional intestinal disturbances, together with abnormal bacterial proliferation. These aggravate the malnutrition and explain the difficulties of restarting GI feeding. Abnormal intestinal bacterial flora, in either qualitative or quantitative terms, suggest changes in the gastric and intestinal defense systems. The gastric bactericidal barrier is modified because of mucosal atrophy and a decrease in hydrogen ion secretion. In the intestine, apart from oral gastric contamination, other factors combine to explain the abnormal bacterial proliferation, for example, reduced intestinal motility, reduction in biliary and pancreatic secretions, excess of residual intraluminal unabsorbed nutrients, reduction in immunoglobulin (Ig)A secretion, and adherence to the mucosa of bacteria such as *Escherichia coli*. Changes in the mucosal barrier and intestinal permeability also allow endotoxin absorption and transfer of bacterial and alimentary antigens conducive to gram-negative sepsis and perhaps to an immunoallergic process.[24] Morphologic changes are variable and may be characterized by mucosal atrophy with the disappearance of the villous structure, a reduction in the mitotic index, and cellular infiltration of the lamina propria.[25] On the other hand, there may only be structural changes in the enterocytes, which are visible only with electron microscopy at the brush border and in the endoplasmic reticulum.[26] Most of the enzyme activities are invariably reduced.[25] Specific disturbances of vitamin B_{12} and conjugated bile acid absorption in the ileum and of sodium-potassium exchange and water absorption in the colon are also frequent.[27] Conditions for impaired digestion and increased malabsorption of nutrients, water, and electrolytes are therefore present.

Depression of the Immune System

A high incidence of severe infections is observed in malnourished infants owing to specific, nonspecific, and nutritional immunity depression.[28] More specifically, it may be a result of protein, energy, vitamin, and mineral deficiencies, acting separately or in association, directly or indirectly, on each of the immune response systems. Cellular immunity is impaired during malnutrition as shown by delayed hypersensitivity reactions to various antigens and impairment of the lymphoblastic transformation test.[28] Lymphocyte distribution is changed with a relative and absolute reduction in the number of T lymphocytes, mainly CD4+. The ratio CD4+-to-CD8+ seems to be a good marker of PEM. The number of B lymphocytes remains constant. The mechanism and the significance of these various abnormal responses are complex, probably multifactorial, and related to thymic atrophy, lymphoid depletion, and involution of the thymus-dependent peripheral areas accompanied by reduction of cell proliferation and protein synthesis. All of these features are reversible when the malnutrition is treated. They are attributable primarily to protein-energy deficiency but vitamin or trace element deficiencies including iron, folate, pyridoxine, and zinc.[28]

Plasma levels of the various classes of immunoglobulins are generally normal, which compares with the normal number of B lymphocytes but does not exclude the possibility of a defective humoral response; additional infection may lead to an increase in immunoglobin level. Isohemagglutinin titers are normal, but antibody responses to viral, bacterial, or parasitic infections may be abnormally low in malnourished children. The production of secretory IgA 11S in nasopharyngeal secretions, tears, and saliva may be normal but is usually reduced, and this may account for the entry of organisms responsible for infections of the respiratory and GI tracts.[28] There may be a correlation between this disorder and the reduced synthesis of IgA by the fewer IgA plasma cells in the submucosa and/or decreased synthesis of the secretory component secondary to villous atrophy.

NUTRITIONAL SUPPORT

Initial Management and Prevention of Refeeding Syndrome

If PN is required because of severe malnutrition and inability of the GI tract to cover the protein-energy requirements, it has to be provided very carefully. Indeed, refeeding syndrome may be observed in severely malnourished patients receiving concentrated calories via PN.[29] Refeeding syndrome was also described in patients receiving enteral nutrition.[30] This syndrome includes the metabolic and physiologic consequences of the depletion, repletion, compartmental shifts, and interrelationships of the following: phosphorus, potassium, magnesium, glucose metabolism, vitamin deficiency, and fluid resuscitation.[11,29–31] Indeed, the net effect of the hormonal and metabolic changes of starvation is to facilitate survival by a reduction in basal metabolic rate, conservation of protein, and prolongation of organ function, despite the preferential catabolism of skeletal muscle tissue. Infants and children who have suffered from malnutrition for weeks or months will also experience a significant loss of visceral cell mass. Refeeding the malnourished child disrupts the adaptive state of semistarvation.

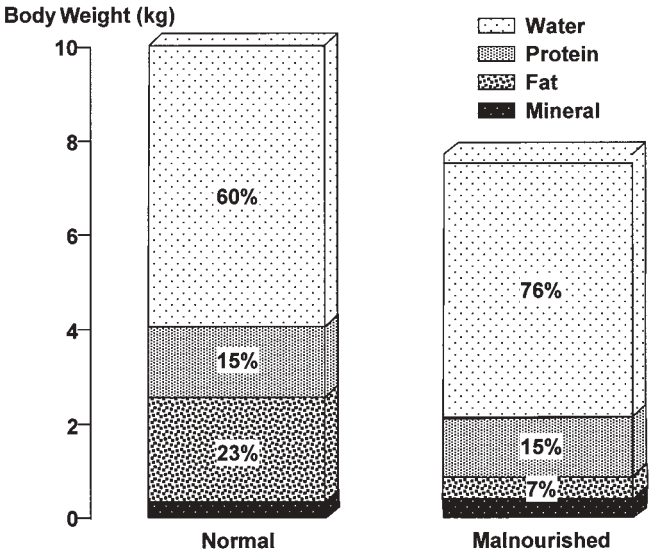

FIGURE 44-1 Changes in body composition during protein-energy malnutrition.

As refeeding is initiated, there is a rapid reversal in insulin, thyroid, and adrenergic endocrine systems. Basal metabolic rate increases, and glucose becomes the predominant cellular fuel. The body immediately begins the process of rebuilding lost tissue. Anabolism is accompanied by positive balance of intracellular minerals. As minerals shift to intracellular spaces, serum levels may plummet. Body fluid compartments redistribute as intracellular fluid increases; extracellular fluid may increase or decrease depending on the previous intake, the persistent digestive losses, and the refeeding regimen. These rapid changes in metabolic status can create life-threatening complications, so the nutritional regimen must be chosen wisely and monitored closely. Several potential metabolic complications of the refeeding syndrome are listed in Table 44-1.

To reduce the risk of refeeding complications, several conditions are required at the initial phase of renutrition of severely malnourished infants and children:

- *Prevention of water and sodium overload.* It is necessary to reduce the patient's water and sodium intake, depending on the hydration state, to prevent water and sodium overload resulting from their excessive retention, accentuated by increased secretions of vasopressin and aldosterone. Early weight gain may be the consequence of fluid retention. Monitoring of water and electrolyte intake must include uncontrolled losses as well as those from the Gl tract. One of the difficulties in such situations is the need to take into account a third sector, such as intraperitoneal or intestinal fluid retention. Monitoring of body weight changes, urine collection, assessment of blood, and urinary electrolytes are essential.
- *Oncotic pressure restoration.* The infusion of macromolecules aims to restore oncotic pressure and to minimize hemodynamic problems, worsened by a water-electrolyte imbalance. Albumin is the best infusate, but fresh frozen plasma or blood may be required in cases of anemia and/or coagulation disorders. Artificial ventilation may be required in those, generally few, cases with a poor cardiorespiratory status.
- *Carbohydrate intake.* Constant administration of carbohydrate is required to maintain blood glucose homeostasis as the reserves are very low; parenteral administration of glucose requires care because of the risk of hyperglycemia with osmotic diuresis and hyperosmolar coma.
- *Potassium repletion.* Correction of potassium depletion is of great importance but should be achieved progressively with monitoring of renal and cardiac functions. It can be dangerous to try to correct the deficiency too rapidly at a stage at which the capacity for fixing potassium remains low because of reduced protein mass; excessive intake leads to the cardiac risk of hyperkalemia.
- *Body temperature monitoring.* It must be monitored because PEM can lead to hypothermia, often associated with hypoglycemia and bradycardia. On the other hand, hyperthermia or excessive reheating increases water loss as well as energy expenditure. Maintenance of a stable body temperature between 36°C and 37°C by appropriate warming techniques is essential. Careful daily nursing to prevent cutaneous lesions and musculotendinous retractions is also very important.
- *Prevention of infection.* The infective, metabolic, and GI problems must be constantly borne in mind during treatment of pediatric patients with severe PEM. The

TABLE 44-1 Metabolic Disorders Associated with Refeeding Syndrome

Hypophosphatemia
Cardiac: altered myocardial function, arrhythmia, congestive heart failure, sudden death
Hematologic: altered red blood cell morphology, hemolytic anernia, white blood cell dysfunction, thrombocytopenia, depressed platelet function, bleeding
Hepatic: liver dysfunction
Neuromuscular: acute areflexic paralysis, confusion, coma, cranial nerve palsies, diffuse sensory loss, Guillain-Barré–like syndrome, lethargy, paresthesias, rhabdomyolysis, seizures, weakness
Respiratory: acute ventilatory failure
Hypokalemia
Cardiac: arrhythmias, cardiac arrest, increased digitalis sensitivity, orthostatic hypotension, electrocardiographic changes (T-wave flattening or inversion, U waves, ST-segment depression)
Gastrointestinal: constipation, ileus, exacerbation of hepatic encephalopathy
Metabolic: glucose intolerance, hyporeflexia, paralysis, paresthesias, respiratory depression, rhabdomyolysis, weakness
Renal: decreased urinary concentrating ability, polyuria and polydipsia, nephropathy with decreased glomerular filtration rate, myoglobinuria (secondary to rhabdomyolysis)
Hypomagnesemia
Cardiac: arrhythmias, tachycardia, torsade de pointes
Gastrointestinal: abdominal pain, anorexia, diarrhea, constipation
Neuromuscular: ataxia, confusion, fasciculations, hyporeflexia, irritability, muscle tremors, painful paresthesias, personality changes, positive Trousseau's sign, seizures, tetany, vertigo, weakness

risk of infection, an expression of both specific and nonspecific immunity depression, may jeopardize the prognosis and aggravate nutritional problems at any time. Clinical and paraclinical investigations must be performed repeatedly to look for widening foci of infection (respiratory, GI, skeletal, and urinary) and for their systemic spread. When a localized or systemic infection is identified, specific treatment is urgently required. The routine use of antibiotics in the absence of bacteriologic evidence in a malnourished child is inadvisable; antibiotics should be given only if sufficient indirect evidence points to the likelihood of infection. Active intestinal parasitosis should, of course, be vigorously treated. Evidence or suspicion of an infection is an essential factor in modifying water, electrolyte, and nutrient intake and also in the choice of the feeding technique.

- *Protein and energy intake.* It is difficult to suppress protein catabolism under these conditions of stress and low energy intake. Excessive nitrogen intake may lead to hyperammonemia and/or acidosis by exceeding the renal clearance capacity for H+ and phosphate ions. An intake of 0.5 to 1 g/kg of parenteral amino acids or oral peptide is sufficient to maintain the plasma amino acid pool. The protein-energy deficiency and other related disorders must be corrected during the days following the initial period of stress. This type of correction should be made carefully and gradually because the deficits are profound and of long standing. It is essential to provide both nitrogen and calories simultaneously and in the correct ratio. The increase in energy intake, if progressive, avoids acute episodes of sodium and water retention accompanied by oliguria and a fall in urinary sodium and potassium output. It is likely that these changes are carbohydrate dependent because their occurrence and equally rapid reversal develop with changes in glucose rate of infusion. This antinatriuretic effect of glucose appears to be similar to the antinatriuresis observed during feeding after a phase of experimental fasting. The insulin secreted induces sodium tubular reabsorption, and the alkalosis that develops might be attributable to increased tubular absorption of bicarbonate.
- *Micronutrients.* The provision of appropriate nutrient solutions requires an understanding of the nutritional relationships between nutrients, electrolytes, vitamins, and trace elements. It is during this initial phase that any deficit owing to incorrect intake will become apparent through either clinical or laboratory signs. These deficits can usually be prevented by giving them in the following proportions: 200 to 250 kcal, nitrogen 1 g, calcium 1.8 mmol, phosphorus 2.9 mmol, magnesium 1.0 mmol, potassium 10 mmol, sodium and chloride 7 mmol, and zinc 1.2 mg. Similarly, it is essential to adapt the intake of copper, manganese, chromium, iron, iodine, cobalt, and fluoride and the group B vitamins especially, as well as the intakes of EFAs, tocopherol, and selenium.
- *Adaptation of intake.* After the initial phase of renutrition, most complications can be prevented by careful supervision and the provision of appropriate intakes. It is essential that the infusion rate, body temperature, cardiac and respiratory function, urinary volume, twice-daily weight, and digestive output are continuously monitored. During the first 5 days, and also when the osmotic load is increased, urine should be checked for osmolality, pH, glucose, and protein. The plasma and urinary ion data, plus the calcium, phosphorus, magnesium, glucose, and hematocrits, should be obtained twice during the first week and then once weekly; plasma proteins, albumin, bilirubin, alkaline phosphatase, and transaminase values should be assessed routinely. These data, as well as knowledge of the patient's state and age, should make it possible to progressively regulate and control the intake and avoid problems of overload or depletion.

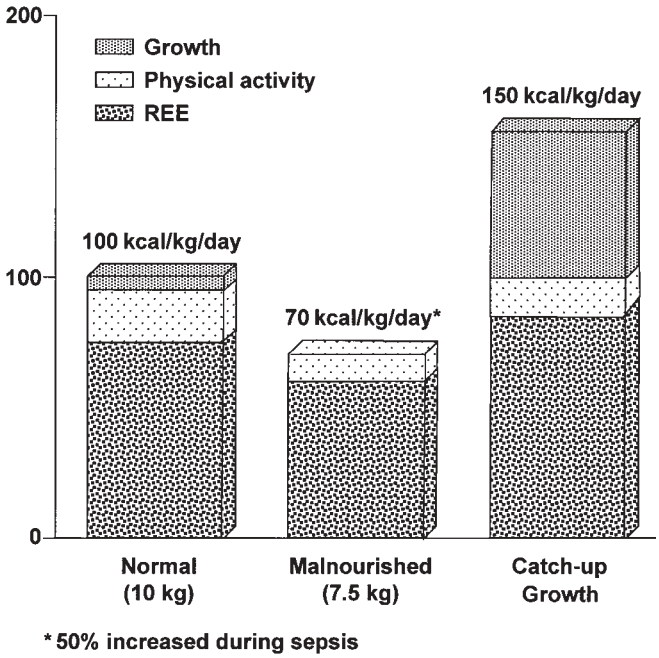

FIGURE 44-2 Changes in energy expenditure during severe protein-energy malnutrition and catch-up growth. REE = resting energy expenditure.

Route of Refeeding

Chronic diarrhea with malabsorption can be the result of a large number of causes (Table 44-2). It is obvious that dietetic and nutritional interventions are important in each of these conditions. However, in circumstances in which the disease is well identified, it is clear that the selection of the proper feeding management is also well defined (eg, celiac disease, saccharase-isomaltase deficiency, congenital chloridorrhea). As the full discussion of each condition is beyond the scope of this chapter, we instead limit our attention to severe protracted and intractable diarrhea of infancy (PDI and IDI).[32]

Enteral Feeding Enteral feeding (EF) makes it possible to use the functioning GI tract to nourish compromised pediatric patients. Digestive disease leading to an anatomic

TABLE 44-2 Main Causes of Chronic Diarrhea

Disorders of enterocyte digestive/absorptive functions
Sucrase-isomaltase deficiency
Glucose-galactose malabsorption
Congenital chloridorrhea
Congenital sodium-losing diarrhea
Microvillous inclusion disease
Epithelial dysplasia (tufting enteropathy)
Short-bowel syndrome
Celiac disease
Acrodermatitis enteropathica
Cow's or soy milk protein intolerance
Autoimmune enteropathy
Eosinophilic gastroenteropathy
Protracted gastrointestinal infections (viral, bacterial, protozoal)
Protein-calorie malnutrition
Small-bowel bacterial overgrowth
Drug-induced enteropathies
Disorders of intraluminal digestion
Cystic fibrosis
Schwachman syndrome
Congenital absence of lipase
Chronic pancreatitis
Enterokinase deficiency
Protein-calorie malnutrition
Cholestasis
Primary bile acids malabsorption
Secreting tumor diarrhea
Disorders of transport from the enterocyte
a-β-lipoproteinemia
Lymphangiectasia

or functional reduction of the absorption capacity of the small bowel represents the main indication for EF, including short-bowel syndrome,[33] severe diarrhea with villous atrophy,[34–38] and inflammatory bowel disease.[39] The physiologic basis of continuous EF is of great interest in patients with GI disorders and PEM. However, some patients with severe PDI and those with IDI fail to respond to continuous EF and require PN. We studied 60 infants who required at least 1 month of total PN.

The main data of this survey are provided in Tables 44-3 and 44-4. Two-thirds of patients had severe PDI from various origins, including multiple food allergy or persistent postenteritis diarrhea. In this setting, PDI has an evident effect on nutrition, leading to the well-known vicious circle of diarrhea-malnutrition-diarrhea. The pathogenesis of this condition is complex and variable (Figure 44-3). This translates into a wide range of small intestinal, mucosal, morphologic, and biochemical changes. Intestinal mucosa may appear from normal to villous atrophic mucosa with continuous or patchy appearance, brush border, and/or intraluminal digestive enzyme deficiencies and variable degrees of increased permeability, to the presence of intraluminal bacterial overgrowth.

As such, it is clear that optimal nutritional management becomes fundamental. Feeding choices that would allow both the resolution of the PDI episode and nutritional repletion are not simple. The digestion of lactose is most frequently impaired, but the absorption of monosaccharides can also be impaired as a result of a reduced surface area. On the other hand, increased concentration of deconjugated bile acids is known to inhibit active glucose transport.[35]

The practical nutritional approach for infants and children with PDI in developed countries is to remove cow's milk proteins and lactose from the diet. A formula whose nitrogen component is based exclusively on a nutritional complete and a balanced solution of free amino acids may be used. Such formulas are, by definition, unable to trigger any allergic reaction. It may be indicated in children with persistent symptoms of formula protein intolerance after treatment with protein hydrolysates, as already reported.[36]

In wasted children with a poor appetite or with digestive intolerance and insufficient weight gain, continuous enteral (nasogastric tube) feeding (CEF) is required.[37]

Physiologic Changes during CEF Continuous gastric emptying related to continuous infusion rate can be achieved if the infusion rate, caloric load, and osmolarity of the mixture are not excessive. Below 3 kcal/minute, the gastric emptying rate increases with increasing caloric load up to the same level as the enteral feeding infusion rate. Excessive infusion rate, caloric load (> 1 kcal/mL), and/or osmolarity (> 350 mosm/L) of the nutritive solution increase the risk of nausea and vomiting.[40] The type of triglyceride, for example, long-chain (LCT) versus medium-chain triglyceride (MCT), may change gastric emptying.[41]

Motor migrating complex, as during fasting, is observed during CEF. The nature of triglycerides and/or the molecular weight of peptides and proteins modify the jejunal motility. Gallblader motility is maintained during enteral infusion, as assessed by ultrasonography. The type of infused lipids, MCT versus LCT, may influence gallblader motility.[42] However, biliary complications, such as sludge or cholelithiasis, are rare, even during long-term CEF.

The gastric secretion depends mostly on protein intake and, in the case of an elemental diet, on the composition of amino acids.[43] It is not demonstrated that the type of diet, elemental, semielemental, or polymeric, modifies gastric acid secretion. Cholecystokinin secretion and pancreatic secretion remain under CEF. There is a correlation between the secretion of chymotrypsin and lipase and the amount of nitrogen infused within the jejunum.[44] Secretory responses do not differ between elemental or polymeric nitrogen intakes.[45]

Experimental CEF in animals has shown that the absorption capacity of the distal small bowel and colon, despite a normal architecture of enterocytes' enzymatic and functional capacity, is decreased; in addition, DNA and quantity of protein are reduced.[46] This could be the consequence of the almost complete absorption of nutrients within the proximal part of the small bowel, leading to a lack of stimulation of the distal segment. On the other hand, it has been suggested that the beneficial effect of CEF, such as in the treatment of severe protracted diarrhea, might be mediated by the suppression of protein dietary antigens. However, recent studies in rats demonstrated that CEF does not modify growth and mucosal morphology but decreases the number of intraepithelial lymphocytes and epithelial expression of major histocompatibility complex

TABLE 44-3 Main Characteristics of Infants with Protracted (PDI) and Intractable (IDI) Diarrhea of Infancy (Personal Data)

	PDI	*IDI*	*p*
Gestational age (mo)	38.5 ± 1.2	38.2 ± 1.7	NS
Birth weight (g)	2,910 ± 340	2930 ± 462	NS
Onset of diarrhea (d)	120 ± 49	38 ± 17	.02
PN duration (mo)	5 ± 11	24 ± 8	.01
Mortality (%)	2.5	23.8	.05

NS = not significant' PN = parenteral nutrition.

TABLE 44-4 Cause and Outcome of Protracted and Intractable Diarrhea of Infancy (Personal Data)

Cause	*Patients (n)*	*Deceased (n)*
Protacted diarrhea	39	1
Multiple food intolerance	15	0
Infectious enteritis	14	0
Colitis (including 2 CMV)	6	1
CDG syndrome	1	0
Ganglioneuroblastoma	1	0
Unknown	2	0
Intractable diarrhea	21	4
Abnormalities of the enterocyte		
Intestinal epithelial dysplasia	6	1
Microvillous atrophy	3	0
Autoimmune enteropathy	5	3
Phenotypic diarrhea	3	0
Undefined	4	0

CMV = cytomegalovirus.

(MHC) II antigens regardless of the molecular form of nitrogen supply.[47]

The thermogenic effect of alimentation is related to the increase of energy expenditure following ingestion of food. The increase of energy expenditure induced by CEF in normal subjects is lower than that for the same nutrient load as bolus.[48] Thus, the constant administration of energy substrates could reduce the energy storage and maintain homeostasis at a lower energy expenditure.[49]

Finally, CEF, by the slow and continuous administration of nutrients into the GI tract, allows it to achieve its optimal use, despite its pathology. By changing the conditions of flow and contact of the nutritive solution, CEF may increase the capacity of intraluminal digestion and intestinal absorption. This feeding technique seems logical and efficient when the absorptive surface is reduced, such as in some forms of severe PDI with villous atrophy.

Nutritive Solution Composition and Regulation of Intake

Techniques for delivering EF and related complications are presented in Chapter 10, "Protein-Energy Malnutrition: Pathophysiology, Clinical Consequences, and Treatment."

The nutritive solutions should have an osmolarity below 320 mosmol/kg and contain substrates, which are rapidly transferred across the intestine and leave no intraluminal residue. In the case of severe protracted diarrhea, all substrates requiring intraluminal hydrolysis (proteins, starches, LCTs) should be excluded, as should potentially highly antigenic substrates (cow's milk proteins, gluten, and soya). All solutions must be sterile because of the high risk of bacterial proliferation and translocation. Initial EF can require a diet in which each of the constituents is modified independently and thus introduced sequentially.

Nitrogen The absorption of amino acid is more rapid and efficient when given in the form of short peptides than free amino acids.[50,51] In addition, the quality, in terms of

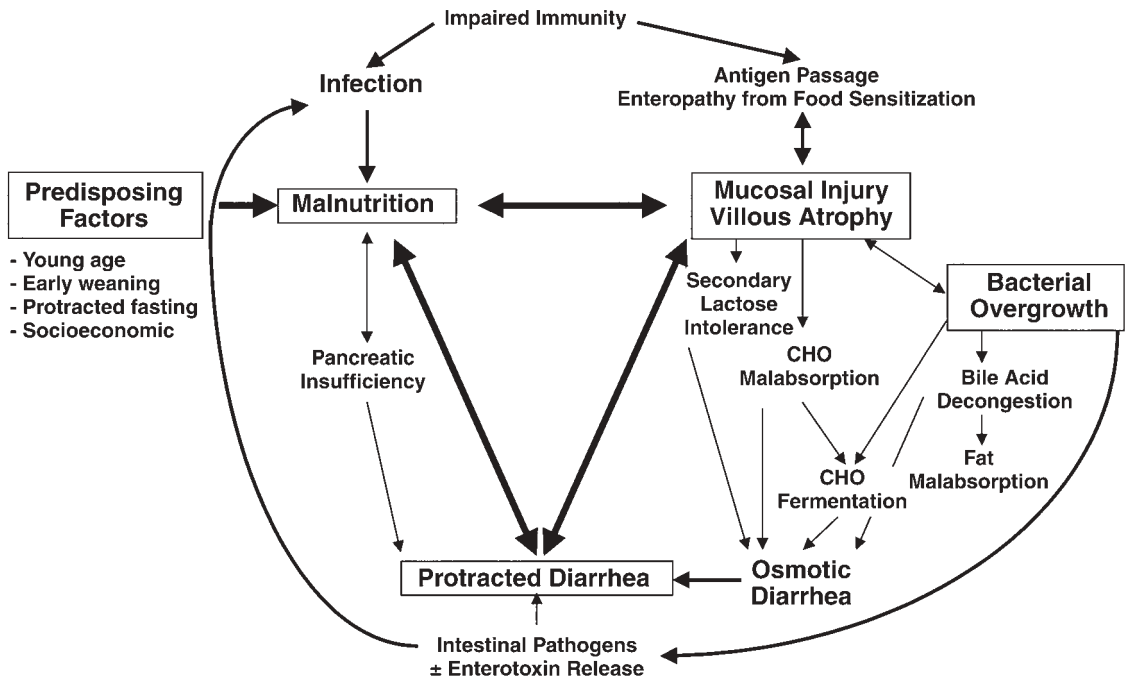

FIGURE 44-3 Pathogenic scheme in protracted diarrhea of infancy. CHO = carbohydrate.

digestion and intestinal absorption of protein hydrolysates, depends on the type of hydrolysate; for example, lactalbumin is better than casein.[52] Thus, the initial use of a solution of polypeptides with a lower osmolality than that of a mixture of amino acids is recommended. However, a free amino acid–based diet has been successfully used in cases of severe PDI.[36,53] More data are required for establishing recommendations for the use of such an amino acid–based diet. Nitrogen needs vary depending on tolerance and range from 350 to 500 mg/kg/day or even more in some highly catabolic situations. The nitrogen-to-calorie ratio must be considered, with protein intakes accounting for 10% of the energy intake.

Carbohydrates Disaccharidase enzymatic activity is depressed in severe malnutrition states and digestive disease. Lactase appears to be the most sensitive to injury and the last of the disaccharidases to recover. In addition, certain drugs, such as neomycin or colchicine, depress the intestinal disaccharidases. Thus, it is important to avoid dietary sources of lactose. Other disaccharides should be given in limited amounts at initial feeding as their corresponding brush border enzymatic activities are reduced. Nevertheless, if the carbohydrate intake during the initial days of EF is exclusively glucose, its high osmolality (5.5 mosmol/g) limits the rate at which it can be infused and thus the total amount given. The subsequent introduction of low-osmolality oligosaccharides may allow the intake to reach 20 or even 24 g/kg/day, especially in infants, without overpassing a solution osmolality of 350 mosm/L.

Lipids The behavior of MCTs within the intestinal lumen and its absorption characteristics are primarily owing to their greater water solubility. They are hydrolyzed faster than LCTs in the small intestine by pancreatic lipase; they are converted almost exclusively into free fatty acids and glycerol and reach directly the portal circulation and liver. Nevertheless, in the case of pancreatic insufficiency, MCTs may be absorbed intact. The excessive use of a diet rich in MCTs can lead to osmotic diarrhea as a result of the rapid hydrolysis of MCTs. Dicarboxylic aciduria has been described in infants supplemented with MCT-rich formulas without any proof of a deleterious effect.[54] The provision of EFAs must be considered because MCTs contain no EFAs. In addition, the administration of MCTs decreases the absorption of LCTs; supplementation with linoleic acid to an MCT formula may be insufficient to prevent EFA deficiency, leading to providing EFA parenterally. However, most of the formulas containing MCT also include up to 50% of lipids as LCTs. By stimulating biliary and pancreatic secretions, LCTs promote increased intestinal motility; an excess of LCTs in the intestinal lumen, especially if they are hydroxylated by bacteria, reverses the rate of water and electrolyte absorption and worsens malabsorption. In these conditions, the addition of cholestyramine may be appropriate associated with an EFA supplementation. Finally, an intake of 3 to 4 g/kg/day of lipids may be achieved, depending on absorption capacity and digestive tolerance.

Other Constituents Recommendations for vitamins and trace elements intakes are provided in Chapter 6, "Trace Elements," and Chapter 7, "Vitamins."

Commercially available semielemental diet formulas containing protein hydrolysate and MCTs can be used safely in children by slowly increasing the volume and the concentration of the solution. The low osmotic load of these products allows increasing concentration if necessary up to 1 kcal/mL. Thus, nutritional solutions in which each of the constituents is modified independently are mostly used in special situations of severe or selective malabsorption.

EF can be used after a prolonged period of PN or simply after a brief phase of peripheral venous infusion. EF is progressively introduced depending on the child's clinical state and the digestive disease. The first step includes the progressive reduction of the PN intake and stepwise EF increase according to digestive tolerance. The water and sodium intake should be increased to compensate for the intestinal losses generally induced by the start of EF; the tolerance is estimated from the weight of the child, the volume and osmolality of urine samples taken at 6-hour intervals, and the plasma osmolality. The tolerance and needs are estimated from 24-hour urine analyses, while attempting to maintain a natriuresis of 2 to 3 mmol/kg/day. At the same time, potassium intakes are adjusted as a function of the nitrogen and energy intake. Glucose is used initially, and the amount is increased progressively and controlled according to the stool volume, pH, and absence of reductory bodies. In the first days of feeding, at least a molar ratio of glucose and sodium is maintained. Protein hydrolysates are gradually introduced according to digestive tolerance.

The weaning period varies from a few days to several weeks or months. Anorexia can be avoided by the maintenance of sucking and swallowing functions during the period of CEF. In addition, it has been demonstrated that non-nutritive sucking during EF enhances growth and intestinal maturation in premature babies.[55] Weaning includes a period of continuous nighttime feeding supplemented by five or six meals in the daytime until the latter account for 50% of the total intake. Oral feeding must be carefully increased because of the relatively low intestinal activity owing to long-term CEF.

Parenteral Nutrition

Infants with IDI require long-term PN. Those who have congenital disease of intestinal mucosa and permanent intestinal failure require indefinite PN and intestinal transplantation. Thus, long-term PN is based on very rigorous methods aiming to avoid PN-related complications (see Chapter 57, "Parenteral Nutrition," for details of management).

Vascular Access Peripheral venous administration is the easiest and least hazardous method, requiring rigorous asepsis, especially in malnourished children, from severe PDI. However, only iso-osmolar solutes, providing insufficient protein-energy intake, can be used because of the risk of superficial phlebitis. In some cases, a further limiting factor can be that access to superficial veins is restricted or

impossible. Infusion into the superior vena cava with a central venous catheter (CVC) is accompanied by specific complications, such as thrombosis or sepsis. Only silicone CVC should be used, the size of which is selected according to the child's weight and age. The CVC can be inserted percutaneously, either via an epicranial vein or via an upper limb superficial vein or in a jugular or subclavian vein in older children.[56] Surgical insertion of the CVC requires adapted techniques to avoid vascular injury, bleeding, or infection. CVC with a Dacron cuff, ensuring efficient anchoring, may be inserted either percutaneously or surgically. In each case, the cutaneous and venous entry sites should be separated by a 5 to 10 cm subcutaneous tunnel; one must be careful because subcutaneous tissue is particularly thin in severely malnourrished children. The cutaneous exit site should be given meticulous daily care using iodinized disinfectants and be protected by an occlusive dressing, which is changed every day. The use of a 0.22 mm antibacterial membrane filter between the catheter and the administration tubing during perfusion remains a controversial issue. The choice of pump is important, satisfying three criteria: reliability at low flow rates, easy to use, and fitted with a safety alarm capable of signaling a change in flow rate, an air bubble, or a blockage leading to increased pressure. Solutions for PN must be prepared under strict asepsis by using antibacterial filters under a laminar flow hood.

Parenteral Nutrition Intakes The composition of the intravenous feeding solution should be adjusted at least daily according to the clinical and biologic criteria and as a function of the recovery from malnutrition and/or the transition from parenteral feeding to EF. Parenteral intakes are progressively introduced, according to tolerance, to cover the requirements of protein, energy, and trace elements.

Nitrogen Intake. PEM secondary to chronic disease as well as acute illness such as injury or infection is associated with the loss of body fat and skeletal-muscle mass. When the disease is prolonged and the child is severely malnourished, a variety of clinical events may occur in association with catabolic state. These alterations include immunosuppression, delayed wound healing and tissue repair, and loss of muscle strength. The accelerated breakdown of body protein can be slowed by the administration of adequate quantities of energy, protein (amino acids), and other essential nutrients. However, measurements of body composition and substrate-flux studies indicate that it is extremely difficult to maintain or replenish body protein during catabolism.[57] Thus, reducing the debility associated with catabolic process could potentially enhance recovery and decrease the consequences of illness on protein retention and height growth velocity.

Nitrogen intake depends on the age and degree of malnutrition.[58] In infants, it varies from 400 to 800 mg/kg/day when GI losses are great.[59] In older children, 300 mg/kg/day is usually sufficient.[60] Such intakes, which are higher than the growth requirement, cover excessive nitrogen losses induced by catabolism. Greater amounts are unsuitable because with a constant caloric intake, there is a negative correlation between nitrogen intake and the amount retained with a danger of hyperaminoacidemia, metabolic acidosis, or iso-osmolar coma. Such intakes may also be responsible for some of the reported anomalies in phosphorus and calcium metabolism.[61] Nitrogen source available for PN comes from various mixtures of crystalline L-amino acids shown to be effective in clinical use, providing appropriate nitrogen use and retention. Amino acid solutions for use in PN are selected according to the following criteria[62,63]: (1) whether the solution contains all or only some of the naturally occurring amino acids, (2) the total amino acid nitrogen content, (3) the osmolality and electrolyte content, and (4) the amount of essential amino acids per gram of total nitrogen (E:T).

Pediatric solutions appear to be better suited for use in newborns, premature babies, or malnourished infants (Primene, Baxter, Maurepas, France; Vaminolac, Fresenius, Kabi, Germany). Both products have an E:T ratio greater than 3 and differ from standard solutions with a higher percentage of branched-chain amino acids, modified aromatic amino acid contents (one-third reduction in phenylalanine), and modified sulphur-amino acid content, with methionine reduced by 50% and an increase in cysteine. Both solutions also contain taurine, which is absent from standard solutions and increased lysine contents.

Because the efficacy of PN cannot be easily improved by quantitative modifications, the addition of specific amino acids or other sources of nitrogen to the feeding formulas might be logical in critically ill children. Glutamine (Gln), being the most abundant amino acid in the body, is absent from the currently available amino acid solutions. Gln is considered unstable in aqueous solutions and during heat sterilization with the formation of pyroglutamic acid and ammonia. Although Gln is a nonessential amino acid, the nutritional requirement for this amino acid during catabolic illness may differ greatly from those during health. During starvation or stress, the concentration of free Gln in the intracellular amino acid pool of skeletal muscle rapidly decreases. Gln exported from the muscle is used primarily by visceral organs; in the kidney, it serves as an ammonia donor; in the GI tract, it serves as a primary oxidizable fuel source for enterocytes and colonocytes.[64] Gln also supports other rapidly proliferating tissue, such as fibroblasts or lymphocytes. Gln-supplemented total parenteral nutrition (TPN) has been shown to preserve gut structure and to improve gut immune function in animal models.[65] Recent studies have shown the clinical benefits of Gln-supplemented TPN in adult patients undergoing bone marrow transplantation.[66,67] The use of Gln-containing dipeptides is proposed regarding the instability of free Gln. Improved nitrogen balance has been shown in patients receiving alanyl-glutamine–supplemented TPN.[68] In addition, Gln dipeptide–supplemented PN prevents intestinal atrophy and increased permeability in critically ill adult patients.[69]

Ornithine α-ketoglutarate (OKG) is a salt formed with two molecules of ornithine and one molecule of α-ketoglutarate. OKG has been sucessfully used by the enteral and parenteral route in burn, traumatized, and sur-

gical patients and in chronically malnourished patients. The mechanism of action of OKG is not fully understood, but it was clearly demonstrated that it is a precursor of Gln.[70] In addition, the secretion of anabolic hormones (insulin, human growth hormone) and the synthesis of metabolites (polyamines, arginine, keto acids) may be involved.[71,72]

In the near future, more specific therapeutic approaches of protein metabolism might be achieved. This perspective is of great importance for children regarding the consequences of inadequate protein metabolism on growth velocity during recovery from malnutrition.

Energy Intake. The infusion rate of glucose must be kept constant without exceeding a rate of 1 g or 1.5 g/kg/hour. Under these conditions, the appearance of a glucosuria indicates a technical problem with the infusion or some stress, particularly an infection. Energy intake is closely correlated with that of nitrogen. In infants, intake varies from 100 kcal/kg/day to 120 kcal/kg/day, but the intake is reduced to 60 to 80 kcal/kg/day in older children.[73]

TPN for infants and children used to provide most of the energy as glucose, although it is not precisely known how much of the intravenously administered glucose is oxidized.[74] Glucose-based TPN has been shown to cause an adverse effect related to glucose storage, particularly as fat. This might account for the extensive lipid deposition reported both in liver and adipose tissue.[75] In these conditions, fat infusion further increases fat deposition and may result in fat overloading. Thus, substitution of part of the glucose calories avoids the undesirable effects reported with glucose-based TPN. In addition, it has been shown that the use of intravenous fat emulsion (IVFE) improves nitrogen retention.[76,77] IVFE provides a highly concentrated source: 2.2 kcal/mL for the 20% emulsion compared with 0.68 kcal/mL for a 20% dextrose solution. The concentrated calories and low osmolality of IVFE make it ideal for peripheral PN. In addition, TPN without lipids creates a metabolic situation likely to produce an EFA deficiency.[78] Glucose infusion stimulates secretion of insulin, which reduces lipolytic activity and prevents release of tissue linoleic acid reserves. The onset of EFA deficiency is even more rapid when there is a preexisting nutritional lack, such as in very young or malnourished infants. Seventy percent of infants less than 1 year old on TPN without lipids develop an EFA deficiency within 1 to 2 weeks.[79] The restart of anabolism can, because of adequate energy and nitrogen intakes, lead to the onset of EFA deficiency. A linoleic acid supply of about 2 to 3% of the total energy input is recommended.[80] A daily supply of 4% or 450 mg of linoleic acid per 100 kcal is often necessary to correct a preexisting deficiency. The lipid supply should also include α-linolenic acid ($C_{18:3}$ n-3). Although its function and requirements are still poorly defined, an intake of about 40 to 50 mg/kg/24 hours, equal to about 0.5% of the total energy intake, is normally provided.

Carnitine is necessary for optimal oxidation of fatty acids. Carnitine, in the form of acyl carnitine, transfers free fatty acids into mitochondria, where they are recombined with coenyzme A (CoA) to form acyl CoA. Plasma levels of carnitine decrease rapidly in premature newborns and small-for-gestational-age neonates during the first days of life if no exogenous carnitine is provided,[81] raising the question of carnitine supplementation for children on TPN.[82] In the absence of specific recommendations, a supplement of 1 to 2 mg/kg/day may be advisable. A supplementation with α-tocopherol as an antioxidant, at a dose of 0.6 mg/g of unsaturated fatty acids, is recommended.[83]

Despite the advantages of IVFE and the need to correct any EFA deficiency, there are restrictions to the administration of lipids to malnourished infants. Malnutrition reduces lipoprotein lipase (LPL) activity, but this reappears with the onset of anabolism.[84] The substrate itself also stimulated LPL synthesis. It is therefore recommended that IVFE should not be administered until a few days after the start of PN. There may also be several classic contraindications to the use of IVFE during the initial phase, such as sepsis, thrombocytopenia, disseminated intravascular coagulation, respiratory distress syndrome, or metabolic acidosis.

Traditionally, IVFE has been prepared with soybean oil; other emulsions are now available. IVFEs containing MCTs are rapidly oxidized when used as a calorie source. Fatty acids from the hydrolysis of MCTs are the primary substrate for ketogenesis. Carnitine is needed to transport long-chain fatty acids into the mitochondria, but malnourished and seriously ill patients may be carnitine depleted. An energy source able to bypass this route into the mitochondria would, in theory, be useful for such patients. Medium-chain fatty acids can enter the mitochondria by simple diffusion, independent of the carnitine enzyme, and produce an elevation of plasma ketones.[85] MCTs have been shown to improve nitrogen balance in postoperative patients, but this positive effect remains controversial according to several other studies.[86,87] The use of MCTs in malnourished infants with severe protracted diarrhea indicates, after 15 days on TPN, that it is well tolerated and can provide advantages in terms of nitrogen metabolism by supplying the equivalent of 25% non–protein-energy intake.[88] MCT emulsion is also well tolerated on long-term TPN.[89]

A new 20% IVFE containing 17% olive oil and only 3% soybean oil is currently available and will probably be available for pediatric patients.[90]

Optimal Glucose-to-Fat Ratio. Studies performed in infants or neonates have assessed glucose and fat use and have determined the optimal lipid intake.[91,92] Fat infusion aiming at a significant contribution to the coverage of energy expenditure requires that glucose oxidation be equal to or lower than maximal oxidative glucose disposal. Hence, glucose infusion rates should be lower than 18 g/kg/day.[91] A study in malnourished infants and young children has shown a maximal lipid use rate of about 3.3 to 3.6. g/kg/day.[93] Above these values, there is an increased risk of fat deposition secondary to the incomplete metabolic use of infused lipid. Pierro and colleagues showed similar results in a short-term study performed in surgical neonates on TPN.[92]

Thus, administration of 2 to 3 g/kg/day of lipid is required as soon as the clinical situation permits, representing up to 30% of non–protein-energy intakes. A slow infusion rate, such as 0.1 to 0.2 g/kg/hour, allows the best

metabolic use and may avoid fat overload and reticuloendothelial system involvement.[94] IVFE may be infused either as a piggyback or as a ternary mixture. Use of an all-in-one mixture is not currently widespread in pediatric patients compared with adult patients.

Adaptation of Intake. Following the initial phase of refeeding (see above), water and electrolyte intake must be varied according to the age, degree of malnutrition, and water-electrolyte status, needing adjustment, for example, if there are intestinal losses. Infants require 120 to 140 mL/kg and older children 80 to 100 mL/kg/day. All normal infants and children need 3 to 5 mmol of chloride, sodium, and potassium per kilogram per day. When there are losses owing to vomiting or gastric aspiration, 8 mmol of sodium, 1 mmol of potassium, 6 mmol of H+ ions, and 12 mmol of chloride should be added to each 100 mL of water. In the case of enterostomy, 15 mmol of sodium, 1 mmol of potassium, 10 mmol of chloride, and 5 mmol of bicarbonate should be added to each 100 mL of water.

With a nitrogen intake of 400 mg/kg/day and a calcium intake of 1.7 mmol/kg/day, the daily requirement of phosphorus is 2.3 mmol/kg for bone growth and nitrogen anabolism. If the phosphorus intake is lower or the intake of nitrogen and/or calcium is higher, severe phosphorus depletion results. Magnesium requirements are usually satisfied by 1 mmol/kg/day.

Vitamin and trace element intakes are provided as a function of the intake of the respective nutrients and their anabolism. For infants and older children, adherence to the recommendations in Chapters 6 and 7 helps to prevent depletion or excess. These intakes should be adjusted in cases of catabolic stress, such as an infection or intestinal losses. Complications of PN are listed in Chapter 57, "Parenteral Nutrition."

When PN has to be continued after the initial phase of renutrition, if the metabolic and nutritional status permits, cyclic PN should be started. The advantages of cyclic infusion are metabolic, physical, and psychological.[95] In addition, cyclic PN allows the patient to be discharged home if long-term PN is required.[96]

PERMANENT INTESTINAL FAILURE

The term "intestinal failure" is now often used to describe GI function insufficient to satisfy body nutrient and fluid requirements. The first recognized condition of intestinal failure was short-bowel syndrome. Severe motility disorders such as chronic intestinal pseudo-obstruction syndrome in children and congenital intractable intestinal mucosa disorders are also responsible for intestinal failure because no curative treatment for these diseases is yet available. PN and home PN remain the mainstay of therapy for intestinal failure, whether it is partial or total, provisional or permanent.[96,97] However, some patients develop complications while receiving standard therapy for intestinal failure and are considered for intestinal transplantation. The main long-term PN-related complications include catheter-related sepsis (CRS) and thrombosis, liver disease both being potentially life threatening.

Complications of Long-Term PN

Catheter-Related Sepsis and Thrombosis CRS is one of the most serious complications that can arise during PN, and the use of a CVC undoubtedly increases the risk of infection. The care of the child should be undertaken by physicians and nurses who have been specifically trained in this technique. Fever or clinical signs suggestive of CRS should lead to a thorough search for a source of sepsis, together with a white blood cell count, C-reactive protein, and coagulation tests. Samples for blood culture should be taken via the catheter and from a peripheral vein. If the body temperature remains elevated, antibiotic therapy should be started, using antibiotics against *Staphylococcus*. Removal of the catheter is not considered unless the PN program is close to completion, and in other cases, it can be considered only if the patient continues to deteriorate even when appropriate antibiotic therapy had been started. With good technique, displacement or obstruction of the catheter and thrombosis of the superior vena cava are rare.

PN-Associated Liver Disease Liver disease can occur rapidly because many factors are involved in hepatobiliary complications in patients with permanent intestinal failure.[98–104] The main factors related to liver disease are as follows: (1) severe necrotizing enterocolitis in premature or small-for-gestational-age babies, (2) bowel rest suppresses or reduces biliopancreatic and digestive secretions, (3) disruption of the enterohepatic cycle (ileal disease or resection), (4) bacterial overgrowth and translocation (endotoxinemia), and (5) recurrent CRS. Other factors are directly related to PN such as inadequate amino acid content of PN solutions, aluminum overload, excessive glucose intake, or excessive lipid intake (lipid peroxidation, reticuloendothelial system overload).

The first and most sensitive laboratory indications are increases in alkaline phosphatase and γ-glutamyltransferase activities. An increase in transaminase activity is also an early and specific sign, but it is less sensitive. Steatosis is the first histologic manifestation, followed by cholestasis and portal and periportal cell infiltration. Hepatic fibrosis indicates severe liver disease but is fortunately rare if PN is performed correctly and/or for a short period of time.

Some measures have been found to limit liver disease effectively: (1) stimulation of the enterobiliary axis by the ingestion of LCTs or breast milk or by the injection of cholecystokinin analogs; (2) suppression of intraluminal bacterial overgrowth caused by intestinal stasis by giving metronidazole; (3) by using ursodeoxycholic acid (10 to 20 mg/kg/day); (4) by decreasing the aluminum content of the PN solution; (5) by limiting glucose intakes to reduce hepatic fat accumulation; (6) by using an appropriate type and amount of lipid emulsion, which provides EFAs and reduces glucose load; (7) by using the new pediatric adapted amino acid solutions, which provide appropriate amino acids as well as taurine; and (8) cyclical PN, which contributes to decreasing hyperinsulinism and reducing liver steatosis.

PN-Related Bone Disease The so-called PN-related bone disease may occur in cases of protracted PN. It resembles rickets, with fractures of the limbs, which are sometimes asymptomatic and are discovered only after routine radiographic examination.[104] The most constant laboratory features are an elevated alkaline phosphatase activity and hypercalciuria, with normal or subnormal levels of vitamin D metabolites and parathyroid hormone. Bone histology shows osteomalacia-like changes with reduced mineralization and an excess of osteoid tissue. The etiology of these bone lesions is probably multifactorial: excess vitamin D or disorders of its metabolism mean that it must be given very carefully on long-term PN. It is also possible to reduce the hypercalciuria by ensuring that the supplies of phosphorus, nitrogen, and energy are properly balanced, while reducing the supply of amino acids, especially the sulfur-containing amino acids. Finally, it is necessary to ensure that the solutions used for children are not contaminated with aluminum.[105] Prevention of this "'bone disease" depends primarily on regular measurements of urinary calcium, which should not exceed 5 mg/kg/24 hours, and serum alkaline phosphatase activity.

INTESTINAL TRANSPLANTATION

Recent advances in immunosuppressive treatment and the better monitoring and control of acute rejection have brought intestinal transplantation into the realm of standard treatment for intestinal failure. In the early 1990s, two advances made intestinal transplantion a promising option for the treatment of end-stage intestinal failure: the combination with liver transplantation and the development of tacrolimus.[106,107] The results from the Intestinal Transplant International Registry indicate that intestinal transplantation is currently an acceptable clinical modality for selected patients with permanent intestinal failure.[108,109] Although it has been used in humans for the past two decades, this procedure had a slow learning curve. According to the current results, this challenging procedure may be performed in children only under certain conditions.

Indications for Intestinal Transplantation

Indications for intestinal transplantation involve mostly pediatric patients and may be divided into three main groups: short-bowel syndrome, intestinal motility disorders, and congenital disease of epithelial mucosa.

Shortly, in patients with short small bowels on long-term PN, intestinal transplantation can be envisaged only once it has been formally shown that the remnant bowel cannot adapt.[110,111] Surgical approaches such as lengthening of the small bowel, loop interposition, or assembly of a "reverse" intestinal loop should be attempted.[112–114] Trophic factors such as recombinant human growth hormone might be helpful in some patients and might contribute to decreasing the need for intestinal transplantation in the near future.[115–117] Therefore, only a small number of patients with short-bowel syndrome are candidates for intestinal transplantation in the absence of life-threatening complications, especially progressive liver disease, which raises another problem. The prevalence of complicated home PN-related liver disease increases with a longer duration of PN.[118]

Motility disorders in childhood include extensive Hirschsprung's disease and chronic intestinal pseudo-obstruction syndrome (CIPOS). The first causes the same problems as short-bowel syndrome, with two main differences. The nonfunctioning colon is excluded and the Hirschsprung's disease–free small bowel has motility disorders. Therefore, when normally innervated small bowel is shorter than 60 cm, the probability of long-term PN dependency is high. Logically, this situation requires a combined colon transplantation. CIPOS is a very heterogeneous condition with regard to clinical presentation, histopathologic features, severity of motility disorders, and outcome.[119–121] In our experience, 20 to 25% of patients will become definitively dependent on PN.[120] Recent data reported that intestinal transplantation or multivisceral transplantation has been performed in CIPOS patients, including some with associated urinary tract involvement.[122,123] Munchausen syndrome by proxy causing intestinal pseudo-obstruction must be recognized, even if difficult, and never justifies intestinal transplantation, as previously reported.[124]

Two congenital intractable epithelial mucosal diseases are responsible for permanent intestinal failure and are currently recognized as requiring intestinal transplantation: microvillous inclusion disease and epithelial dysplasia. Both are autosomal recessive inherited disorders with neonatal onset of severe watery diarrhea and total malabsorption. Microvillous inclusion disease involves the intracellular pathway of brush border development,[125] whereas epithelial dysplasia is associated with abnormal enterocytes and basement membrane.[126] The primary inherited defect is currently not known for either of these diseases. Children with one of these two mucosal diseases have undergone successful small bowel transplantation (SBTx) in isolation or in combination with the liver.[127–129]

Complications after Intestinal Transplantation

The intestine differs from other solid organs in its association with a large lymphoid system, the gut-associated lymphoid tissue. This complex lymphoid system includes Peyer's patches, mesenteric lymph nodes, plasma cells, and mature T lymphocytes disseminated within the intestinal mucosa. The sensitization of recipient lymphocytes to alloantigens in the Peyer's patches and mesenteric lymph nodes favors the homing of mature alloreactive T cells into the intestinal graft. On the other hand, the intestine is permanently exposed to potentially harmful pathogens, a major threat for recipients of intestinal grafts, amplified during rejection by the destruction of the epithelial barrier. These singularities of the gut may impede intestinal transplantation for several reasons: (1) the gut-associated lymphoid tissue can induce graft-versus-host disease (GVHD) and may enhance allograft rejection and the subsequent risk of gram-negative sepsis; (2) the secretion of lymphokines or the production of cytotoxic T cells in response to intraluminal pathogens may impede the induction of tolerance and

thereby favor allograft rejection; (3) the need for heavy immunosuppressive treatment increases the risk of developing opportunistic infection and post-transplantation lymphoproliferative disorders. GVHD has been extensively studied in animal models of intestinal transplantation. In humans, despite the presence of circulating donor-derived lymphocytes during the first few weeks after transplantation, clinical signs of GVHD have rarely been reported.[130] GVHD is therefore not a major complication after intestinal transplantation.

Intestinal allograft rejection remains the major complication after intestinal transplantation. As a result of increased immunosuppressive treatment, graft rejection may further precipitate opportunistic infections that become additive factors in patient and graft losses. As rejection can occur rapidly and can be life threatening, close monitoring is required. This has led to the development of numerous diagnostic methods, which have not been validated in human intestinal transplantation or have limited value.[131–133] Therefore, regular biopsies of the proximal and distal ends of the graft for histologic or immunohistochemical analysis are required.[134–136] Clinical signs of rejection occur later than histologic and immunohistochemical signs and correspond to a relatively advanced rejection process with marked histologic lesions. In addition, clinical manifestations are nonspecific markers of rejection. It is thus of importance to differentiate other sources of potential intestinal allograft disease that may clinically mimic rejection, such as post-transplantation lymphoproliferative disorders, Epstein-Barr virus, cytomegalovirus, adenovirus, or other bacterial/viral enteritis. Rejection and sepsis can be intimately related after SBTx, when rejection compromises normal intestinal barrier mechanisms and bacterial translocation results, with consequent multiorgan failure.

Intestinal Graft Function

Provided that the small intestine survives ischemia and reperfusion injury, long-term graft absorptive function depends on the effects of denervation, lymphatic disruption, immunosuppressive treatment, rejection, and infection.[137–140] These factors may explain impaired function of the intestinal graft and a delay in achieving intestinal autonomy. Studies performed in animals have shown that intestinal transplantation disturbs the absorption of carbohydrates, lipids, glutamine, water, and electrolytes.[141–145] The intrinsic motor activity of the small intestine is preserved, for the most part, although there is some discoordination between proximal and distal elements in the fed state.[146–156] Studies in dogs have shown extrinsic reinnervation of the intestinal graft wall along the arterial axis.[155] This process requires a prolonged period. In a syngeneic Lewis rat model, it was shown that nitric oxide and peptidergic neurons markedly decreased just after transplantation and that nitric oxide neurons recovered faster.[156]

Feeding must resume as early as possible after transplantation because this ensures optimal mucosal trophicity and reduces gastrointestinal stasis, which is a source of intraluminal bacterial overgrowth. Clinical experience has demonstrated that because of water-electrolyte malabsorption, abnormal motility, and impaired lymphatic drainage, it may take several weeks to achieve normal intestinal transit and stool volume. If the recipient has no colon, combined small-/large-bowel transplantation has physiologic advantages in terms of water and electrolyte reabsorption, slowing intestinal transit and trophic factors through colonic synthesis of short-chain fatty acids. Finally, it is currently considered that intestinal transplantation restores an enteral axis capable of ensuring digestion and absorption and that full function enables PN to be withdrawn completely.

Post-Transplantation Nutritional Management

Maximizing post-transplantion nutritional status is believed to increase the probability of a successful outcome. To achieve this objective, the following nutritional goals have to be met during the post-transplantation period: (1) continuation of PN during the early post-transplantation course, (2) initiation and adjustment of EFs, (3) oral stimulation and initiation of oral feeding, (4) maintenance of vitamin and mineral status, and (5) restoration of normal growth.

During the initial post-transplantation period, TPN is administered continuously, with modifications made to the electrolyte and macronutrient content of the solution based on serum and urine laboratory indices. Hyperglycemia may result from initial high steroid doses and steroid recycling during early rejection episodes and/or from tacrolimus. Post-transplantation pancreatitis may also affect glucose metabolism. Thus, insulin may be required in patients with severe hyperglycemia to maintain adequate caloric balance. Impaired renal function may require the limitation of nitrogen intake required for post-transplantation wound healing, and fluid restrictions may prohibit the ability to provide enough TPN volume to supply adequate calories. Use of intravenous lipid emulsion whenever possible, according to metabolic tolerance and infectious state, is recommended to achieve adequate calorie intake and the provision of EFAs. The type of emulsion has never been evaluated in such a situation and might be controversial. In our practice, we preferentially use MCT/LCT emulsion without overpassing 1.5 g/kg/day.

Continuous EFs through a gastrostomy or from proximal jejunostomy are started once intestinal motility occurs, generally within 1 week. EFs are initiated and advanced slowly unless contraindicated, as in the presence of severe diarrhea or vomiting and, of course, in the presence of an acute graft rejection. In our experience and elsewhere, the patients initially receive a low antigenic and low-fat formula and are subsequently transitioned over a period of weeks and months to a more complex product with intact macronutrients. The use of an amino acid–versus a peptide-based enteral product remains a controversial issue in the nontransplanted critically ill patient with impaired GI function. Nitrogen absorption from free amino acids and di- and tripeptide solutions without the presence of carbohydrate or fat are felt to be absorbed similarly, although by different active transport systems.[157] In the presence of carbohydrate and fat, however, nitrogen

absorption has been reported to be greater with a 100% elemental free amino acid protein source.[158] Moreover, the presence of free glutamine in powdered amino acid–based formulas bas been shown to be beneficial in protecting GI mucosa and reducing bacterial translocation.[159] Conversely, peptide-based elemental formulas are generally lower in osmolality, which may make them more suitable for use in the presence of increased stool output. A peptide-based isotonic formula used under such circumstances may also promote greater nitrogen uptake than an amino acid–based product, given that there would be less need to dilute the solution. It is impossible to identify significant differences in outcome as measured by the length of time until the patients are completely weaned from TPN, length of hospital stay, ileostomy output, or time until transition to oral intake alone by the type of enteral formula used. Most studies are limited by the small number of patients who received a peptide- or hydrolyzed casein–based enteral formula versus an amino acid preparation. Post-transplantation impaired lymphatic drainage with either chylous ascite or intestinal lymphangiectasia limits lipid intake. Low-fat and MCT-rich formulas are recommended at initiation of EF. Fat content can be adapted according to the occurrence of inadequate lymphatic drainage. In our experience, children with inferior vena cava thrombosis are at high risk of chylous ascite and must be fed very slowly, with adapted lipid intake (eg, MCT-rich formula). Commercially available formulas can limit the use of a combined low-fat/-amino acid preparation. More complex products with intact macronutrients are progressively introduced according to graft status, digestive tolerance, and capacity of eating. In children with eating disorders, EF can be progressively achieved by using a polymeric diet. PN weaning is a crucial objective, allowing intestinal transplantation to be considered successful.

Chronically ill infants and children are at risk for oral aversion caused by the loss of the sucking or swallowing reflex in those maintained on TPN or tube feeding for an extended period of time without oral intake. Further orally associated problems, including delayed speech and language development, may also result from this aversion. Pretransplantation management of eating disorders and early and adequate post-transplantation stimulation of oral feeding can reduce food aversion. It is essential to insert a digestive access (gastrostomy or proximal jejunostomy) at the time of transplantation surgery, especially in patients felt to have eating disorders. Psychological evaluation and assistance are, of course, required in each case. In our experience, all patients achieved oral feeding, sometimes up to 2 years after transplantation.

Finally, the course of post-transplantation nutritional therapy includes the period of initiation of EFs to achieve full digestive autonomy (discontinuation of PN) and complete oral feeding. It can take several weeks or months, depending on the pretransplantation nutritional status, rate of post-transplantation complications, and intestinal graft recovery and function. Data from the registry indicate that full nutritional autonomy with complete discontinuation of PN has been achieved in 77% of cases, and partial recovery was documented in another 14%, for a total rehabilitation rate of 91% in survivors.[110] In our experience, among 25 survivors after isolated (n = 5) or combined intestinal-liver transplantation (n = 20), all patients were weaned from PN, with delay ranging from 4 weeks to 3 years. In the absence of major complications, recipients of an isolated intestinal allograft can be weaned from PN relatively quickly within 4 to 6 weeks. The longer time to achieve full enteral nutrition after small bowel–liver transplantation (SBLTx) reflects a more prolonged recovery from the surgical procedure compared with isolated SBTx. Thus, the ultimate goal of independence from PN is achieved for the majority of patients. By using stool balance analysis in 12 PN-weaned transplanted children, we have shown that lipid absorption rate is decreased, ranging between 72 and 87%. With increased intakes according to Recommended Dietary Allowance, normal growth may be achieved in most children.

Nutritional Outcome

Beside the enteral or oral feeding approach, nutritional evaluation following intestinal transplantation is mandatory. However, only few nutritional data are available in children after intestinal transplantation.[160–164] We studied 13 children (8.8 ± 3.5 years) with at least 12 months follow-up (median 27 months).[165] PN was stopped 110 ± 84 days after grafting. They were on unrestricted oral feeding with enteral supplementation in 6 patients with varying degrees of eating disorders. At 12 months post-transplantation, body weight for age and height for age were decreased, at 89 ± 13% and 93 ± 5%, respectively. Body weight for height was increased (105 ± 9%), with fat body mass being 20.1 ± 4.3% of body weight. Growth velocity was decreased 6 months before and after grafting at 67 ± 38% and 57 ± 46% of normal for age, respectively, but was increased at 142 ± 64% of normal for age during the last 6 months of follow-up. Bone mineral density, measured by using dual-energy x-ray absorptiometry (DXA), was decreased in all children according to age. Nutritional parameters showed normal albumin and prealbumin plasma levels as well as plasma tocopherol. Conversely, both vitamin A and retinol binding protein plasma levels were decreased, as well as serum iron and ferritin.

Weight gain with excessive fat body mass and catch-up growth may be achieved after intestinal transplantation in most cases in our experience. However, in some cases, there is evidence of severe inhibition of linear growth at the time of transplantation, with no evidence of catch-up after transplantation.[163,164] Growth velocity is severely altered both before and just after transplantation owing to liver disease and high-dose steroids. Thus, catch-up growth is delayed. Thus, a follow-up period of 6 months is too short to observe positive trends in height/length. Despite normal growth, bone mineral density is low, and some nutritional biologic parameters are altered, such as vitamin A plasma levels. Monitoring should not be restricted to growth parameters but should include recording body composition and biologic parameters for achieving nutritional supplementation if required. In addition to these simple nutritional parame-

ters, future studies of post–intestinal transplantation nutrition therapy should evaluate bone mineral density on a longitudinal basis. DXA is undoubtedly required to assess bone mineral density. Indeed, insufficient bone mineral density may be attributable to previous long-term PN and might be worsened with high-dose steroids.

Candidates for Intestinal Transplantation

Intestinal transplantation is theoretically indicated for all patients permanently dependent on PN. Functional grafts lead to gastrointestinal autonomy (weaning off PN). However, as PN is generally well tolerated, even for long periods, each indication for transplantation must be carefully weighed in terms of survival rate, morbidity, and quality of life.[166–168] Intestinal transplantation is often accompanied by numerous life-threatening complications, such as those briefly reviewed above, leading to recurrent or long-term hospitalization and sometimes a poor outcome. An evaluation of the quality of life after intestinal transplantation among home PN has to be performed in transplanted patients using a validated quality of life instrument in the form of a self-administered questionnaire.[168] Intestinal transplantation recipients with functioning grafts reported a significant improvement in their quality of life. This information is encouraging and should be used toward future advancement in intestinal transplantation.

When long-term PN is effective and well tolerated, it can thus be used pending further progress in intestinal transplantation. In contrast, when PN has reached its limits, especially those associated with extensive thrombosis, recurrent sepsis, severe metabolic disorders, or advanced liver disease, intestinal transplantation must be undertaken. Patients with irreversible intestinal failure and end-stage liver disease are certainly candidates for a life-saving procedure such as combined SBLTx. Patients with irreversible intestinal failure and PN dependency without consistent liver disease must satisfy rigorous criteria to be considered candidates for isolated SBTx. They must fulfill at least one of the following criteria: extensive thrombosis impeding the ability to administer PN, recurrent life-threatening sepsis, severe metabolic disorders preventing nutritional requirements from being met with consequent failure to thrive in children, and underlying disease with high water-electrolyte losses with the risk of life-threatening dehydration in the case of PN disruption (eg, IDI from congenital intestinal mucosal disease). Some patients with severe chronic intestinal pseudo-obstruction may be disabled because of chronic, massive gastrointestinal dilation refractory to stomal decompression or partial enterectomy. They might be considered for intestinal transplantation, although the usual indications, including progressive liver disease, the threatened loss of vascular access, and recurring life-threatening sepsis, have not developed.

Finally, as pediatric patients represent almost two-thirds of the indications for SBTx, appropriate therapeutic strategies should be developed for all phases of intestinal failure. It is first required to recognize as early as possible the patient with irreversible intestinal failure such as extreme short-bowel syndrome or congenital disease of the intestinal mucosa or total aganglionosis. These patients should be referred at an early stage to multidisciplinary teams involved in SBTx in optimal nutritional status. For other patients, attempts at achieving intestinal autonomy (PN weaning) require appropriate management, as previously emphasized. Intestinal transplantation thus requires a strategy based on long-term medicosurgical management, aimed at demonstrating the irreversibility of intestinal failure, to avoid the complications of long-term PN and to refer early selected patients requiring this procedure.

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CHAPTER 45

SHORT-BOWEL SYNDROME, INCLUDING ADAPTATION

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Short-bowel syndrome provides the clinician with multiple challenges in nutritional therapy, perhaps more than any other single medical condition. It is a complex disorder that results in multiple disruptions of normal intestinal anatomy and physiology and produces a variety of nutritional, infectious, and metabolic complications. Short-bowel syndrome is usually defined functionally and is considered to exist when the patient has malabsorption in the presence of a shortened small intestine.[1] Malabsorption may involve nutrients, fluid, or electrolytes. Many of the clinical challenges lie in recognizing the many nutritional deficiency states that occur as a result of malabsorption secondary to the reduced absorptive surface area.

The prognosis of patients with short-bowel syndrome has been changing markedly over the past several years. The development of parenteral nutrition was a major step forward, permitting patients with shortened small intestine to live for extended periods beyond the development of the short-bowel state. Subsequent refinement in solutions, techniques, and catheters and new improved enteral feeding solutions had further impact on the prognosis in patients with short-bowel syndrome.[2,3] This disorder, which was formerly fatal, is now often compatible with long-term survival and potentially even a normal life span. The recent advent of intestinal transplantation is currently further altering the perspective of short-bowel syndrome. This chapter discusses the pathophysiology associated with short-bowel syndrome and the therapeutic steps that must be taken to permit patients with short-bowel syndrome to achieve their full potential.

ETIOLOGY

In most pediatric patients with short-bowel syndrome, the disorder begins at or near birth. However, a number of conditions later in life may result in the development of short-bowel syndrome in older children and adults. Neonates with short-bowel syndrome can be subdivided into those with and those without congenital anomalies.

Neonates who begin with normal intestinal anatomy constitute a large number of patients with short-bowel syndrome, which, in most of these cases, follows intestinal resection for necrotizing enterocolitis.[2–4] This occurs predominantly in the premature infant. The actual cause of this condition appears to be multifactorial, but ischemic injury to the small intestine may produce nonviable bowel, which subsequently must be resected. In this instance, ileal or proximal colonic resections are most common and extensive resection often results in compromised intestinal function. Later in life, anatomically normal patients may develop Crohn's disease, whereas patients with malrotation may develop a volvulus with intestinal ischemia. Tumors and radiation enteritis secondary to radiation therapy for neoplastic diseases are also common causes of short-bowel syndrome in older children and adults. Occasionally, Hirschsprung's disease may involve a portion of the small intestine in addition to the colon.

Short-bowel syndrome may also be the result of congenital anomalies. Atresia may occur anywhere in the small intestine, and these may be either isolated or multiple. Multiple atresias may result from anomalies of the superior mesenteric artery, known as "apple peel" or "Christmas tree" deformities of the small intestine. Congenital short-bowel syndrome, or shortened small intestine, may be present at birth. Patients with gastroschisis, an abdominal wall defect, may also have some degree of intestinal shortening, either congenitally or as a result of resection for ischemia or bowel injury.

There is little difference between these two groups from a functional perspective. However, certain anatomic considerations may have great impact on the patient's long-term prognosis and may alter the interventional steps required.

PHYSIOLOGIC ABNORMALITIES

Marked differences exist in the functioning of the proximal versus the distal small intestine, and these differences have a major impact on the management of patients with short-bowel syndrome. Typically, the jejunum has long villi, a large absorptive surface, and a high concentration of enzymes and transport carrier proteins. The epithelium is characterized by relatively large tight junctions between the epithelial cells. Because the tight junctions are the location of the paracellular pathway for transport and large quantities of fluid and smaller molecules pass through this pathway, the jejunal epithelium is relatively porous, allow-

ing free and rapid flux of water and electrolytes from the vascular to the intraluminal space. It is also the site of greatest nutrient absorption in the small intestine. On the other hand, the ileum is characterized by shorter villi, more lymphoid tissue, less absorptive capacity, and a tighter epithelium. Smaller tight junctions permit less flux of fluid from the vascular space to the lumen; therefore, the epithelium in the ileum is more effective in the conservation of fluid and electrolytes. Nutrients are absorbed less rapidly in the ileum than in the jejunum. The ileum also has certain capabilities that the jejunum does not have, mainly the absorption of vitamin B_{12} and bile salts through site-specific receptors. Normally, a large influx of fluid and electrolytes flows into the proximal small intestine to dilute highly concentrated nutrients delivered into the duodenum. Rapid mixing, digestion, and subsequent carrier-mediated transport of monosaccharides, amino acids, and dipeptides occur predominantly in the jejunum. Although some of these functions certainly occur in the ileum as well, the ileal epithelium is better suited to the reabsorption of water and electrolytes that were passively secreted owing to the osmotic gradient into the jejunum. The patient with a jejunostomy and a major ileal resection will therefore be susceptible to fluid losses from osmotic diarrhea, especially in association with carbohydrate feedings. However, patients with jejunal resection may tolerate such feedings better with less fluid loss.

Following ileal resection, patients may initially absorb more nutrients, although absorption will rapidly adapt as the ileum assumes jejunal function. Although the ileum can develop the absorptive capacity of the jejunum for various macro- and micronutrients, site-specific carrier-mediated transport of vitamin B_{12} and bile salts will never occur in the jejunum, and the patient will permanently malabsorb these substances following ileal resection. Many gastrointestinal hormones are also produced in the ileum, especially those that affect small intestinal motility, such as enteroglucagon and peptide YY. Ileal resection may impair regulation of gut motility by nutrients, especially fat. The antimotility effect of fat in the ileum is known as the ileal brake and is important in ensuring adequate fat absorption from the small intestine. Gastrin secretion is also increased in patients with short-bowel syndrome, probably because of the loss of the normal feedback mechanism owing to ileal resection. This abnormality partly explains the frequent occurrence of acid peptic disease and esophagitis in patients with short-bowel syndrome.

The ileocecal valve has two important functions. It serves as a barrier for reflux of colonic bacteria from the colon into the small intestine. It also appears to regulate the exit of fluid and nutrients from the small intestine. Consequently, its resection may have major negative effects on physiology following small-bowel resection.[2,3] A greater influx of bacteria from the colon into the small intestine results in bacterial overgrowth in the small intestine, resulting in a number of complications, to be discussed later. In addition, rapid transit of nutrients from the small intestine into the colon may exacerbate malabsorption and increase sensitivity to osmotic loads. More recent evidence suggests that the ileocecal valve may be less important than originally thought, and the adverse effects of ileocecal valve resection on the long-term outcome of short-bowel syndrome do not appear to be as great as originally thought.[5]

The major consequence of resection of the small intestine is malabsorption. This is primarily owing to reduction of the absorptive surface area with a concomitant loss of digestive enzymes and transport carrier proteins.[6] The consequences of nutrient malabsorption are easily demonstrated in patients with short-bowel syndrome. For example, malabsorption of rapidly digested carbohydrates produces tremendous osmotic diarrhea following resection of the ileum as reabsorption of water is impaired. Larger molecules such as proteins, which are usually ingested in smaller quantities, produce few symptoms when malabsorbed. Fats are also large molecules, and although they may be poorly absorbed, malabsorption of fat creates little additional fluid loss from the small intestine. However, fat absorption requires greater mucosal surface area; therefore, the coefficient of fat absorption may be less than for proteins and carbohydrates in patients with short-bowel syndrome. Fat-soluble vitamins may also be malabsorbed in large quantities in patients with short-bowel syndrome; therefore, vitamin deficiency states, especially fat-soluble vitamin deficiency states, are common. Following extensive ileal resection, reabsorption of bile salts may be impaired to such a degree that the patient will become bile salt depleted. Bile salt concentrations will fall below the critical micellar concentration, and fats cannot be solubilized. Fat-soluble vitamins and fats are therefore malabsorbed to a greater degree. Because it is thought that fat is not absorbed by a carrier-mediated saturable process, the total quantity absorbed may be increased by increasing dietary fat content, even though the coefficient of absorption may be reduced. Additional calories in the form of carbohydrate cannot be absorbed, however, once transport carriers are saturated. The possible exception is the fermentation of some malabsorbed carbohydrate to short-chain fatty acids in the colon or possibly in the distal small intestine if bacterial overgrowth is present. Colonic absorption of these substances may permit recovery of some additional calories. Consequently, preservation of the colon may be important not only for control of fluid and electrolyte losses but also for the potential provision of additional calories from short-chain fatty acids.[7]

Motility abnormalities are also found following intestinal resection. Transit time is greater in the jejunum following ileal resection. Gastric emptying is also more rapid following ileal resection but can be normalized if the colon is retained.[8] Additional functional abnormalities may result with time, often owing to compensatory changes that occur within the gastrointestinal tract. Intestinal transit time may increase as the intestine adapts in an attempt to increase nutrient contact time with the small-bowel mucosa. Mucosal surface area will likewise increase as the small intestine dilates. Unfortunately, both of these changes result in increased bacterial content in the small bowel, which results in a variety of complications that will be subsequently discussed.

Fortunately, the intestine is capable of significant adaptation resulting in enhanced absorption with time. These changes significantly alter physiology in short-bowel syndrome.

DESCRIPTION OF THE ADAPTATION PROCESS

Intestinal adaptation is characterized by hyperplasia of the mucosal epithelium.[9–13] An increase in crypt cell production rate precedes mucosal hyperplasia and results in increased crypt depth and subsequent lengthening of the intestinal villi. As a result, some dilatation of the small intestine occurs with increased folding of the mucosa and subsequent increase in mucosal surface area. As the process is hyperplasia and not hypertrophy, growth in cell number rather than cell size predominates. This observation is evidenced by parallel increases in mucosal DNA, protein, and weight. Increasing length of intestinal villi necessitates an increase in the rate of migration of cells from the crypt up the villus and also an increased rate of cell renewal. Cell number is the primary determinant of villus and microvillus surface area.[14] Increased absorption of almost all nutrients has been demonstrated following completion of the adaptation process, mostly in animal studies.[15–18] Disaccharidase digestion, monosaccharide absorption, and absorption of trace metals, vitamins, fluids, and electrolytes all increase significantly following resection. Within 8 weeks in the rat, enhanced glucose-dependent electrogenic sodium transport can be measured using Ussing chamber techniques.[19]

Electron microscopic studies demonstrate little change in enterocyte ultrastructure after 60% proximal small intestinal resection. The general structure of the single enterocyte is preserved, and all subcellular organelles appear morphologically intact. Resected animals demonstrate some dilatation of intracellular spaces on the tips of the villi. Microvillus surface also decreases as a function of time after proximal resection. No significant difference in the relative areas of mitochondria, rough endoplasmic reticulum, and nuclei are seen as a function of time following resection.[20]

Functional improvement of absorption does not immediately follow an increase in absorptive surface area. Digestive enzymes such as lactase, sucrase, and maltase are often decreased in hyperplastic epithelium, suggesting some functional immaturity. Replicative enzymes such as thymidine kinase are often increased. This functional immaturity appears to change gradually with time as absorptive function improves.[15–18] However, functional adaptation appears to be a diverse process. Improved absorption of some nutrients occurs much more rapidly than that of others.[21] Substantial confusion exists regarding the extent of improvement in intestinal function, primarily because of differences in expressing the data from the animal studies.[22,23] Tissue preparations—such as intestinal sacs or rings, isolated enterocytes, or membrane vesicles—commonly suggest impaired absorption because data are most often expressed based on a parameter of mucosal mass, such as DNA, protein, or weight. However, the marked increase in mucosal mass that occurs following resection actually results in an increase in intestinal function. Whenever possible, data should be expressed per centimeter of small intestine or related to small intestinal absorptive surface in some other way. When calculations are performed in this way, intestinal function improves in nearly all studies.

Analysis of transport kinetics defines the functional changes in hyperplastic mucosa. No changes in Km occur, suggesting no alterations in thickness of the unstirred layer. However, V_{max} for several substrates may be reduced by 50% when the data are expressed per unit of mucosal surface area. Individual enterocytes in the hyperplastic epithelium are likely to contain fewer carrier proteins than are found in the physiologic state. Nonetheless, reduced enterocyte function is overcome by the larger absorptive surface area.[24,25] Digestive enzyme function may vary significantly. In one study, specific activity of sucrase appeared to increase, but lactase decreased following resection. Analysis of messenger ribonucleic acid (mRNA) suggested that sucrase changes were pretranslationally regulated, but the decrease in lactase activity was a post-translational event.[26] Unfortunately, most studies have been performed 2 to 3 weeks postoperatively in an experimental model. It is not known for certain whether further maturation of the absorptive function occurs with time, but clinical experience strongly suggests that it does.

Functional adaptation may also occur independently of villus hyperplasia.[27] Increased glucose uptake has been observed even in the absence of increases in intestinal mass.[28] Differences in adaptive rates of glucose as well as amino acids have also been measured. Administration of higher nutrient concentrations can cause adaptive changes in the small bowel without changing morphology. Carbohydrate content, when increased, may result in marked enhancement of glucose transport without changing villus architecture or mucosal mass. Normally, the proximal small bowel contains greater mucosal mass than the distal small bowel, and villus length is increased over the distal small intestine. Consequently, there is a proximal to distal gradient in the transport of several nutrients, especially glucose. However, the gradient in the case of glucose is much more pronounced than the gradient for intestinal mass, suggesting that there is a functional adaptive response to the high concentrations of glucose, which occurs independently of the effect of nutrients on jejunal morphology. These morphologically independent adaptive changes in transport appear to be nutrient specific. For example, a high-carbohydrate, low-protein diet results in enhanced glucose transport but reduced amino acid transport. Likewise, a high-fructose diet induces fructose absorption, whereas glucose absorption is not altered. Conversely, high-glucose diets will stimulate glucose transport independently of fructose transport.

These morphology-independent changes may occur quite rapidly.[29,30] Glucose transport may be increased within 1 to 3 days of a change in dietary carbohydrate. Comparable changes in morphology may take 1 to 3 weeks. Synthesis of transporters and brush border diges-

tive enzymes appears to occur rapidly in response to large quantities of intraluminal nutrients.

Animal studies, mainly in dogs and rats, have been used to develop most of our understanding of intestinal adaptation. In the rat, mucosal adaptation occurs rapidly. Cell replication increases in the crypt as early as within 24 to 48 hours.[1] Likewise, in the rat, the villus hyperplasia process is often nearly complete by 2 to 3 weeks. Little corresponding information is available in humans, although clinical experience suggests that the adaptive process proceeds more slowly. The adult patient with short-bowel syndrome is likely to reach potential much more rapidly than a child. Data from rats have demonstrated that 3-week-old rats have less potential for total adaptation than 8-week-old animals, probably because the smaller animals were already under enough stimulation just to meet their growth needs alone and had little potential to adapt beyond their natural capacity.[31] In old animals, the adaptive response occurs much more slowly, although the capacity to adapt remains intact.[32] In children, a substantial potential exists for lengthening of the small intestine. Because little lengthening is possible in adults, growth in bowel length can greatly enhance the prognosis in infants with short-bowel syndrome. Children with very short bowels have a great capacity to increase bowel length when resection is performed in the neonatal period.[33] Extensive linear growth is observed in the normal small intestine during the first year of life and continues somewhat more slowly beyond that point. It is not clear whether there is much opportunity to enhance linear growth beyond that which normally occurs over a given segment of bowel, however. Clinical experience has taught us that pediatric patients may not reach their full adaptive potential following neonatal small-bowel resection until the fifth year of life.

Although most data have been derived from animal studies, some data are available regarding functional adaptation in humans. In children, a marked increase in glucose absorption was observed following an extensive resection using intestinal perfusion technique. Sucrose hydrolysis was increased in the same proportion as glucose absorption. Also, studies of human children have demonstrated intestinal hyperplasia, that is, an increased number of enterocytes per unit length of villus and a suggestion of increased villus length, although not statistically significant.[34]

IMPORTANCE OF ENTERAL NUTRITION

Enteral nutrition is extremely important in stimulating intestinal adaptation. Atrophy has been observed in the small intestine deprived of nutrient contact either by bypassing the small intestine surgically or by using parenteral nutrition.[35] Intravenous feeding following small-bowel resection results in slight mucosal atrophy, whereas enteral nutrition stimulates mucosal hyperplasia. The mechanism by which nutrients stimulate adaptation is complex.

Nutrient contact with the intestinal epithelium stimulates adaptation. Jejunal villi are normally longer than ileal villi, probably because they are exposed to high concentrations of nutrients. Therefore, when a segment of ileum is transposed into the jejunum, ileal mucosal mass increases rather markedly to the point where the length of the villi and the transposed ileum may actually exceed the length of villi in the adjacent jejunum.[36] Therefore, high nutrient concentration in the jejunum appears to stimulate villus length. Ileal villi appear to be as sensitive to nutrient concentrations as jejunal villi. However, the length of the small intestinal villi also appears to be genetically regulated as grafts of fetal duodenum develop longer villi than grafts of fetal ileum even in the absence of the influence of intraluminal factors.[37]

Enteral nutrition is also important for stimulating regeneration of the mucosa following injury. The combination of parenteral and enteral nutrition is superior to parenteral nutrition in stimulating intestinal regeneration of disaccharidases in a group of patients with protracted diarrhea of infancy.[38] A more rapid resolution of malabsorption and diarrhea following enteral nutrition alone versus parenteral nutrition in the same disorder has also been observed.[39] Enteral nutrition is also important in maintaining mucosal mass. Maintenance of mucosal mass and glucose absorption has been demonstrated to be improved following enteral versus parenteral nutrition, apparently as a result of direct nutrient contact. Direct nutrient contact is also important in the maintenance of normal glucose transport.

Stimulation of nutrient-sensitive epithelial cell proliferation appears to be a complex process. Originally, increased nutrient content was thought to produce hyperplasia by providing increased nutrition to enterocytes. It is more likely, however, that trophic factors, secreted locally and acting through a paracrine mechanism, work to stimulate epithelial cell proliferation and reduce apoptosis carbohydrates.[40] Nonmetabolized substances that require active transport are just as capable of stimulating adaptation as glucose.[41] Functional workload, therefore, appears to be the major stimulus for intestinal adaptation. Certain enteral nutrients may be more effective stimulants than others, probably because they require greater energy for digestion and absorption or because they result in enhanced release of trophic hormones. For example, hydrolyzable disaccharides induce greater mucosal adaptation than constituent monosaccharides.[41] Hydrolysis of the disaccharide in conjunction with subsequent absorption of the monosaccharide components appears to exert a greater functional workload on the intestinal mucosa. Inhibition of the sucrase enzyme with acarbose can abolish the stimulatory effect of sucrose on adaptation by eliminating the functional workload of sucrose hydrolysis. Likewise, lactulose, a nonabsorbable, nonmetabolized carbohydrate, requires no workload from the intestine and exerts no stimulatory effect on mucosal hyperplasia.[42]

Enteral nutrition also appears to promote adaptation through the stimulation of secretion of trophic gastrointestinal hormones. Thiry-Vella fistula models have been extensively used to demonstrate these effects. Thiry-Vella fistulae have an intact blood supply, but as they are isolated from the flow of enteric contents, they have no exposure to intraluminal nutrients (Figure 45-1). Enteral feedings are capable of stimulating intestinal adaptation not only in the

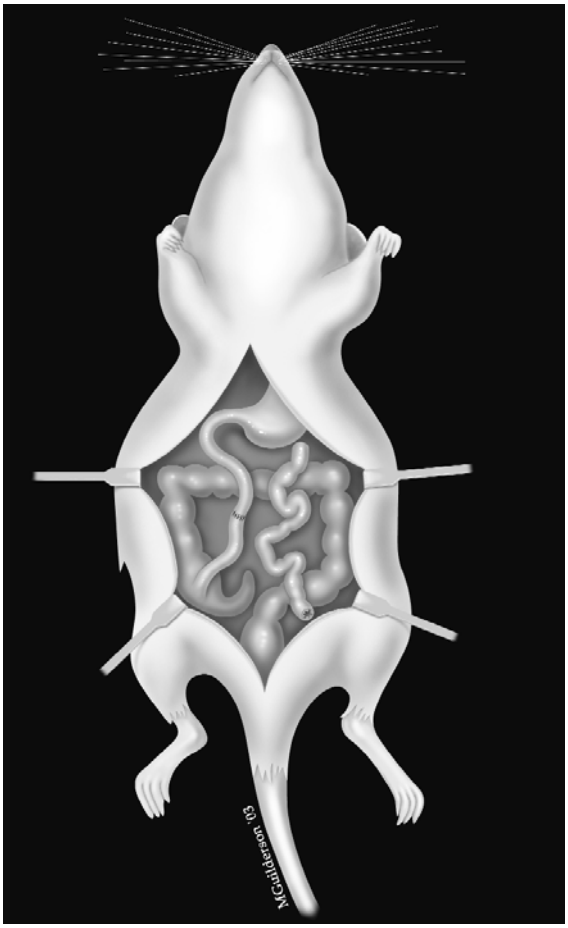

FIGURE 45-1 A Thiry-Vella fistula. A segment of distal jejunum and proximal ileum has been removed from continuity, its blood supply left intact, and ostomies created at both proximal and distal ends of the fistula.

small intestine but also in Thiry-Vella fistulae. Intravenous feeding, in contrast to enteric feeding, results in atrophy not only in the intact bowel but also in the Thiry-Vella fistula.[43] These findings are confirmed when mucosal mass in self-emptying blind loops is evaluated in animals receiving an 85% jejunoileal bypass in which mucosal mass markedly exceeds that in animals receiving only a 25% bypass. This observation suggests that the defunctionalized bowel responds to a greater adaptive stimulus produced from a reduction in the functioning small intestine.[44] Trophic gastrointestinal hormones circulating via the bloodstream appear to be an important means whereby intraluminal nutrients stimulate intestinal adaptation.

Additional evidence for this concept is derived from studies using parabiotic animals (Figure 45-2). In these experiments, one animal undergoes partial small-bowel resection. Blood is then cross-circulated between the two animals, and increased mucosal cell proliferation can be observed not only in the resected animal but also in its parabiotic partner.[45]

Intestinal adaptation can also be stimulated by increased production of gastrointestinal secretions. For example, transplantation of the ampulla of Vater into the distal small intestine may result in hyperplasia in the ileum in response to enteric feedings.[46,47] Pancreatic and biliary secretions entering the distal small bowel through the ampulla appear to stimulate villus hyperplasia. Diversion of pancreatic and biliary secretions into self-emptying ileal loops also induces villus hyperplasia.[48]

CANDIDATE TROPHIC HORMONES

At present, determination of hormones that regulate intestinal adaptation is an area of extensive research. Many hormonal mediators have been suggested (Table 45-1). Enteroglucagon, structurally similar to glucagon, has perhaps been studied most extensively. Patients with enteroglucagon-secreting tumors were initially found to develop massive mucosal hyperplasia, which resolved once the tumor was resected.[49] Therefore, the trophic effect of enteroglucagon in the small bowel became apparent. Enteroglucagon is known to be produced in highest concentration in the distal small intestine, which has the greatest potential for adaptation. Measurement of enteroglucagon levels and enteroglucagon mRNA levels reveals that they are increased following intestinal resection or jejunoileal bypass, situations in which mucosal hyperplasia is present.[50–52] Other studies have suggested that enteroglucagon may not play an important role in intestinal adaptation. Immunoneutralization of endogenous enteroglucagon by monoclonal antibodies does not obliterate the adaptive response.[53] Administration of enteroglucagon and glucagon to animals fails to stimulate mucosal hyperplasia.[54] In fact, the hormone appears to have antiproliferative properties when studied in an in vitro cell culture system.[53] Precursors to enteroglucagon have recently been demonstrated to be elevated following resection and may be the means through which enteroglucagon stimulates intestinal hyperplasia.[55] Ileal proglucagon mRNA levels rise rapidly following resection.[56]

Gastrin levels are also highly elevated following intestinal resection, and gastrin is a known trophic hormone to the stomach and proximal small intestine.[57,58] Hypergastrinemia appears to result in hyperplasia only in the very proximal small intestine, however, and is therefore not a likely candidate for regulation of the adaptation process. Neurotensin is found mainly in the central nervous system but is also present in the distal small intestine and appears to be an important regulator of intestinal motility. It has also been found to stimulate hyperplasia in the small intestine, although it may have a more important regulatory function in the growth of colonic mucosa.[59] Secretin and cholecystokinin have been shown to prevent mucosal hypoplasia when infused into parenterally fed dogs.[60,61] The effects of secretin, cholecystokinin, and neurotensin may all be explained by the stimulatory effect that these hormones have on pancreatic or biliary secretions.[62]

Epidermal growth factor (EGF), otherwise known as urogastrone, is a hormone that is present in breast milk and is known to stimulate proliferation of the intestinal epithelium. Its effects are most pronounced in the stomach, but it has been a recent candidate for involvement in the adaptation process.[63] It appears to stimulate ornithine decarboxylase,

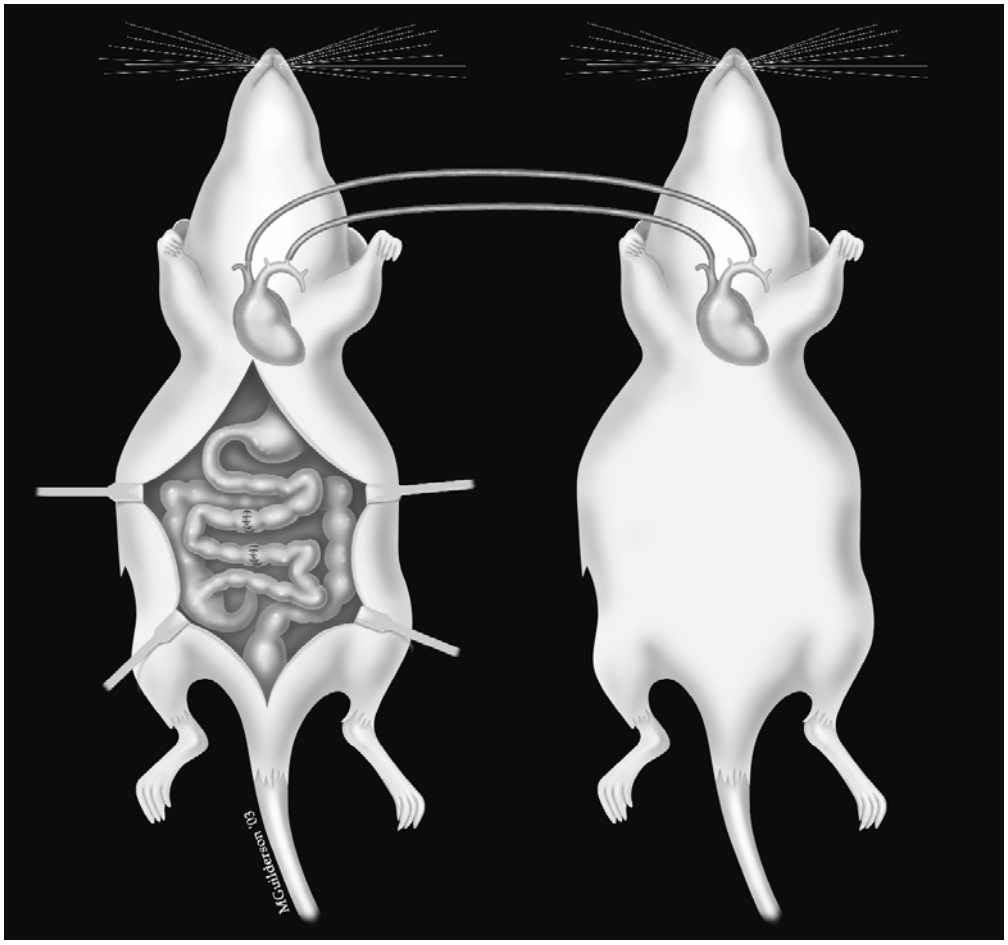

FIGURE 45-2 Parabiotic animals. Blood is cross-circulated between the two animals, one of which has undergone partial small intestinal resection.

important in polyamine synthesis, in the small intestine. Subsequent mucosal proliferation has been observed.[64] EGF receptors are present in the small intestine in high numbers, and this hormone is known to stimulate DNA synthesis.[65] High concentrations of EGF are found in the salivary and Brunner's glands, suggesting that EGF may exert its primary influence in the proximal small intestine. It may be important in maintaining normal mass in the physiologic state.

Insulin-like growth factor I (IGF-I) is a hormonal substance structurally similar to insulin. Also known as somatomedin C, this growth factor is responsible for many of the regulatory effects of growth hormone. Because plerocercoid growth factor, a growth hormone analog produced by a tapeworm, was shown to stimulate intestinal adaptation, the importance of growth hormone in regulating intestinal adaptation has received substantial interest.[66] Growth hormone itself has produced equivocal results, and studies showing a positive response in intestinal adaptation were hampered by the lack of control of nutrient intake.[67,68] Further studies using IGF-I and a truncated analog, des-IGF-I, in rats following small-bowel resection, however, demonstrated augmentation of the adaptation process.[69] Using a transgenic mouse model, further studies have demonstrated the importance of both IGF-I and growth hormone in regulating intestinal mass.[70] Studies in piglets demonstrated that colostrum, rich in IGF-I, had no benefits in inducing adaptation.[71] IGF-I appears to play a role in the adaptation process, perhaps independently of growth hormone.

Peptide YY may also be involved in intestinal adaptation. Elevation of peptide YY levels has been associated with enhanced adaptation produced by administration of menhaden oil. Concentrations of this hormone are markedly elevated in patients with short-bowel syndrome.[72] Because the hormone reduces gastrointestinal motility and also increases nutrient contact with the epithelium, peptide YY might potentially play a regulatory role in adaptation through its effect on motility. Additional factors of 4,500 and 1,500 daltons have also been identified that appear to

TABLE 45-1 Hormones Thought to Be Important in Intestinal Adaptation

Enteroglucagon
Gastrin
Secretin
Cholecystokinin
Epidermal growth factor
Insulin-like growth factor I
Peptide YY

be associated with nutrient-induced gut adaptation.[73] Antitrophic hormones probably also exist. Transforming growth factor β-1 has been shown to induce stem cell quiescence in the intestinal mucosa of the rat.[74]

The most interesting trophic factor at the present time is glucagon-like peptide 2 (GLP-2). GLP-2 promotes nutrient absorption by expansion of the mucosal epithelium by stimulation of crypt proliferation and inhibition of apoptoses in the small intestine. GLP-2 also reduces epithelial permeability and decreases meal-stimulated gastric acid secretion in gastrointestinal motility. The specificity of GLP-2 in the intestine appears related to the highly localized expression of the GLP-2 receptor in the intestinal epithelium.[75] In rat models of intestinal adaptation, GLP-2 has been shown to induce morphologic adaptation.[76] In humans, GLP-2 has been shown to improve the intestinal absorption of energy and increased crypt depth and villus height.[77]

PROSTAGLANDINS

Prostaglandins may also play a role in regulating epithelial cell proliferation.[78] Prostaglandins have been shown to be trophic to numerous cell types, and inhibition of prostaglandin synthesis reduces the mitogenic effect of some gastrointestinal hormones.[79] In addition, 15,15-dimethylprostaglandin E_2 increases mucosal mass and intestinal length in rats. These effects are primarily present in the gastric antrum and very proximal small intestine. The 16,16-dimethylprostaglandin E_2 stimulates intestinal adaptation following resection.[80,81] Likewise, inhibition of prostaglandin synthesis using aspirin reduces the stimulatory effect of resection on intestinal mucosal mass, predominantly in the ileum.[81] Dietary arachidonic acid appears to facilitate the adaptation process by acting as a substrate for the synthesis of prostaglandins and not through derivatives of lipoxygenase, such as leukotrienes or thromboxanes.[82]

ROLE OF POLYAMINES

Polyamines are polycationic compounds present in all procaryotic and eucaryotic cells.[29,83] Putrescine is formed from the decarboxylation of ornithine by ornithine decarboxylase, the rate-limiting step in polyamine biosynthesis (Figure 45-3). Spermine and spermidine are subsequently synthesized. Ornithine carboxylase is present in low concentrations in resting and nondividing tissues. However, both the enzyme and polyamine concentrations are high in rapidly proliferating tissue such as the small intestinal epithelium.[84] Polyamines appear to be essential for normal cell growth and differentiation. Polyamine content increases during all proliferative states in the small intestine such as adaptive hyperplasia, recovery from mucosal injury, lactation, and poststarvation refeeding.[85–88] Ornithine carboxylase elevation is one of the earliest cellular events occurring following transition of epithelial cells from quiescence to active proliferation.[89]

Polyamines are known to stimulate mucosal hyperplasia. Blocking polyamine synthesis by ornithine decarboxylase reduces adaptation.[90] Likewise, blocking polyamine degradation using aminoguanidine increases intestinal adaptation.[91] In addition to the trophic effects, polyamines also appear capable of inducing maturation of sucrase isomaltase synthesis and sodium/glucose transport, probably mediated by both transcriptional and post-transcriptional events.[92] Unfortunately, using polyamines to stimulate adaptation may be difficult because of their short half-life. *Saccharomyces boulardii* has been shown to synthesize polyamines and, as such, might serve as a potential source of therapeutic polyamines. However, administration of *S. boulardii* to rats was not successful in inducing adaptation following small-bowel resection.[93]

POTENTIAL APPLICATIONS OF ADAPTATION

Dietary manipulation of the adaptation process has a major role in the treatment of short-bowel syndrome. Certain nutrients appear to be more capable of stimulating adaptation than others (Table 45-2). Most data evaluating the importance of various nutrients on stimulating adaptation have been obtained from experimental models, primarily in rats. Complex diets induce greater adaptation than elemental diets. This is likely because they demand a greater functional workload for assimilation.[94] When specific dietary components are evaluated, however, it appears that hydrolyzed protein appears to be more capable of stimulating adaptation than intact protein.[95] Two studies have demonstrated that long-chain fats are more trophic than medium-chain fats to the small bowel.[96,97] High-fat diets also appear to reduce starvation-induced mucosal injury more rapidly than diets high in carbohydrate or protein.[98] A higher percentage of long-chain triglycerides in the form of essential fatty acids may be of benefit when compared with formulas deficient in essential fatty acids as essential fatty acid deficiency appears to impair the adaptation process.[99] Menhaden oil, a highly unsaturated fish oil containing a high percentage of eicosapentaenoic acid, appears much more trophic to the small bowel than other fats, including safflower oil or beef tallow.[100] The beneficial effects of menhaden oil do not appear to be related to enteroglucagon but are associated with a small but signifi-

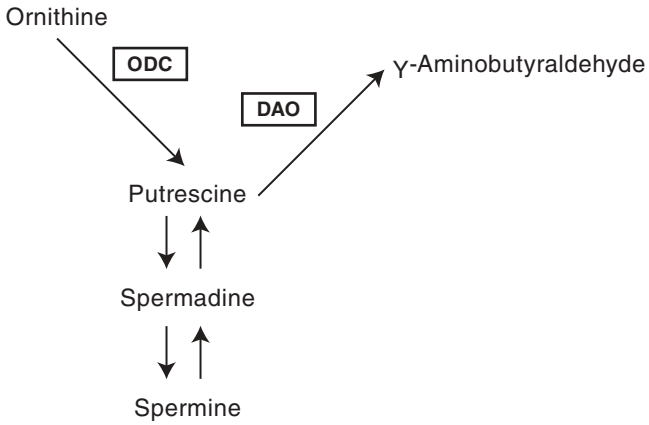

FIGURE 45-3 A diagram showing the synthesis and degradation of polyamines. DAO = diamine oxidase; ODC = ornithine decarboxylase.

TABLE 45-2 Nutrients That May Stimulate Adaptation More Than Others

Long-chain fats
Omega-3 fatty acids
Short-chain fatty acids
Fiber
Glutamine?

cant increase in peptide YY levels.[101] Other lipids may also be important in adaptation, including short-chain fatty acids. When added to parenteral nutrition solutions, atrophy is reduced. The addition of short-chain triglycerides to a chemically defined diet enhanced both jejunal and colonic adaptation compared with a control diet containing medium-chain triglycerides.[102] Mucosal atrophy associated with parenteral nutrition can likewise be reversed by administration of short-chain fatty acids.[103] Short-chain fatty acids may be useful to enhance intestinal adaptation following resection.[103]

Glutamine has received substantial interest in the treatment of a variety of gastrointestinal disorders primarily because of its apparent role in the nutrition of the small intestinal mucosa. Administration of glutamine reduces bacterial translocation in the small intestine and prevents mucosal atrophy in certain models. Intravenous glutamine also appears to have some trophic effect on the small intestine.[104] However, some studies have failed to demonstrate a trophic effect of glutamine even when used in pharmacologic concentrations.[105]

More recent evidence suggests that the use of glutamine and growth hormone may not be helpful in patients with short-bowel syndrome. The administration of glutamine and growth hormone in an experimental model appears to be effective in inducing adaptation but only when animals are maintained on parenteral nutrition and not given enteral feedings.[106] In another animal study, this time using supplemental enteral feedings, glutamine supplementation alone had no remarkable effects on bowel adaptation but appeared to enhance the supplemental beneficial effect of growth hormone.[107] However, in humans, growth hormone alone or in combination with glutamine with or without a low-fat diet demonstrated marginal, if any, benefit.[108] In a double-blind, placebo-controlled, crossover study in humans, no beneficial effects of oral glutamine and a high-carbohydrate, low-fat diet were observed.

Fiber may also enhance intestinal adaptation. Its effects are probably most important in the colon and are likely to be mediated through production of short-chain fatty acids. Pectin, when added to an elemental diet, improves adaptation in the jejunum, ileum, and colon following resection.[109–111]

COLONIC ADAPTATION

The colon also undergoes some adaptive changes following partial small-bowel or partial colon resection. If the right colon is removed, gradual improvement in sodium and water absorption occurs in the left colon.[112] In the rat, intestinal resection does not appear to alter absorption rates of sodium chloride and water in the cecum or colon, probably because of the large cecum present in the rat colon. Resection of the cecum in addition to massive small-bowel resection, however, results in a doubling of sodium and water absorption in the remaining colon. Growth of the cecum, therefore, appears to be an important compensatory mechanism in the rat following intestinal resection.[113]

The entire colon functionally adapts after small-bowel resection, but morphologic adaptation appears to occur only after massive resection of as much as 80%.[114] IGF-I appears to be important in colonic adaptation as well as small-bowel adaptation. IGF-I significantly enhances colonic mucosal growth and water absorption following resection and postresection up-regulation of colonic IGF-I mRNA. Alterations of the binding protein (BP) IGF-BP-3 and IGF-BP-4 mRNA expression have also been observed following small-bowel resection.[115] If a segment of colon is interposed into the small bowel, where it is exposed to higher concentration of undigested nutrients, some studies have even suggested that the colon is capable of assuming some small intestinal function. The exact extent of such adaptation, as well as whether it actually occurs, is controversial.[116] As in the small intestine, both glucose and glutamine can be used by colonic epithelial cells through the glycolysis pathway. However, the short-chain fatty acid butyrate can be used equally as well for fuel for colonocytes. Its oxidation does not appear to be adversely affected by either glucose or glutamine.[117] Fiber may therefore be an important fuel in short-bowel syndrome not only because of the trophic effect of short-chain fatty acids but also because of the importance of short-chain fatty acids for fuel for colonocytes.

CLINICAL MANAGEMENT

Parenteral Nutrition

Clinical management (Table 45-3) of patients with short-bowel syndrome is best considered in stages.[1,118–120] Initially, total parenteral nutrition is used for a short period of time to stabilize fluid and electrolyte status. The immediate postoperative period is characterized by a transient ileus, and all nutrients must be given parenterally. Patients then develop large-volume fluid and electrolyte secretions once the ileus resolves, and gastric fluid and ostomy losses may be high. Because these losses may vary significantly with time, placing the patient on a standard parenteral nutrition solution containing all appropriate macro- and micronutrients and normal concentrations of fluid and electrolytes for metabolic needs is often optimal. Excessive fluid losses from gastric tubes, gastrostomies, and diarrhea or ostomy fluid losses can then be replaced based on the electrolyte content of these secretions as determined in the laboratory. It is preferable to measure the volume of these secretions and replace them every 2 hours using a separate fluid and electrolyte solution. Losses tend to be high in sodium content, and solutions with at least 80 to 100 mEq/L of sodium are often required to maintain fluid

TABLE 45-3 Clinical Management of Short-Bowel Syndrome

Parenteral nutrition
Correct fluid and electrolyte losses
Replete nutritional deficiency states
Enteral nutrition
Slowly convert from parenteral to enteral nutrition
Use elemental diet containing adequate long-chain fats
Administer by continuous enteral infusion
Gradually increase enteral, decrease parenteral nutrition as tolerated
Dietary therapy
Reduce osmolality
High fat
High protein
Low carbohydrate
Provide macro- and micronutrients
Compensate for malabsorbed nutrients
Treat complications
Total parenteral nutrition liver disease
Push enteral feedings
Minimize infections and bacterial overgrowth
Bacterial overgrowth
Nutritional deficiency states
Monitor micronutrient, fat-soluble vitamin levels
Monitor success of therapy
Remember that not all supplements will be absorbed
In case of failure, consider transplantation or supplemental surgical procedures

and electrolyte homeostasis. As ostomy losses decrease, fluid replacement is reduced accordingly. The use of dual pumps, one for parenteral nutrition and the other for replacement solutions, may seem cumbersome, but a reduction in the wastage of parenteral nutrition solution and the reduced need for laboratory monitoring will compensate for the additional expense.

The first stage of therapy is also the time to replete any nutritional deficiency states that may have existed at the time of resection. In small infants, adequate nutritional therapy may have been delayed because of the transient ileus or poor gastrointestinal motility. Deficiencies in energy stores are not uncommon, and protein stores may be compromised as well. In older children, resection may have resulted from the preexistence of bowel disease, such as Crohn's disease, and unless preoperative management was optimal, a variety of macro- and micronutrients may well be deficient. Consequently, nutritional assessment and appropriate repletion of nutritional deficiencies remain an important early goal in the management of short-bowel syndrome.

Initiation of Enteral Nutrition

When fluid and electrolyte losses have decreased, a continuous enteral infusion is initiated. Most commonly, elemental diets are used in this setting.[121,122] Usually, these are started slowly, and the concentration is rapidly increased to 0.67 kcal/mL in infants or 1 kcal/mL in children and adults. Once this is done, the volume of enteral feedings can then be gradually increased as the volume of parenteral feedings is decreased. Initial advancement of concentration rather than rate of enteral feeding solution allows the transition from parenteral to enteral feeding to be conducted without overloading the patient with fluid.

Continuous enteral infusion is gradually advanced based on several parameters. A marked increase in stool loss by more than 50% is usually a contraindication to advancing enteral feedings. Likewise, stool losses greater than 40 to 50 mL/kg/day or ostomy output strongly positive for reducing substances suggests that enteral feedings should not be advanced. In patients with an intact colon, a decrease in stool pH below 5.5 is frequently indicative of carbohydrate malabsorption. Further advancement of enteral feedings is likely to result in a significant increase in osmotic diarrhea in such patients, and a delay in advancement is usually indicated.

The use of continuous enteral infusion in short-bowel syndrome is usually advantageous to the patient because feedings are frequently better tolerated in this fashion, permitting a greater percentage of total nutrition by the enteral route. Emesis is likewise reduced.[1] When continuous enteral infusion is used, carrier proteins are continuously saturated and intestinal function is optimized. The increased enteral calories also give one the opportunity to increase the functional workload of the small intestine, resulting in additional stimulation of intestinal adaptation. Administration of extra calories through the enteral route reduces the need for parenteral nutrition and thereby reduces the risk of parenteral nutrition liver disease, the major cause of morbidity and mortality in short-bowel syndrome.

Despite the inconvenience of enteral feeding, portable pumps and backpacks permit children with short-bowel syndrome to have reasonable mobility even if they are receiving their continuous enteral feedings 24 hours a day. Solids can also be initiated while patients are on continuous enteral feeding. If nasogastric tubes are in place, solids can be fed around the nasogastric tube without difficulty. Small bolus feedings are often tolerated well in these patients. Institution of solid feedings at the usual time and continued administration of small bolus feedings at least two or three times a day are important. They teach the infant how to suck and swallow and lessen the likelihood of feeding difficulties once tube feedings are discontinued.

The appropriate solids to give initially to patients with short-bowel syndrome are a matter of controversy. Tradition has suggested the use of high-carbohydrate diets. High-carbohydrate diets, however, are broken down rapidly to small molecules, creating an osmotic load in the small intestine and resulting in excessive fluid secretion. This is especially true in patients with ileal resections, in whom the jejunum is susceptible to fluid losses from osmotic overload. Feeding fats or proteins that are broken down to larger molecules and create less osmotic load results in less fluid loss. In addition, the role of fat as a trophic agent to the small intestine is another reason why the early introduction of fats is important. Recent data in experimental animals have demonstrated that (low-fat) diets actually result in reduced ability to transport lipids and that low-fat diets induce significantly lower final body weight in plasma lipids when compared with normal diets.[123] Consequently, patients may benefit from being given meat as their initial solid, and once some degree of tolerance has been achieved, the diet can

be expanded. Simple sugars, especially in high volumes or concentrations, should still be avoided because of the osmotic load.

Enteral Formulas

Patients with short-bowel syndrome are normally given elemental or chemically defined diets.[121,122,124] Truly elemental diets are not available for pediatric use. It is actually difficult to define what is meant by elemental diets. Normally, these are considered to be diets that contain amino acids rather than peptides. However, most protein is absorbed in the form of di- and tripeptides, so the concept of an elemental diet can probably be extended in pediatrics to the predigested partially elemental formulas known as extensive protein hydrolysates, available from several manufacturers. The most common protein source in North America is hydrolyzed casein. Carbohydrates are usually present from one or more sources, including partially hydrolyzed starch and disaccharides such as sucrose. A mixture of medium- and long-chain fats is included. Adult elemental formulas are usually inappropriate in pediatrics as they may be deficient in vitamins, minerals, and essential fatty acids. They also tend to be high in carbohydrate content and therefore are more likely to result in osmotic diarrhea. These formulas can be modified somewhat if a pure amino acid formula is desired or needed in infants because of protein allergy or intolerance. Addition of extra vitamins, minerals, and fats may permit their use in pediatrics with little difficulty.[122,124] In addition, increased fat content in pediatric formulations may be beneficial because of the stimulatory effect of fat on adaptation in the small intestine. Long-chain fats are more trophic to the small intestine than medium-chain fats (Figure 45-4). Furthermore, highly saturated fats derived from fish oil may prove to be even more effective in stimulating intestinal adaptation (Figure 45-5).

Commercially available protein hydrolysate formulas containing a mixture of medium- and long-chain fats are ideal for use in small infants with short-bowel syndrome. Examples include Alimentum (Ross, Columbus, OH) and Pregestimil (Mead Johnson, Evansville, IN). Both are relatively high in fat content, reducing the osmotic load in the small intestine. Both formulas contain substantial amounts of long-chain fats, important for their trophic effect. In older infants and toddlers, fiber-supplemented complex formulas may be instituted as they produce a firmer stool, and fiber, through its effect on short-chain fatty acid production, may also play a role in maximizing intestinal adaptation. (For enteral formulas, see the Appendix.) Newer formulas containing amino acids as a protein source and also a high percentage of fat are now available (Neocate, SHS; Elecare, Ross). Although they do not confer any absorption advantage, their added hypoallergenicity may be important, especially in small infants.

Advancing Enteral Nutrition

As parenteral nutrition is decreased and enteral nutrition is increased, intermittent parenteral nutrition can be used. The patient is given the parenteral portion of his nutrition over an 8- to 16-hour period each day. It is important to institute these changes in the hospital before the patient is discharged as intermittent parenteral nutrition improves the patient's freedom in the home and makes care much easier.[121,125–127] In small infants, parenteral nutrition may be required for the greater part of the 24-hour day, but soon the interval "off" parenteral nutrition can gradually be increased as the patient's tolerance of enteral calories increases with age. This is often a gradual change, taking several months to years. As tolerance improves, the rate of enteral administration is increased, and the duration of parenteral nutrition is decreased until the patient can be taken off parenteral nutrition for one or more nights per week. Changes should be

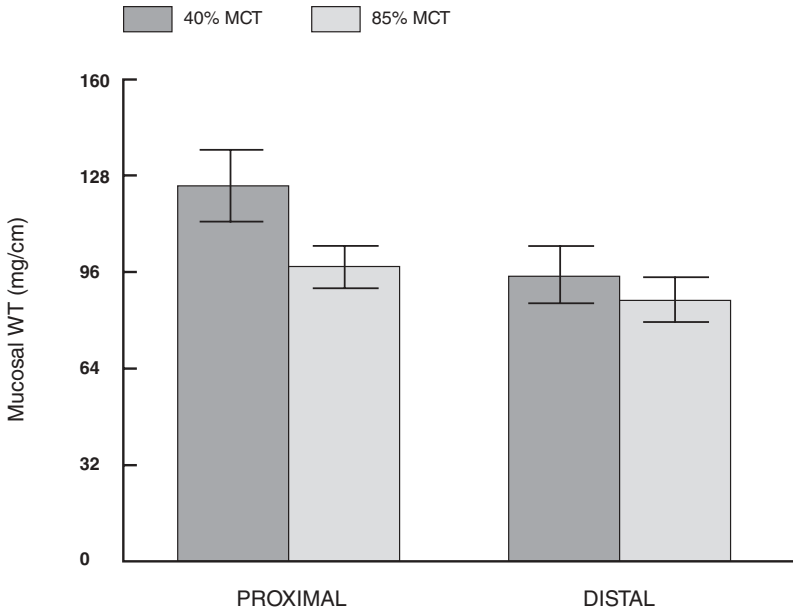

FIGURE 45-4 Mucosal weight in rats fed diets containing either 40% or 85% of their total lipid concentration as medium-chain triglycerides (MCT) for 3 weeks following 85% jejunoileal resection.

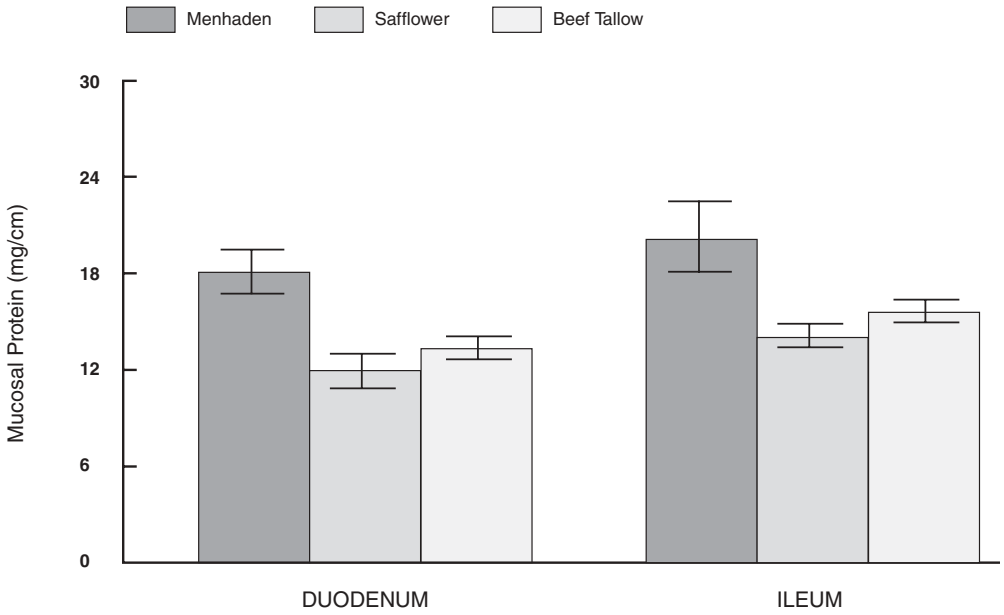

FIGURE 45-5 Mucosal protein concentration in rats fed menhaden oil, safflower oil, or beef tallow for 3 weeks following 85% jejunoileal resection.

isocaloric as the caloric density of the parenteral and enteral solutions may differ. Caloric changes are gradually increased, based on the child's growth needs, to ensure that the child parallels the 50th percentile for both height and weight. Excessive caloric administration is often a problem at this stage of management as the child is incapable of regulating his/her own nutrient intake. The physician must carefully monitor the child's growth to make certain that the patient's weight gain is appropriate for length.

Fluid losses are often substantial during early stages of short-bowel syndrome management. Ostomy output may have sodium concentrations of 80 to 100 mEq/L. The enteral diets may be diluted with oral electrolyte solution and the rate of administration increased accordingly to replace these losses and simplify patient management as well as improve absorption.[128] In the absence of small-bowel bacterial overgrowth, the antimotility agents, such as loperamide, may occasionally be useful in slowing intestinal transit and increasing fluid and nutrient retention. Long-acting release intramuscular octreotide has also been shown to be efficacious in this situation but is not commonly used.[129]

Early in the course of therapy, preparations for home parenteral nutrition should be made. Home parenteral nutrition reduces the cost of long-term management in patients with short-bowel syndrome and decreases family stresses and nosocomial infections. It has now become the standard of care in patients with short-bowel syndrome, and prolonged hospitalizations are rarely necessary, except for complications that may arise.

CHRONIC COMPLICATIONS

Managing the many chronic complications in short-bowel syndrome is difficult. Many of these complications result from parenteral nutrition, such as catheter-related problems, sepsis, and total parenteral nutrition liver disease. Others, such as bacterial overgrowth and micronutrient deficiency, may be more problematic after parenteral nutrition has been discontinued.

Bacterial Overgrowth

One of the least-recognized complications of short-bowel syndrome, but also one of the most treatable, is bacterial overgrowth. Bacterial overgrowth is considered to occur when bacterial content increases in the small intestine above normal levels.[130] Normal bacterial counts vary from 10^3 proximally to much higher concentrations in the distal small intestine. Gastric acid and bile normally limit the number of bacteria that can successfully colonize the small intestine. Bacteria are normally eliminated from the small intestine through a combination of antegrade peristalsis and mucosal immune factors. However, in short-bowel syndrome, many of these factors are disrupted. Anatomy may be abnormal, and motility is frequently impaired. Bacterial content of the proximal small intestine uncommonly exceeds 10^5. When motility is slowed, the bowel is dilated, and the ileocecal valve is absent, one can predict that bacterial overgrowth is present. Reduction in gut-associated lymphoid tissue following resection may also impair the immune response in short-bowel syndrome.[3]

Most commonly, the bacteria present are facultative organisms and a variety of anaerobic bacteria. These bacteria deconjugate bile salts, and this results in rapid reabsorption of bile acids, which depletes the bile salt pool. Micellar solubilization is therefore incomplete, and steatorrhea and malabsorption of fat-soluble vitamins result. Bacterial overgrowth also results in mucosal inflammation, which can impair adaptation and further exacerbate nutrient malabsorption. Additionally, bacterial over-

growth may compete with the host for vitamin B_{12} and perhaps other nutrients. Bacterial overgrowth symptoms include bloating, cramps, diarrhea, or gastrointestinal blood loss. When these symptoms are observed in patients with seemingly adequate gut length, bacterial overgrowth should be considered in the differential diagnosis. Bacterial overgrowth should also be considered when previously stable patients with short-bowel syndrome begin to deteriorate or lose weight.

Diagnosis of bacterial overgrowth, by definition, is based on the demonstration of increased bacterial content in the small intestine. This is usually assessed by aspiration of the small intestine and culture of the fluid. However, these techniques are often cumbersome, difficult to perform, and unreliable. Consequently, screening for bacterial overgrowth is helpful and, today, is most commonly performed through the use of breath hydrogen determination. Markedly elevated fasting breath hydrogen levels or a rapid rise in breath hydrogen following oral administration of glucose (2 g/kg up to a maximum of 50 g) suggests bacterial overgrowth. If the patient has rapid transit through the small intestine, rapid entry of the malabsorbed glucose into the colon may falsely elevate breath hydrogen content. Additional screening studies that are useful include urine indican and serum D-lactate. Small-bowel biopsies demonstrating inflammatory changes with no other apparent cause often suggest bacterial overgrowth. This occurs especially when the small intestine is dilated, motility is poor, or partial obstruction is present.

Additional complications of bacterial overgrowth include D-lactic acidosis and small-bowel colitis. D-Lactic acidosis results because bacteria are capable of producing both D- and L-lactate, but humans metabolize only D-lactate poorly. Lactic acid is produced in both forms from the malabsorbed carbohydrate, and D-lactate accumulates in the blood, resulting in neurologic symptoms varying from disorientation to frank coma.[131,132] Bacterial overgrowth also causes colitis or ileitis. Large ulcerations similar to Crohn's disease may be present. No granulomas are identified, however.[133] Arthritis or other rheumatologic symptoms occasionally occur in these patients, suggesting that the disorder may be immune complex related, possibly to absorbed bacterial antigens.[134,135] Occasionally, this complication responds to antimicrobial therapy, although sulfasalazine or more aggressive immunosuppression is often required. A short course of corticosteroids may produce marked improvement in patients with enterocolitis induced by small bowel bacterial overgrowth.

Treatment for bacterial overgrowth should be initiated with broad-spectrum antibiotics. These are initially given intermittently, usually the first 5 days of each month (Table 45-4). Oral metronidazole, 20 mg/kg/day, either alone or in combination with trimethoprim/sulfamethoxazole, is frequently effective. Oral gentamicin may also be used. It is minimally absorbed and well tolerated. Several other combinations are also helpful. Refractory patients may require continuous antibiotic therapy, and in this event, antibiotics may be rotated periodically to prevent overgrowth with resistant organisms. Need for rotation is variable but is often necessary every 2 to 3 months.

In some children, absence of an ileocecal valve results in severe overgrowth in the distal small intestine. This complication increases as children age, are capable of controlling their bowel movements, and attempt to defecate less frequently. Voluntary defecation several times a day can be encouraged in such patients, and clinical improvement may result. If not, daily saline enemas or, occasionally, enteral lavage with polyethylene glycol solutions are required to reduce bacterial content. Antimotility agents such as loperamide may exacerbate bacterial overgrowth and may be contraindicated for patients in whom gastrointestinal motility is already delayed. In the absence of bacterial overgrowth, such agents may be helpful in improving nutrient contact with the mucosa and may actually improve absorption.

Watery Diarrhea

Excessive fluid secretion frequently occurs in short-bowel syndrome. Often, it is simply a matter of excessive osmotic fluid load in the small intestine, usually as a result of excessive carbohydrate administration. This complication occurs more frequently with bolus than with continuous enteral feeding. Elevated serum gastrin levels, which are often present in patients with short-bowel syndrome, may occasionally result in secretory diarrhea and may respond to histamine$_2$ receptor antagonists. This form of therapy is usually disappointing, and, in our experience, this complication is rare. Somatostatin analogs have been used in a limited number of short-bowel patients with secretory diarrhea, with varying results.[135–137] Subjects often improve initially, but the favorable response is usually transient.[138] Cholestyramine is sometimes helpful in short-bowel syndrome with watery diarrhea. Cholestyramine binds bile acids, and as bile acid concentrations are increased in the colon following ileal resection owing to bile acid malabsorption, secretory diarrhea may occur. However, in the case of massive ileal resection, patients may have bile acid deficiency, which may be exacerbated by cholestyramine through binding of the few available bile salts left to facilitate fat absorption (Table 45-5).

Nutritional Deficiency States

Once patients are free of parenteral nutrition, they are subject to a wide variety of nutritional deficiency states.

TABLE 45-4 Treatment for Bacterial Overgrowth

Antibiotics
Intermittent
Continuous cyclical
Surgery
Tapering
Lengthening
Prevention of colonic stasis
Frequent bowel movements
Saline enemas
Enteral lavage

The compromised intestinal function becomes a major problem in ensuring adequate nutrient stores. Usually, macronutrients such as carbohydrates, fats, and proteins can be absorbed in adequate quantities. Micronutrients, including trace minerals and vitamins, are often less well absorbed and are more likely to become deficient. Malabsorption of fat-soluble vitamins, especially A, D, and E, is common. Trace metal deficiencies are likely to occur, with iron and zinc being most common. A low serum zinc level, especially in association with a low serum alkaline phosphatase, suggests zinc deficiency. Zinc deficiency may result in poor growth as well as impaired intestinal adaptation. The typical clinical picture may include acrodermatitis enteropathica, with crusting rash around the eyes, nose, mouth, and anus and loss of hair. Both zinc and serum alkaline phosphatase levels are commonly low, and the syndrome usually responds to supplemental oral zinc.[139] Selenium absorption may also be impaired.[140] Low serum levels of calcium and magnesium are also frequently observed. Extra vitamin D and calcium may correct the calcium deficiency, but magnesium deficiency is more difficult to treat. Enterally administered magnesium salts often result in osmotic diarrhea, although some magnesium salts are better tolerated than others.[141]

Evidence of bony demineralization radiographically merits careful attention to vitamin D status as well as appropriate calcium and phosphorus administration, remembering that significant malabsorption of all vitamins and minerals is likely and that, occasionally, enteral repletion of all of these nutrients may be difficult, if not impossible. Occasionally, the supplemental parenteral vitamins, minerals, micronutrients, and even fluid may be required even if the patient is able to absorb enough calories and protein to meet growth needs.

The ileum is solely responsible for bile acid and vitamin B_{12} absorption, and following ileal resection, patients should be monitored carefully for vitamin B_{12} deficiency. Parenteral administration of vitamin B_{12} may be required every 1 to 3 months. Vitamin B_{12} deficiency may take years to develop, and periodic attention to this possibility is required.

Parenteral Nutrition Liver Disease

The major cause of death in children with short-bowel syndrome is parenteral nutrition liver disease. This disorder is common in children receiving long-term parenteral nutrition. The incidence increases in inverse proportion to age; therefore, it is more common in small infants.[2–4,6] There is much argument about how parenteral nutrition induces liver injury. Toxicity of amino acids, competition of amino acids with bile acids for transport across the canalicular membrane, production of toxins in the underused bowel, excess nutrient administration, toxic substances in parenteral nutrition solutions, and nonstimulation of gastrointestinal hormones that normally control biliary secretions have all been postulated. However, aggressive use of enteral feedings, in the hope of ensuring at least 20 to 30% of the total daily caloric intake through the enteral route, prevention of bacterial overgrowth in the small intestine, and reduction in catheter-related sepsis all appear to be helpful in reducing the risk of parenteral nutrition liver disease (Table 45-6). The newer parenteral nutrition solutions, especially designed for infants, are less likely to produce liver disease.

TABLE 45-5 Effects of Bile Salt Malabsorption

Mild
Secretory diarrhea
Severe
Fat malabsorption
Loss of calories
Loss of fat-soluble vitamins

Biliary disease may also occur in children on parenteral nutrition.[142] Twenty percent of infants receiving parenteral nutrition may develop cholelithiasis. This appears to be a multifactorial problem resulting from a combination of malabsorbed bile acids, altered bilirubin metabolism, and gallbladder stasis. In some centers, early cholecystectomy is advocated for patients on long-term parenteral nutrition.[142]

Catheter-Related Complications

Complications related to chronic indwelling central venous catheters occur frequently in patients with short-bowel syndrome.[143] In one series, central venous catheter replacement was needed a mean of every 200 days, with septic episodes typically occurring more frequently than once per year. Complications appear to be higher in infants less than 1 year of age. Catheter thrombosis is also a common problem. Central venous catheter infections appear to result from either poor catheter care or bacterial overgrowth, with subsequent seeding of the catheter from the blood with gut bacteria. Most catheter infections in children appear to be related to poor catheter care, even when the infections are caused by enteric organisms. A careful analysis of catheter techniques should always be the first step in evaluating patients with frequent central venous catheter infections.

SURGICAL ALTERNATIVES

Patients with short-bowel syndrome, especially those with bacterial overgrowth, may have anastomotic strictures. Further resection of an already shortened small intestine may be avoided by using a tapering enteroplasty, stricturoplasty, or serosal patching.[144] Bacterial overgrowth may be reduced through such procedures, and normal flow of luminal contents through the small intestine may resume. Occasionally, dramatic clinical improvement will occur following such procedures, especially if bacterial overgrowth has been clearly demonstrated.

Several procedures have been designed to slow intestinal transit.[145–150] These include reverse segments of small bowel or colon interposed to slow delivery of nutrients through the small intestine and creation of valves that produce a partial obstruction to disrupt the normal flow of contents through the small intestine. Unfortunately, these

TABLE 45-6 Prevention of Total Parenteral Nutrition Liver Disease

Aggressive use of enteral feedings
Prevention of catheter sepsis
Prevention of bacterial overgrowth

procedures produce an increase in bacterial overgrowth. They are usually contraindicated in patients with preexisting bacterial overgrowth, in which case, they will do more harm than good. It is unlikely that they will be of much benefit in children with short-bowel syndrome.

Increasing the length of the small intestine through the use of the intestinal lengthening or Bianchi procedure is helpful in a subgroup of patients with short-bowel syndrome.[151–157] In this procedure, the bowel is transected longitudinally, preserving the blood supply to both sides of the small intestine. A segment of bowel is thereby created that is twice the length and half the diameter of the original segment. The procedure should be performed only if the small intestine is dilated. It allows reduction of the diameter of the dilated bowel without loss of surface area and consequently reduces bacterial overgrowth. It should be considered primarily as a means of reducing bacterial overgrowth without loss of intestinal surface area. However, through progressive dilatation, an eventual increase in absorptive surface area results. In one series of 13 pediatric patients, marked improvement in absorptive capacity as measured by decreased parenteral nutrition and fluid requirements was achieved in most.[158] Although the procedure is successful only in the jejunum and the ileum, attachment of the antimesenteric side of the small intestine to the liver or abdominal wall may be performed. Vasculature will then grow into the bowel from the surface, and the small intestine can be divided laterally. This has been partially successful in at least one patient.[159]

Advances in parenteral nutrition and long-term management have made it possible for some children with under 15 cm of small intestine to survive and to eventually become independent of parenteral nutrition. Although the presence of an ileocecal valve markedly improves prognosis, some of these children have survived massive resection and adapted well, even in the absence of an ileocecal valve. As a general rule, patients with greater than 25 cm of small intestine at the time of neonatal resection who have an ileocecal valve or those with greater than 40 cm of small intestine at the time of neonatal resection who do not have an ileocecal valve have a reasonably good prognosis. In such instances, it is at least possible that the patient could eventually become independent of parenteral nutrition.[2–4,6,160] However, these numbers apply only to patients resected in the neonatal period, probably because substantial linear growth in the small intestine occurs during the first few months of life. Application of these numbers to older children results in excessive optimism. Ultimately, predicting the outcome in patients following a massive resection is difficult.[153–161] A recent multivaried analysis suggested that only residual small-bowel length was a significant predictor of the duration of parenteral nutrition in short-bowel syndrome. However, the study suggested that the use of breast milk or amino acid–based formulas might also play a role in accelerating adaptation.[162] The beneficial effects of amino acid formulas suggested the possibility that allergic inflammatory changes might play a role in prolonging the need for parenteral nutrition in some short-bowel patients.

Despite aggressive treatment of bacterial overgrowth, aggressive enteral feeding to stimulate adaptation, and the appropriate use of intestinal lengthening procedures and other forms of surgical therapy, many patients will never become independent of parenteral nutrition. If a resection is performed in a neonate, and that patient is still dependent on parenteral nutrition beyond 4 or 5 years of age, ultimate success without parenteral nutrition is unlikely. Parenteral nutrition is expensive, averaging about $100,000/year and frequently costing much more.

TRANSPLANTATION

To date, several hundred bowel transplantations have been performed, predominantly combined liver/bowel transplantations and isolated intestinal transplantations,[163–168] Presently, post-transplantation 1- to 2-year survival is better than 70%, with intestinal graft survival long term slightly better than 50%. Infection appears to be a greater problem in patients with small-bowel transplantation than in those with liver transplantation and is especially common in patients with combined liver/bowel transplantation. Apparently, the breakdown of the intestinal mucosal barrier during episodes of allograft dysfunction and rejection contributes to the recurring infection problem. Translocation of bacteria and fungi into the bloodstream is likely to remain a significant problem.

The key to success with intestinal transplantation appears to be aggressive immunosuppression. However, increased need for immunosuppression raises concern about the development of post-transplantation lymphoproliferative syndrome. This malignancy is related to the Epstein-Barr virus and is a significant problem following intestinal transplantation. It may respond to a reduction or cessation of immunosuppression, but loss of the graft is common following a reduction in immunosuppression.

The value of intestinal transplantation is now more defined. Intestinal transplantation is now considered appropriate for a subset of children with intestinal failure who remain dependent on parenteral nutrition and are likely to develop life-threatening complications arising from this therapy. Such life-threatening complications include parenteral nutrition–associated liver disease, recurrent sepsis, and threatened loss of central venous access.[169] Concern persists regarding post-transplantation lymphoproliferative syndrome, late-onset complications including rejection and other malignancies, and infectious complications. Greater experience should be sought before recommending this procedure for patients who are otherwise stable on parenteral nutrition (Table 45-7). The combined liver/bowel transplantation appears to be a potential option in patients with irreversible total parenteral nutri-

TABLE 45-7 Problems to Overcome in Intestinal Transplantation

Early diagnosis of rejection
Determining appropriate immunosuppression
Controlling sepsis
Preventing lymphoproliferative disease
Controlling graft-versus-host disease

tion liver disease, and because of donor shortage, patients should be referred for transplantation once liver disease is considered irreversible. Preliminary experience suggests that isolated intestinal transplantation may have a more benign course and should probably be considered as a possibility at the early onset of liver disease to avoid a combined liver/bowel transplantation.

In children with intestinal failure associated with short-bowel syndrome and complicated by liver failure from parenteral nutrition, isolated orthotopic liver transplantation may occasionally be indicated.[170] This should be considered only in carefully selected children who have developed parenteral nutrition–induced liver disease who have not had an adequate trial of aggressive attempts to adapt to enteral feeding and who appear to have an adequate length of remaining small intestine without underlying bowel disease. Here, isolated orthotopic liver transplantation may be performed and followed by aggressive use of enteral nutrition to induce adaptation in the remaining gut. A recent report has suggested that a majority of such patients can be successfully weaned from parenteral nutrition without recurrence of the liver injury. This, therefore, avoids the much greater risk of complications associated with intestinal transplantation relative to isolated liver transplantation. In adults, a few cases of isolated ileal segment transplantation have been reported with what appears to be a reduced risk of rejection. However, ethical considerations have limited the usefulness of these patients and should probably not be attempted in children.[171]

With aggressive nutritional therapy, most patients with short-bowel syndrome do well. Careful attention to detail and monitoring for nutritional deficiency states and bacterial overgrowth are important factors in success. Surgical procedures, such as intestinal lengthening procedures, are helpful in a few patients, and in those for whom no other option exists, intestinal transplantation may offer a viable long-term alternative. Therefore, short-bowel syndrome should not be considered a fatal disorder as once was the case.

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CHAPTER 46

THE CRITICALLY ILL CHILD

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Critical illness and surgical intervention in the pediatric patient are associated with a set of metabolic changes that are profound yet predictable. Over a half century ago, Sir David Cuthbertson described the fundamental aspects of this metabolic response to injury in the adult.[1] Research regarding the pediatric stress response has shown that although neonates and children share similar qualitative metabolic sequelae to illness with adults, significant quantitative differences exist.

An understanding of the metabolic events that accompany critical illness and surgery of the child is the first step in implementing adequate nutritional support. The goal of nutritional support therapy in this setting is to augment the short-term benefits of the pediatric stress response while minimizing the long-term harmful consequences. Ultimately, an individualized determination of nutrient requirements must be made to provide appropriate nutrients.

METABOLIC RESPONSE TO CRITICAL ILLNESS: AN OVERVIEW

Children, similar to adults, rely on the metabolic breakdown and transfer of protein, carbohydrates, and lipid to meet the catabolic demands of critical illness. Figure 46-1 illustrates the basic pathways involved in the pediatric metabolic response. In general, the metabolic stress response is characterized by an increase in net muscle protein degradation and enhanced movement of the free amino acid products through the circulation. These amino acids serve as the building blocks for rapid synthesis of proteins that act as inflammatory mediators for tissue repair and the inflammatory response. Remaining amino acids not used in this way are channeled through the liver, where their carbon skeletons are used to create glucose through gluconeogenesis. Although the catabolism of muscle protein is an effective short-term adaptation for the child, it is of limited duration and potentially damaging owing to reduced body stores.

Carbohydrate and lipid turnover is also increased several fold during the pediatric metabolic response. Although these metabolic alterations would be expected to increase overall energy requirements, recent data show that any increase is variable and far less than originally proposed. Overall, the energy needs of the critically ill child are governed by the severity and persistence of the underlying illness.

Finally, a unique hormonal and cytokine profile is found in the child with critical illness. Such patients demonstrate an elevation in serum levels of insulin, the catabolic hormones (glucagons, cortisol, catecholamines), and specific cytokines known to interact with the inflammatory process. Current research in this field is focused on ways to manipulate these hormonal and cytokine alterations to minimize the deleterious consequences induced by the stress response itself.

BODY COMPOSITION AND METABOLIC RESERVES

Table 46-1 outlines the macronutrient metabolic reserves of the neonate, child, and adult patient in terms of the percentage of total body weight.[2–4] The most striking difference in body composition between the adult and child is the quantity of protein in reserve and available at times of illness. As a percentage of body weight, the protein stores of adults are nearly twice those of the neonate. In contrast, carbohydrate stores remain constant and do not afford significant reserve at any age. Lipid concentrations are low at birth and increase gradually during development; premature infants have even lower proportions of stored lipid at birth.

In addition to the reduced macronutrient reserves in the child, both neonates and children have much higher baseline requirements. The resting energy expenditure for neonates is up to three times that for adults when standardized for weight.[5,6] This inverse relationship between energy expenditure and body weight is constant throughout mammalian species and is partially related to body surface area. The recommended protein and energy requirements of the healthy neonate, child, and adult can be found in Appendix 2. The protein requirements of the full-term neonate are nearly three times that of the adult. Moreover, premature neonates require a minimum of 2.8 g/kg/day of protein to maintain growth rates similar to those in utero, and this is 3.5 times the requirement for protein balance in the adult.[7] Thus, the critically ill child

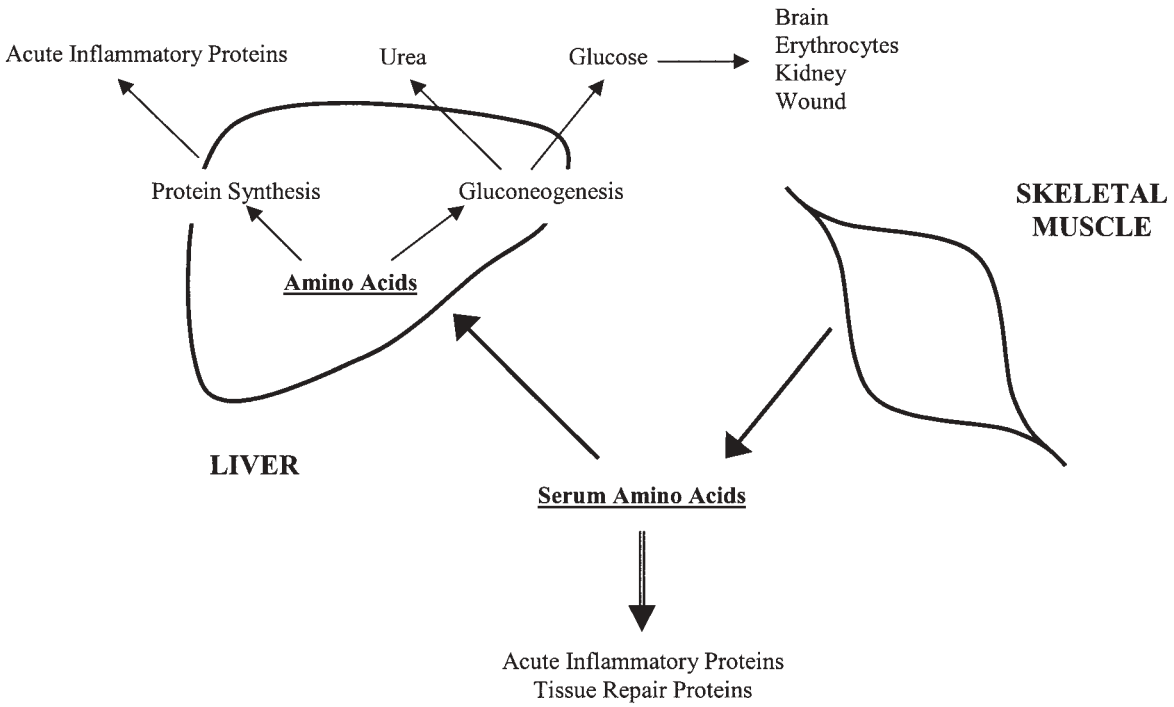

FIGURE 46-1 Illustration of the basic pathways in the metabolic response to critical illness.

has the potential to be much more susceptible to the harmful effects of protracted catabolic stress, and the prompt implementation of adequate nutritional support must be a priority in the patient's care.

NUTRIENT METABOLISM

Protein Metabolism

Amino acids are the key building blocks required for growth and tissue repair. The vast majority (98%) are found in existing proteins, with the remainder residing in the free amino acid pool. Proteins themselves are not static as they are continually degraded and synthesized in the process of protein turnover. The reuse of amino acids released by protein breakdown is extensive; protein turnover contributes more than two times the amino acids derived from protein intake. As a reference, healthy newborns have a protein turnover of approximately 6.7 g/kg/day, and adults have a protein turnover of approximately 3.5 g/kg/day.[8] An advantage of high protein turnover is that a continuous flow of amino acids is available for synthesis of new proteins. In this way, maximal physiologic adaptability is present at times of injury or illness.

TABLE 46-1 Body Composition of Neonates, Children, and Nonobese Adults as a Percentage of Total Body Weight

Age	*Percent Protein*	*Percent Fat*	*Percent Carbohydrate*
Neonates	11	14	0.4
Children (age 10 yr)	15	17	0.4
Adults	18	19	0.4

In the metabolically stressed patient, such as adults with severe burn injury or children with significant cardiorespiratory failure requiring extracorporeal membrane oxygenation (ECMO), protein turnover is double that of normal subjects.[9,10] Specifically, this process involves a redistribution of amino acids from skeletal muscle to the liver, wound, and other tissues taking part in the inflammatory response. The mediators of the inflammatory response—enzymes, serum proteins, and glucose (via gluconeogenesis)—are thus synthesized. Evidence for this process can be seen in the serum by the marked increase in hepatically derived acute-phase reactants (C-reactive protein, fibrinogen, α_1-antitrypsin, α_1-acid glycoprotein) and the reduction in transport proteins such as albumin and retinol binding protein.

Importantly, although children with critical illness have increases in both whole-body protein degradation and whole-body protein synthesis, it is the former that predominates during the stress response. Thus, these patients manifest net negative protein and nitrogen balance. Clinically significant negative protein balance is characterized by skeletal muscle wasting, weight loss, and immune dysfunction.[11]

Apart from the need for acute-phase protein production in the inflammatory response, another driving force for increased protein catabolism is the obligate production of glucose from amino acids through the process of gluconeogenesis. This process is essential as glucose is the preferred substrate for the brain, erythrocyte, and renal medulla and

is a versatile energy source for tissues involved in the inflammatory response. In this process, free alanine and glutamine are first produced by muscle protein degradation. These amino acids are then transported to the liver for glucose production. Alanine, through deamination to pyruvate, contributes a three-carbon unit toward gluconeogenesis, in the glucose-alanine cycle.[12] Glutamine is first converted to alanine in the intestinal mucosa and then transported through the portal vein to the liver, to be used in glucose production. Whereas in fasting subjects, alanine and glutamine account for over 60% of total amino acids released from muscle, this ratio is further accentuated in critical illness. From neonates to adults, increased gluconeogenesis is known to occur during illness and injury. On a per kilogram basis, this process is particularly prominent in patients with low body weight, presumably because of an elevated brain-to-body weight ratio and hence an increased requirement for glucose as an energy source.[13]

Because hepatic gluconeogenesis incorporates deamination of these amino acids to cleave the carbon skeleton, the ammonia moiety by-product is detoxified by the liver through the urea cycle. Urea is thus generated as a soluble and relatively nontoxic metabolite that can be safely excreted in the urine. In addition, glycolysis is often initiated for energy production given the anaerobic environment of injured tissue. Although this process is exceedingly inefficient compared to the aerobic oxidation of glucose, its end product, lactate, can eventually be reduced to pyruvate and shunted back into gluconeogenesis via the Cori cycle.

Although the catabolism of muscle protein to generate glucose and inflammatory response proteins is an excellent short-term adaptation, it is ultimately limited because of the reduced protein stores available in children and neonates. Interestingly, the provision of dietary glucose alone is ineffective in reducing the endogenous glucose production via gluconeogenesis in the metabolically stressed state.[14] Therefore, without elimination of the inciting stress for catabolism (ie, the critical illness or injury), the progressive breakdown of muscle leads to untoward consequences. Loss of diaphragmatic and intercostal muscle mass leads to respiratory compromise, and the subsequent loss of cardiac muscle predisposes to fatal arrhythmia. Fortunately, the provision of amino acid nutritional supplementation has been shown to improve overall protein balance in the premature neonate.[15,16] The mechanism for this change appears to be an increase in protein synthesis, whereas the rate of protein degradation remains constant.[17]

As expected, the amount of protein required to optimally enhance protein accretion is higher in critically ill than in healthy children. Infants demonstrate 25% higher protein degradation after surgery, a 100% increase in urinary nitrogen excretion with bacterial sepsis, and a 100% increase in net protein breakdown while on ECMO.[9,17] Children under treatment for cancer have also been shown to have increased net protein breakdown.[18]

The provision of dietary protein sufficient to optimize protein synthesis, facilitate wound healing and the inflammatory response, and preserve skeletal muscle protein mass is the single most important nutritional intervention in critically ill children. The quantities of protein recommended for critically ill neonates and children are outlined in Table 46-2.[9] Certain severely stressed states, such as significant burn injury or patients requiring ECMO, may require additional protein supplementation to meet metabolic demands. Hence, growth rates and other indices for protein accretion (ie, prealbumin levels) must be monitored closely in chronically ill patients. Excessive protein administration should be avoided as toxicity has been documented, particularly in children with marginal renal and hepatic function. Studies using protein allotments of 6 g/kg/day have found toxicity in neonates as demonstrated by azotemia, pyrexia, strabismus, and a lower IQ score.[19,20]

Although the precise amino acid composition to best increase whole-body protein balance has yet to be fully determined, stable isotope techniques now exist to study this issue.[21–23] Neonates, in particular, have immature biosynthetic pathways that may alter their ability to synthesize specific amino acids. For example, histidine is a conditionally essential amino acid until 6 months of age, and data suggest that biosynthetic pathways for cysteine, taurine, and proline may be of limited capacity in the premature neonate.[21–25] These immature amino acid pathways may have clinical relevance. Given that cysteine is essential for the production of the antioxidant glutathione, our laboratory has demonstrated that, in very low birth weight neonates, glutathione concentrations in erythrocytes are only 30 to 40% of that in normal infants (unpublished data). In addition, proline demand has been shown to increase significantly in patients with severe burns.[10] Therefore, it is likely that specific disease states may accentuate specific amino acid requirements, and further research is needed to determine optimal dietary protein supplementation for such conditions.

Energy Metabolism

During critical illness, increases in the metabolic turnover of protein, carbohydrate, and lipid provide an increased basal energy requirement for the pediatric patient. However, the question of whether total energy expenditure is actually increased in this cohort has drawn much interest. The question is important as the caloric provision for the critically ill child has significant consequences. For example, protein retention can be optimized by an adequate caloric allotment, and this is particularly true when protein intake is marginal.[26] Conversely, the dietary provision of excess calories from glucose results in an increased production of CO_2, with no change in loss of lean body mass.[27,28] Recent data have also shown a possible paradoxical increase in net protein degradation from excess carbo-

TABLE 46-2 Estimated Protein Requirements for Injured Children of Various Age Groups

Age (yr)	*Estimated Protein Requirement (g/kg/d)*
0–2	2.0–3.0
2–13	1.5–2.0
13–18	1.5

hydrate intake.[29] Therefore, a careful appraisal of energy requirements in the critically ill pediatric patient is required as both underestimates and overestimates can lead to injurious results.

Resting energy expenditure can be measured using direct or indirect methods. The direct method measures the heat released by a subject at rest and is based on the principle that all energy is eventually converted to heat. In practice, the patient is placed in a thermally isolated chamber, and the heat dissipated is measured for a given period of time.[30] Although precise, this method is not practical for most pediatric or critically ill patients. The indirect methods estimate energy production based on quantities of O_2 consumption or CO_2 production by the whole body during a specific time interval. The classic indirect method, indirect calorimetry, measures V_{O2} (the volume of oxygen consumed) and V_{CO2} (the volume of CO_2 produced) and uses a correlation factor based on urinary nitrogen excretion to calculate the overall rate of energy production.[31] This method uses the metabolic cart, a leak-free system with a computer-controlled gas exchange measurement device as well as 24-hour urine collection. Indirect calorimetry provides a measurement of the overall respiratory quotient (RQ), defined as the ratio of CO_2 produced to O_2 consumed, for a given patient. However, this method is not accurate in subjects with uncuffed endotracheal tubes or on an ECMO circuit. Newer techniques using stable isotopes to measure energy expenditure are now well validated and in use. Using ^{13}C-labeled bicarbonate and doubly labeled water ($^2H_2{}^{18}O$), studies in pediatric surgical patients have accurately measured total energy expenditure.[9,32] These techniques have been shown to correlate well with the gold standard of indirect calorimetry and have been used to measure energy expenditure of critically ill neonates in a variety of settings.[33]

Using these techniques to measure energy expenditure, it has become apparent that the severity and duration of the critical illness govern the energy needs of the ill child. In general, any increase in energy expenditure during illness or after operation is variable, and recent studies suggest that the increase is far less than originally hypothesized. In children with severe burns, the initial resting energy expenditure during the flow phase of injury is increased by 50% but then returns to normal during convalescence.[34] In neonates with bronchopulmonary dysplasia, in which the illness increases the patient's work of breathing, a 25% elevation in energy requirement is evident.[35] Newborns undergoing major surgery have only a transient 20% increase in energy expenditure that returns to baseline values within 12 hours postoperatively provided that no major complications develop.[36,37] Stable, extubated neonates 5 days after operation have been shown to have resting energy expenditures comparable to normal infants.[38] Effective anesthetic and analgesic management may play a significant role in muting the stress response of the neonate; studies have demonstrated no discernable increase in resting energy expenditure in neonates undergoing patent ductus arteriosus ligation who receive intraoperative fentanyl anesthesia and postoperative intravenous analgesic regimens.[37] Finally, by using stable isotopic methods, we have found that the mean energy expenditures of critically ill neonates on ECMO are nearly identical to age- and diet-matched nonstressed controls.[39] There was, however, a greater variability in energy expenditure among the critically ill cohort in this study. The one exception to this pattern may be children with head injury who have been shown to demonstrate a variable elevation in energy expenditure, presumably secondary to a marked rise in serum catecholamines.[40]

These studies suggest that critically ill neonates have only a small and perhaps negligible increase in energy expenditure. How can this be explained in the presence of a corresponding increase in illness-induced metabolic turnover of nutrients? Total energy requirement for all patients includes resting energy expenditure, energy allotted to physical activity, and diet-induced thermogenesis. By definition, resting energy expenditure also encompasses the energy requirement for growth. Although critically ill children have increased energy requirements from increased metabolic turnover, their growth is often halted or slowed during physiologic stress.[41] In addition, owing to the nature of the illness and administration of sedation and paralytic agents, levels of physical activity are low in the critically ill child.

Thus, for practical purposes, the recommended dietary caloric intake for healthy children represents a reasonable starting point for the upper limit of caloric allotment in the critically ill child.[42] Excessive caloric allotments can be harmful, leading to synthesis of excess fat and increased CO_2 production. Children fed through enteral administration require a further 10% increment in caloric regimen to account for obligate malabsorption. Owing to the high individual variability in energy expenditure, particularly in the most critically ill patients, the actual measurement of resting energy expenditure (ie, by indirect calorimetry) is recommended. It should be noted that predictive equations used with stress factors to account for the degrees of illness have proven inaccurate in determining individual energy expenditures; the preferred method to measure energy expenditure remains indirect calorimetry, when available.[43]

Once protein needs have been met, safe caloric provisions using carbohydrate and lipid energy sources have similar beneficial effects on net protein synthesis and overall protein balance in critically ill patients. The rational partitioning of these substrates requires knowledge of carbohydrate and lipid use in critical illness.

Carbohydrate Metabolism

Glucose production and availability are a priority of the metabolic response in critically ill children. Glucose is the primary energy used by the brain, erythrocyte, and renal medulla and is useful in the repair of injured tissue. Glycogen stores are limited and quickly depleted in illness or injury, resulting in the need for gluconeogenesis. In injured and septic adults, a threefold increase in glucose turnover and oxidation has been demonstrated as well as an elevation in gluconeogenesis.[44,45]

A significant feature of the metabolic stress response is that the provision of dietary glucose does not halt gluco-

neogenesis. Consequently, the catabolism of muscle protein to produce glucose continues unabated.[14] However, it is clear that a combination of dietary glucose and amino acids effectively improves net protein balance in critical illness. This occurs primarily through the augmentation of protein synthesis and has little, if any, effect on protein breakdown.[17,46]

In early nutritional support regimens for critically ill patients, excessive glucose allotments were used to attempt to overcome the need for gluconeogenesis and, in effect, protein degradation. As expected, the excess glucose was converted to fat, resulting in the net generation of CO_2. The synthesis of fat from glucose has an RQ of approximately 8.7. Clinically, this high RQ is not attained as glucose is never purely used for fatty acid synthesis. Nonetheless, the provision of excess glucose results in an elevated RQ and thus increases the ventilatory burden on the child. The mean RQ in postsurgical neonates fed a high-glucose diet is approximately 1.0, whereas comparable neonates fed with reduced quantities of glucose in combination with a standard concentration of lipid have an RQ of 0.83.[47] Using high-glucose total parenteral nutrition, hypermetabolic adult patients fed excess caloric allotments have a 30% increase in O_2 consumption, a 57% increase in CO_2 production, and a 71% elevation in minute ventilation.[27] In addition, aforementioned studies have found that excess glucose provisions may worsen negative protein balance in neonates requiring ECMO.[29]

Thus, avoidance of excess calories from glucose provisions and the use of a mixed-fuel system employing both carbohydrates and lipid are theoretically and practically useful in critically ill children, many of whom already have respiratory challenges from the nature of their illness. This approach also helps to alleviate difficulties with hyperglycemia in the relatively insulin-resistant stressed child.

Lipid Metabolism

Analogous to protein and carbohydrate metabolism, lipid turnover is generally accelerated by critical illness, surgery, and trauma.[46] Although lipid use is compromised in the initial, brief ebb phase following acute trauma or sepsis, overall lipid turnover increases dramatically during the predominant flow phase. Adult patients demonstrate two- to fourfold increases in lipid turnover compared with healthy controls, and this increase is proportional to the degree of illness.[48,49] This process involves the recycling of free fatty acids and glycerol into and from triglycerides. Approximately 30 to 40% of the free fatty acid moieties are oxidized for energy, and the RQ values postinjury are approximately 0.8. Infants and children subjected to uncomplicated abdominal surgery have also shown a reduction in RQ along with a decline in plasma triglyceride levels.[50] Recently, it has been shown that critically ill children do, indeed, have a higher rate of fat oxidation.[51] Thus, this suggests that fatty acids are, in fact, the prime source of energy in metabolically stressed children. Glycerol, released along with free fatty acids from the breakdown of triglycerides, may be converted to pyruvate and thereby shunted into the gluconeogenesis pathway. Again similar to protein catabolism, the provision of dietary glucose does not decrease glycerol clearance or overall lipid turnover.

Because of the increased demand for lipid use in critical illness coupled with the limited lipid stores in the pediatric patient, critically ill children are susceptible to the evolution of biochemical essential fatty acid deficiency if administered a fat-free diet.[52,53] In infants, linoleic and linolenic acid are considered essential, whereas arachidonic acid and docosahexaenoic acid are thought to be conditionally essential. If the body lacks dietary linoleic acid, the formation of arachidonic acid (a tetraene) by desaturation and chain elongation cannot take place. The same pathway then converts available oleic acid to 5,8,11-eicosatrienoic acid (a triene). Empirically, an elevated triene-to-tetraene ratio is characteristic of essential fatty acid deficiency.[54] Clinically, this syndrome presents as dermatitis, alopecia, thrombocytopenia, increased susceptibility to bacterial infection, and overall failure to thrive. To avoid essential fatty acid deficiency in critically ill or injured infants, the allotment of linoleic and linolenic acid is recommended at concentrations of 4.5% and 0.5% of total calories, respectively.[55]

The provision of commercially available lipid solutions to parenterally fed critically ill children reduces the risk of essential fatty acid deficiency, results in improved protein use, and does not significantly increase CO_2 production or metabolic rate.[56] There are disadvantages, however, with lipid administration including hypertriglyceridemia, increased rates of infection, and decreased alveolar oxygen diffusion capacity.[57–59] Most centers, therefore, start lipid supplementation in ill children at 1.0 g/kg/day and advance over a period of days to 2 to 4 g/kg/day, with monitoring of triglyceride levels. Lipid administration is generally restricted to a maximum of 30 to 40% of total calories, although this practice has not been validated by clinical trials.

Of note, normal ketone body metabolism is also markedly affected by critical illness. The product of incomplete fatty acid and pryruvate oxidation is acetyl coenzyme A, which forms the ketone bodies acetoacetate and β-hydroxybutyrate through a condensation reaction within the hepatocyte. In starved healthy subjects, a major adaptation to preserve skeletal muscle mass is the production of these ketone bodies, which can then be used as an energy source for the brain. However, in the 3-day period following trauma, there is a negligible elevation in serum ketone body levels.[60] This observation may be explained in part by the elevated serum insulin concentrations found during the metabolic stress response. Even low concentrations of insulin inhibit ketogenesis, a fact made evident by the absence of ketotic complications in type 2 diabetics. Hence, the elevated insulin concentrations seen in severe illness and injury serve to negate the ketotic adaptation found in starvation.

Electrolyte Metabolism

Requirements for the basic electrolytes—Na+, K+, Cl^-, HCO_3–, Ca2+—must be evaluated frequently in the critically ill patient. In addition to routine electrolyte monitoring, careful attention to phosphate and magnesium levels

is recommended. Hypophosphatemia may lead to hemolytic anemia and respiratory muscle dysfunction and may also be seen with refeeding syndrome in the ill child. Renal failure can result in the retention of phosphate, and nutritional allotments must be reduced accordingly. Deficiency of magnesium can cause fatal cardiac arrhythmia.

Abnormalities of acid-base physiology in the critically ill child can also influence the nutritional regimen. For example, head-injured patients often develop an iatrogenically induced respiratory alkalosis. If a metabolic alkalosis secondary to active diuresis or gastric suction is also present, Cl^- administration should be used to correct the alkalosis. Untreated alkalemia tends to inhibit the respiratory drive, shift potassium intracellularly, and decrease ionized calcium concentrations by increasing the affinity of albumin for calcium. Metabolic acidosis can also be seen in critically ill children, often from associated hypotension or ischemic etiologies. In this case, the provision of acetate instead of Cl^- in the parenteral nutrition regimen should be used so as not to worsen the existing acidemia. The provision of excess acetate at 1 mEq/kg/day is usually a safe adjunct to limit metabolic acidosis.

Vitamin and Trace Mineral Metabolism

Vitamin and trace mineral metabolism in critically ill and postoperative patients has not been extensively studied. For the neonate and the child, required vitamins include fat-soluble vitamins (A, D, E, and K) and water-soluble vitamins (ascorbic acid, thiamin, riboflavin, pyridoxine, niacin, pantothenate, biotin, folate, and vitamin B_{12}), and these are routinely administered. Because vitamins are not stoichiometrically consumed in biochemical reactions but rather act as catalysts, the administration of large supplements of vitamins in stressed states is not logical from a nutritional standpoint.

The trace minerals required for normal development are zinc, iron, copper, selenium, manganese, iodide, molybdenum, and chromium. Trace minerals are used in the synthesis of active sites of a ubiquitous and extraordinarily important class of enzymes termed metalloenzymes. As with vitamins, the role of metalloenzymes is to act as catalysts. Hence, unless there are excessive losses, such as increased zinc loss with severe diarrhea, large nutritional requirements in critical illness should not be anticipated. The Recommended Dietary Allowances of vitamin and trace mineral needs of healthy children and neonates are reviewed periodically and are well defined in the literature.[42] These recommended levels have been used in critically ill patients, and little evidence exists that they are nutritionally inadequate. In children with severe hepatic failure, copper and manganese accumulation can occur; thus, parenteral trace mineral supplementation should be reduced.

ROUTES OF NUTRITIONAL PROVISION

In the critically ill child with a functioning gastrointestinal tract, the enteral route of nutrient administration is preferable to parenteral nutrition. Enteral nutrition is physiologic and has been shown to be more cost-effective without the added risk of nosocomial infection inherent in parenteral nutrition.[61,62] The postpyloric feeding tube, placed at the bedside or with fluoroscopic guidance, helps to decrease the risk of aspiration and is a useful tool in the nutritional management of the critically ill child. Continuous feedings using standard formulas can adequately nourish the majority of injured patients. Diarrhea can often be avoided by carefully controlling the infusion rate until tolerance is established. At the time of extubation, tube feeds are held for 6 to 12 hours to lower the corresponding risk of aspiration. It is also recommended not to use enteral feeds with patients who are hypotensive or who have evidence of bowel ischemia so as to limit the risk of small-bowel necrosis associated with rapid enteral feeding.[63]

If the gastrointestinal tract is not functional and parenteral nutrition is necessary, central venous access is obtained to facilitate the administration of concentrated nutritional solutions. This obviates fluid overload from less concentrated solutions and avoids the risk of sclerosis of smaller peripheral veins. Percutaneously placed intravenous lines that are threaded centrally and standard central venous catheters are the preferred routes of administration. Intravenous lines in the groin are not preferred owing to their propensity for infection but may be necessary on a temporary basis in patients who have chronic access issues. In most pediatric intensive care unit patients, central access may be performed successfully at the bedside. Once gastrointestinal function has been re-established, the patient can usually be converted to an enteral nutrition regimen.

MECHANISMS OF THE METABOLIC RESPONSE

Although research continues to elucidate the metabolic changes associated with the pediatric stress response, future studies will aim to uncover the mechanisms behind these metabolic alterations. The goal of this research is ultimately to gain the knowledge necessary to control and modulate the response. In this way, many of the deleterious consequences associated with the metabolic stress response can potentially be circumvented. Two integrated and complex systems are involved: neuroendocrine pathways and inflammatory cytokines.

The neuroendocrine response to critical illness is relatively well defined, and its features are common to both children and adults. Beginning soon after the initial insult, a unique hormonal profile takes hold. Catecholamines are released from the adrenal medulla on stimulation by the sympathetic nervous system. The secretion of adrenocorticotropic hormone mediated by the anterior pituitary results in an increase in serum cortisol and aldosterone levels. Growth hormone and antidiuretic hormone are secreted by the anterior and posterior pituitary glands, respectively. In addition, glucagon levels rise with the surge in catecholamines. After a brief, initial decline, a rapid increase in serum insulin concentrations is found.[64–66] Overall, the hormonal changes in neonates and infants have been shown to

be of greater magnitude but shorter duration than those found in older children and adults.

The alterations in intermediary metabolism inherent in the metabolic response can be attributed, at least in part, to these hormonal changes. The mobilization of amino acids from muscle, the increased rate of gluconeogenesis in the liver, and the increased lipolysis from adipocyte stores can be explained by the elevations in glucagon, cortisol, and the catecholamines. The increase in net protein degradation, however, is not consistent with the persistent elevation of insulin, a known anabolic hormone. In this way, it has been postulated that injury-induced protein degradation is the result of a postreceptor defect in insulin action.[67] This hypothesis is further supported by the finding that burn patients do not demonstrate the same degree of inhibition of protein breakdown compared with normal controls when subjected to hyperinsulinemic euglycemic conditions.[68]

The presence of inflammatory cytokines can be found in the circulation within hours of elective surgery or trauma. These peptides are secreted by leukocytes in a variety of settings and help to mediate the inflammatory response. In general, the prototypical cytokine response in neonates does not markedly differ from that of older children or adults.

Interleukin (IL)-6 has been found in increased concentrations in the serum of children within hours after surgery, and this increase persists up to 24 to 48 hours postoperatively.[69] IL-6 levels have also been shown to be significantly elevated in critically ill children requiring ECMO.[39] IL-6 levels have been directly correlated with increased protein turnover and catabolism as well as a higher incidence of postoperative complications and mortality.[66,67] Tumor necrosis factor (TNF) has also been shown to increase in neonatal critical illness such as necrotizing enterocolitis and sepsis. It is hypothesized that TNF is involved in the release of prostaglandins, thereby mediating the hypotension associated with the septic state. The release of IL-2, IL-8, IL-11, interferon-γ, and other growth factors is also known to augment the immunologic and hormonal response to injury, although the precise effect of these cytokines on metabolism has not been fully defined.

CONCLUSION

The pediatric metabolic response to critical illness and injury is composed of a significant increase in the turnover of protein, carbohydrate, and lipid substrates. This process allows for the production of inflammatory response proteins that participate in the associated inflammation and wound healing. Extreme protein loss, consistent with the severity of the illness or injury, is a hallmark of this metabolic process. Interestingly, recent research has demonstrated that the overall energy expenditure of the child is not necessarily increased during this metabolic response. It is thought that the child shifts energy resources from normal growth and activity to provide fuel for the increased turnover of substrate.

Implementing an appropriate nutritional regimen to minimize the protein loss and to meet the energy requirements of the child is of paramount importance in the long-term management of children suffering from critical illness or major injury. Maintaining positive protein balance in the face of protein loss requires substantially increased protein allotments, especially in neonates. Excessive carbohydrate provisions do not blunt the metabolic response and, indeed, have been shown to have deleterious consequences. In addition, because the energy expenditure of these patients does not appear to increase significantly, the recommended caloric intake for healthy children in a similar age group represents a reasonable starting point for the upper limit of caloric allotment in critically ill children. Finally, exact measurement of energy expenditure using indirect calorimetry should be used in complicated patients and when patients do not respond over time to an appropriate nutritional regimen.

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CHAPTER 47

HYPERLIPIDEMIA AND CARDIOVASCULAR DISEASE

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Atherosclerotic heart disease is a major cause of adult morbidity and mortality in the United States; coronary heart disease (CHD) affected 12.6 million Americans and caused nearly 530,000 deaths in 1999. Other atherosclerotic complications, including stroke and peripheral vascular disease, affect millions more.[1] The causes of atherosclerotic cardiovascular disease are multifactorial; however, nutrition is related to many traditional cardiovascular risk factors. Increased total cholesterol is an important risk factor for atherosclerosis and was found in half of the Framingham Heart Study adult cohort who sustained a myocardial infarction.[2] Reducing cholesterol by 8% reduces the risk of CHD by 19%.[3] Nutrition is an important determinant of lipid values. Other important cardiovascular risk factors include hypertension and obesity, and these factors are also modified by diet. Taking these facts into consideration, health care providers who deliver care to young persons can be assured that millions of today's youth, and a significant fraction of our practices, will sooner or later fall victim to atherosclerotic vascular disease.

Several lines of evidence suggest that atherosclerotic vascular changes begin by adolescence and that early intervention on a population basis and, for severe cases, on an individual basis is warranted. These lines of evidence, and the arguments for and against various screening and treatment strategies, are laid out in the comprehensive report of the National Cholesterol Education Program (NCEP) Expert Panel on Children and Adolescents.[4] These consensus guidelines were promulgated in 1991 by the American Academy of Pediatrics.[5] The NCEP pediatric guidelines have become somewhat dated in the dozen years since their initial presentation, but they still form the basis of updated recommendations for pediatric lipid practice from the American Academy of Pediatrics.[6]

In this chapter, we present evidence supporting the early onset of atherosclerosis in childhood, including new thinking in pathophysiology; briefly review lipid biochemistry; and describe different pediatric hyperlipidemias, nutritional and pharmacologic treatments, and practical clinical approaches to children with hyperlipidemia. We make specific note of examples in which our current practice or recommendations diverge from those of the NCEP.

PEDIATRIC ORIGINS OF ADULT ATHEROSCLEROSIS

Atherosclerosis usually takes decades to develop. Symptoms and sequelae from atherosclerotic vascular disease are extremely rare in children and adolescents and are limited to patients with profound genetic dyslipidemias. However, both the disease process itself and the nutritional habits that propagate the disease begin early. Autopsy studies of cohorts as early as the Korean War have shown atherosclerotic coronary artery disease in the second decade of life on gross examination[7] and by microscopy.[8,9] These pathology findings were correlated with hyperlipidemias in young persons in the United States in a landmark study termed Pathological Determinants of Atherosclerosis in Youth (PDAY),[10] among others.[11] In the PDAY study, fatty streak precursor lesions were present by age 15 years in the coronary arteries of children who died of noncardiac causes. Both the prevalence and extent of fatty streaks, and the degree of progression to raised vascular lesions (early atherosclerosis) by young adulthood, were directly related to increased non–high-density lipoprotein (HDL) cholesterol—that is, low-density lipoprotein (LDL) plus very-low-density lipoprotein (VLDL)—and decreased HDL cholesterol measured at the time of death.

Epidemiologic Evidence of a Connection between High Cholesterol in the Young and Heart Disease

Epidemiologic studies have shown that countries with higher rates of CHD have higher pediatric population mean total cholesterol.[12] Cholesterol levels in the pediatric age group are important because they predict adult cholesterol levels to a substantial degree. Cholesterol "tracks" quite well; children with very high cholesterol levels are highly

likely to be adults with high cholesterol. This has been demonstrated in a decades-long cohort project in Iowa, the Muscatine Study: nearly half of subjects with high cholesterol as children had high cholesterol levels as adults.[13]

There are data connecting cholesterol levels in young adults with CHD. Starting in the late 1940s, cholesterol levels were available for cohorts of Johns Hopkins University medical students. High total cholesterol values in the students predicted greater risk of CHD, mortality from CHD and overall mortality later in adult life.[14] This study provides the most compelling link between measured cholesterol levels in young persons and subsequent risk of heart disease 30 or 40 years later. Long-term intervention studies demonstrating a link between cholesterol levels in school-aged children and CHD in the fifth and sixth decades of life and showing that interventions in this age range prevent future disease have not been done; the length of follow-up is daunting. Therefore, the interventions we discuss below are based on inference, adult studies, and short-term intervention results in the young.

High-Risk Groups

Compared with the general population, specific identifiable groups of young people are at high risk of early atherosclerosis owing to hyperlipidemias. These include heart transplant recipients[15,16] and renal transplantation patients,[17,18] in whom the problem is related only in part to chronic transplant rejection. Children with diabetes mellitus are also at particular risk for cardiovascular disease in the long run. In assessing risk for individual children, solid organ transplantation and juvenile-onset diabetes can reasonably be considered to count as two risk factors in determining whether a child is a candidate for pharmacologic therapy.

EMERGING CONCEPTS IN ATHEROSCLEROSIS: APPLICATIONS IN CHILDREN AND ADOLESCENTS

The fact that half of adults in the Framingham Heart Study who had myocardial infarctions had normal cholesterol levels,[2] a finding supported by other studies,[19,20] has prompted researchers to search for other contributions to atherosclerosis. Although the prevailing theory of atherosclerotic disease since the 1960s has focused on cholesterol, recent thinking places emphasis on vascular and systemic inflammation as instrumental in the pathophysiology of atherosclerosis. A simple marker, serum C-reactive protein (CRP), is proving to be a valuable tool for assessing cardiovascular disease risk in adults. CRP is an acute-phase reactant. Transient inflammation, from minor infections for example, can readily raise the CRP level above a population upper limit of normal, 0.5 mg/dL. However, a highly sensitive CRP assay (hsCRP) detects variations in levels of less than 0.1 mg/dL. At these low levels, previously deemed normal, differences in CRP levels in the population predict cardiac risk. Studies examining adults having myocardial infarctions show abnormally elevated CRP; higher peak values predict worse outcomes[21] and larger infarcts.[22] Adults who have abnormal CRP levels even months or years after an acute coronary event have a significantly greater risk of recurrence.[23,24] Prospective evaluation in large cohort studies reveals that men and women without clinical atherosclerotic disease who have CRP values higher than the normal range are at risk for future cardiovascular disease.[25,26]

Relation of CRP Findings to Pediatric Lipid Disorders and Cardiac Risk

Inflammation probably has a role in the increased risk of future cardiovascular disease in pediatric patients. Only a fraction (between 23 and 43%) of the offspring of parents with early myocardial infarction have high LDL cholesterol.[27,28] This suggests that at least part of familial cardiac disease risk is not related to hypercholesterolemia and might be related to a hyperinflammatory state. In fact, one study found that children with first-degree relatives who had myocardial infarctions have abnormally elevated CRP levels.[29] Despite these intriguing results, no data available in late 2002 demonstrate a specific role for hsCRP as a screening tool in pediatric lipid practice. However, the test might be valuable in present practice in some individual patients at high risk as assessed by family history or by lipid levels and will likely have greater use in risk prediction in the future. The exact relationship between CRP and coronary risk is unclear. It is possible that ongoing, mild vascular inflammation contributes both to atherosclerosis and the increased CRP level.

The understanding of the role of inflammation in atherosclerosis has led to new thinking about therapies in adults, including acetylsalicylic acid, vitamins E and C, and betacarotene. However, a recent large study in adults found no difference in 5-year mortality, despite increases in serum levels of vitamins E and C and betacarotene; there is more to learn on this subject.[30] There have been no studies of these therapies in pediatric patients.

Homocysteinemia and Pediatric Evaluation for Cardiac Risk

Elevated level of the nonstructural amino acid homocysteine is another coronary artery disease risk factor that has lately become better understood. Three lines of evidence link homocysteine levels to atherosclerotic disease: (1) in large adult cohorts, including the Framingham Heart Study, mild hyperhomocysteinemia is predictive of coronary events[31]; (2) homocysteine itself causes vascular disease in animal models[32]; and (3) young patients with profound hyperhomocysteinemia owing to the rare genetic defect cystathionine-β-synthase deficiency (homocystinuria) have dramatic elevation in thrombosis risk. Dietary deficiencies of vitamin B_{12} (cobalamin), folate, or vitamin B_6 (pyridoxine) can all lead to hyperhomocysteinemia, as can genetic defects in absorption or metabolism of these vitamins.

The most common genetic association is with a heat-labile form of methylenetetrahydrofolate reductase, caused by a 677C-to-T polymorphism and present in more than one-quarter of Caucasians.[33] In the presence of this polymorphism, relative folate deficiency with resultant mild

elevation in homocysteine levels is fairly common in adults with poor folate intake. However, just as the significance of relative folate deficiency was becoming clear in the late 1990s, universal folate supplementation of cereals and enriched grain products to prevent neural tube defects was enacted, clouding the data on the relationship between folate supplementation and CHD. In a large cohort of pediatric patients studied for lipid nutritional intervention, the Dietary Intervention Study in Children (DISC), hyperhomocysteinemia was rare among several hundred subjects.[34]

LIPID BIOCHEMISTRY

Lipids, including cholesterol and other sterols, triglycerides, and free fatty acids, are essential for life. In humans, all but the essential fatty acids can be endogenously synthesized, but diet is a major contributor to total body lipid stores in typical diets in developed countries. Essential fatty acids include the basic precursors of the polyunsaturated fatty acids (eg, linoleic acid or linolenic acid).

Cholesterol is partially absorbed from the diet and partially synthesized by the liver. The only dietary source of absorbed cholesterol is animal products; 30 to 50% of dietary intake is absorbed. Strict vegans synthesize 100% of their cholesterol needs as vegetables contain no cholesterol. After absorption, cholesterol is esterified and carried in the serum on lipoprotein particles, as described below.

Fat, in the form of fatty acids and triglycerides (three fatty acids esterified to glycerol), is derived both from dietary sources and from endogenous synthesis, including excess carbohydrates and even proteins. Fatty acids can be "saturated," with hydrogen at each carbon; "monounsaturated," with one double carbon bond; or "polyunsaturated," with two to six double bonds. Naturally occurring dietary fatty acids are in the "*cis*" configuration at each double bond. Polyunsaturated fats are prone to spoilage by oxygen, light, and heat; therefore, food processing, especially catalytic hydrogenation processing, used to avoid rancidity, leading to non-natural fatty acid chemistry, including a "*trans*" bond configuration. Readers will be familiar with "partially hydrogenated" oils from the list of ingredients in many processed foods, especially snack foods. In general, the larger the proportion of partially hydrogenated fats, the larger the proportion of undesirable transconformation fatty acids. Dietary cholesterol (usually not much more than 300 mg/day) is re-esterified to fatty acids in plasma. Dietary triglycerides (typically dozens of grams daily) are degraded by lipase in the gut, absorbed, and re-esterified to re-form triglycerides. Dietary fat is distributed to body tissues, primarily the liver, in the form of chylomicrons.

Cholesterol esters and neutral fats such as triglycerides are negligibly soluble in water and therefore are carried in the bloodstream by lipoproteins. Free fatty acids in plasma are carried mainly on albumin and are rapidly taken up by tissues for re-esterification or for combustion as fuel. Lipoproteins are made up of hydrophobic lipids (triglycerides and cholesterol ester) on the inside and apoproteins, phospholipids, and unesterified cholesterol on the outside.

There are several types of lipoproteins, classified by density as determined using plasma ultracentrifugation: chylomicrons, which float as a creamy supernatant: HDLs, LDLs, and VLDLs.

Chylomicrons are synthesized in the intestine from dietary triglycerides, cholesterol, and apolipoproteins synthesized in the liver. Chylomicrons have the lipoproteins apo A, apo C, and apo C-II. The chylomicron delivers the triglyceride to muscle and adipose tissue, where it is modified by lipoprotein lipase, losing triglycerides, apo A, and apo C and gaining apo E. The chylomicron remnants are taken up by the liver via the apo E receptor and degraded.

HDL is the densest and smallest lipoprotein. The major proteins (apoproteins) in HDL are apo A-I, apo A-II, apo C, and apo E. HDL is the primary lipoprotein responsible for reverse cholesterol transport, returning cholesterol from other tissues back to the liver. HDL also transports cholesterol from other lipoproteins, such as LDL, and cell membranes to VLDL and chylomicrons.

LDL is the main reservoir of circulating cholesterol esters, supplying cell membranes and tissues. Each LDL particle carries an apolipoprotein B molecule, the protein responsible for LDL clearance by its cognate receptor. Cholesterol synthetic mechanisms are present in nearly all mammalian cell types, but exogenous sources are used prior to endogenous synthesis. Delivery to tissues is regulated by the number of LDL receptors, and a tight negative feedback system prevents cholesterol synthesis and downregulates LDL receptors in normal humans when extracellular LDL is abundant. Recent studies have noted an increased risk of atherosclerotic events in people with particularly dense LDL particles.

VLDL is manufactured in the liver, particularly during fasting, as the main source of triglycerides when chylomicrons are absent. VLDL is secreted into the bloodstream and triglycerides are removed in the periphery by lipoprotein lipase. The VLDL remnants are metabolized by the liver and serve as the precursor for LDL production.

HYPERLIPIDEMIA

Normal cholesterol levels are age dependent; children have lower levels than adults do. The NCEP guideline cutoffs for borderline and overt hypercholesterolemia, as well as for normal levels of HDL, triglycerides, and LDL, are shown in Table 47-1.

Establishing a Diagnosis

Hypercholesterolemia and hyperlipidemia are both multifactorial and polygenic traits. It is useful to distinguish primary (familial or sporadic) from secondary hyperlipidemia. In pediatrics, most cases of hyperlipidemia are primary; however, secondary causes of hyperlipidemia should be considered, evaluated, and ruled out because several of the secondary causes are treatable. Secondary causes of hyperlipidemia (Table 47-2) are often readily identified by a medical history and examination, with simple laboratory testing as indicated.

Among primary hyperlipidemias, dietary transgressions, lack of exercise, glucose intolerance, and obesity

TABLE 47-1 NCEP and Population Age-Based Percentiles for Lipid Values in Children

Classification/ Percentile	*Total Cholesterol, mg/dL**	*Low-Density Lipoprotein,† mg/dL**	*High-Density Lipoprotein, mg/dL**	*Triglycerides, mg/dL**
Acceptable	< 170	< 110	—	—
Borderline	170–199	110–129	—	—
Elevated	> 200	> 130	—	—
5th Percentile				
Age 5–9 yr				
Boys	125	65	39	31
Girls	130	70	37	33
Age 10–14 yr				
Boys	123	66	38	33
Girls	128	70	38	38
Age 15–19 yr				
Boys	116	64	31	38
Girls	124	61	36	40
50th Percentile				
Age 5–9 yr				
Boys	164	93	56	53
Girls	168	101	54	57
Age 10–14 yr				
Boys	160	97	57	61
Girls	163	97	54	72
Age 15–19 yr				
Boys	150	96	47	71
Girls	160	96	53	70
75th Percentile				
Age 5–9 yr				
Boys	180	106	65	67
Girls	184	118	63	73
Age 10–14 yr				
Boys	178	112	63	80
Girls	179	113	60	93
Age 15–19 yr				
Boys	170	112	54	94
Girls	177	114	63	90
95th Percentile				
Age 5–9 yr				
Boys	209	133	76	104
Girls	211	144	75	108
Age 10–14 yr				
Boys	208	136	76	129
Girls	207	140	72	135
Age 15–19 yr				
Boys	203	134	65	152
Girls	209	141	76	136

Adapted from National Cholesterol Education Program (NCEP).[4]
Acceptable, borderline, and elevated cholesterol values according to the NCEP pediatric guidelines are shown for total cholesterol and low-density lipoprotein (LDL). For comparison, percentile values are shown for these measures and for high-density lipoprotein (HDL) and triglycerides. See National Cholesterol Education Program[4] for full percentile tables.
*Values are reported as serum; to convert to plasma values, divide by 1.03.
†LDL and HDL values for Caucasian subjects.

TABLE 47-2 Medical, Physiologic, and Pharmacologic Causes of Secondary Hyperlipidemia

Endocrine and metabolic states
- Diabetes mellitus
  - Type I: with concomitant primary hyperlipidemia, very high vascular risk
  - Type II: particularly related to high triglycerides
  - Insulin resistance states without overt diabetes (check for acanthosis nigricans)
- Pregnancy
- Hypothyroidism
- Hypopituitarism*
- Anorexia nervosa

Hepatic disease
- Hepatitis of any etiology
- Congenital biliary atresia†
- Acute intermittent porphyria
- Glycogen storage disease†
- Benign recurrent intrahepatic cholestasis

Renal disease
- Nephrotic syndrome†
- Any renal inflammatory state
- Hemolytic uremic syndrome
- Idiopathic hypercalcemia

Lysosomal storage disease
- Cholesterol ester storage disease
- Niemann-Pick disease
- Other conditions, such as Tay-Sachs disease, Gaucher's disease

Recognizable genetic syndromes
- Klinefelter's syndrome
- Progeria (Hutchinson-Gilford disease)

Systemic inflammatory states
- Trivial inflammation (eg, viral illnesses, simple urinary tract infection, sinusitis) can raise triglyceride levels; "healthy day" testing recommended
- Systemic lupus erythematosus: severe vascular risk if combined with primary hyperlipidemia
- Burns

Drugs and other agents
- Corticosteroids (systemic): primarily hypertriglyceridemia
- Thiazides
- Beta-blockers
- Oral contraceptives (third-generation oral contraceptive pills have beneficial effect on HDL, which can appear as benign elevation in total cholesterol)
- Antiepileptic medications
- Ethanol: low-dose, regular consumption increases salutary HDL; in excess, hypertriglyceridemia

*If hypopituitarism is suspected, thyroid-stimulating hormone alone, as advocated for primary screening, is not sufficient to rule out central hypothyroidism.
†Elevations can be severe with xanthomas.
HDL = high-density lipoprotein.

often accompany sporadic high cholesterol levels and complicate familial lipid disorders. Several of the familial lipid disorders are dominantly inherited with a gene dosage effect: heterozygous individuals have elevated lipids but are generally asymptomatic until the condition manifests as early stroke, angina, myocardial infarction, or sudden death in the fourth or fifth decade of life. However, homozygotes can manifest xanthomas, arcus cornea, and thickened tendons even before puberty and can have cardiovascular end points in early adulthood. Although multiple genes affect lipid levels, several monogenic conditions have been distinguished and can be readily recognized if family history and laboratory data are available. A simple guide for diagnosis based on lipid profile and family history is presented in Table 47-3.

Familial combined hyperlipidemia is the most common type of inherited hyperlipidemia. It is autosomal dominant and is found in 1 in 100 individuals. Of patients with early coronary heart disease, 10 to 15% carry this diagnosis. The

lipid abnormalities are moderate. About one-third of patients with familial combined hyperlipidemia have increased LDL primarily, one-third have increased triglycerides without altered LDL, and another third have increased triglycerides and increased LDL. The three types frequently coexist within a family.

Familial hypercholesterolemia, though rare, is the genetic lipid disorder best understood at a biochemical level. The cause is genetic defects in the LDL receptor gene. Heterozygotes have a decrease in the number of active receptors and homozygotes have absence or near absence of functional receptors. Heterozygous deficiency has a prevalence of 1 in 500 individuals in the United States (0.2%), but heterozygotes account for 5% of early myocardial infarction survivors. These individuals usually have total cholesterol levels in the range of 200 to 500 mg/dL (5.2 to 13 mmol/L). They have a family history of high cholesterol and early coronary disease and require pharmacologic treatment. Premature atherosclerosis is seen in 30% of adults heterozygous for familial hypercholesterolemia.[35]

Some populations with elevated familial hypercholesterolemia prevalence because of founder effects include French Canadians, Dutch Afrikaners in South Africa, and Lebanese Christians. Individuals with homozygous LDL receptor defects are rare, about one in a million individuals, and have very high total cholesterol levels of 500 to 1,000 mg/dL (13 to 25.9 mmol/L). These are children who could have myocardial infarctions and require not pharmacologic treatment, which is usually ineffective, but plasmapheresis or liver transplantation. In the complete absence of LDL receptors (familial hypercholesterolemia patients homozygous for null mutations), statins are utterly ineffective at standard doses. LDL apheresis with devices such as Liposorber columns is very effective, and carries lower risk than does liver transplantation. Gene therapy approaches have been attempted,[36] but long-term benefit remains to be demonstrated.[37]

TABLE 47-3 Phenotype and Family History Commonly Found among Pediatric Lipid Clinic Patients

Common Phenotypes	*Family History*	*Likely Diagnosis*
Elevated LDL* and total cholesterol only	Xanthomas/early heart disease†	Familial hypercholesterolemia (total cholesterol 500–1,000 mg/dL found in homozygotes)
Elevated triglycerides + low HDL, often with obesity	Type 2 diabetes or similar lipid patterns	High risk for metabolic syndrome
Moderately elevated triglycerides and LDL	Elevated triglycerides, LDL, or both	Familial combined hyperlipidemia
Low HDL only	Low HDL, early coronary heart disease	Familial hypoalphalipoproteinemia
High HDL (> 60 mg/dL), normal LDL	Often negative for early heart disease	Normal variant; in 20% of children with elevated total cholesterol, high HDL is the only abnormality; intervention not required

Cholesterol, HDL, and triglyceride values measured in a fasting state. Combination of phenotype with typical family history suggests diagnosis.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
*LDL is calculated from fasting values using the Friedewald formula, in which LDL = TC – (HDL + TG/5).
†Early heart disease is defined as myocardial infarction before age 55 in men and before in 60 in women.

Familial defective apoplipoprotein B is clinically similar to familial hypercholesterolemia, with similar prevalence for heterozygote and homozygote forms. Familial defective apolipoprotein B is attributable to decreased binding of LDL to its receptor because of a mutation in the apolipoprotein B protein itself rather than a receptor mutation. The condition is rare. The biochemical findings in untreated patients are indistinguishable from heterozygous familial hypercholesterolemia. However, response to pharmacologic therapy, including statins and other agents, tends to be poor, because the up-regulation of hepatic LDL receptors, a key step in the mechanism of action for statins and for bile-binding resins, will not increase clearance of the mutant particles from the blood.

Familial hypertriglyceridemia is characterized by high triglyceride levels, sometimes accompanied by low HDL. This is a very common profile, of polygenic origin, exacerbated by type 2 diabetes and obesity. Rare monogenic disorders cause chylomicronemia and profound hypertriglyceridemia. Homozygous deficiency of lipoprotein lipase or its cofactor, apolipoprotein C-II, causes isolated increase in chylomicrons, presents in children as recurrent pancreatitis, and is autosomal recessive. Affected individuals have xanthomas but do not have an increased risk of early myocardial infarction.

Familial hypoalphalipoproteinemia exists, but in the general population, low HDL is a common trait, and low HDL is especially prevalent among young survivors of myocardial infarction. With notable but rare exceptions, the exact genetic basis of low HDL is obscure. One allele of the apo A-I gene was found in 32% of adults with severe coronary artery disease and in 3 to 4% of those without CHD.[38]

A number of rare, inherited disorders of lipoprotein metabolism have been described. These are beyond the scope of this chapter.

Metabolic Syndrome

Lipoprotein (a) and Cardiovascular Risk Lipoprotein (a), or Lp(a), is a variant LDL particle with a covalently bound protein portion, termed apolipoprotein (a). This particle is not measured on standard lipid profiles. High levels are thought to be atherogenic because the particle not only participates in atheromatous plaques (as does LDL) but also impairs fibrinolysis because apolipoprotein (a) prevents normal plasminogen activation.[39] Lp(a) is genetically determined, and high levels are associated with increased risk of coronary artery disease. The levels within the population are not normally distributed. The majority of humans have normal levels of less than 30 mg/dL, but levels greater than 30 mg/dL are common in lipid clinic

settings. Very high levels (more than 100 mg/dL) deserve particular attention, but there is no pharmacologic treatment that specifically targets Lp(a). Lovastatin has produced some reduction in adults,[40] and others with severe CHD have been treated with plasmapheresis.

Metabolic syndrome, previously called syndrome X, is a collection of cardiovascular risk factors associated with a higher rate of atherosclerotic disease. In adults, metabolic syndrome involves hypertension, elevated fasting glucose levels, central obesity, low HDL, and high triglycerides.[41] This syndrome has not yet been well characterized in children, although it is likely that having a collection of risk factors such as these would put a child at increased risk for atherosclerotic disease in adulthood and therefore should alert the clinician to screen for dyslipidemias and other cardiovascular risk factors and to emphasize modification of lifestyle, including diet. Body mass index (BMI) above the 95th percentile for age in childhood is likely to be a risk factor for future metabolic syndrome.

Cholesterol Screening

Whom to Screen The NCEP and the American Academy of Pediatrics have recommended selective screening of children with risk factors for atherosclerosis, including family history of hypercholesterolemia or early coronary artery disease (Figure 47-1), after age 2 years. Universal screening of all children is not advocated, for these reasons:

- The cost of screening some 60 million young persons is not worth the marginal gain in identifying the small number of patients not identified by family history.
- Based on the NCEP screening algorithm presented in Figure 47-1, rescreening costs for the 15 million US children above the 75th percentile would be even higher.
- It would be rare to discover children by universal screening who would require medication before adulthood, and all children should follow a prudent (Step One) diet and exercise regularly.
- Labeling children unnecessarily as hypercholesterolemic could cause harm.

Nevertheless, several studies have shown that selective screening misses some children because of its dependence on family history—often the full family history is not available,[42] and very young children might have grandparents too young to have had early heart disease—and family history might be less predictive in black children than in white children.[43,44] Therefore, patients with unknown family histories can be screened at physician discretion, according to the NCEP guidelines. Health care providers might also check fasting lipid profiles or total cholesterol in children who have personal risk factors such as obesity, hypertension, or smoking.

What to Test The 1991 pediatric NCEP guidelines suggest initial screen by nonfasting total cholesterol only for children with a family history of hypercholesterolemia. False-negative and false-positive results are common,

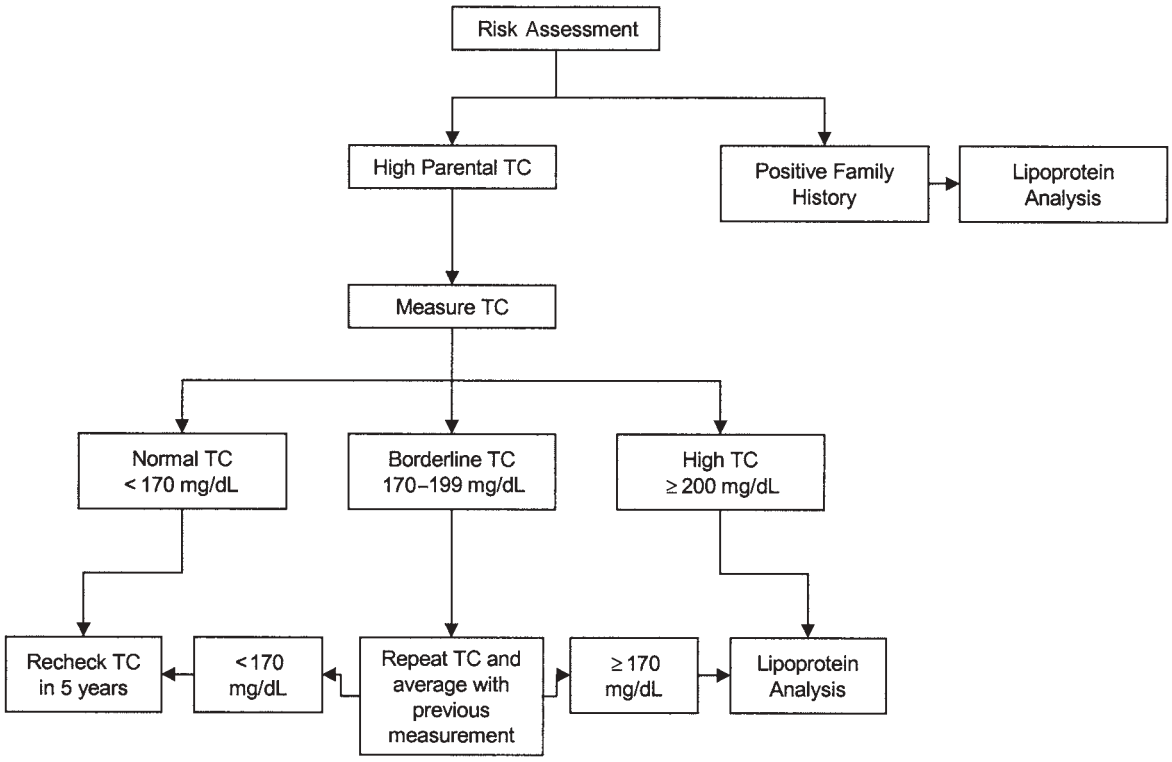

FIGURE 47-1 Selective screening approach recommended by the National Cholesterol Education Program Expert Panel on Children and Adolescents. Note that screening total cholesterol (TC), with a 75th percentile cutoff, requires a large volume of retesting because a single value between 170 and 200 mg/dL has limited positive predictive value.[75]

based in part on HDL cholesterol variance. By contrast, current NCEP guidelines for adults suggest screening with nonfasting total cholesterol *and* HDL cholesterol rather than total cholesterol alone.[45] Adding HDL to the screen adds to the initial cost but dramatically improves sensitivity and specificity of the screen; we believe it is well worthwhile. We recommend screening nonfasting total cholesterol and HDL cholesterol to primary care colleagues in our practice.

NUTRITION AND CHOLESTEROL IN CHILDREN

Dietary habits among American children have changed over the past several decades. Children, like all Americans, eat out more often, consuming 32% of their calories outside the home between 1994 and 1996 compared with 18% in 1977–78. Food eaten outside the home is usually higher in total and saturated fats and lower in calcium, iron, and fiber than food eaten at home.[46] Fruit juice has been recognized as a major source of calories; high intake has been associated both with poor growth and also with obesity, and some studies have shown higher total cholesterol to HDL ratios and lower absolute HDL with high intake of some types of juice.[47] There have been suggestions in recent years that dietary habits in infancy can have a significant impact on childhood cholesterol patterns and even on levels in adulthood. A recent meta-analysis of 1,532 British children and adults showed that breast-feeding was associated with higher total cholesterol and LDL in childhood and lower total cholesterol and LDL in adulthood.[48]

Management of obesity is covered elsewhere in this volume (see Chapter 54). From a lipid management point of view, in patients who are prone to hypertriglyceridemia on a genetic basis and for patients with obesity or at family history of type 2 diabetes, trends toward "super-sized" fast-food meals, juice, and sedentary lifestyle are highly detrimental.

TREATMENT FOR DYSLIPIDEMIAS

Dietary treatment is the first line of intervention in all childhood dyslipidemias, as it is in the adult population. Diet modification is emphasized even more in the pediatric age range than for adults because pharmacologic agents have been tested primarily in adults and safety data are somewhat limited in children. The NCEP has recommended a two-level nutritional approach, adopted with variations by the American Heart Association and the American Academy of Pediatrics. Step One reduces total fat intake to less than 30% of total calories, with a goal of saturated fat representing less than 10% of total calories and cholesterol intakes of less than 300 mg/day.[45] The Step Two diet restricts saturated fat intake to less than 7% of daily calories.

In practice, a Step One diet is readily achieved. Relatively few US children now eat too much cholesterol, in the form of eggs, for example. Some suggestions we provide to our patients for Step One diets are shown in Table 47-4. Professional nutritional counseling is very helpful for patients aiming for a Step Two diet. Dietary intervention trials in adults with fat reductions more stringent than the NCEP Step One diet show a total cholesterol reduction of between 10 and 15%.[49] Several studies demonstrate the efficacy of dietary interventions in children. One study showed that the Step One diet decreased total cholesterol and LDL cholesterol by 12%, although there was significant loss to follow-up of two-thirds of the enrollees.[50] Other studies have found decreases in total and LDL cholesterol of between 6 and 11%.[51,52]

Other dietary interventions have an impact on cholesterol levels in the pediatric ages. One small study of children with hypercholesterolemia showed that fiber supplementation decreases cholesterol while preserving HDL and is more effective than simply following the Step One diet alone.[53] Fiber seems to have an independent effect of reducing cholesterol in children.[54] Recently, counseling has focused not on eliminating fat from the diet so much as exchanging saturated fat for monounsaturated fat. Fat elimination can lead to substitution with refined sugars and carbohydrates that increase triglyceride levels, whereas increased intake of monounsaturated fats can raise HDL levels and improve the cardiovascular risk profile. The Mediterranean diet, one focusing on mono- and polyunsaturated fats, has been associated with a reduced risk of cardiac mortality and morbidity in adults after their first myocardial infarction.[55] It has not been systematically evaluated in children, although many practitioners recommend it to their patients and families. Weight loss in children has been shown to effectively decrease total cholesterol and triglycerides and to increase HDL.[56]

Some pediatric practitioners have raised concerns that these diets will hamper pediatric growth and development; however, the Dietary Intervention Study in Children (DISC) demonstrated that children on a Step One diet had the same growth and development, with somewhat lower cholesterol levels, than did children on a diet close to the usual American intake.[57] The Special Turku Coronary Risk Factor Intervention Project (STRIP) showed that dietary consumption of fat, saturated fat, and total cholesterol did not affect neurodevelopment, although higher protein intake was associated with better neurodevelopmental out-

TABLE 47-4 Simple Substitutions for the Step One Diet

For	*Substitute*
Fatty meats	Fish, skinless chicken, lean beef
Saturated fat (eg, butter)	Monounsaturated fat
Partially hydrogenated oils (*trans*-fatty acids) in regular margarines	Canola or olive oil, monounsaturated margarines (eg, Smart Balance)
Regular peanut butter (partially hydrogenated)	"Natural" peanut butter
Ice cream	Frozen yogurt
Whole milk	Skim or 1% milk
Regular cheese	Low-fat cheese
Lunch meats	Low-fat equivalents
Chocolate (saturated oils)	Cocoa flavoring
Less healthful lunch purchased at school	Lunch packed at home

come in boys, demonstrating that some degree of fat restriction is safe even in children less than 5 years old.[58]

Other interventions that have been explored, but not well exploited, are community-based programs. For example, school-based interventional strategies show some promise. In one study, after 5 years of group nutritional teaching, 2 hours per week, average total cholesterol was lower in children at the intervention schools than in the comparison groups.[59] Another similar study in Greece showed smaller increases in BMI and fat and saturated fat intake and larger decreases in total cholesterol in the intervention schools than in the control schools.[60] The DISC is the largest published experience with school-based interventions. The investigators found that even in the control schools, with modest education rather than formal interventions, cholesterol values improved. The American Heart Association Web site (<http://www.americanheart.org>) is an excellent resource for community-based interventions. The jumpSTART program offers a curriculum for third to fifth graders (<http://www.nhlbi.nih.gov/health/prof/heart/other/jumpstrt.htm>).

Special Nutritional Interventions: Stanol-Containing Margarines and Omega-3 Fatty Acids

Several specific nutritional tools modify lipid profiles. Certain sterols, similar in structure to cholesterol but not absorbed by the small intestines, lower cholesterol by inhibiting absorption of cholesterol, both dietary and in the form of bile acids. As part of a low-fat diet in adults, stanols decrease total cholesterol by 8 to 10%, in addition to the 7% reduction from the low-fat diet alone.[61] Few studies have been performed in children; one trial of stanol ester margarine in 24 children found a decrease from pretreatment levels in total and LDL cholesterol by 14 and 18%, respectively, after 12 weeks, although betacarotene and tocopherol levels also decreased.[62] In adults, n-3 polyunsaturated fatty acids (omega-3 fatty acids) have been shown to reduce the risk of cardiovascular mortality after a myocardial infarction,[63] but, of course, no such data are available for children. Fish are a rich source of omega-3 fatty acids and should be recommended. Flax oil and ground flaxseed are reasonable substitutes for fish for children who will not eat fish.

Pharmacologic Intervention

Adult studies demonstrate significant reduction in cardiovascular morbidity and mortality with cholesterol-lowering medications, not just in severely affected patients or those who have existing heart disease but also as primary prevention in patients with only moderate hypercholesterolemia.[64] As in adults, lipid-lowering drugs can be very effective in children. However, not enough data are available to weigh the potential long-term benefit against very low short-term risk of heart disease in young patients, together with the expense and potential risk of the medications.

In addressing this difficult choice, the NCEP recommendations take a compromise approach: after approximately a year of nutritional and lifestyle changes, children aged 10 years or older with severe hyperlipidemia, defined as LDL cholesterol of more than 190 mg/dL or greater than 160 mg/dL with two additional risk factors for cardiovascular disease, are eligible for consideration for pharmacologic treatment. In practice, we follow this guideline approximately, with the following modifications: we are less likely to consider medication in prepubertal patients if the beneficial HDL levels are high (consistent with the current adult guidelines, which take HDL cholesterol of more than 60 mg/dL as a negative risk factor). Conversely, we occasionally consider and treat children less than 10 years of age with medication for very abnormal profiles with severe family history. Usual dosages are shown in Table 47-5.

The few trials that have been done in children show efficacy rates for decreasing cholesterol levels that are similar to those of adults. Cholestyramine and colestipol are resins that bind to cholesterol in the gut and can lower cholesterol by 10 to 15%.[65,66] The bile acid binding medications are not absorbed, so there are no systemic effects; however, they have a gritty texture in powdered form and can cause constipation, so many children cannot tolerate them. Tablet forms of colestipol and cholestyramine are presently off the market. Colesevelam tablets are available and can be used in patients who do not tolerate the powdered forms but are old enough to swallow the large pills. Because they bind to lipophilic and acidic drugs, bile binding agents are challenging to use in patients on multiple crucial medications such as post-transplantation immunosuppressive agents. In these special patients, it would be reasonable to consider statin use earlier in a patient's course. Compliance with bile acid binding medications can be a problem that limits their usefulness, particularly in the younger child who might not understand the point of a preventive medication. Teenagers might have compliance issues as well, particularly with medications that require multiple doses per day.

Other lipid-lowering medications are systemically absorbed and are used with even more caution in children. Niacin can be an effective adjunct to lipid therapy in some adult settings, but flushing, abdominal discomfort and risk of hepatotoxicity limit its use in children.[67]

3-Hydroxy-3-methylglutaryl CoA reductase inhibitors, or statins, are the clear first-line agents for adults with elevated LDL cholesterol levels and have been used in selected, high-risk pediatric and adolescent patients for many years, but formal studies of safety and efficacy are few. Pravastatin was tested in 8- to 16-year-old boys and found to decrease total cholesterol by 25% and LDL cholesterol by 33%, without side effects, after 12 weeks of follow-up[68]; other short-term studies have supported these findings.[69,70] The longest trial of a statin medication reported to date is a 48-week follow-up trial in boys that showed significant efficacy, with a reduction of LDL cholesterol by 25% and no long-term endocrinologic or other sequelae.[71] Gemfibrozil and other fibric acid derivatives are indicated for hypertriglyceridemia in adults but are used only rarely, and only for very severe cases, in teenagers and almost never in younger patients.

TABLE 47-5 Dosages of Medications Commonly Used in Hyperlipidemia

Bile Binding Resins	*Dosage Forms*	*Typical Dosage Range*	*Comments*
Cholestyramine powder (eg, Questran, Lo-Cholest)	Generic powder is unflavored; Questran Light and Lo-Cholest are flavored	Weight < 40 kg: start with 2 g bid, increase to 4 g bid if well tolerated Weight > 40 kg: start as above, to 6 g bid; max. adult dose, 24 g/d	Not systemically absorbed; side effects of bloating, constipation fairly common
Colesevelam (Welchol)	625 mg tablets	Adult dose: 1,875 mg bid; pediatric dose: approx. 30 mg/kg bid, with liquids	Tablets are large; can be difficult for children to swallow
Statins†			
Lovastatin (eg, Mevacor)	10, 20, 40 mg tablets	Pediatric dose*: 10–20 mg qd or divided bid; adult dose: 20–80 mg qd or divided bid	Generic form available, inexpensive; works best with bid dosing; is the drug with longest experience and most pediatric safety data available
Pravastatin (eg, Pravachol)	10, 20, 40, 80 mg tablets	Adult dose: 10–40 mg qhs	
Simvastatin (eg, Zocor)	5, 10, 20, 40, 80 mg tablets	5–80 mg qhs	
Atorvastatin (eg, Lipitor)	10, 20, 40, 80 mg tablets		

Dosages are provided as a guide only and should be reviewed independently prior to prescribing.
*Children heavier than 40 kg are considered nearly adult sized and are dosed as adults.
†Statin therapy is contraindicated in pregnancy. Liver function tests (LFTs) should be monitored at baseline, after 6 weeks therapy, and then intermittently if normal. Caution patients about rare rhabdomyolysis; creatine phosphokinase should be checked if patient has myalgias. Sleep disturbances and abdominal discomfort are infrequent side effects.

Other Approaches for Severe Hypercholesterolemia

For patients with severe hypercholesterolemia unresponsive to diet or pharmacologic intervention, plasmapheresis or LDL apheresis with a Liposorber column has been successfully used in adults, lowering total cholesterol, LDL, triglycerides, and lipoprotein (a), and perhaps a slowing of the progression of atherosclerosis.[72] The technique has also been used in selected pediatric patients with success,[73] although the issue of vascular access is a difficult one. An interesting new medication approved for use in adults by the US Food and Drug Administration in late 2002 is ezetimibe, a selective inhibitor of cholesterol absorption that reduces LDL by approximately 20% in 12 weeks.[74] This trial included seven participants aged 12 to 17 years, with no particular mention of ill effects in these children; however, the medication has not yet been systematically studied in pediatric patients.

MULTIDISCIPLINARY LIPID CLINIC APPROACH

Because atherosclerosis has a complex and multifactorial pathophysiology, pediatric lipid treatment programs that employ a multidisciplinary approach are more likely to be successful. In our center, the approach is combined nutritional and aerobic activity counseling, along with risk assessment and lipid monitoring. Our impression is that lifestyle habits can be more malleable in children, and changes put into place in younger children might be more likely to have an impact for years to come. This is the prime rationale for seeing children at young ages, along with their families, even if they will not require medication before adulthood.

Contrary to the trend in adult lipid practice, we, along with most groups who see many children with hyperlipidemias, strive to avoid pharmacotherapy and only occasionally use medication in the most severely affected patients. Figure 47-2 describes one such approach to patient management.

Clinic sessions should include group and individual nutritional education, laboratory work (or a review of previously obtained laboratory results), and a session with a clinician. A 3-day food recall provides a basis for individual nutritional counseling at the initial visit and in follow-up. Patient and family group education can include the basics of "good" and "bad" cholesterol, saturated and *trans*–fatty acids, protein, sugars, and fiber, etc. Parents can be taught to read labels and to read between the lines on labels, and children can learn the concept of budgeting their fat and sugar intake so that birthday cake, for example, is not completely off limits but requires a lean period in compensation. It is useful to show children the actual amount of sugar in a can of soda or a serving of juice or the appearance of fat clogging a tube that represents an artery. Methods of "dieting" for children can include using the plate method (Figure 47-3). We stress that "diet" does not mean weight loss for slender patients with genetic hyperlipidemia, but weight loss is paramount in patients with moderate to severe obesity, even when genetic hyperlipidemia is present. In general, emphasizing substitution of foods, as opposed to restricting or eliminating food, is more positive and seems more effective. Table 47-4 presents some simple suggestions for dietary modifications in hyperlipidemia.

The physician or nurse practitioner portion of the visit should involve a review of family history, general medical history, level of physical activity (or lack thereof), and an evaluation of lipid values. Twelve-hour fasting lipid values are the most valuable for children referred to a specialist clinic as it is important to have accurate triglyceride and LDL levels, at least on one or two occasions. At the Children's Hospital, Boston clinic, a healthful breakfast is pro-

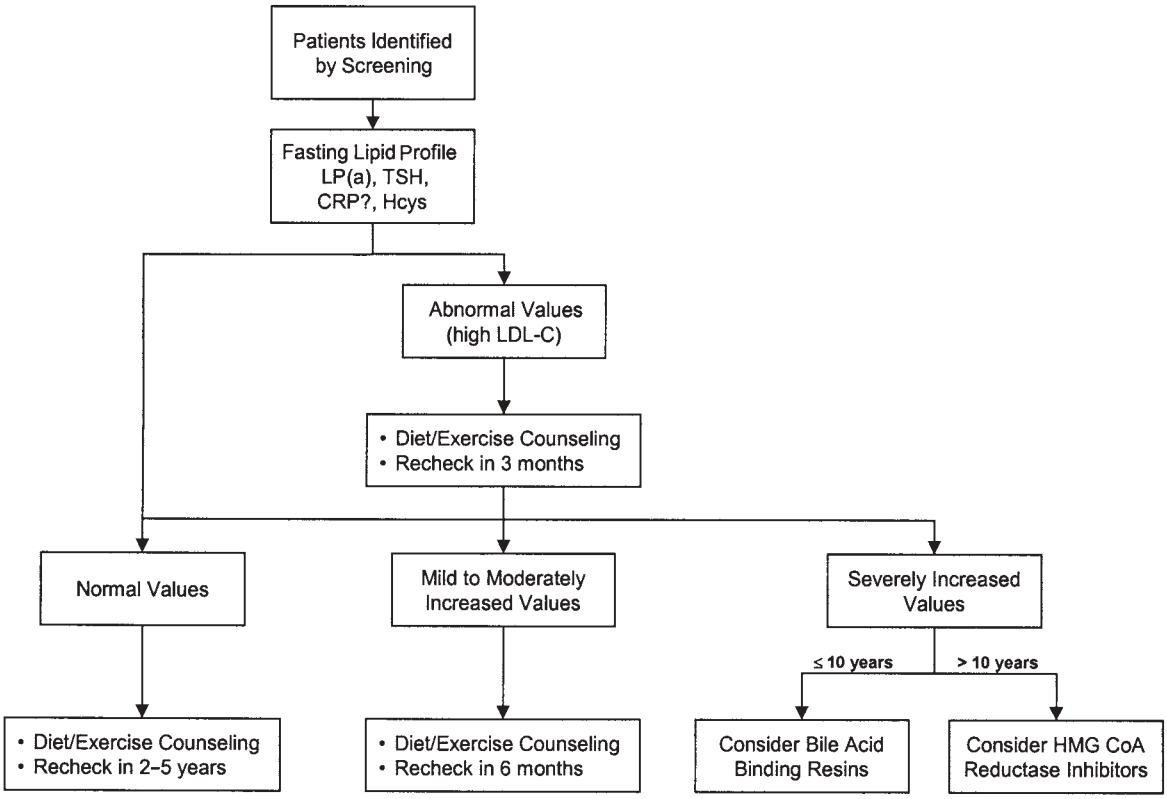

FIGURE 47-2 Proposed approach to young patients ascertained to have high cholesterol on screening. Thyroid-stimulating hormone (TSH) serves as an inexpensive screen for primary hypothyroidism. Lipoprotein (a) (Lp[a]) is an independent risk factor for premature atherosclerosis. The role of highly sensitive C-reactive protein (hsCRP) or homocysteine (Hcys) screening is not defined in pediatrics. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

vided to children after their laboratory samples are drawn, allowing modeling of good eating habits. Because severely affected children in a pediatric lipid setting usually have severely affected parents, we have found that often the most pressing medical issue for the child is having his or her parents tested for hyperlipidemia. It is important to ask about cigarette smoke exposure, to encourage children not to smoke, and to encourage parents not to smoke around their children because it has been shown that children exposed to cigarette smoking have lower HDL levels.[75,76] We stress the need to find physical activities that the child will enjoy.

We try to emphasize that for most children, these issues are not an emergency but rather are long-term modifications that are important not for present health but for cardiovascular risk 30 to 40 years in the future (a nearly unimaginable length of time for most children). This helps parents and children to view this as a long-term project and removes the pressures of enforcing an immediate turnaround. Having only appropriate food in the home is helpful in making choices easier. Lifestyle changes seem to be more effectively made if the entire family joins in the effort. Often, suggested changes are indicated for multiple family members, even if only one child in the family was referred. Follow-up is crucial for monitoring progress, medication compliance, and somatic growth.

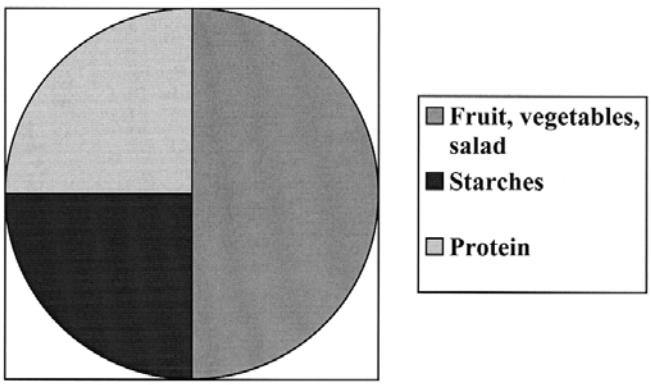

FIGURE 47-3 The "plate method" is a simple means for balancing the diet and reducing carbohydrate consumption without counting calories or grams of fat. The method is highly effective for hypertriglyceridemia and for obesity, if given with a few suggestions: (1) the entire family, not just the patient, should try the method for 4 to 6 weeks and then recheck lipids and weight; (2) the patient must finish the entire plate before having second helpings; and (3) "seconds" cannot be just starches but must again be balanced.

SUMMARY

Pediatric lipid disorders contribute to future cardiovascular risk and as such should be addressed aggressively. Yet at the same time, in the majority of cases, pediatric hyperlipidemias might be most safely, and perhaps most effectively, treated with a multidisciplinary approach that includes aerobic activity, nutritional counseling, and individualized interventions. Care should be exercised to prevent the establishment of negative behavioral patterns because the health implications of dyslipidemias are, for

the most part, far in the future. Future research should focus on longer-term evaluation of antihyperlipidemic medications in young patients and on developing markers of preclinical disease that can be used to evaluate the efficacy of interventions for atherosclerosis prevention.

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CHAPTER 48

CARBOHYDRATE ABSORPTION AND MALABSORPTION

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Carbohydrates are a major dietary source of energy, accounting for 50 to 60% of the calories ingested in the average Western diet after early infancy. The disaccharide lactose is the principal carbohydrate offered to most young infants, whether they are nursed or fed commercial cow's milk formula. Throughout the first year of life, however, sucrose and starch are introduced progressively into the diet as solids and juices; by early childhood, starch will have become the major dietary carbohydrate.

The proportion of newborns in the United States who breast-feed has been increasing.[1–4] In 1971, only about 6% of 6-month-old infants nursed. However, by 1995, about 60% of new mothers initiated breast-feeding and 25% of 6-month-old infants continued to nurse. During the first 6 months of life, human milk and commercial formula account for more than 50% of the total calories in the diet in the United States.[5,6] Human milk has a very high lactose content compared with the milk of other mammals; human milk and commercial formulas contain about 37 and 42% of their calories, respectively, in the form of carbohydrate.[7] Use of soy-based formulas has increased over the past 30 years; as many as 25% of infants in the United States now receive these formulas.[8–10] Soy-based formulas contain carbohydrate as cornstarch, cornstarch hydrolysate, tapioca starch, or sucrose rather than lactose.[8] The carbohydrate content of these formulas is similar to human milk and cow's milk–based formulas.

Baby foods provide less than 10% of the calories ingested by an average 3-month-old infant, with half of this amount coming from cereal.[6] During the entire first year of life, about 20% of the total caloric intake is provided by baby foods. By 12 months of age, table foods account for more than 50% of the calories in an infant's diet.[5] Of the solid foods, fruits become a significant source of carbohydrate by 4 months of age and remain the highest nonformula source of carbohydrate throughout the first year of life (G. H. Johnson, unpublished data). In an average diet for an older child or adult, about 50% of the carbohydrate is in the form of starch; lactose accounts for a decreasing proportion of the total carbohydrate calories, becoming only a minor fraction for many adults.

CARBOHYDRATE DIGESTION AND ABSORPTION

Although carbohydrate is ingested largely in the form of starch and disaccharides, only monosaccharides are actually able to move from the intestinal lumen through the mucosal barrier. Therefore, digestion of complex carbohydrates (ie, hydrolysis) is required for assimilation to occur.

Starch

Most dietary starch consists of either straight chains of glucose with α-(1,4) links (amylose) or straight chains with additional α-(1,6) branches accounting for about 5% of the total linkages (amylopectin). Amylopectin is the major form of starch in the human diet. The primary enzyme of starch digestion, α-amylase, acts only on the interior α-(1,4) linkages of starch. The oligosaccharides released are maltose (2 glucose units), maltotriose (3 glucose units), and the α-limit dextrins, oligosaccharides consisting of up to 6 glucose units with one or more α-(1,6) links, which come from amylopectin. The glucose released is negligible; therefore, the products of starch hydrolysis require further digestion prior to absorption. Amylase is unable to cleave the α-(1,6) linkages of amylopectin and the α-limit dextrins or the β-(1,4) linkage of cellulose.

Carbohydrate digestion begins with the oral exposure of starches to salivary α-amylase (Table 48-1). The role of salivary α-amylase in starch digestion has been uncertain because this enzyme is inactivated at gastric pH. However, starch and the oligosaccharide products of starch digestion have been found to protect the activity of salivary amylase in this pH range, even in the presence of pepsin.[11,12] In neonates, saliva is likely to be an important source of amylase activity, even though salivary enzyme activity is low in premature infants.[12] This function of salivary α-amylase appears to be analogous to the role that lingual lipase serves in fat digestion in newborns.[13]

Human milk, unlike cow's milk, is rich in α-amylase activity (the sum of several salivary isoenzymes).[14,15] This amylase, like salivary α-amylase, may partially compensate for the low level of pancreatic α-amylase activity

TABLE 48-1 Principal Enzymes of Carbohydrate Digestion in Humans and Their Common Substrates

Enzyme	*Substrate*
α-Amylase	
Pancreatic	Starch (interior α-l,4 links)
Salivary and human milk (may be important in neonates)	
Oligosaccharidases	
Sucrase-isomaltase (α–dextrinase)	Sucrose Maltose Maltotriose α-Limit dextrins (α-1,4 and α-1,6 links)
Maltase-glucoamylase	Short glucose polymers (α-1,4 links, activity is greatest for linear polymers) Maltose Maltotriose Starch (α-1,4 links)
Lactase	Lactose

in the duodenum of newborns (see below), in a manner similar to the role that human milk lipase appears to have in neonates.[16] During the first 3 months of life, the α-amylase activity in duodenal fluid is actually lower than the activity in an equivalent volume of the milk ingested by a nursing infant. Amylase activity levels do not vary between preterm and term human milk, throughout a feeding, or between feedings.[17] Storage of expressed human milk for at least 24 hours does not reduce amylase activity levels, even at 15°C to 25°C.[18] Pasteurization of human milk results in only a 15% reduction of activity (in contrast to lipase activity, which is completely abolished).[19]

In the adult, the pancreas secretes α-amylase in marked excess of the normal requirements for starch hydrolysis.[20] When intestinal contents reach the distal duodenum, hydrolysis is essentially complete. Although α-amylase will adhere to the intestinal brush border, intraluminal activity is more than adequate to account for the total amount of starch digested. In fact, adults with pancreatic insufficiency and secondary steatorrhea are usually able to digest starch adequately despite decreased levels of pancreatic α-amylase as well as the absence of electrophoretically identifiable salivary amylase in the duodenal fluid. Auricchio and colleagues demonstrated that infants less than 6 months of age typically have a low concentration of α-amylase activity in the duodenal fluid and a concomitant inability to completely hydrolyze amylopectin following a test meal containing this starch.[21] This pattern of low α-amylase activity in the first 6 months of life has been confirmed by others as well.[22,23] Infants can digest various cooked starches in limited quantities: at 1 month of age, 10 g per day (comparable the amount of starch in formula), and at 3 months of age, 23 g per day (comparable to the quantity of starch taken in cereal and formula at this age).[24] After the first year of life, children have high concentrations of α-amylase activity in their duodenal fluid, and their capacity for digestion of a test meal of starch is comparable to that of adults.

In healthy adults, the form in which starch is offered will greatly influence the degree to which it is digested.[25,26] As much as 10 to 20% of the carbohydrate in a bread composed of wheat flour may not be absorbed in the small intestine, whereas the starch from low-gluten wheat or rice bread (even with added gluten) appears to be completely absorbed. Wheat flour consists of granules of starch surrounded by a protein shell, and this layering effect may interfere with starch digestion. Variable susceptibility to digestion of the starches from a number of cereals has also been shown in vitro.[27] Amylase-resistant starch is a good substrate for colonic fermentation, resulting in short-chain fatty acids (see "Consequences of Carbohydrate Malabsorption" below) and has been used in the treatment of diarrhea.[28]

OLIGOSACCHARIDES

Oligosaccharides, including the products of starch digestion and the dietary disaccharides, are not absorbed intact but must first be split into monosaccharides. Hydrolysis of the oligosaccharides occurs at the luminal surface of the small bowel and is catalyzed by a group of enzymes, the oligosaccharidases (also, although less accurately, called the disaccharidases). These enzymes reside on the exterior surface of the brush border (the microvillus membrane) of the surface epithelium (enterocytes) of the small intestine. The oligosaccharidases are glycoproteins and consist of about 30 to 40% carbohydrate by weight, covalently linked to a protein moiety.[29] These enzymes are composed of a hydrophobic region, which serves as an anchor in the lipid-rich brush border membrane, and a hydrophilic region, which extends into the small bowel lumen and contains the active site.[30]

The surface of the small bowel is covered by a continuous sheet of epithelium. The epithelium proliferates in the crypts and migrates to the villus tips over a period of 3 to 5 days. During this migration, the epithelial cell or enterocyte matures both morphologically and functionally. Oligosaccharidase activity is associated with the mature villus enterocytes but not with the crypt cells. In addition to the normal variation in oligosaccharidase activity along the villus-crypt axis, activity varies along the length of the small intestine, with maximal levels in the proximal jejunum and minimal levels in the proximal duodenum and terminal ileum.[31] The process of synthesis of the oligosaccharidases within the enterocyte and their subsequent transport to the brush border, a region devoid of its own apparatus for protein synthesis, is incompletely understood but has been best studied with the enzyme complex sucrase-isomaltase.[32–34] There is evidence that this protein is synthesized and partially glycosylated in the endoplasmic reticulum. Further glycosylation takes place in the Golgi apparatus, and the nascent enzyme is subsequently incorporated into the brush border membrane.[35] Sucrase and isomaltase are synthesized as one large polypeptide, which is incorporated into the brush border membrane and then split into two subunits by exposure to pancreatic proteases.[33,34,36]

The developmental changes in both sucrase and lactase activities in the neonatal period and the distribution of activity along the small intestine in rodents correlate with the abundance of sucrase-isomaltase and lactase messenger ribonucleic acids (mRNAs), respectively.[37–39] In both rodents and humans, sucrase-isomaltase and lactase mRNAs appear to be absent from crypt epithelial cells and most prominent in the lower to midvillus enterocytes, demonstrated by in situ hybridization, correlating with the distribution of activity.[40–42] As shown in Table 48-1, a number of the oligosaccharidases have the ability to cleave to more than one substrate. The oligosaccharidases are classified as α-glucosidases (including sucrase-isomaltase and maltase-glucoamylase) and a β-galactosidase (lactase), depending on the type of carbohydrate linkage that is split. Many factors are known to influence enzyme activity, including the presence of substrate, hydrolytic products, pancreatic enzymes, and bile, as well as damage to the brush border. Ingestion of a diet rich in substrate sugar generally leads to an elevation in the complementary disaccharidase activity.[43–45] The reduction in sucrase-isomaltase activity associated with elimination of sucrose and starch from the diet can be accounted for by conversion of the enzyme to an inactive protein.[46] Lactase appears to be an exception, and the influence of chronic ingestion of a diet rich in lactose on lactase activity is small and probably not of physiologic importance.[47] It does not appear that this enzyme can be induced by diet in individuals with lactase deficiency, nor does lactase activity drop in individuals with normal levels when given a lactose-free diet.[48,49]

The half-life of the oligosaccharidases in vivo is in the range of 4 to 16 hours. Because migration of the enterocyte to the villus tip occurs over several days, there must be continued synthesis and degradation of these enzymes by the mature enterocyte. It appears that pancreatic proteases, and possibly bile acids and lysolecithin as well, play a key role in the degradation of these enzymes.[50–52] After removal of pancreatic enzymes or bile from the intestinal lumen in laboratory animals, the level of activity of the oligosaccharidases rises, and turnover of enzyme protein is decreased.[50,52] Paradoxically, lactase activity rises in the proximal bowel but falls in the mid–small bowel on removal of these secretions.[53] Treatment of pancreatic insufficiency with enzyme replacement returns the oligosaccharidase activity to normal. With the exception of lactase, this elevation of enzyme activity in pancreatic insufficiency has been demonstrated in humans as well.[54]

During fetal life, there is a characteristic pattern of development of the activities of each of the oligosaccharidases in the small bowel.[55] In humans, lactase is the last of these enzymes to reach the level found in full-term newborns. Because lactose is the major carbohydrate in human milk and most infant formulas, this observation has potential importance when the tolerance of dietary carbohydrate by premature infants is considered.

The oligosaccharidases, with the exception of lactase, have the capacity to hydrolyze substrates at a rate more rapid than the rate at which the resultant monosaccharide products can be absorbed.[56,57] Therefore, monosaccharide absorption, rather than oligosaccharide digestion, is the rate-limiting step for assimilation of these sugars. However, lactose is split at a rate that is lower than that of the mucosal uptake of the glucose and galactose products.[56] Therefore, lactase activity is rate limiting for lactose absorption. Furthermore, in normal individuals, the level of activity of lactase is always lower than the level of activity of sucrase. Lactose hydrolysis has been shown to be inhibited by monosaccharide products but by fructose as well, suggesting that the presence of other disaccharides (eg, sucrose) may also inhibit lactose hydrolysis.[58,59] All of these phenomena contribute to the observation that lactose intolerance is the most common of the acquired oligosaccharide intolerances.

The α-limit dextrins that result from amylopectin hydrolysis are digested by the complementary action of three brush border oligosaccharidases: sucrase, isomaltase (α-dextrinase), and glucoamylase.[60] Glucose monomers are removed in sequence from the nonreducing end of the oligosaccharide. Although all three enzymes are capable of splitting α-(1,4) links, isomaltase appears most active when four or more glucose residues remain; sucrase is most active for three or fewer glucose residues (ie, maltotriose and maltose). Only isomaltase is capable of splitting the α-(1,6) branches. Glucoamylase is especially active for straight-chain glucose polymers with about six glucose units.[61] Studies done in humans suggest that starch and disaccharides ingested in test meals are essentially completely absorbed by the time the intestinal contents reach the distal jejunum.[20,62,63]

Monosaccharides

Most of the monosaccharide that is presented to the intestinal surface during digestion results from hydrolysis of dietary starch and oligosaccharides. Monosaccharides released at the brush border by the oligosaccharidases can either be absorbed directly or can diffuse back into the lumen of the intestine to be absorbed at another site. Because of the size and hydrophilic nature of the monosaccharides, they are not able to move across the brush border membrane by diffusion. Glucose and galactose appear to be absorbed by the same carrier-mediated active process, whereas fructose appears to move across the brush border membrane by facilitated transport in association with a different carrier.[64,65] Infants less than 1 year of age have a decreased capacity for glucose absorption in comparison with adults.[66]

Evidence from in vitro studies has made a strong case for Na+-coupled active transport as the primary mechanism for absorption of glucose and galactose.[64] In the human intestine, about 95% of the dietary glucose ingested by an adult is absorbed by carrier-mediated transport.[67] This finding is in contrast to earlier studies, which had suggested a more important role for passive absorption. Transport of each sugar is saturable, and competitive inhibition suggests that both sugars are transported by the same membrane carrier. All of the sugars transported by this carrier have closely related structures. D-Xylose,

although a pentose, can be transported by the glucose-galactose carrier.

Glucose absorption by enterocytes occurs in two steps: (1) The Na+/glucose cotransporter (SGLT1), a transmembrane protein that is believed to aggregate as a homotetramer, is responsible for active transport across the brush border membrane.[68,69] Glucose is able to bind to the extracellular domain of this protein complex only in the presence of Na+; this interaction causes a conformational change in this transmembrane protein, moving glucose into the cell.[69] (2) Glucose moves out of the enterocyte by facilitated diffusion across the basolateral membrane in association with the transporter GLUT 2.[70] Both carriers have been cloned, sequenced, and expressed.[68,70] In studies in rabbit intestine, SGLT1 mRNA can be found by in situ hybridization in villus but not crypt epithelial cells, and abundance of this mRNA increases sixfold from the base to the tip of the villus.[71] SGLT1 protein has been found only associated with the brush borders of mature enterocytes.[71] Expression of both transporters is increased by exposure to glucose.

Although glucose is absorbed down a concentration gradient during meals, absorption continues as intraluminal glucose concentrations drop below tissue levels. Sodium concentration gradients appear to be the driving force for this transport system. The basolateral membrane transporter GLUT 2 maintains a low intracellular concentration. Therefore, although glucose movement is against a concentration gradient, it is coupled to Na+ movement down an electrochemical gradient. In studies in which Na+ has been removed from a solution bathing the intestine, in vivo or in vitro, glucose transport has been reduced or eliminated.[72,73]

Fructose absorption occurs by facilitated diffusion (ie, carrier mediated but not active transport). Fructose assimilation occurs at the brush border in association with a high-affinity transporter, GLUT 5.[74] Fructose then crosses the basolateral membrane associated with the carrier GLUT 2.[75] Expression of both transporters is increased by the presence of fructose. The capacity of the small intestine to absorb fructose in humans is limited and can be surpassed in some individuals during ingestion of a diet rich in fructose.[76] Excess fructose in the diet of infants, in addition to sorbitol, can be a factor in the development of toddler's diarrhea.[77]

There is another membrane transport mechanism that has been demonstrated for monosaccharides: the hydrolase-related transport system.[78] When intestinal preparations have been studied under conditions in which glucose transport has been saturated, further absorption of glucose could be achieved by introducing a glucose-containing disaccharide into the bathing solution. This transport is Na+ independent. Both glucose and fructose can be transported by this system when the disaccharide is sucrose; however, it is doubtful that this system is of physiologic importance.

CONSEQUENCES OF CARBOHYDRATE MALABSORPTION

The pathophysiologic consequences of carbohydrate malabsorption are similar for all carbohydrates and all underlying etiologies. The range of symptoms and the nutritional effects of carbohydrate malabsorption have been well characterized. The net capacity of the small bowel for carbohydrate absorption is influenced by several variables: (1) the functional capacity of the bowel mucosa for each of the steps of carbohydrate assimilation, (2) the amount of small bowel surface area available (influenced by bowel resection or mucosal damage), and (3) the rate of transit of luminal contents through the intestine. In the past, the small intestine was thought to be the only region of the gastrointestinal tract in which carbohydrate could be absorbed. However, the work of Bond and Levitt (described below) indicates that the colon is capable of conserving malabsorbed carbohydrate and has changed some of our ideas about the factors that influence the consequences of carbohydrate malabsorption.[79–81]

The complete symptom complex of carbohydrate malabsorption can include nausea, crampy abdominal pain, intestinal gas, bloating, abdominal distention, and watery diarrhea. However, not all of these symptoms need occur in every individual with carbohydrate intolerance. Patients may have abdominal pain with little or no diarrhea. Likewise, diarrhea may be present without other symptoms. Because a delay in the onset of symptoms after carbohydrate ingestion can occur, the association may not be obvious.

The surface of the gastrointestinal tract provides a hydrophobic barrier to the passive diffusion of carbohydrate. Therefore, if any step in the assimilation of carbohydrate is blocked, carbohydrate remains in the luminal contents and passes distally. The stomach and proximal small bowel are permeable to water and electrolytes; therefore, nonabsorbed carbohydrate in the lumen of the proximal gastrointestinal tract is diluted with water and electrolytes that have moved across the mucosa to maintain isotonicity. When a mixture of lactose and a nonabsorbable marker, polyethylene glycol (PEG), has been fed to normal individuals, dilution of PEG occurs in the duodenum, and progressive concentration of PEG is found in aspirates from the distal small bowel (Figure 48–1).[82] The increased concentration of PEG represents a decrease in intraluminal volumes resulting from net fluid absorption because PEG does not cross the small-bowel surface. For lactose-intolerant individuals, dilution of the lactose solution occurs in the duodenum as well; however, the concentration of PEG remains low throughout the distal small bowel, suggesting a lack of subsequent reabsorption of intraluminal water. Although net absorption of fluid does occur in the colon in these subjects, it is at a decreased rate. Furthermore, increased transit through the small bowel has been found to occur when carbohydrate is incompletely absorbed.[83] The net secretion of fluid and electrolyte in the small bowel, decreased reabsorption in the colon, and possibly the rapid transit through the small bowel all contribute to the production of a watery diarrhea rich in electrolyte. This has been called an osmotic diarrhea because the diarrhea results from the presence of a poorly absorbed osmotically active solute in the intestinal lumen.[84] These diarrheas are characterized by (1) the fact that they stop when the solute is removed from the diet and (2) a stool osmolality that is at least 50 mOsm/kg greater than twice the sum of stool sodium

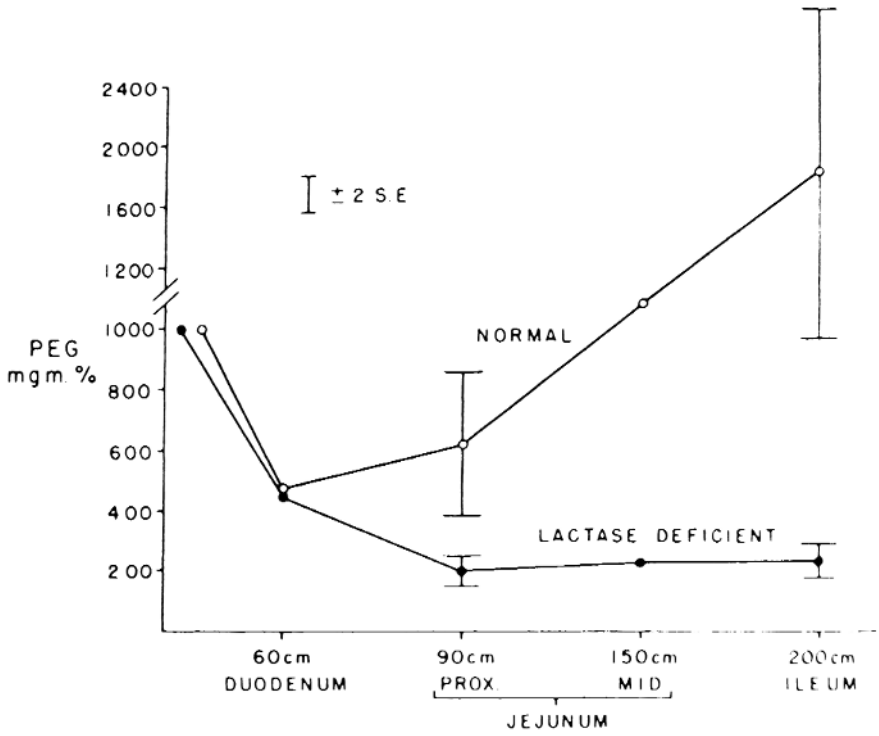

FIGURE 48-1 Polyethylene glycol (PEG) concentration is shown in different regions of the small bowel following ingestion of lactose and PEG by two normal and five lactase-deficient individuals. The small intestinal contents have become diluted in proximal bowel and then concentrated in distal bowel of normal but not lactase-deficient individuals. Reproduced from Christopher NL and Bayless TM.[82]

and potassium concentrations (ie, there is another osmotically active solute present in addition to electrolyte).[83,84]

Unabsorbed carbohydrate reaching the colon is fermented by bacteria, which produce short-chain fatty acids, CO_2, hydrogen (H_2), and methane. This process increases the osmolality of the colonic contents and stool by splitting carbohydrate into smaller units. Gas production and the increased fluid volumes in the intestine probably cause abdominal cramps by distention and altered motility. It is estimated that 1 g of malabsorbed carbohydrate (including the resultant short-chain fatty acids) results in an increase in stool weight of about 30 to 35 g.[85,86]

Bond and Levitt estimated that normal subjects absorbed 92 to 100% of a 12.5 g lactose load in the small bowel, whereas subjects with lactase deficiency absorbed only 22 to 60% of the load. This estimate was derived by collecting ileal contents after ingestion of a mixture of ^{14}C-labeled lactose and a nonabsorbable marker.[80] However, only about 15% of the ^{14}C from the malabsorbed lactose was recovered in the stool, suggesting further assimilation in the colon. Debongnie and colleagues obtained similar results offering subjects cow's milk, except that in two of their four lactase-deficient subjects, lactose malabsorption was not demonstrable (ie, only 0 and 7% of the ingested lactose was recovered from the ileum).[83]

The influence of lactose malabsorption on the absorption of other nutrients has been controversial. One can find studies that suggest that lactose intolerance either does or does not lead to malabsorption of protein or fat. Although small amounts of protein and fat may be malabsorbed along with lactose, this finding does not appear to be nutritionally important.[83] Lactose malabsorption is associated with increased recovery of calcium, magnesium, and phosphate from the ileum, suggesting that there is increased loss of these minerals with lactose malabsorption. Although lactose intolerance has been associated with osteoporosis in adults, causality has not been demonstrated. In situations in which gastrointestinal tract function is compromised (eg, the short-bowel syndrome), steatorrhea secondary to lactose intolerance may become clinically apparent.

Much of the carbohydrate malabsorbed in the small bowel may be conserved in the colon. In patients with lactose intolerance, a greater amount of ^{14}C from radiolabeled lactose is recovered in ileal aspirates than in the stool.[80] In germ-free rats, carbohydrate is not absorbed intact in the colon; fecal bacteria must first ferment the carbohydrate to short-chain fatty acids (including acetic, propionic, and butyric acids), which are then rapidly absorbed.[81,87] Absorption of ^{14}C-labeled sucrose has been compared in healthy subjects and patients with jejunoileal bypass (ie, short bowel).[79] The bypass patients were unable to absorb up to 84% of a 50 g dose of ^{14}C sucrose. For most of these patients, more than 60% of the ^{14}C that passed the ileum was absorbed in the colon. The normal individuals absorbed 95 to 98% of the sucrose load in the small bowel, and less than 1% of the ^{14}C was recovered in the stool. These studies suggest that in clinical situations in which there is malabsorption of carbohydrate, a large proportion of the carbohydrate can be salvaged in the colon by fermentation to short-chain fatty acids, which are then absorbed. Of the ^{14}C that remained in the feces, the major portion was nondialyzable (either incorporated into macromolecules or bound to nondialyzable components of the feces) and was, therefore, neither available for absorption nor osmotically active. It has been calculated that up

to 540 kcal per day in the form of short-chain fatty acids may be absorbed in the colon of an adult.[87] In the normal subjects, the amount of sucrose reaching the terminal ileum was only a small part of the total dose but was great enough to cause an osmotic diarrhea if not removed in the colon. Variability of the factors influencing this mechanism of colonic conservation of carbohydrate (eg, changes in colonic flora) may explain, in part, the wide range of symptoms that can occur with similar degrees of carbohydrate malabsorption. Variability of other gastrointestinal disorders such as irritable bowel, chronic constipation, and antibiotic-related diarrhea may have a similar basis.

TESTS OF CARBOHYDRATE INTOLERANCE

A wide array of tests are available to identify carbohydrate maldigestion and malabsorption. Each test has advantages and disadvantages, but none correlates perfectly with clinical symptoms. Most tests evaluate bowel function by measuring carbohydrate absorption or malabsorption, although disaccharidase assays measure mucosal enzyme activity directly. Clinical suspicion of a carbohydrate intolerance may be aroused when the introduction of a particular carbohydrate or group of carbohydrates into the diet results in diarrhea or abdominal pain. A typical example would be diarrhea that starts when sucrose-containing solids (eg, fruits) are introduced into the diet of an infant with congenital sucrase-isomaltase deficiency. Similarly, the resolution of diarrhea with the removal of a carbohydrate from the diet may be a clue to the diagnosis. As an example, diarrhea following a viral gastroenteritis may be secondary to a transient lactose intolerance and, if so, will resolve when lactose is removed from the diet.

Screening tests for carbohydrate intolerance include evaluation of stool-reducing substances and pH, as well as measurement of stool osmolality and electrolyte concentration. Examination of stool for reducing sugars is a simple bedside test that is especially useful in infants.[88] The test is done using Clinitest tablets (Ames), and the method is similar to that for measuring glucose in the urine. Five drops of stool are mixed with 10 drops of water, and a Clinitest tablet is added. Trace or 0.25% is not considered abnormal, but a greater reaction is considered a positive test. It must be remembered, however, that sucrose is not a reducing sugar. Therefore, it is recommended that if the patient has been given a sucrose-containing diet, the stool must first be heated to boiling with 0.1 normal HCl, instead of water, to hydrolyze the sucrose. The test is then carried out as described previously. Unfortunately, the proportion of both false-positive and false-negative reactions is high when the stool is evaluated for sucrose.[89] Breast-fed neonates will normally have some lactose in the stool; therefore, a positive Clinitest reaction in this group is not necessarily abnormal. We have seen a purple Clinitest reaction, occurring in an infant with phenolphthalein-induced, factitious diarrhea.[90] Presumably, this color was a combination of a blue negative reaction of the Clinitest plus a pink indicator reaction on alkalinizing the stool with Clinitest. If the amount of carbohydrate malabsorbed is small, the diarrhea is mainly secondary to the osmotic effect of luminal organic acids and associated cations; however, as the amount of malabsorbed carbohydrate becomes greater, unmetabolized carbohydrate makes a large contribution to the diarrhea.[91] This may explain some of the false-negative stool Clinitest reactions in individuals with carbohydrate malabsorption and diarrhea. Stool pH may also be a sign of carbohydrate malabsorption. As described previously in the section on consequences of carbohydrate malabsorption, when carbohydrate reaches the colon, it is fermented by bacteria, and organic acids (short-chain fatty acids) are produced. Depending on the buffering capacity of the stool, this process may lower the pH. A fecal pH < 5.6 has also proved to be a reliable screening test for carbohydrate malabsorption, as demonstrated in human volunteers with diarrhea induced by nonabsorbable carbohydrates.[84,89] The pH may occasionally be abnormal during carbohydrate malabsorption, despite a negative Clinitest, and this additional information can be useful.

The measurement of stool osmolality, as well as sodium and potassium concentration, will identify osmotic diarrhea of any etiology. As noted previously, if the osmolality of a stool is greater than two times the sum of the sodium and potassium concentration in the stool (this number includes the associated anions), an osmotic diarrhea is likely. Malabsorbed carbohydrate and osmotic cathartics are the two most common groups of solutes to cause an osmotic diarrhea.

Starch malabsorption is rarely a clinical problem, and no routine clinical studies specifically identify this disorder. Duodenal α-amylase activity can be quantitated using a standardized secretin-pancreozymin test.[22,23]

Carbohydrate Tolerance Tests

Carbohydrate tolerance tests have been among the most readily available and most widely performed tests of carbohydrate absorption in the past. Following ingestion of a carbohydrate, the patient is evaluated for a rise in blood sugar, which, when present, suggests that absorption has occurred. Symptoms that develop during the test can also be correlated with the results. The advantages of this test include its simplicity, lack of sophisticated equipment, relatively noninvasive character (compared to small-bowel biopsy), and potential correlation with symptoms. The disadvantages are not insignificant, however, and include a high rate of both false-positive and false-negative studies as well as the necessity of drawing repeated blood specimens. Factors other than an individual's capacity for carbohydrate absorption can alter the blood sugar level and include the rate of gastric emptying, hormonal influences on blood glucose, and the rate of peripheral metabolism of glucose. Delayed gastric emptying has been a common cause of false-positive tolerance tests in children. This problem can be circumvented by administering the carbohydrate directly into the duodenum using a nasoduodenal tube; however, this method reduces the simplicity of the test.

Tolerance tests have been used most commonly to study absorption of glucose, xylose, lactose, and sucrose. None of these tests has been well standardized. The quan-

tity of sugar administered can vary from 0.5 to 2.0 g/kg (maximum 50 to 100 g), usually given in a 10% aqueous solution. The timing for collection of blood samples varies from as frequent as 0, 15, 30, 45, 60, 90, and 120 minutes to a single sample 45 to 60 minutes after ingestion. Generally, a rise in blood sugar of 20 mg/dL is interpreted to represent adequate absorption. Both glucose and xylose require the glucose-galactose carrier system for uptake; malabsorption of these sugars has generally been used as an indirect measure of mucosal damage or decreased surface area (eg, the short-bowel syndrome). Glucose metabolism is influenced so greatly by factors other than mucosal absorption that D-xylose, a pentose that is not metabolized, has been used preferentially. Commonly, xylose is given as 0.5 g/kg; fasting and 1-hour blood samples are collected for measurement of blood xylose levels. In older children and adults, a 5-hour urine sample can be collected and analyzed to determine the percentage of the dose of xylose that is excreted. However, there are studies both supporting and questioning the usefulness of xylose absorption as a screening test for mucosal damage.[92–95] The most common clinical situation in which this test might be of use is in evaluating a patient for celiac disease. Unfortunately, one cannot always rely on an adequate rise in blood xylose level to exclude celiac disease.

Disaccharide tolerance tests have been useful in screening for lactase and sucrase deficiencies. However, the breath H_2 test, which is described below, is simpler and more accurate and has largely replaced the use of tolerance tests. Because glucose is released on hydrolysis of both lactose and sucrose, absorption should lead to an elevation of blood glucose. In one study of the standard lactose tolerance test performed in adults with normal lactase activity (demonstrated by small-bowel biopsy), 28% of the subjects had a maximal rise of blood glucose of less than 20 mg/dL.[96] When the administration of 50 or 100 g of lactose was compared, there was no difference in the percentage of individuals with normal curves. In 50% of the individuals, the blood glucose value had peaked at 15 minutes. Some investigators have felt that the reliability of this test can be increased by the use of capillary samples rather than venous blood.[97] An older test, which is rarely used now, involves the simultaneous ingestion of lactose and ethanol. The ethanol inhibits conversion of galactose to glucose, and the blood galactose level is then measured.

Disaccharidase Assay

Quantitation of oligosaccharidase activity in the mucosa of the small intestine has been the standard against which other tests of disaccharide intolerance have been measured. Tissue from the distal duodenum or proximal jejunum is obtained for study by capsule or endoscopic biopsy.[98,99] If the tissue is immediately frozen, these enzymes will remain stable for months. Assays are done by homogenizing the tissue in buffer, incubating the homogenate with the appropriate substrate (usually a disaccharide) at 37°C, and measuring the quantity of glucose released during a given period of time.[100] Although disaccharidase assays are generally performed in this manner, there are minor variations among laboratories, including the type of buffer used and the pH at which the incubation is done. Therefore, mean values and ranges may vary somewhat from one laboratory to another for any substrate studied, but these figures ought to be fairly consistent within the same laboratory. The enzyme activities most commonly assayed are sucrase, lactase, and maltase, using the substrates for which they are named. The substrate frequently used for the measurement of isomaltase activity has been palatinose because highly purified isomaltase is not readily available. Activities are usually expressed per gram wet weight of the mucosa and per gram mucosal protein (ie, specific activity).

Disaccharidase activities are easily quantitated in this manner. However, activity levels may not always correlate well with symptoms.[101] Although the small-bowel biopsy sample is taken from a region of the bowel that ought to exhibit near-maximal disaccharidase levels, it is, nevertheless, a sample of only a small area and may not be representative of the total bowel activity. This problem may occur with a disorder that causes patchy damage to the bowel or with the short-bowel syndrome. Alterations in the colonic conservation of carbohydrate will also influence symptoms.

Breath Hydrogen Test

The breath hydrogen test remains the most widely used method of analysis of carbohydrate intolerance. Carbohydrate that is malabsorbed in the small bowel will be fermented by bacteria in the colon, releasing hydrogen, CO_2, and methane gas. A portion of this gas is absorbed and subsequently expired in the breath (about 15 to 20% of the H_2 produced in the colon).[102,103] Although the original technique of measuring expired H_2 involved a continuous, closed, rebreathing system for collection, sampling is now usually done at 30-minute intervals, and a rise in H_2 content of more than 10 to 20 ppm over the fasting value (measured by gas chromatography) is considered consistent with carbohydrate malabsorption. The measurement of breath hydrogen content is therefore an indirect, semiquantitative test of carbohydrate malabsorption. It offers the advantage of being a simple, noninvasive, and sensitive study.

The method of collection of breath samples has been adapted for use with infants and children.[104] In addition, samples may be collected in the field and stored for later analysis. In fact, many of the most recent epidemiologic studies of lactose intolerance have incorporated this technique.

Breath methane concentration has been used to enhance the reliability of breath testing for carbohydrate malabsorption. However, the likelihood of methane production is low before 3 years of age. Individuals who produce methane and not H_2 gas are rare, and the sensitivity and specificity of the breath methane test are lower than those of the breath hydrogen test for lactose malabsorption.[105]

Bond and Levitt demonstrated the excellent correlation of breath H_2 content with lactose malabsorption by studying lactose-tolerant and -intolerant adults who had ingested 12.5 g of radiolabeled lactose.[80] Lactose malab-

sorption in the small bowel was determined by measuring the radiolabeled lactose in aspirates from a peroral tube placed in the distal ileum. Simultaneous breath samples were collected and analyzed for H_2 content. For each subject, breath hydrogen was also analyzed after the ingestion of a standard amount of nonabsorbable carbohydrate (lactulose). Comparison with this standard made it possible to quantitate the amount of carbohydrate malabsorbed by an individual through measurement of the H_2 excreted in the breath. The resultant plot of lactose malabsorption, shown in Figure 48–2, demonstrated the excellent correlation of breath H_2 excretion with ileal aspiration of malabsorbed lactose (coefficient of correlation = .94).

For infants and children, it is generally possible to identify either lactose or sucrose intolerance by collecting samples at 30-minute intervals for a total of 90 minutes after ingestation of 1 to 2 g/kg and up to 50 g of the sugar of interest.[105,106] A rise in breath H_2 content of either 10 or 20 ppm has been recommended as the cutoff for a positive test; a threshold of 10 ppm is associated with greater sensitivity but lower specificity compared with 20 ppm.

Many uses have been described for the breath hydrogen test and include the identification of isolated lactose or sucrose intolerance, small-bowel mucosal damage or decreased surface area (eg, short bowel), and bacterial overgrowth. However, potential problems in interpretation of the breath hydrogen test exist. As with all of the other tests for carbohydrate intolerance, a positive study is not always accompanied by symptoms (or even a history of previous symptoms). Because breath hydrogen analysis is a more sensitive measure of carbohydrate intolerance than many of the previously available tests, it is likely that identification of subclinical carbohydrate malabsorption will occur more frequently. Conversely, about 2% of the population lack the bacterial flora necessary to produce hydrogen gas in the colon and can therefore have a negative test despite carbohydrate malabsorption.[107] The use of antibiotics shortly before the test may alter the intestinal flora and influence colonic fermentation, thereby reducing the breath hydrogen level. If the ability of an individual to produce hydrogen gas is in question, this problem can be settled by performing a breath hydrogen study following the administration of lactulose. Ingestion of this poorly absorbed sugar should lead to hydrogen production, and a negative result indicates a lack of ability to produce hydrogen gas. A diarrheal illness or the presence of rapid transit may affect results as well. In addition, the breath hydrogen concentration rises during both sleep and cigarette smoking. Finally, a lower rate of H_2 production has been demonstrated when lactose has been given in whole milk rather than in an aqueous solution.[108]

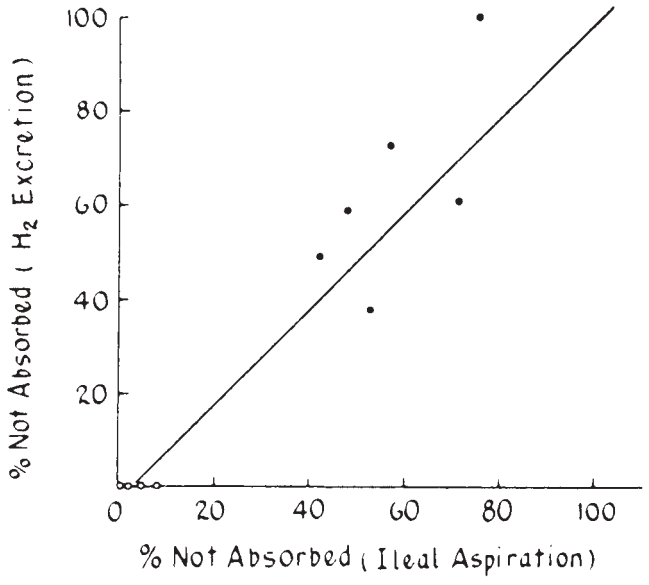

FIGURE 48-2 Correlation of lactose breath test with ileal aspiration as a measure of lactose malabsorption. Reproduced from Bond JH and Levitt MD.[80]

PRIMARY DISORDERS OF CARBOHYDRATE ABSORPTION

Starch Intolerance

Clinically apparent starch malabsorption is uncommon. Infants less than 6 months of age normally have very low levels of α-amylase activity in the duodenum and therefore do have the potential for starch malabsorption.[22] Although starch malabsorption is uncommon, Lilibridge and Townes have described an infant with chronic diarrhea that appears to have been secondary to starch intolerance.[109] In a 1-month-old infant, starch provided 7% of the infant's dietary calories, and this proportion had increased to 16% by age 4 months. However, no α-amylase activity was found in a duodenal aspirate. Treatment by removal of starches from the diet resulted in improved stools, accelerated growth, and a drop in the intake from 300 to 120 kcal/kg/day. When the infant reached 1 year of age, the duodenal fluid contained low levels of α-amylase activity. At that time, starches were reintroduced into the diet without incident. In addition to this child, a patient with isolated absence of pancreatic amylase activity from the duodenal fluid and with chronic gastrointestinal symptoms suggesting malabsorption has been described by Lowe and May.[110] Although this patient had low trypsin activity, lipase activity was normal. In addition, salivary amylase was present.

Lebenthal and colleagues found reduced glucoamylase activity in 3% of assays performed in small-bowel biopsy samples from 511 children with chronic diarrhea.[111] In about 40% of the small group with reduced activity, glucoamylase deficiency was considered to be secondary to mucosal damage, and in the remainder, it was considered to be a primary deficiency. A subgroup of the children with glucoamylase deficiency was studied, and in some but not all of the children, symptoms appeared to be related to starch ingestion.

As mentioned previously, Anderson and colleagues have demonstrated that when starch is offered in the form of wheat flour, adults frequently have evidence of small-bowel malabsorption.[25] This observation has raised the possibility that some of the "functional" bowel diseases

might be caused or at least influenced by starch malabsorption. In addition, these investigators have suggested that the symptoms of some organic bowel diseases (eg, inflammatory bowel disease) might be potentiated by wheat in the diet.

Primary Disaccharidase Deficiencies

Primary Lactase Deficiency Lactose intolerance is the most frequent of all of the clinical syndromes of carbohydrate malabsorption. Although secondary disorders of lactose digestion are common in infancy, the primary disorders are of greater importance in older children and adults. There are three primary disorders of lactase deficiency: (1) developmental, (2) congenital, and (3) late onset (adult onset).

Lactase, unlike the other commonly measured disaccharidases, develops to the level of activity seen in full-term newborns late in the third trimester of gestation only.[55] Therefore, it is thought that premature infants commonly have low levels of lactase activity proportionate to their degree of immaturity.

MacLean and Fink evaluated a group of 22 healthy infants, ranging from 29 to 38 weeks of gestational age, who received a commercial infant formula containing lactose.[112] Serial measurements of breath hydrogen excretion were made. It was found that hydrogen excretion increased during the first 3 weeks of life and that, by this age, all of the infants were excreting levels that would be consistent with lactose intolerance in an older infant. The lack of evidence of lactose intolerance in some of the younger infants probably reflected the small volumes of formula taken initially. This study suggests that all premature infants probably do malabsorb lactose, although this is rarely symptomatically significant. Calculations based on the H_2 excretion over a period of time after feedings suggested that an average of about 65% of the lactose ingested by these infants reached the colon. However, all of the infants gained weight well, and the mean stool output was only 6 g per day. This finding suggests that colonic conservation of carbohydrate (see "Consequences of Carbohydrate Malabsorption") was likely to have been operative in these infants. In addition, there was no evidence that feeding the infants lactose stimulated more rapid development of lactase activity. It appears, therefore, that lactose malabsorption may be a normal event in premature infants, although it is usually not associated with symptoms. In fact, this process may encourage the development of a fecal flora, which prevents colonization of the colon with enteropathogens. It may not be necessary or even optimal to restrict lactose ingestion by asymptomatic premature infants.

Congenital lactase deficiency is an extremely rare disorder that has been infrequently reported, in contrast to late-onset hypolactasia, which is common (discussed later).[113–115] Diagnosis of the congenital form requires severely reduced or absent small bowel lactase activity in the newborn period, in association with normal mucosal histology and normal levels of the other disaccharidases. Lactase activity remains abnormal throughout life. The low levels of lactase activity that can be found in this disorder have been thought to be secondary to nonspecific hydrolysis of lactose by lysosomal acid–β-galactosidase rather than brush border lactase.[116] The former enzyme does not appear to play a physiologic role in lactose digestion. In a study in which brush border proteins from four children with congenital lactase deficiency were separated on polyacrylamide gels, the protein band corresponding to lactase was markedly reduced or absent in each case.[117] The mobility of the lactase band was normal, suggesting that activity was reduced because of decreased amounts of enzyme protein but not because of the synthesis of an altered protein.

The most common and most extensively studied of the disaccharide intolerances has been adult-onset hypolactasia (also known as adult-onset or late-onset lactose intolerance). Although this entity is never apparent at birth, it is a primary disaccharidase deficiency that appears later in life. Epidemiologic evidence suggests that this deficiency is an autosomal recessive characteristic, although this has not been definitely confirmed.[118–120] Late-onset lactose intolerance actually is not an abnormality or disease; if one considers the world's population, only a minority of people have the persistence into adulthood of the elevated lactase levels of infancy. Lactose intolerance beyond weaning, in fact, is typical of all mammals other than humans. Therefore, it is the people who have persistence of these high levels of lactase activity into adulthood who really are "atypical" or "abnormal." Nevertheless, because humans continue to eat and drink dairy products beyond infancy, they have the potential for the development of symptoms from lactase deficiency.

One of the most interesting aspects of late-onset hypolactasia is the variable prevalence of this trait among different racial and ethnic backgrounds. Lactose intolerance is common among adult Semitics, Asians, Africans, Eskimos, and American Indians (North and South), occurring in up to 80 to 90% of unmixed populations.[121] However, it is rare in Northern Europeans as well as in several tribes from Africa and India, occurring in only 10 to 20% of unmixed populations.[120] In the United States, up to 70% of blacks but less than 20% of whites have been found to be lactose intolerant.[122]

Two explanations have been offered for the difference in lactose tolerance among populations. One explanation is that lactase activity might be induced by substrate and that certain populations have had high levels because they ingest greater amounts of lactose. The bulk of the evidence in studies of animals and humans suggests that lactase is not an enzyme that can be induced to any useful extent.[48,123] The alternative explanation has been that lactose tolerance is genetically determined and has had a selective advantage in groups that historically have consumed dairy products as a major component of their diet. This hypothesis is consistent with the dietary practices of those populations that are known to be largely lactose tolerant.

A number of studies have confirmed the impression that lactose intolerance is inherited as an autosomal recessive trait.[118,119,124] In a study of Nigerian families, if both parents were lactose intolerant (21 families), only 1 offspring in

56 was lactose tolerant.[119] If one parent was lactose tolerant, 55% of the offspring were lactose tolerant. In a study including 156 American Indians, the likelihood of having lactose intolerance, identified by breath hydrogen excretion following an oral lactose load, was in direct proportion to the percentage of Indian blood of an individual.[118]

Despite the name "late-onset hypolactasia," the age of onset of this entity is quite variable among ethnic backgrounds and often occurs in early childhood. In Thailand, nearly all native adults have been lactose intolerant. In a study of 172 Thai infants and children, lactose intolerance was demonstrated to occur by 2 years of age in about 85% of this group; a standard lactose tolerance test was used.[125] Some of the children had sucrose or glucose tolerance tests as well, and these tests were virtually always normal, suggesting that the lactose intolerance was not secondary to generalized mucosal damage. The levels of lactase activity measured in small-bowel biopsies from a limited group of the Thai children supported the impression that lactase deficiency was widespread in this group. The age of onset of lactose intolerance was delayed in village children compared with institutionalized children, although still usually less than 2 years of age. The investigators speculated that environmental factors might have influenced the age of onset and specifically noted that, although nutrition was comparable in the two groups, episodes of acute enteritis were more common in the institutionalized children. Newcomer and colleagues studied a group of American Indians (Leech Lake Indian Reservation, Minnesota) in which 66% of the subjects demonstrated lactose intolerance using the breath hydrogen test.[118] Lactose intolerance was already present by 5 years of age, the youngest subjects studied. Johnson and colleagues demonstrated intolerance in 7 of 11 Pima Indians, aged 3 to 5 years, using a lactose intolerance test.[126]

Late-onset hypolactasia, identified by the standard lactose tolerance test, has been found to develop in blacks in the United States between the age of 6 and the teenage years.[127] Although Welsh and colleagues have suggested that the reduced lactase levels of late-onset lactose intolerance may develop by as early as 3 years of age in blacks, this finding has not been well documented. Both Lebenthal and colleagues and Welsh and colleagues have found that among whites, abnormal lactase levels are not seen before 5 years of age.[128,129] As in blacks, the incidence of symptomatic late-onset lactose intolerance probably increases gradually into the teenage years. These findings have led to the observation that if evidence of lactose intolerance (by breath hydrogen or standard lactose tolerance test) is found in a black under 3 years of age or a white under 5 years of age, one should always consider the possibility that there has been damage to the intestinal mucosa.[130]

The identification of lactose intolerance by screening tests does not necessarily correlate with the presence of symptoms and has resulted in confusion in the interpretation of these tests. Although the quantity of lactose that an individual ingests influences the degree of symptoms of lactose intolerance, the threshold for development of these symptoms varies among individuals. This observation may result from variation in the levels of residual lactase activity along the length of the bowel but is more likely to be related to factors that influence the colonic conservation of carbohydrate. Among individuals with late-onset lactose intolerance, symptomatic tolerance for lactose may range from the quantity present in half a glass up to 1 quart or more of milk. Bedine and Bayless evaluated the threshold for symptoms of lactose malabsorption among 20 adults with lactose intolerance (6 of whom were asymptomatic).[131] Of this group of subjects, 75% developed symptoms, which included abdominal fullness, bloating, flatulence, or diarrhea, within 3 to 4 hours after ingesting 12 g or less of lactose (Figure 48–3). This amount is equivalent to the quantity of lactose in one glass of milk. However, only about two-thirds of the subjects who developed these complaints had a previous history of symptomatic intolerance in association with the ingestion of one glass of milk. Above the threshold for an individual, symptoms became more severe with greater amounts of lactose. Interestingly, the threshold did not appear to correlate well with the jejunal lactase level. Similar findings have been observed in a study from Denmark.[132] However, more recently, individuals who considered themselves to have severe lactose intolerance were able to tolerate as much lactose as in an 8-ounce glass of milk daily without symptoms.[133] Individuals who do become symptomatic with the ingestion of lactose should tolerate an equivalent amount of a glucose and galactose mixture without any problem.[122]

Studies of schoolchildren and hospitalized adults suggest that lactose-intolerant individuals as a group do tend to drink less milk than individuals who are lactose tolerant.[122,134] Newcomer and colleagues found that among individuals with lactase deficiency, symptomatic lactose intolerance is more common in adults than in children.[118] Likewise, when subjects were given 50 g of lactose (or 2 g/kg if this were lower), children were less likely to develop symptoms than adults at an equivalent quantity of lactose per kilogram of body weight (Figure 48–4). In a double-blind study of the symptoms associated with lactose intolerance among healthy teenagers (including 42 lactose-tolerant and 45 lactose-intolerant individuals), no statistical difference was found for the occurrence of symptoms noted by either group after drinking 8 ounces of either a lactose-containing or placebo drink.[135] After ingesting 16 ounces of the lactose drink, however, 16% of the intolerant subjects did have symptoms that seemed to be related to the lactose.

As described in the section on consequences of carbohydrate malabsorption, Bond and Levitt demonstrated in their study of lactose absorption that lactose-tolerant individuals malabsorbed up to 8% of a 12.5 g lactose load, whereas intolerant individuals malabsorbed 42 to 75% of the load in the small bowel (Figure 48–5).[80] However, only a small fraction of the lactose was actually recovered in the stool because of bacterial degradation of the sugar and colonic absorption of the resultant short-chain fatty acids.

The extent to which late-onset lactose intolerance contributes to the etiology of recurrent abdominal pain of childhood (RAP) has been an area of great interest. RAP is probably the most common chronic symptom of child-

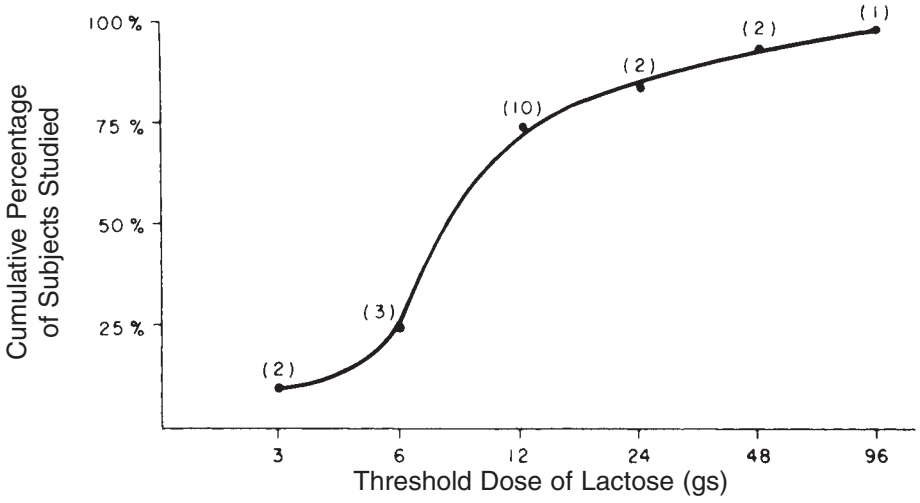

FIGURE 48-3 Cumulative percentage of subjects developing symptoms with increasing quantities of lactose. The number of subjects first symptomatic at each dose is given in parentheses. From Bedine MS and Bayless TM.[131])

hood, occurring in more than 10% of school-aged children.[136,137] Yet it is often not possible to identify an organic etiology. In 1971, Bayless and Huang described a group of five children (6 to 13 years of age) with RAP that appeared to be caused by lactose intolerance, despite the absence of diarrhea.[138] These observations and others have stimulated speculation that lactose intolerance might be the etiology for a large segment of RAP in childhood. Barr and colleagues reported that 40% of a group of 80 children with RAP studied prospectively were lactose malabsorbers, as defined by the breath hydrogen test.[106] However, among these lactose-intolerant children, it was not possible by history to associate symptoms with lactose ingestion. Although there was a trend toward more frequent symptoms following a lactose load among the lactose-intolerant individuals, 68% of the tolerant individuals complained of symptoms that could have been associated with lactose malabsorption as well. Of the malabsorbers, 28 participated in diet trials with and without lactose; 71% reported more frequent symptoms on the lactose-containing diet. Although this study suggests that lactose intolerance might have an important etiologic role in RAP, the diet trial was neither blinded nor controlled. In addition, two subsequent studies have not confirmed this hypothesis. Lebenthal and colleagues found that although about 40% of a group of patients with RAP had resolution of symptoms on a milk-elimination diet continued for 1 year, this percentage was no greater than the frequency of resolution of symptoms in groups of lactose absorbers fed either a similar or an unrestricted diet for the same period of time.[139] Wald and colleagues reported a prospective study of 40 children with RAP.[140] They demonstrated that 30% of the children were lactose malabsorbers when defined by a breath test using a load of 2 g/kg (maximum of 50 g) of lactose. This lactose load and the response were similar to those reported by Barr and colleagues[106]; however, when the breath tests were repeated using 12.5 g of lactose (equivalent to one glass of milk), only about 30% of the individuals previously identified as malabsorbers had abnormal studies. The presence of symptoms during the breath test did not discriminate between lactose-tolerant and lactose-intolerant individuals. Patients were then given lactose-elimination diets without knowledge of the results of their breath hydrogen tests. Although 25% of the lactose malabsorbers showed improvement in their symptoms of pain, 18% of the lactose absorbers also improved, and these response rates were not statistically different from one another. In addition, none of the three children who demonstrated abnormal breath hydrogen tests when given only 12.5 g of lactose improved during the lactose-free period. Considering all of these

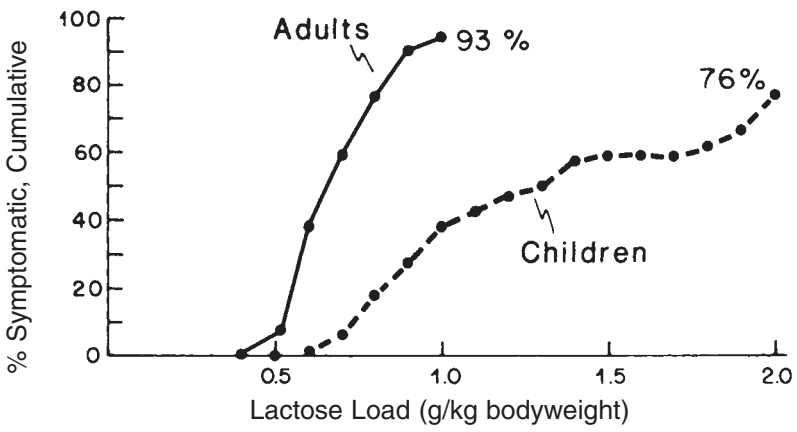

FIGURE 48-4 Cumulative percentage of subjects developing symptoms with increasing quantities of lactose (expressed g/kg body weight) is compared for adults and children. From Newcomer AD et al.[118]

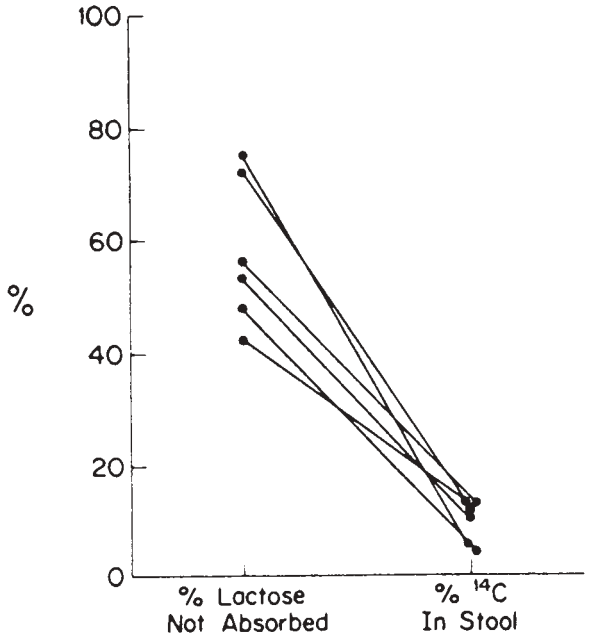

FIGURE 48-5 Comparison of the quantity of lactose not absorbed as determined by ileal aspiration with that derived from stool ^{14}C after ingestion of radiolabeled lactose by six lactase-deficient subjects. From Bond JH and Levitt MD.[80])

studies, it seems that lactose intolerance is undoubtedly the cause of RAP in a small proportion of patients but probably not in the 30 to 40% of these patients originally described. The extreme sensitivity of the breath hydrogen test, the large lactose loads used in these studies, and the high rate of placebo effect of diet treatment have probably led to an overestimation of the importance of lactose intolerance as a primary etiology of RAP.

Perhaps of greater importance is the possibility that lactose intolerance might exacerbate the symptoms of other gastrointestinal disorders (eg, inflammatory bowel disease [IBD]). Because late-onset lactose intolerance is common, it is inevitable that among individuals with another disorder, a subgroup will have lactose intolerance as well. This finding has led to some confusion about the role of lactose intolerance in the production of symptoms in patients with other gastrointestinal disorders. Despite the clinical impression that lactose intolerance can at times contribute to symptoms in IBD, lactose intolerance has been observed to be no more common in a group of children with IBD than in a group with RAP.[141] Although a comparison with normal subjects was not made, the prevalence of lactose intolerance is probably no greater in patients with IBD than in a healthy population of similar ethnic background. As mentioned previously, normal individuals commonly malabsorb small amounts of ingested lactose in the small bowel.[80] Patients with other gastrointestinal diseases, such as IBD, may be unable at times to compensate for even the small quantity of lactose that normally reaches the colon, and this factor may contribute to their symptoms.

It has been demonstrated that lactase enzyme from the small bowel of individuals with late-onset lactose intolerance has normal motility on polyacrylamide gel electrophoresis, but the enzyme is present in the brush border in decreased quantities.[117] Subsequently, similar observations have been made using the more sensitive technique of crossed immunoelectrophoresis.[142] Although decreased amounts of lactase protein were found in brush border membranes, the enzyme had normal activity per unit of enzyme protein, and no variants with abnormal mobility were found. This study suggests that individuals with late-onset lactose intolerance have either decreased synthesis or increased degradation of brush border lactase but do not produce an inactive enzyme.

In individuals without adult-onset hypolactasia (ie, those who have persistently high small-bowel lactase activity as adults), lactase mRNA is found uniformly in all villus enterocytes, and lactase protein, as well as lactase activity, is present uniformly at the brush border.[42] Individuals with adult-onset hypolactasia may have different patterns of development of lactase deficiency as a result of alterations at the transcriptional or translational level.[143–146] Even on a single villus from an individual with adult-onset hypolactasia, some enterocytes may have (1) no detectable lactase mRNA, (2) lactase mRNA but no detectable brush border lactase protein, (3) lactase protein but no activity, or (4) lactase protein and lactase activity.[42,147] Some enterocytes contain as much lactase mRNA as seen in the enterocytes of individuals without hypolactasia. Thus, enterocytes with different phenotypes are present on the same villus. Enterocytes with different patterns of lactase expression occur in a patchy distribution, indicating that they are not arising in a clonal pattern. The mechanism of this variable expression remains to be elucidated. Perhaps differences in the proportion of enterocytes with each pattern of expression explain the differences in mechanisms of adult-onset hypolactasia among individuals.

Studies of Finnish families with adult-onset hypolactasia have found no DNA variations in the coding or promoter region of the lactase gene but instead a variant of a *cis*-acting element roughly 14 kb upstream from the lactase gene. Evaluation of additional DNA samples from four different populations demonstrated the same pattern.[148] Studies indicate that the mutation causing the rare disorder congenital lactase deficiency lies outside the region of the lactase gene as well.[149]

Congenital Sucrase-Isomaltase Deficiency In humans, a congenital deficiency of small intestinal sucrase is always associated with a deficiency of isomaltase, and this entity is known as congenital sucrase-isomaltase deficiency.[150–154] This deficiency is much less common than late-onset lactose intolerance. It is found in about 0.2% of North Americans and in up to 10% of Greenland Eskimos.[153] Congenital sucrase-isomaltase deficiency appears to be hereditary and transmitted as an autosomal recessive trait. The association of these two enzyme deficiencies is, in fact, no surprise because these enzymes are synthesized together, inserted into the brush border membrane as one large protein, and subsequently cleaved into two units, which continue to remain closely associated.[32,34,36]

Characteristically, congenital sucrase-isomaltase deficiency first presents at the time of introduction of sucrose into the diet. This sugar may be introduced in a sucrose-containing formula (usually soy based) or in solid foods (especially fruits). The symptoms are typical of all of the syndromes of carbohydrate malabsorption: diarrhea, bloating, flatulence, and cramps. Failure to thrive may be a prominent component in young infants. On clinical presentation, these infants may be mistakenly thought to have gluten-sensitive enteropathy; however, they can also present with mild symptoms and adequate growth, suggesting chronic nonspecific diarrhea.[150,151] A rarer presentation has been protracted diarrhea in infants fed glucose polymer formula.[152] Older children with congenital sucrase-isomaltase deficiency can develop an aversion to sucrose-containing foods, which limits their intake of this sugar.

A suspicion that this disorder may be responsible for a patient's symptoms can first arise from the results of routine screening tests for sugar intolerance. The diagnosis should be confirmed by the characteristic pattern of small-bowel disaccharidase activity: extremely low or absent levels of activity of sucrase and isomaltase coincident with a normal level of lactase activity. Typically, the activity of lactase is the most sensitive to mucosal damage and the most greatly reduced in secondary disaccharidase deficiency. Therefore, the enzyme pattern seen with congenital sucrase-isomaltase deficiency should not be confused with the pattern of mucosal damage.

There have been conflicting hypotheses about the molecular basis of congenital sucrase-isomaltase deficiency. Dubs and colleagues, in 1973, reported studies of patients with this disorder, which included immunofluorescent staining of small-bowel biopsies with an antibody against the human sucrase-isomaltase complex.[155] They were able to demonstrate the presence of an immunoreactive protein in the brush border region of the villi of most of the patients studied and believed that this demonstrated the presence of an inactive enzyme. In 1974, Preiser and colleagues reported studies in which they performed gel electrophoresis with small intestinal brush border preparations from two siblings with congenital sucrase-isomaltase deficiency[156]; they observed the absence of the protein band usually associated with sucrase-isomaltase activity. Because no new protein band was identified, these investigators believed that this disorder resulted from a decrease in the amount of sucrase-isomaltase protein rather than the presence of an altered enzyme. In 1976, Gray and colleagues used a sensitive radioimmunoassay to demonstrate the complete absence of enzyme protein (both active and inactive) in seven patients with congenital sucrase-isomaltase deficiency.[153] A curious observation was that the fraction of total enzyme protein in the inactive form was greater for relatives of patients with congenital sucrase-isomaltase deficiency than for normal individuals. The investigators suggested that voluntary sucrose restriction in the diet of these family members might have influenced enzyme activation.

Several phenotypes of sucrase-isomaltase deficiency have been identified by localization of sucrase-isomaltase protein in small-bowel biopsies using monoclonal antibodies.[157] In different individuals, enzyme protein accumulates in the endoplasmic reticulum or Golgi or is transported to the brush border with reduced activity. These findings suggest the likelihood of at least three mutations causing different phenotypic expressions of sucrase-isomaltase deficiency. Consistent with this observation, mutations of the sucrase-isomaltase gene have been demonstrated to result in sucrase-isomaltase proteins that are either secreted and lost at the cell surface or retained in the endoplasmic reticulum and Golgi.[158–160]

Congenital Trehalase Deficiency Trehalase deficiency is a common disaccharidase deficiency in Greenland, occurring in about 8% of the population.[161] However, this deficiency does not appear to have nutritional importance.

Primary Monosaccharide Intolerance

Glucose-galactose malabsorption is the only known primary monosaccharide intolerance. It is an extremely rare disorder, with less than 25 cases having been reported.[162] Infants with this disorder present with diarrhea shortly after the first feeding that contains glucose, galactose, or any oligosaccharide composed of either of these sugars. Lactose, the principal carbohydrate of human milk, consists of glucose and galactose subunits; therefore, infants with this disorder will not be spared symptoms by nursing. Furthermore, infants with congenital glucose-galactose malabsorption will not tolerate sucrose (glucose-fructose), invert sugar (glucose + fructose), or glucose polymers. In fact, this diagnosis should be considered when a neonate has diarrhea in association with carbohydrate malabsorption and is found to tolerate fructose alone. The disorder is thought to be hereditary with an autosomal recessive mode of transmission, and many of the children reported have been the products of consanguineous matings.[162]

In vitro studies with radiolabeled glucose and galactose have demonstrated that the small-bowel mucosa from patients with congenital glucose-galactose malabsorption cannot concentrate these sugars, in contrast to the mucosa from normal subjects.[163,164] Small-bowel perfusion studies have also demonstrated decreased absorption of these sugars in vivo.[162] The mucosal histologic appearance and the capacity for absorption of fructose have both been shown to be normal. It is thought that this disorder represents a deficiency or defect in the specific glucose-galactose carrier protein of the brush border of the small intestine. Although the transport of glucose and galactose is markedly reduced in this disorder, no further decrease in uptake occurs with the in vitro introduction of phloridzin, which competitively binds to the carrier.[163] This observation has raised the possibility that there is a defect in the binding site of the glucose-galactose carrier. With the cloning of SGLT1, two siblings have been described with a mutation in the *SGLT1* gene leading to a defect in the Na+/glucose cotransporter and secondary glucose-galactose malabsorption.[165] Remission of symptoms with increasing age has been described even though active jejunal glucose transport remains absent in these patients.[166]

Patients with primary glucose malabsorption have been identified using the breath hydrogen test with a relatively small glucose challenge (0.1 g/kg), in the absence of any associated symptoms.[162] With greater quantities of glucose or galactose (0.5 or 1.0 g/kg, respectively), loose, acidic stool developed and contained reducing substance; however, fructose (2.0 g/ kg) was well tolerated.

SECONDARY DISORDERS OF CARBOHYDRATE ABSORPTION

Many forms of injury to the mucosa of the small bowel may lead to transient carbohydrate intolerance. Often histologic abnormalities will be noted to be concomitant with the carbohydrate intolerance; however, the mucosa can appear relatively normal by light microscopy, especially with a transient disaccharide intolerance. Infants seem to be more prone to secondary disorders than older individuals, and carbohydrate intolerance commonly occurs in association with infantile gastroenteritis. Intolerance for disaccharides alone or in combination with monosaccharides may occur, but the former is more common. Acquired monosaccharide intolerance usually suggests severe small-bowel mucosal damage, manifested as moderate to severe villous atrophy on light microscopy and damaged microvilli on electron microscopy.[167]

During acute infantile diarrhea, malabsorption of both monosaccharides and disaccharides has been demonstrated by small-bowel intubation studies.[168] Occasionally, transient lactose intolerance can persist for a period of months. The likelihood that this will occur seems to correlate with the severity of the diarrheal illness and the degree of malnutrition.[169] Aside from this association with transient lactose intolerance, there is a suggestion that malnutrition may potentiate the initiation of late-onset lactose intolerance at an earlier age.[170] A substantial proportion of childhood infectious diarrhea is caused by viruses (primarily rotavirus); the pathogenesis of this diarrhea involves acute damage to mature villus epithelial cells with replacement by rapidly migrating but immature crypt epithelial cells.[171] These immature epithelial cells exhibit decreased disaccharidase activity as well as decreased capacity for glucose absorption. When a group of patients with rotavirus gastroenteritis were evaluated with a lactose breath hydrogen test during the acute illness, an abnormal study was noted in most of these children, but 1 week later, the test was normal in all.[172]

Bacterial overgrowth in the small intestine may be associated with both mono- and disaccharide intolerance.[173] In fact, this overgrowth may be the mechanism of the sugar intolerance that occasionally follows gastrointestinal surgery in neonates.[174] An animal model for bacterial overgrowth, which has been extensively studied, has been surgically prepared blind loops of bowel in the rat.[175–178] A reduction of disaccharidase activity in these blind loops appears to be secondary to an increase in brush border glycoprotein degradation rather than decreased synthesis.[176] Although increased amounts of deconjugated bile salts have been thought to be a mediator of the disaccharidase deficiency in bacterial overgrowth, this may not be the case.[177] Bacterial extracts prepared from anaerobic organisms isolated from blind loops have been shown to have the ability to remove disaccharidases from isolated brush borders, most likely as a result of an elastase-like protease activity.[178]

Some species of *Bacteroides* have been shown to have what appears to be a unique ability to secrete proteases, which release maltase and sucrase when incubated with human brush borders.[179] Similar protease activity has been found in fluid aspirated from the small intestine of patients with bacterial overgrowth. Other clinical disorders that have been associated with secondary carbohydrate intolerance include giardiasis, gluten-sensitive enteropathy, cow's milk protein intolerance, and protracted diarrhea of infancy. Recently, an association of abnormal lactose breath hydrogen tests with cancer chemotherapy has been demonstrated.[180] Therefore, a wide variety of agents may produce damage to the small bowel mucosa and secondary carbohydrate intolerance, which can occasionally be slow to resolve.

TREATMENT OF CARBOHYDRATE INTOLERANCE

Attempts to induce enzyme activity as a treatment for patients with oligosaccharidase (disaccharidase) deficiencies have not been successful. Chronic ingestion of lactose by individuals with late-onset lactose intolerance does not alter their ability to digest lactose or their level of small-bowel lactase activity.[48,123,125] Although the ingestion of a diet rich in fructose will stimulate an increase in the level of small bowel sucrase activity in normal individuals,[181] Greene and colleagues were able to demonstrate only a slight rise in sucrase activity, which did not reach a normal level, when a child with congenital sucrase-isomaltase deficiency was given a diet rich in fructose.[182]

The most direct method of treatment of sugar or starch intolerance has been the elimination of the malabsorbed carbohydrate from the diet. For young infants, special formulas are available that are lactose, sucrose, or even carbohydrate free. The carbohydrate-free formulas require an added sugar. In addition, formulas are available with glucose polymers (five to nine glucose units in length). The use of these polymers rather than an equivalent amount of glucose results in a reduction in the intraluminal osmolality in the small bowel.[183] Infants with an acquired monosaccharide intolerance caused by small-bowel mucosal damage will exhibit net fluid secretion during perfusion of the jejunum with glucose.[184] If the glucose is replaced with an equal concentration of a short-chain glucose polymer, the secretion will be decreased or even reversed.[184] Presumably, the lower osmolality of the polymer improves fluid balance. However, there is at least one case report in which an infant recovering from chronic protracted diarrhea tolerated oral glucose but not a glucose polymer.[185]

Infants with congenital glucose-galactose malabsorption tolerate dietary fructose well.[163,164] However, a secondary monosaccharide intolerance will usually involve all of the monosaccharides, and, if severe, a period of total parenteral nutrition (TPN) may be necessary. The use of a modular formula will allow a gradual increase in dietary

TABLE 48-2 Comparison of Lactose Content of Various Milk Products

Product	*Lactose (g)*
1 cup (approximate)	
Milk	11–12
2% milk (low fat)	9–13
Skim milk	12–14
Chocolate milk	10–12
Buttermilk	9–11
Low-fat yogurt	11–15
Cottage cheese	5
Cottage cheese (low fat)	7–8
Ice cream	9–10
Sherbet, orange	4
1 ounce (approximate)	
Cheddar cheese	0.4–0.6
American cheese	0.5
Swiss cheese	0.4–0.6
Cream cheese	0.8
Parmesan cheese (grated)	0.8
Butter (2 pats)	0.1

Adapted from Welsh JD.[187]

monosaccharide, as tolerated, and a simultaneous decrease in the proportion of calories provided by TPN.[186]

For carbohydrate intolerance, restriction of other carbohydrate-containing foods and drinks becomes critical once infants are no longer taking formula alone. Lists are available that provide the lactose or sucrose content of common foods (Tables 48–2 and 48–3),[150,187] but it is often useful to have a trained dietitian help with diet planning. How vigorously the diet needs to be restricted will depend on the individual's symptomatic response to dietary treatment. The use of commercially prepared lactase enzyme to split the lactose in milk (described later) has simplified the treatment of lactose intolerance. Of course, a combined secondary lactase and sucrase deficiency is more difficult to treat because the diet becomes so restrictive. It should be mentioned that although congenital sucrase deficiency is always associated with isomaltase deficiency and isomaltase is active in starch digestion (especially in the digestion of α-limit dextrins), starch intolerance is generally not a problem in this disorder, and there is usually no need for restriction of starch intake.

Lactase-deficient individuals tolerate yogurt with fewer symptoms than anticipated, considering the amount of lactose in this milk product (see Table 48–2). A lactase enzyme has been identified in yogurt, which is inactive prior to ingestion but active at body temperature (37°C) and small intestinal pH (7).[188] This enzyme is active in small-bowel contents and allows lactase-deficient individuals to absorb a large fraction of the lactose in a yogurt meal. The use of probiotic agents has been considered in the treatment of lactose intolerance, but efficacy has not been established.[189,190]

In addition to food intolerances, it is important to remember that medications contain sugars, which may be a source of symptoms for some patients. Lists of sugar-free drugs are periodically available in the pharmaceutical literature, and drug companies should be consulted directly if there is concern about a specific medication.[191] Patients with disaccharide intolerance will usually tolerate sugar substitutes, although it is important to keep in mind that the use of these products does restrict the caloric intake. Sorbitol, a poorly absorbed polyalcohol sugar used in many "sugar-free" products, may produce an osmotic diarrhea as well as gas, bloating, and cramps.[192] For patients on low-sugar diets, it is important to consider sorbitol as a potential cause of chronic symptoms suggestive of a sugar intolerance.

Commercially produced lactase enzyme products are available to add to foods or take with meals containing lactose to reduce symptoms.[193] This enzyme is prepared by extraction of bacterial or yeast β-galactosidases. If added to cow's milk at room or refrigerator temperature and when allowed to sit for a specified period of time, it will hydrolyze up to 95% of the lactose. Taste acceptance of the milk prepared in this manner is good. This kind of product allows for bulk production of low-lactose dairy products. This technical advance may have excellent possibilities in areas of the world where the majority of individuals are lactase deficient and where cow's milk products could be an important staple in the diet (see Appendix, Tables A-16 and A-24).[98] Sacrosidase, an enzyme with sucrase activity isolated from *Saccharomyces cerevisiae*, has been studied in the treatment of congenital sucrase-isomaltase deficiency.[194] This

TABLE 48-3 Food with Low Sucrose Content

Foods	*Less Than 1% Sucrose*	*Between 1% and 2% Sucrose*
Fruits, fruit juices	Gooseberries	Boysenberries
	Blackberries	Cherries (Bing)
	Currants	Grapes (Tokay or Thompson seedless)
	Lemon	Guava
	Rhubarb	Lime juice
	Pomegranate	Pear
	Cranberries	Figs
	Loganberries	Raspberries
		Strawberries
Vegetables	Tomato	Beans (lima)
	Tomato juice	Carrot
	Bamboo shoots	Rutabaga
	Beans (snap, string, green)	Squash (golden, crookneck)
	Cabbage	Bean sprouts
	Cauliflower	Black-eyed peas
	Celery	
	Corn	
	Cucumber	
	Eggplant	
	Lettuce	
	Potato (white)	
	Pumpkin	
	Radishes	
	Squash (Hubbard, butternut)	
Grains, cereals, nuts, sweetening agents	Corn meal	Wheat flour
	Puffed rice	Whole-grain cereals, crackers with whole wheat
	Rice (brown, white)	
	Wheat flour (patent)	
	Macaroni, spaghetti	Honey
		Pecans

Adapted from Ament ME et al.[150]

treatment has been shown to decrease symptoms of gas, abdominal cramps, bloating, and diarrhea.

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CHAPTER 49

NUTRITIONAL ANEMIAS

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Anemia is defined as an inadequate circulating red cell mass to prevent tissue hypoxia. Anemia can be related to blood loss, decreased red cell production, increased red cell destruction, or a combination of these events. When anemia occurs as a consequence of a nutritional deficiency, any of these pathologic processes may be involved. Vitamin deficiencies that have been implicated as causes of anemia in humans include vitamin A, members of the vitamin B group (pyridoxine, riboflavin, folic acid, and vitamin B_{12}), vitamin C, and vitamin E. Among minerals, iron and copper are recognized as essential for optimal erythropoiesis. Complex nutritional disturbances, such as those observed in starvation and protein-calorie deficiency states, can also result in anemia.

Hemoglobin, hematocrit, and red cell indices (mean cell volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]) are the initial laboratory assessments used to diagnose anemia. It is important to recognize and adjust for the age-related changes in these parameters when assessing anemia in the pediatric age group (Table 49-1). An initial evaluation of these parameters can help to classify the anemia as one caused by decreased red cell production versus increased red cell destruction, acute blood loss, or impaired hemoglobin production. If the anemia is secondary to inhibited hemoglobin synthesis, the anemia will be microcytic and hypochromic (decreased red cell indices). Conversely, if the anemia results as a consequence of a disturbance in cell maturation, the anemia may be macrocytic (increased red cell indices). If the deformability of the red cell membrane is altered, the anemia will have a hemolytic component, an elevated reticulocyte count, and normocytic or macrocytic red cell indices. Nutritional deficiency states may result in a combination of decreased hemoglobin synthesis, abnormal red cell maturation, and increased red cell destruction. In some nutritional deficiency states, such as protein-calorie malnutrition, decreased red cell production is also noted.

The most common nutritional deficiency responsible for anemia is iron deficiency. Nutritional deficiencies of folic acid or vitamin B_{12} are also occasionally encountered, and patients with chronic illness may have other vitamin, mineral, and protein deficiencies contributing to anemia. This chapter reviews relationships between nutritional deficiencies and anemia and discusses responsible mechanisms. The etiology of many of the vitamin and mineral deficiencies is not discussed in detail as this information is provided elsewhere in this book

VITAMIN DEFICIENCY ANEMIAS

Vitamin A Deficiency

Chronic deprivation of vitamin A results in an anemia with certain characteristics similar to those observed in iron deficiency. Mean red cell volume and MCHC are reduced, anisocytosis and poikilocytosis may be present, and serum iron values are low.[1–4] Unlike iron deficiency, however, liver and marrow iron stores are increased, serum ferritin values are normal, serum transferrin concentration is usually normal or decreased, and the administration of therapeutic doses of iron may not correct the anemia. These findings suggest that the basis for this hypochromic, microcytic anemia may be related to a failure of iron transport from storage sites to active metabolic pools.

Nutritional surveys conducted in developing countries have supported a relationship between serum concentration of vitamin A and blood hemoglobin concentration.[5] An excellent correlation was demonstrated in a study of 532 children in Karachi, Pakistan, between retinol levels and hemoglobin, hematocrit, and red blood cell levels.[6] A correlation between plasma retinol and hemoglobin was observed experimentally in adult men in the United States with induced vitamin A deficiency confirming a causal relationship of vitamin A to anemia.[2] Finally, studies in underdeveloped countries with a high prevalence of vitamin A deficiency have shown that treating anemia with vitamin A in combination with iron is more effective than treatment with iron alone, supporting a causal relationship.[2,7–10]

Pyridoxine Deficiency

The vitamin B_6 group includes pyridoxal, pyridoxine, and pyridoxamine. These substances are all phosphorylated to pyridoxal-5-phosphate, which is an essential cofactor in heme biosynthesis mediated by d-aminolevulinic acid synthetase.[11,12] In some experimental animals, pyridoxine deficiency produces anemia and ringed sideroblasts.[13] Experimental induction of vitamin B_6 deficiency in two infants was associated with a hypochromic, microcytic anemia,[14] and a malnourished patient has been described whose hypochromic anemia failed to respond to iron therapy but subsequently responded to the administration of vitamin B_6.[15]

TABLE 49-1 Red Blood Cell Values at Various Ages: Mean and Lower Limit of Normal (–2 SD)*

	Hemoglobin (g/dL)		*Hematocrit (%)*		*RBC Count (10^3/L)*		*MCV (fL)*		*MCV (pg)*		*MCHC (g/dL)*	
Age	*Mean*	*–2 SD*	*Mean*	*–2 SD*	*Mean*	*–2 SD*	*Mean*	*–2 SD*	*Mean*	*–2 SD*	*Mean*	*–2 SD*
Birth (cord blood)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1–3 d (capillary)	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29
1 wk	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28
2 wk	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28
1 mo	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29
2 mo	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29
3–6 mo	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30
0.5–2 yr	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30
2–6 yr	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31
6–12 yr	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31
12–18 yr												
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31
18–49 yr												
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	26	34	31
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	26	34	31

*These data have been compiled from several sources. Emphasis is given to recent studies employing electronic counters and to the selection of populations that are likely to exclude individuals with iron deficiency. The mean ± 2 SD can be expected to include 95% of the observations in a normal population. Adapted from Dallman PR. In: Rudolph A, editor. Pediatrics. 16th ed. New York: Appleton-Century-Crofts; 1977.
MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume.

Nutritional deficiencies of pyridoxine are extremely rare, although occasionally patients receiving therapy with antituberculosis drugs such as isoniazid, which interferes with the transport of pyridoxine to cells,[13,16,17] develop a microcytic anemia, which can be corrected with large doses of pyridoxine.[18,19] A small percentage of patients who have congenital or acquired sideroblastic anemia improve while on pharmacologic doses of pyridoxine.[20,21] There are also reports of sideroblastic anemia owing to vitamin B_6 deficiency in patients on hemodialysis.[11] Coadministration of pyridoxine with isoniazid or during dialysis should decrease the risk of these complications.

Riboflavin Deficiency

Although anemia secondary to riboflavin deficiency has been demonstrated in several animal models, it has been difficult to establish a direct casual role in humans.[22] The best evidence is provided by experimental studies. Human volunteers with malignancies maintained on a riboflavin-deficient diet and fed the riboflavin antagonist galactoflavin develop pure red cell aplasia.[23] Vacuolated erythroid precursors are evident prior to the development of aplasia. Red cell indices are normal, and the reticulocyte count is low. This anemia can be corrected by the administration of riboflavin. Confirmation of this response to riboflavin supplementation has been seen in both human adult and pediatric populations with anemia.[24,25] Riboflavin-deficient children given riboflavin demonstrated a decrease in serum iron and transferrin saturation accompanied by an increase in hemoglobin if the initial hemoglobin was below 13.5 g/mL, suggesting a relationship between riboflavin and iron use.[25]

Rat studies have shown that riboflavin deficiency is associated with reduced iron absorption and increased iron loss.[26,27] It has been proposed that this enhanced iron loss is the result of an accelerated rate of epithelial turnover in the small intestine.[28] In addition, ferrokinetic studies in humans receiving the riboflavin-deficient diet and galactoflavin demonstrated prolonged plasma clearance and distribution of iron primarily to liver and spleen in contrast to bone marrow in normals. Clearly, riboflavin has an important role in erythropoiesis probably by altering iron metabolism.

Riboflavin deficiency produces a decrease in red cell glutathione reductase activity.[29,30] Glutathione reductase is necessary for glutathione peroxidase to effectively regulate cellular redox potential.[31,32] Under normal conditions, the decrease in glutathione reductase activity is not associated with an increased sensitivity of the red cell to oxidant-induced injury.[33] It is possible that certain conditions in conjunction with riboflavin deficiency will leave the red cell vulnerable to oxidation injury, causing hemolytic anemia; however, this has not been described in humans.

Vitamin C (Ascorbic Acid) Deficiency

It is still unclear whether ascorbic acid has a direct role in hematopoiesis or whether the anemia observed in subjects with ascorbic acid deficiency, scurvy, is a result of the interactions of ascorbic acid with folic acid and iron metabolism. Although approximately 80% of individuals with scurvy are anemic,[34] attempts to induce anemia in human volunteers by severe restriction of dietary ascorbic acid have been unsuccessful.[35,36] Confusion arises because the anemia observed in subjects with scurvy may be hypochromic, normocytic, or macrocytic, and the marrow may be hypocellular, normocellular, or hypercellular. In about 10% of patients, the marrow is megaloblastic.[34]

Ascorbic acid is required to maintain folic acid reductase in its reduced, or active, form. Impaired folic acid reductase activity results in an inability to form tetrahydrofolic acid, the metabolically active form of folic acid. It has been demonstrated that patients with scurvy and

megaloblastic anemia excrete 10-formylfolic acid as the major urinary folate metabolite. Following ascorbic acid therapy, 5-methyltetrahydrofolic acid becomes the major urinary folate metabolite in these patients. This observation has led to the suggestion that ascorbic acid prevents the irreversible oxidation of methyltetrahydrofolic acid to formylfolic acid.[37] Failure to synthesize tetrahydrofolic acid or to protect it from oxidation in scurvy ultimately results in the appearance of a megaloblastic anemia. Under these circumstances, ascorbic acid therapy will produce a hematologic response only if sufficient folic acid is present to interact with the ascorbic acid.[38]

Iron deficiency in children often occurs in association with ascorbic acid deficiency. Scurvy may cause iron deficiency as a consequence of external bleeding. Iron balance may be further compromised by ascorbic acid deficiency because this vitamin facilitates intestinal iron absorption.[39] Ascorbic acid increases the bioavailability of iron through two mechanisms. First, it can reduce Fe^{3+} to Fe^{2+}, which is more soluble and less likely to form insoluble hydroxides at low pH than Fe^{3+}. Second, it forms a stable complex with iron, preventing iron from complexing with dietary constituents, such as tannins and phytates, which block transport into gastrointestinal mucosal cells.[40] Patients with scurvy, particularly children, often require both iron and ascorbic acid to correct a hypochromic, microcytic anemia,[41] and, rarely, a combination of iron, ascorbic acid, and folate may be required.[42]

Despite the evidence linking ascorbic acid deficiency to alterations in either folic acid or iron metabolism, many patients with scurvy have a normocytic, normochromic anemia accompanied by a persistent reticulocytosis of 5 to 10%. Ascorbic acid has antioxidant properties, and it is possible that a deficiency of this vitamin renders the cell susceptible to oxidant injury. This is of particular interest in regard to the possible reducing effects of ascorbic acid on oxidized vitamin E, much like those described above for folic acid.[43] Administration of ascorbic acid to patients with scurvy who have hemolysis produces an initial increase in reticulocyte count, followed by a rise in hemoglobin concentration and an ultimate correction of hematologic abnormalities.[44]

Folic Acid and Vitamin B_{12} Deficiencies: The Megaloblastic Anemias

The fundamental biochemical defect that results from deficiency of either folic acid or vitamin B_{12} is decreased synthesis of deoxyribonucleic acid (DNA). This decreased synthesis of DNA appears to be the result of the inadequate conversion of deoxyuridylate to thymidylate and is largely owing to inadequate quantities of 5,10-methylenetetrahydrofolate for participation in the necessary single-carbon transfer reaction.[45] Vitamin B_{12} is required for the release of folate from its circulating and stored methyl form so that it can return to the tetrahydrofolate pool for conversion to 5,10-methylenetetrahydrofolate. In vitamin B_{12} deficiency, folate is trapped as methylfolate, which is metabolically inactive. This event is known as the "folate trap" hypothesis.[46–48]

The morphologic representation of this decreased DNA synthesis is the megaloblast. Megaloblasts are nucleated red blood cells that display a lacy nuclear chromatin and prominent parachromatin pattern and an apparent dyssynchrony of maturation between the nucleus and the cytoplasm. This dyssynchrony is produced by the slow DNA synthesis in the nucleus in relation to the near-normal synthesis of ribonucleic acid (RNA) in the cytoplasm. Although the morphologic abnormalities present in the maturing erythroid precursors are regarded as the hallmark of folic acid or vitamin B_{12} deficiency, morphologic abnormalities are also evident in the myeloid and megakaryocytic cell lines, resulting in morphologic abnormalities in granulocytes and platelets. Owing to the involvement of multiple cellular elements in marrow, the diagnosis of megaloblastic anemia can be confused with the diagnosis of acute myelogenous leukemia.

Nutrient deficiency of either folate or vitamin B_{12} will eventually result in a similar megaloblastic anemia. However, not all megaloblastic anemias are attributable to a lack of these vitamins because any abnormality that limits DNA synthesis can produce megaloblastosis. Other examples include orotic acid, which is a precursor of uridine, thiamin deficiency, Lesch-Nyhan syndrome, congenital dyserythropoietic anemias, and as a complication of chemotherapeutic agents (methotrexate and cytosine arabinoside), antimalarial agents, and antibacterial agents (trimethoprim). Some of these antifolates have an affinity for dehydrofolate reductase (DHFR), and when intracellular folate concentrations are low, they may inhibit DHFR activity and cause folate deficiency.

In an established case of megaloblastic anemia, the circulating red cells are macro-ovalocytic, and their MCV is increased to a range of 105 to 160 fL. The presence of simultaneous iron deficiency may obscure the macrocytosis, resulting in a normocytic anemia. In either folate or vitamin B_{12} deficiency, polychromia and fine basophilic stippling of the erythrocytes are observed, and Howell-Jolly bodies, which are nuclear remnants normally extruded from the erythrocyte during cell maturation, may be present. The concentration of serum iron is usually increased owing to impaired erythrocytosis. The red cell life span is modestly reduced, perhaps owing to an abnormality in membrane properties related to the dyserythropoietic state. A significant degree of ineffective erythropoiesis is present.[49] This may be reflected by an increase in the serum bilirubin concentration and an increase in serum lactate dehydrogenase (LDH).[50] Unconjugated serum bilirubin concentration may reach a range of 2.0 to 3.0 mg/dL.

The earliest morphologic change in the megaloblastic anemias is alteration in the circulating granulocytes. The polymorphonuclear leukocytes are hypersegmented. In the normal child, 2.6 segments are the average; in patients with folate or vitamin B_{12} deficiency, the average number of nuclear lobes generally exceeds a mean value of 3.0. In the normal subject, fewer than 3.0% of the circulating leukocytes have five lobes; in contrast, in megaloblastic anemias, nuclear hypersegmentation will result in the presence of polymorphs with six or more nuclear segments.[50] In severe forms of deficiency, both neutropenia and thrombocytopenia can be present.

Folate or vitamin B_{12} deficiency may occur as a result of inadequate ingestion, absorption, or use owing to congenital or acquired defects or increased requirement, excretion, destruction, or loss of these nutrients. Deficiencies of either folate or vitamin B_{12}, from any mechanism, are uncommon in the pediatric population in the United States.

Folic Acid Deficiency

The folic acid molecule consists of a pteridine moiety, coupled by a methylene bridge to a *p*-aminobenzoic acid molecule, which, in turn, is covalently bound to a glutamic acid residue. Natural folic acid occurs primarily as polyglutamates. These polyglutamates must be broken down to monoglutamates before intestinal absorption can occur. This reaction requires the presence of the enzyme γ-glutamylcarboxypeptidase (conjugase), which is present in the mucosal border of the small bowel. A folate binder exists on the enterocyte surface. Monoglutamates are absorbed through both active and passive mechanisms. An etiologic and pathophysiologic classification of folate deficiency is shown in Table 49-2.

Most of the folate in the blood is in the form of 5-methyltetrahydrofolic acid and is transported in free form or loosely associated with serum proteins.[51] Specific folate binding proteins also have been found in plasma and tissues that have similarities to receptors on the surface of some cells.[52] Only small quantities of folate are normally found in the urine; this excretion of 1 to 10 μg per day is a result of both the tight plasma binding of folate and the tubular resorption of any filtered vitamin. The fecal content of folate may be as high as 500 mg/day and is a consequence of bacterial synthesis, which occurs primarily in the large bowel. Some folate is lost daily in sweat and desquamated skin. Patients with severe burns have extensive loss of folate through the skin.

The clinical manifestations of folate deficiency include megaloblastic changes (not necessarily anemia or pancytopenia); gastrointestinal symptoms such as glossitis, anorexia, gastrointestinal discomfort, or occasional diarrhea; humoral and cellular immune defects; and neurologic abnormalities including depression, poor judgment, and some affective disorders.[53]

The Adequate Intake (AI) of folate for infants is 65 μg/day until 6 months of age and 80 μg/day from 7 to 12 months. The Dietary Reference Intake (DRI) for children is 150 μg/day from 1 to 3 years of age, 200 μg per day from 4 to 8 years of age, 300 μg/day from 9 to 13 years of age, and 400 μg/day from 14 years to adulthood.[54] Folate is present in a wide variety of foods. Cow's milk, human milk, and proprietary infant formulas normally provide approximately 50 μg L. In contrast, goat's milk contains only 2 to 11 μg/L, and the feeding of goat's milk to infants as the sole source of nutrition will result in the appearance of a megaloblastic anemia.[55] Although dietary folic acid deficiency is a common cause of megaloblastic anemia in developing countries, it appears to be unusual in the United States, where folic acid deficiency is more likely to be the result of defective absorption, increased requirements, or impaired use.

TABLE 49-2 Etiologic and Pathophysiologic Classification of Folate Deficiency

Nutritional causes
Decreased dietary intake
Poverty and famine (associated with kwashiorkor, marasmus)
Institutionalized individuals (psychiatric and nursing homes)
Chronic debilitating disease
Goat's milk, special diets (phenylketonuria, maple syrup urine disease, slimming)
Cultural/ethnic cooking techniques (food folate destroyed) or habits (folate-rich foods not consumed)
Decreased diet and increased requirements
Physiologic
Pregnancy
Lactation
Prematurity, infancy
Pathologic
Intrinsic hematologic disease (extrinsic: AIHA, drugs; malaria, hemoglobinopathy; SCD, thalassemia; membrane defects; HS, PNH)
Abnormal hematopoiesis (leukemia, lymphoma, MDS, agnogenic myeloid metaplasia with myelofibrosis)
Infiltration with malignant disease
Dermatologic (psoriasis, methotrexate dermatopathies)
Folate malabsorption
With normal intestinal mucosa
Some drugs (controversial)
Congenital folate malabsorption
With mucosal abnormalities
Tropical sprue
Nontropical sprue
Regional enteritis
Defective cellular folate uptake
Familial aplastic anemia
Inadequate cellular use
Folate antagonists (methotrexate)
Hereditary enzyme deficiencies involving folate
Drugs (multiple effects on folate metabolism)
Alcohol
Sulfasalazine
Triamterene
Pyrimethamine
Trimethoprim-sulfamethoxazole
Anticonvulsants (diphenylhydantoin, barbiturates)
Acute folate deficiency

Adapted from Antony A. Megaloblastic anemias. In: Hoffman R, et al, editors. Hematology: basic principles and practice. New York: Churchill Livingstone; 1991.
AIHA = autoimmune hemolytic anemia; HS = hereditary spherocytosis; MDS = myelodysplastic syndrome; PNH = paroxysmal nocturnal hemoglobinuria; SCD = sickle cell disease.

Developmental changes in folate balance are seen during infancy. Serum and red cell folate concentrations are higher in both preterm and term infants than in normal adults.[56] After birth, serum values decline rapidly, but the decline is most rapid and most severe in infants weighing less than 1,700 g at birth. Approximately two-thirds of low birth weight infants may display subnormal serum folate concentrations between 1 and 3 months of age, but they rarely have a megaloblastic anemia. Administration of supplemental folic acid, in the absence of megaloblastic anemia, has not been demonstrated to produce any increase in the hemoglobin concentration. The normal preterm infant absorbs folic acid without difficulty. The dietary provision

of 20 to 50 μg/day appears adequate to prevent the development of a deficiency. The presence of chronic infection or diarrhea may impair absorption or increase needs in these small infants. Overcooking of foods or boiling of milk can reduce the folate content by approximately 50%.[57]

Folate deficiency may accompany kwashiorkor, and its incidence has been found to range from 10 to 70%. This variation presumably reflects regional dietary practices. Both malabsorption and chronic infection may also contribute to this folic acid deficiency.

Because folate is absorbed primarily from the upper third of the small intestine, structural or functional damage in this area can reduce absorption sufficiently and result in folate deficiency. In chronic diseases, such as gluten enteropathy, tropical sprue, and active Crohn's disease, a megaloblastic anemia may occur. In many of these disorders of the small bowel, there is an apparent loss of intestinal conjugase activity because a small dose of monoglutamate folate produces a prompt hematologic response; large doses of polyglutamate folate, such as those present in food, are poorly absorbed. Impaired absorption has also been described in chronic congestive heart failure and skin disorders such as dermatitis herpetiformis.

Folate malabsorption may be induced by a number of drugs. Patients taking anticonvulsants such as phenytoin (Dilantin) may develop a folate-responsive megaloblastic anemia. It has been proposed that this anemia is a result of phenytoin-induced inhibition of intestinal conjugase, thus interfering with the conversion of dietary polyglutamate to the absorbable monoglutamate form.[58] Folic acid antagonists (folate analogs) such as methotrexate, pyrimethamine, pentamidine isethionate, and trimethoprim, which inhibit the reduction of folate to its metabolically active tetrahydrofolate derivative, may produce a megaloblastic anemia. In addition, a variety of genetic deficiencies of enzymes required for folate metabolism have been described. Some of these patients demonstrate mental retardation, and many, but not all, have a megaloblastic anemia.[59,60]

Folate requirements appear greater per kilogram in the newborn infant and young child[48]; in pregnant women, in whom folate is shunted to the developing fetus and urinary folate loss is increased; and in lactating women, who secrete 50 μg or more into each liter of milk.[43] The folate content of breast milk does not correlate with the mother's plasma folate[61] because folate is concentrated in milk above the level of plasma folate. Some milk folate is bound to the folate binding protein, as indicated above. Other groups of patients with higher than normal folate requirements include persons with sprue and other diseases of the small intestine, persons taking antiepileptic medication, women taking birth control pills, and persons with hemolytic anemia, including those with sickle cell anemia and thalassemia.[53]

Laboratory Diagnosis of Folate Deficiency

In addition to the characteristic laboratory findings of megaloblastic anemia, such as macrocytosis with or without neutropenia, multilobulated polymorphonuclear cells, increased LDH and bilirubin, bone marrow showing megaloblastic changes, increased plasma iron content and saturation of transferrin, and decreased serum cholesterol and lipids, several specific measurements provide direct evidence of deficiency of folate. These include decreased serum folate, decreased erythrocyte folate, homocystinemia and sometimes homocystinuria, and abnormal deoxyuridine suppression test in bone marrow corrected in vitro by addition of *N*-5-methyltetrahydrofolate or other folates and excretion of formiminoglutamate in the urine.[53]

Measurement of folate activity of serum and red blood cells is the most direct and reliable way to determine the folic acid status of the patient. The measurement of serum folate concentration alone reflects short periods (2 weeks) of folate deficiency. Herbert produced folate deficiency by self-experimentation and convincingly demonstrated that a fall in serum folate concentrations precedes the appearance of any other hematologic manifestations (Table 49-3).[62] The concentration of red cell folate is far more useful for documenting the presence of a long-standing deficiency. Only reticulocytes and nucleated red cell precursors are capable of taking up the vitamin from tissue stores. The folate in the mature erythrocyte is nonexchangeable; thus, reduction in red cell folate indicates a deficiency of at least 3 to 4 months duration.

The normal range of serum folate is 3 to 15 ng/mL. Serum folate values in the 1.5 to 3.0 range are regarded as "indeterminate." The red cell folate normally ranges from 150 to 600 ng/mL, and values of less than 150 ng/mL are diagnostic of deficiency. Normal values for the first year of life are depicted in Table 49-4. Microbiologic assays using *L. casei* will produce spuriously low results if the serum used for assay contains antibiotics or chemotherapeutic agents that inhibit the growth of the organism. A therapeutic trial, using 100 μg/day of folic acid, may also be used to make a presumptive diagnosis.

Vitamin B_{12} Deficiency

Vitamin B_{12}, or cobalamin, is an organometallic complex consisting of two major moieties: a corrin nucleus containing a covalently bound cobalt atom and a nucleotide base lying at right angles to the corrin nucleus. The vitamin B_{12} coenzymes, which activate intracellular metabolism, are 5-adenosylcobalamin and methylcobalamin. Hydroxycobalamin is the predominant dietary form of the vitamin. Vitamin B_{12} is synthesized by bacteria and is not present in plants; therefore, it does not occur in vegetables or fruit.

Only two metabolic functions for the vitamin B_{12} coenzymes have been identified in humans. The first of these is

TABLE 49-3 Time Sequence of Hematologic Changes in the Development of Nutritional Folic Acid Deficiency

Hematologic Finding	*Time to Appearance (wk)*
Reduced serum folate	2
Hypersegmentation of leukocytes	6
Reduced red cell folate	17
Macro-ovalocytosis	18
Megaloblastic bone marrow	19
Anemia	19–20

the conversion of L-methylmalonyl-coenzyme A (CoA) to succinyl CoA, a reaction catalyzed by methylmalonyl-CoA mutase and requiring 5-adenosylcobalamin. Defects in the conversion of L-methylmalonyl-CoA to succinyl CoA result in methylmalonicacidemia (MMA) and methylmalonicaciduria. The second reaction in which vitamin B_{12} is a cofactor is the homocysteine 5-methyltetrahydrofolate methyltransferase reaction. This reaction generates methionine from homocysteine using methionine synthase and produces tetrahydrofolic acid from 5-methyltetrahydrofolic acid.[63]

Dietary vitamin B_{12}, primarily in the form of hydroxycobalamin, is absorbed in the terminal ileum and requires the presence of intrinsic factor that has been secreted in the parietal cells of the stomach. Nutritional deficiency of vitamin B_{12} is extremely rare in infants and children. An etiologic and pathophysiologic classification of vitamin B_{12} deficiency is shown in Table 49-5.

It is estimated that the adult and older child require 1.0 μg of vitamin B_{12} per day and the infant 0.1 μg per day to maintain normal erythropoiesis. The normal diet usually contains far more vitamin B_{12} than this minimal requirement. Western diets usually contain 5 to 10 μg daily. The highest concentrations are found in liver, kidney, meat muscle, fowl, shellfish, and dairy products. There is probably no vitamin B_{12} in fruits, vegetables, nuts, or cereal unless they are contaminated with vitamin B_{12}–producing bacteria. Vitamin B_{12} is usually not destroyed by cooking. Under alkaline conditions and the presence of ascorbic acid, some vitamin B_{12} may be lost when milk is boiled or when meat is overcooked.

The average daily vitamin B_{12} output in breast milk is approximately 0.3 μg and closely parallels the serum vitamin B_{12} concentration of the mother.[64] The term infant receives approximately 30 μg of vitamin B_{12} from the mother during the course of gestation. Liver stores are about 26 μg in term infants but only 10 μg in premature infants.[65] Serum vitamin B_{12} values in the newborn are normally much higher than those of the mother. Because of this adequate endowment, vitamin B_{12} deficiency owing to inadequate ingestion in the first year or two of life is seen only when an infant is born to a severely vitamin B_{12}–deficient mother and is exclusively breast-fed by her or placed on a strict vegetarian diet. Megaloblastic anemia in the infants of strict vegetarian mothers has been reported from India.[66] Megaloblastic anemia in breast-fed infants of mothers who either have untreated pernicious anemia or are on vegetarian diets has also been observed in 5- to 6-month-old infants in the

TABLE 49-4 Normal Serum and Red Cell Folate Values during the First Year of Life: Mean (Range)

Age	*Red Cell Folate (ng/mL)*	*Serum Folate (ng/mL)*
Neonate	598 (196–1,256)	24.5 (3–59)
3–4 mo	283 (110–498)	12.2 (5–30)
6–8 mo	247 (100–466)	7.7 (3.5–16)
12 mo	277 (74–995)	9.3 (3–35)

Adapted from Lanzkowsky P.[55]

TABLE 49-5 Etiologic and Pathophysiologic Classification of Cobalamin (Cbl) Deficiency

- Nutritional Cbl deficiency (insufficient Cbl intake)
  - Strict vegetarians, vegans
  - Breast-fed infants of mothers with pernicious anemia
- Abnormal intragastric events (inadequate dissociation of Cbl from food protein)
  - Atrophic gastritis
  - Partial gastrectomy with hypochlorhydria
- Deficient or defective intrinsic factor (IF) molecules (IF-Cbl complex not formed; therefore, Cbl not absorbed)
  - Deficient IF
    - Congenital IF deficiency
    - Loss or atrophy of gastric oxyntic mucosa
      - Partial gastrectomy
      - Autoimmune destruction
        - Adult pernicious anemia
        - Juvenile pernicious anemia
      - Caustic destruction (lye)
      - Total gastrectomy
  - Defective IF
    - IF with no abnormal susceptibility to acid pepsin/trypsin
    - IF with 60-fold lower affinity for IF receptor
- Abnormal events in small bowel lumen
  - Inadequate pancreatic protease (Cbl complex not degraded; therefore, Cbl not transferred to IF)
    - Insufficient pancreatic protease (pancreatic insufficiency)
    - Inactivation of pancreatic protease by gastric hypersecretion (Zollinger-Ellison syndrome)
  - Usurpation of luminal Cbl (inadequate Cbl binding to IF)
    - By bacteria
      - Stasis syndromes (blind loops, pouches of diverticulosis, strictures, fistulae, anastomoses)
      - Impaired bowel motility (scleroderma pseudo-obstruction)
      - Hypogammaglobulinemia
    - By *Diphyllobothrium latum* (fish tapeworm)
- Disorders of ileal mucosa/IF receptors (IF-Cbl not bound to IF receptors)
  - Diminished or absent IF receptors—surgical conditions (ileal bypass, resection)
  - Abnormal mucosal architecture/function—medical conditions (tropical/nontropical sprue, Crohn's disease, tuberculous ileitis, infiltration by lymphomas)
  - Defective IF receptors/post-OF receptor defects
    - Imerslund-Graesbeck syndrome
    - Transcobalamin (TC) II deficiency
    - Drug-induced effects (slow K, biguanides, cholestyramine, colchicine, neomycin PAS)
- Disorders of plasma Cbl transport (TC II-Cbl complex not delivered to TC II receptors)
  - Quantitative deficiency (congenital TC II deficiency)
  - Qualitative deficiency of TC II with decreased Cbl binding
  - Defective binding of TC II-Cbl to Tc II receptors
- Metabolic disorders (Cbl not used by cell)
  - Inborn errors—mutations A–G
    - Cbl A: defective reduction of Cbl II to I
    - Cbl B: defective conversion of Cbl I to Ado-Cbl
    - Cbl C, Cbl D: defective reduction of Cbl III to II
    - Cbl E: inability to maintain Cbl bound to MS in reduced state
    - Cbl F: inability to transport Cbl from endosome/lysosome to cytoplasm
    - Cbl G: defect in MS catalyzed reaction
  - Acquired disorders: Cbl I oxidized to III-N2O inhalation

Adapted from Antony A. Megaloblastic anemias. In: Hoffman R, et al, editors. Hematology: basic principles and practice. New York: Churchill Livingstone; 1991.

United States.[67,68] In many of these cases, the infant presents with evidence of neurologic involvement as well as a macrocytic anemia. Both resolve following treatment with vitamin B_{12}. As yet, megaloblastic anemia owing to dietary vitamin B_{12} deficiency has not been reported in children in the United States as a result of a vegetarian diet if the infant was born of a nutritionally sufficient mother.

The absorption of vitamin B_{12} requires gastric secretion of intrinsic factor, normal pancreatic exocrine secretion, and normal ileal function. The gastric disorders producing inadequate or absent secretion of intrinsic factor include congenital pernicious anemia, juvenile pernicious anemia (with or without one or more endocrine disorders), and extensive gastric resection (Table 49-6). Children with congenital pernicious anemia are born with absence of intrinsic factor and no other abnormalities. The stomach is normal on biopsy and produces normal quantities of gastric acid. There are no antibodies to intrinsic factor or parietal cells. Patients with this disease generally present between 4 and 28 months of age with a megaloblastic anemia or neuropathy. The disease is inherited as an autosomal recessive disorder. One variant of this disorder has been described in which the patient was found to have an immunologically normal, but biologically inert, intrinsic factor.[69] The defective molecule binds vitamin B_{12} normally but attaches poorly to the ileal receptor site.

The juvenile form of pernicious anemia resembles that seen in adults. These children have gastric atrophy, gastric achlorhydria, absent intrinsic factor, and a high incidence of antibody against intrinsic factor. Some children with pernicious anemia, like adults, have associated endocrinopathies such as hypoparathyroidism, hypothyroidism, and Addison's disease. An association of selective immunoglobulin A deficiency with juvenile pernicious anemia has also been observed.

Failure of absorption of vitamin B_{12}–intrinsic factor complex in the ileum may also produce a megaloblastic anemia. This problem has been observed following ileal resection or ileal atresia; in association with celiac syndrome, regional enteritis, severe chronic pancreatitis, and lymphosarcoma of the terminal ileum; and in Imerslund-Graesbeck syndrome. In this latter disorder, which is familial, there is a series of defects in transport of vitamin B_{12} across the enterocyte despite the presence of a structurally normal ileum and intrinsic factor. Vitamin B_{12} absorption is not corrected by the addition of normal human intrinsic factor with vitamin B_{12}.[63]

Inadequate absorption of vitamin B_{12} may also be the result of competition for the vitamin in the gut from intestinal parasites, such as the fish tapeworm, or bacteria in association with the blind loop syndrome or trichobezoar.[55] Inadequate use of the vitamin B_{12} may occur in congenital enzyme deficiencies of vitamin B_{12} metabolism and congenital lack of the vitamin B_{12} transport protein transcobalamin II. In addition, several rare metabolic genetic defects affecting vitamin B_{12} metabolism have been reported. Because these deficiencies do not represent nutritional deficiencies, the reader is advised to consult other sources for more detailed information regarding these inherited abnormalities.[55,63,70]

The biochemical changes associated with vitamin B_{12} deficiency include MMA and methylmalonicaciduria of a magnitude determined by the flow of odd-chained fatty acids, valine and threonine, through the pathway. The secondary effects of MMA accumulation include acidosis, hyperglycinemia, and possibly inhibition of other enzymes and of bone marrow stem cells by accumulated MMA.[71–74] Homocystinemia and homocystinuria can be found. Inadequate levels of tetrahydrofolate in cells, producing defective rates of polyglutamyl folate synthesis and deficiency of folates required for some intracellular reactions, are observed. Defective thymidylate synthesis, defective synthesis of endogenous purines, defective detoxification of formate, and accumulation of formiminoglutamate, 5(4)-amidoimidazole-4(5) carboxyribonucleotide, and other intermediates of folate-dependent reactions are present. Biochemical central nervous system changes, which might relate to defective methylation of myelin basic protein, have been reported.[75–77] Finally, intracellular folate levels are lower than expected for the concentration of folate in plasma.[53]

Clinical Manifestations of Vitamin B_{12} Deficiency

The onset of symptoms is often insidious and may include pallor, apathy, fatigability, and anorexia. These symptoms are not specific for vitamin B_{12} deficiency. A beefy red and sore tongue with papillary atrophy may be observed. Pares-

TABLE 49-6 Vitamin B_{12} Malabsorption in Childhood

	Age at Onset (yr)	*Inheritance*	*Gastric Mucosa*	*Acid Secretion*	*Intrinsic Factor*	*Parietal Cell and Intrinsic Factor Antibodies*	*Associated Abnormalities*
Congenital pernicious anemia	< 3	Autosomal recessive	Normal	Normal	Absent	Absent	Immunodeficiency (?)
Imerslund-Graesbeck syndrome	< 2	Autosomal recessive	Normal	Normal	Present	Absent	Proteinuria
Juvenile pernicious anemia	> 10		Abnormal	Absent	Absent	Present	Polyendocrine failure, mucocutaneous candidiasis, immunodeficiency
Pernicious anemia	> 20		Abnormal	Absent	Absent	Present	Autoimmune disease

Adapted from Kramen B, Meyers P. Megaloblastic anemias. In: Miller DR, et al, editors. Blood diseases of infancy and childhood. St. Louis: Mosby; 1995.

thesias may be reported in the older child. Signs of subacute dorsolateral degeneration are uncommon in children, but loss of vibration and position sense may be seen. When neurologic disease is present, the lower limbs are more severely affected. The neurologic changes may precede the appearance of anemia. A number of gastrointestinal symptoms have been reported. The peripheral blood findings and bone marrow findings in vitamin B_{12} deficiency resemble those observed with folic acid deficiency.

Diagnosis of Vitamin B_{12} Deficiency The general findings secondary to megaloblastic anemia are similar to those indicated above for deficiency of folic acid. Specific measurements for vitamin B_{12} deficiency include decreased serum cobalamin, excess methylmalonic acid in the urine or serum, homocystinemia and sometimes homocystinuria, and abnormal deoxyuridine suppression test in bone marrow, corrected in vitro by addition of MeCbl or 5-formyltetrahydrofolate but not by methyltetrahydrofolate.

The serum vitamin B_{12} level is deficient when it is less than 100 pg/mL (normal 200 to 800 pg/mL). If the dietary history indicates a normal vitamin B_{12} intake, absorption of cobalt-labeled vitamin B_{12} should be performed by the Schilling test. For this purpose, a standard dose of the labeled vitamin (0.5 μg) is given orally after an overnight fast, and then a "flushing dose" of 1,000 μg of vitamin B_{12} is given parenterally 2 hours after the oral dose. Less than 7% of the labeled dose will appear in the urine during the 24-hour collection period if there is a lack of intrinsic factor or malabsorption of vitamin B_{12} for any other reason. If absorption is impaired, the Schilling test is repeated with the simultaneous administration of both intrinsic factor and labeled vitamin B_{12}. Improvement in the urinary excretion of the labeled ascorbic acid confirms the diagnosis of intrinsic factor deficiency. Gastric biopsy, the measurement of gastric acid secretion, and assay of intrinsic factor in gastric juice all help to categorize the nature of the underlying disturbance.

A therapeutic trial may be employed for the diagnosis of vitamin B_{12} deficiency. A dose of 0.5 μg of cyanocobalamin or hydroxycobalamin is given parenterally for 7 to 10 days. A reticulocytosis and increase in hemoglobin concentration should be observed. If the diagnosis has been firmly established, a therapeutic trial may be omitted and the patient treated with daily doses of 25 to 100 μg. If the patient has any form of vitamin B_{12} malabsorption rather than a primary nutritional deficiency, maintenance therapy should consist of monthly injections of 50 to 1,000 μg, depending on the patient's age and weight.

Vitamin E Deficiency

Vitamin E, α-tocopherol, a lipid-soluble antioxidant, was first discovered in 1922. Although a need for vitamin E in human nutrition has been established, precise requirements, the means of determining vitamin E sufficiency, the spectrum of diseases produced by vitamin E deficiency, the interrelationships between vitamin E and other nutrients, and its precise mechanism of action have been topics of continued debate and the subject of excellent reviews.[78–81]

The human fetus at 5 months gestation has a total-body vitamin E content of only 1 mg.[82] The fetus at term has a body vitamin E content of 20 mg. The increase in body vitamin E content during gestation can be linearly related to total body weight or total body fat and averages 3 to 7 mg/kg. The normal adult male averages 50 mg/kg, and the female averages 160 mg/kg. This difference in the ratio of body vitamin E to body weight presumably reflects differences in body fat composition. The ratio of vitamin E to fat remains relatively constant throughout gestation and averages 0.27 mg of vitamin E per gram of lipid; ratios of 0.24:1.00 have been described for adult males and 0.46:1.00 for adult females.[83,84]

Plasma vitamin E levels average close to 0.9 mg/100 mL in the mother at term, with a corresponding value of only 0.2 mg/100 mL in the infant.[85] Although there is a direct relationship between the plasma level of vitamin E in the infant at birth and that of the mother, infants are not born with values above 0.6 mg/100 mL, the value regarded as the lower limit of normal for older children and adults. When vitamin E concentrations are expressed as vitamin E-to-lipid ratios, perhaps a more nutritionally valid means of determining vitamin E deficiency, differences between mothers and their infants disappear. The vitamin E-to-total lipid ratio of mothers at term has been found to average 1.57:1.00, with a ratio of 2.40:1.00 in cord blood.[86]

Infants, both term and preterm, who are fed colostrum and human milk achieve normal plasma vitamin E concentrations by 1 week of age.[46,87] Most of the simulated human milk formulas presently available will produce vitamin E concentrations within the normal adult range when fed to infants during the first 2 weeks of life. The relationship between iron content and vitamin E in the diet may determine the turnover of vitamin E as iron-mediated reactions stimulate lipid peroxidation and increase the requirements for vitamin E.

Hemolytic Anemia and the Premature Infant Prior to 1967, despite the fact that it was recognized that most proprietary formulas fed to low birth weight infants resulted in a prolonged period of vitamin E deficiency, no hematologic abnormalities could be demonstrated.[88,89] In 1967, the presence of a hemolytic anemia that could be corrected by vitamin E or prevented by maintaining vitamin E sufficiency from early infancy was described.[90]

This syndrome was seen almost exclusively in infants with birth weights of less than 1,500 g and was most pronounced during the period of 6 to 10 weeks of life. The hematologic findings consisted of anemia with hemoglobin of 6 to 8 g/dL, reticulocytosis of 4 to 5% or greater, and thrombocytosis. Red cell morphologic changes included the presence of anisocytosis, poikilocytosis, red cell fragments, and irregularly contracted erythrocytes and spherocytes. The hydrogen peroxide hemolysis test was abnormal, and the red cell life span was reduced.[90,91] These findings were all consistent with alterations in the membrane caused by oxidant injury. Treatment with vitamin E, in total doses ranging from 200 to 1,000 mg, produced a prompt rise in hemoglobin, a reduction in the reticulocyte

count, and a gradual decline in the platelet count to the normal range. In addition to the hematologic abnormalities, many of the small infants also displayed edema of the lower legs and scrotum, watery nasal discharge, and, on occasion, tachypnea. The mechanisms responsible for these changes are not known.

Melhorn and Gross studied infants of less than 36 weeks gestation receiving a commercial formula and found that, at 6 to 10 weeks of age, infants who had been supplemented with 25 IU of vitamin E per day from day 8 of life had significantly higher hemoglobin concentrations and lower reticulocyte counts and hydrogen peroxide tests than the unsupplemented infants.[92] It was also found that the daily administration of ferrous sulfate, 10 to 12 mg/kg/day from day 8, exaggerated the hemolytic anemia in the infants not receiving the vitamin E supplement. Williams and coworkers demonstrated that hemolytic anemia owing to vitamin E deficiency occurred in infants receiving iron-fortified formulas only if the formula was unusually rich in polyunsaturated fats.[93]

It has been hypothesized that hemolysis occurs in vitamin E deficiency as a consequence of peroxidation of lipid components of the red cell membrane. The peroxidation is initiated by the generation of a free radical (an unpaired electron) and proceeds autocatalytically in the absence of an antioxidant. Iron, in the reduced state, particularly in the presence of ascorbic acid, is recognized to generate free radicals. The requirements for lipid peroxidation include the presence of a suitable substrate (eg, a long-chain unsaturated fatty acid), a lack of antioxidant (eg, vitamin E), and a source of a free radical generating system (eg, heavy metals, molecular oxygen). Most proprietary formulas have now reduced their polyunsaturated fatty acid (PUFA) content and increased their vitamin E concentration, resulting in vitamin E-to-PUFA ratios in excess of 0.6:1.00, a value generally regarded as sufficient to prevent the development of vitamin E deficiency.[78] The potential for the development of vitamin E deficiency anemia is present when infants receive intravenous lipid preparations without adequate vitamin E supplementation.

The diagnosis should be suspected in an infant who displays anemia in the presence of persistent reticulocytosis, nonspecific red cell morphologic abnormalities, and thrombocytosis. Confirmation of the diagnosis requires (1) evidence of a reduced plasma vitamin E concentration (< 0.5 mg/dL) or a reduced vitamin E-to-total lipid ratio (< 0.6), (2) an abnormal hydrogen peroxide hemolysis test (usually > 30% hemolysis with a normal laboratory value of < 10%), and (3) an increase in hemoglobin and a fall in reticulocyte count after vitamin E therapy. Response should be apparent within 10 days, provided that correction of criteria 1 and 2 has occurred.

Miscellaneous Conditions Patients with various forms of malabsorption will become vitamin E deficient. These include patients with exocrine pancreatic insufficiency (cystic fibrosis), congenital biliary atresia, abetalipoproteinemia, and extensive small-bowel resections. In patients with reduced concentrations of plasma vitamin E, the red cell half-life is usually shortened,[61,79] although anemia is usually not evident or, when present, is usually not correctable by the administration of vitamin E alone. The relative anemia observed in most patients with chronic lung disease with cystic fibrosis will not respond to iron alone but may improve when iron and vitamin E are given concurrently.[94]

Anemia of Starvation

Studies conducted during World War II with conscientious objectors demonstrate that semistarvation for 24 weeks resulted in a mild to moderate normocytic, normochromic anemia.[95] Marrow cellularity was usually reduced and was accompanied by a decrease in the erythroid-to-myeloid ratio. Measurements of red cell mass and plasma volume suggested that dilution was a major factor responsible for the reduction in hemoglobin concentration. In persons subjected to complete starvation, either for experimental purposes or to treat severe obesity, anemia was not observed during the first 2 to 9 weeks of fasting.[96] Starvation for 9 to 17 weeks produced a fall in hemoglobin and marrow hypocellularity.[97] Resumption of a normal diet was accompanied by a reticulocytosis and disappearance of anemia. It has been suggested that the anemia of starvation is a response to a hypometabolic state, with its attendant decrease in oxygen requirements.

Anemia of Protein Deficiency (Kwashiorkor)

From the series of Delmonte and coworkers on the anemia of protein deficiency in rats, it was deduced that oxygen consumption and, therefore, erythropoietin production are reduced.[98] Other studies confirmed this observation but related the reductions to caloric deprivation, with its associated decrease in the blood level of triiodothyronine and thyroxine.[99] As a result, erythropoiesis decreases, and the reticulocyte count falls. The plasma iron turnover and red cell uptake of radioiron are markedly reduced, and the red cell mass gradually declines.[100] Protein deficiency also produces a maturation block at the erythroblast level and a slight decrease in the erythropoietin-sensitive stem cell pool.[101] If exogenous erythropoietin is provided, normal erythropoiesis is restored despite protein depletion,[102] an observation that has explained the empiric but successful use of starved rats in the bioassay for erythropoietin.

In infants and children with protein-calorie malnutrition, the hemoglobin concentration may fall to 8 g/dL of blood,[103,104] but some children with kwashiorkor are admitted to the hospital with normal hemoglobin levels, probably owing to a decreased plasma volume. The anemia is normocytic and normochromic, but there is a considerable variation in the size and shape of the red cells on the blood film. The white blood cells and the platelets are usually normal. The marrow is most often normally cellular or slightly hypocellular, with a reduced erythroid-to-myeloid ratio. Erythroblastopenia, reticulocytopenia, and a marrow containing a few giant pronormoblasts may be found, particularly if these children have an infection. With treatment of the infection, erythroid precursors may appear in the marrow, and the reticulocyte count may rise. When nutrition is improved by feeding high-protein diets (pow-

dered milk or essential amino acids), there is reticulocytosis, a slight fall in hematocrit owing to hemodilution, and then a rise in hemoglobin, hematocrit, and red blood cell count. Improvement is slow, however, and during the third or fourth week, when the children are clinically improved and the serum proteins are approaching normal, another episode of erythroid marrow aplasia devoid of giant pronormoblasts may develop. This relapse is not associated with infection, does not respond to antibiotics, and does not remit spontaneously. It does respond to either riboflavin or prednisone, and unless treated with these agents, children who develop this complication may die suddenly. It has been suggested that the erythroblastic aplasia is a manifestation of riboflavin deficiency.[105]

Although the plasma volume is reduced to a variable degree in children with kwashiorkor, the total circulating red cell mass decreases in proportion to the decrease in lean body mass as protein deprivation reduces metabolic demands.[104] During repletion, an increase in plasma volume may occur before an increase in red cell mass, and the anemia may seem to become more severe, despite reticulocytosis. The erythropoietin level increases as the hemoglobin concentration falls[106] and, more importantly, as oxygen demand increases. The increased oxygen demand may, in part, account for the reticulocytosis. Also, during the repletion period, occult deficiencies of iron, folic acid, and, occasionally, riboflavin, vitamin E, and vitamin B_{12} may become manifest unless these essential nutrients are supplied in adequate amounts.

METAL DEFICIENCIES

Iron Deficiency

Iron deficiency continues to be the most common nutritional cause of anemia worldwide, affecting as many as 4 to 5 billion people.[107] The prevalence of iron deficiency has been declining in industrialized countries over the last few decades, at least partly owing to an increase in breastfeeding and fortification of infant formulas and cereals.[108] Unfortunately, most of the rest of the world has not experienced such a decline; an estimated 90% of cases occur in developing countries, impacting significantly on morbidity, mortality, and national development.[107]

Anemia, a treatable condition, is the most common clinical problem associated with this deficiency. However, the real public health concerns are the cognitive and behavioral impairments seen in infants and children,[109–113] the fatigue and decreased work capability in older children and adults,[109] and the association of severe iron deficiency anemia in pregnant women with prematurity, perinatal mortality, and low birth weight infants.[114–116] Because long-term iron supplementation is an impractical solution, providing fortified staple foods and working to increase the bioavailability of iron in various foods are steps toward decreasing the prevalence of iron deficiency worldwide.[117]

Iron deficiency occurs in various stages. First, there is depletion of iron stores in the body. This stage is unlikely to be diagnosed by any routine screening laboratory tests. Next, there is iron deficiency with anemia, initially with a normal MCV. As the deficiency continues, erythropoiesis is significantly impaired, and the diagnosis becomes more evident with obvious hypochromia and microcytosis on peripheral blood smear, in conjunction with some of the nonhematologic manifestations of this condition.

The body, based on its needs, attempts to maintain a balance between iron stores, recycled iron, and dietary iron intake. One-third of an infant's iron needs come from dietary sources; the remainder is recycled from red blood cell breakdown. Over time this changes, so that by adulthood, an even greater proportion of iron needs come from recycled iron such that there is less reliance on the diet for iron.

Iron is a vitally important nutrient that serves multiple functions in the body. It is the functional group in hemoglobin for oxygen transport and use in the red blood cell and helps with storage of oxygen in myoglobin in muscle. Iron is also present in peroxidase, catalase, and the cytochromes. Excess iron is stored primarily as ferritin and hemosiderin for use when the requirements of the body are greater than the combination of the dietary intake and the available recycled iron.

Fetal-Maternal Relationships The iron content of the normal newborn infant is approximately 75 mg/kg, as determined by carcass analysis of stillbirths.[119] Studies performed during various stages of pregnancy indicate that the iron content of the fetus and the weight of the fetus increase proportionately with age; thus, through gestation, the fetus tends to maintain a constant iron content. Under usual circumstances, 66 to 75% of the infant's iron is present in the red cell mass. Storage iron in the liver and spleen, although subject to great variability, makes up approximately 6% of the total iron, whereas nonhemoglobin iron in the form of cytochromes, myglobin, and other iron-containing enzymes account for approximately 24%.[120]

The bulk of the infant's iron endowment at birth is represented by the red cell mass. As a result, the amount of iron in the body at the time of birth depends on the blood volume and the hemoglobin concentration, and any complications during pregnancy or the perinatal period that result in fetal blood loss will compromise the infant's iron endowment. Unless extreme, the presence of maternal iron deficiency does not appear to compromise the iron endowment of the fetus. The hemoglobin concentration in the cord blood of infants born to anemic iron-deficient mothers does not differ from that of infants born to iron-sufficient mothers until maternal hemoglobin values fall below 6.0 g/dL.[121] With extreme maternal iron deficiency anemia, the placenta is small and the cord blood hemoglobin concentration is reduced. Some studies have observed that women with low serum iron values tend to have infants with lower than normal serum iron levels[122]; other studies have found no difference in the state of the infant's iron nutrition at 6, 12, and 18 months of age regardless of whether their mothers had received iron supplementation during pregnancy.[123,124] The relationship between maternal iron status and pregnancy outcomes is discussed further in Chapter 24, "Maternal Nutrition and Pregnancy Outcome."

Employing plasma ferritin concentrations as an index of iron sufficiency, Rios and coworkers were unable to document any correlation between plasma ferritin concentrations in mothers with high and low values and the plasma ferritin concentrations of their infants at birth or at $1^1/_2$ months of age.[125] It may be concluded from these studies that, except in the most unusual circumstances, maternal iron deficiency by itself does not result in iron deficiency anemia in the infant, either at birth or later in the first year of life. Factors such as rate of growth relative to birth weight, initial iron endowment that has been compromised by blood loss, and infant nutrition seem to be far more important in determining the later appearance of anemia.

At birth, the newborn has a large number of reticulocytes and a relatively high hemoglobin concentration with a mean of 16.6 g/dL.[126] The hemoglobin increases over the first few days and then, as erythropoiesis slows in the marrow and extramedullary spaces, the hemoglobin falls, reaching a nadir in 6 to 8 weeks. Erythropoiesis is then stimulated and the hemoglobin rises to 12.5 g/dL, which is the mean throughout infancy.[126] Preterm infants have a more dramatic fall in hemoglobin to a mean of about 9 g/dL at the nadir, although the marrow recovery is good, and at 6 months of age, these infants have the same mean hemoglobin concentration as a term infant.[127]

Iron Requirements Iron requirements are age dependent. It is rare for a term infant to become iron deficient before 4 months of age, but a preterm infant can become deficient by 2 to 3 months because of relatively faster growth and smaller iron stores at birth.[126] From birth through adolescence, children need iron for growth and increasing blood volume, as well as to replace losses. Although the amounts are small, in an infant averaging 20 μg/kg/day, iron is lost in sweat, urine, bile, and desquamation of skin and intestinal cells and through hair and nail loss.[108] The Committee on Nutrition of the American Academy of Pediatrics made the following recommendations for daily iron requirements for infants, based on approximately 10% absorption[128]: term infant, 1 mg/kg to maximum 15 mg/day, beginning by 4 months; low birth weight infant, 2 mg/kg to maximum 15 mg/day, beginning by 2 months. The DRI is 1 to 3 years: 7 mg/day; 4 to 8 years: 10 mg/day; 9 to 13 years: 8 mg/day; 14 to 18 years: boys, 11 mg/day; girls, 15 mg/day; pregnancy: 27 mg/day.[54]

Etiology Iron is found in many different food sources; however, the bioavailability is highly variable. Studies have shown that breast milk and cow's milk each contain 1 mg/L of iron. However, the bioavailability of iron to the infant is drastically different, with 49% absorption of the former and only 20% absorption of the latter.[129] The absorption from fortified formula is only 3 to 4%, but it contains 12 mg of iron/L.[125] Because the amount of iron in breast milk is not consistent over a long period of time, the addition of iron-fortified cereal is recommended for all infants by 4 to 6 months of age to help keep up with needs and prevent depletion of iron stores. These cereals are fortified with an electrolytic iron powder, resulting in 0.45 mg of iron/g of cereal. Thus, one portion contains 5 mg of iron, but only about 4% is absorbed.[130]

Shortly after starting cereals, most infants also start other foods. Heme iron, from animal sources, is absorbed more efficiently than nonheme iron from vegetable sources. The difference is 15 to 20% compared with 5%. The mechanism of absorption is different. Heme iron enters the intestinal mucosa cell in the intact protoporphyrin. Nonheme iron is absorbed as free iron or protein bound, which makes it more susceptible to influence from other factors that assist or inhibit absorption.

The absorption of iron is affected by the combination of foods and drinks ingested together. For example, orange juice facilitates absorption, whereas tea hinders it. Some of the other enhancers of iron absorption are ascorbic acid, fructose, certain amino acids, meat, fish, and poultry. Inhibitors include phosphates, phytates (common in vegetarian diets), tannins, and oxalates.[117,131] Interestingly, the iron in eggs is not efficiently absorbed, and it also inhibits the absorption of iron from other sources.[131]

By the age of 12 months, infants switch over to whole cow's milk from formula and may or may not continue to be breast-fed as well. It is important to restrict this intake to less than three-quarters of a liter per day because too much can cause milk-induced exudative enteropathy, with blood loss and malabsorption leading to hypoproteinemia, iron deficiency, and anemia, which can be significant.[132] The acidic environment of the stomach helps to convert ferric iron to the more soluble ferrous form of iron. Thus, conditions that affect this acidity, such as partial or total gastrectomy (rare in children), achlorhydria, and antacids, also decrease iron absorption. Rapid gastric emptying, celiac disease, and inflammatory bowel disease also cause malabsorption.[117,118]

Manifestations With the decline in iron deficiency anemia in industrialized countries, children with the manifestations of severe long-standing iron deficiency anemia are rare. Sadly, they are still seen elsewhere. Mild to moderate iron deficiency anemia is most common. Frequently, the first signs and symptoms of iron deficiency anemia are pallor, fatigue, exercise intolerance, and, occasionally, palpitations. The pallor is most notable in the nail beds, conjunctiva, and palms, especially if the individual has dark skin. Fatigue and exercise intolerance have been best documented in studies of adults employed at physical labor, revealing that even mild anemia can affect exercise tolerance in settings involving strenuous energy expenditure and that correction of the anemia increased exercise tolerance.[133–135] The usual phenomenon of pica or compulsive consumption of non-nutritional items such as dirt, clay, cornstarch, laundry detergent, or ice is a characteristic finding of iron deficiency anemia. Ingestion of these items usually exacerbates the underlying iron deficiency by further impairing absorption.[136]

The recognition that iron deficiency produces a broad array of systemic effects has attracted increasing attention.[118,137] A partial list of nonhematologic manifestations of iron deficiency is provided in Table 49-7.[138] Over time, glossitis, stomatitis, and angular cheilosis may develop. These symptoms may be the result of tissue iron deficiency

rather than the anemia itself.[139] Koilonychia, or spooning of the fingernails, is caused by abnormal proliferation of the cells of the nailbed. Other features of severe long-standing iron deficiency anemia can actually make treatment with oral iron supplementation difficult. The presence of esophageal webs, or Plummer-Vinson syndrome, impairs swallowing; atrophic gastritis and abnormal duodenal mucosa can both decrease absorption.

There have been numerous studies investigating immune function associated with iron deficiency anemia.[109,140–149] Interestingly, iron overload has also been shown to impair normal immune function, decreasing lymphocyte proliferation and the ability of macrophages to kill intracellular pathogens.[150] Similarly, both iron deficiency and iron therapy have been associated with increased infection. In one study, anemia was associated with malaria, acute respiratory infection, and diarrhea,[151] and two other studies found fewer episodes of infection in children treated with parenteral or oral iron.[152,153] However, other studies show that individuals with malaria, hepatitis C virus infection, and human immunodeficiency virus infection have worse outcomes if they have excess iron or are treated with iron.[154–156] This conflict may be attributable, in part, to the difficulty in establishing cause and effect and accounting for mediating variables.

Iron plays an important role in brain development, and many studies have indicated that iron deficiency is associated with cognitive impairment, poor motor development, and behavioral problems.[109–112,157–159] This is particularly disturbing as these problems may continue long term, even after correction of the anemia. However, it should be noted that a causal relationship has not been established as important potential confounding variables have not been fully accounted for. It is also not clear that central nervous system effects can be remedied by iron therapy as many of the clinical trials have failed to demonstrate benefit from therapy. A more detailed discussion of the relationship between iron status and behavior, including study limitations, is presented in Chapter 22, "The Behavior of Children."

TABLE 49-7 Nonhematologic Manifestations of Iron Deficiency

Impaired growth
Skin and mucous membranes
Koilonychia
Angular stomatitis
Glossitis
Gastrointestinal tract
Anorexia
Dysphagia with postcricoid webs
Gastric achlorhydria
Malabsorption
Beeturia
Exudative enteropathy and occult bleeding
Central nervous system
Irritability
Decreased attention span
Poor performance in standardized developmental testing
Breath-holding spells
Impaired exercise tolerance
Immunologic response
Impaired lymphocyte mitogen response
Decreased leukocyte killing

Iron is essential to the metabolism of certain amine neurotransmitters.[109] Children with iron deficiency anemia have increased catecholamines in their urine, which return to normal levels after iron therapy.[160] There have been animal studies suggesting abnormal dopamine receptor function in association with iron deficiency anemia.[161] The exact meaning of these findings and how they relate to cognitive and behavioral development remain unclear.

Laboratory Findings The diagnosis of iron deficiency anemia is rarely made based on a single laboratory test but rather on a combination of several tests and the comparison to age-specific norms reflecting the changes that occur as a child grows. Commonly used tests assess the iron storage, erythropoiesis, and severity of the anemia (Table 49-8). Together these tests can help to rule out other causes of anemia.

Peripheral Smear. Often microscopic examination of the blood smear can be normal early in iron deficiency, but as the anemia progresses, hypochromia, microcytosis, anisocytosis, and occasional target cells and elliptocytes are seen.

Hemoglobin. Anemia starts when this value is < 95% for age. Thus, it is essential to use age-based mean hemoglobin values for accurate interpretation of these results.

Red Cell Distribution Width. This is a valuable index to note, especially as a clue early in iron deficiency anemia, because it is a sensitive test, although not very specific.[162] It represents the variation in size of the red blood cells. In thalassemia, infection, and inflammation, it is usually normal, but in iron deficiency anemia, this value is elevated and can be > 20%.[118]

Mean Corpuscular Volume. This value represents the average size of the red blood cell and varies with age. When anemia becomes significant enough to interfere with hemoglobin synthesis, microcytosis occurs (low MCV). This is one of the red cell indices readily available from an electronic counter in the laboratory.

Mean Corpuscular Hemoglobin. As with the MCV, this index is available from an electronic counter. Initially, with iron deficiency, the MCH is normal, but with advancing anemia, the red blood cell becomes more hypochromic, and this change is evident by a low MCH.

Serum Ferritin. Iron inside the cell can be toxic. Ferritin, a protein, helps to compartmentalize it. The serum level correlates with total-body iron. As an acute-phase reactant, ferritin is increased by inflammatory, infectious, and malignant processes, and correlation with body iron stores becomes less reliable. Although a few conditions, including vitamin C deficiency, reduce serum ferritin, values < 10 μg/L are generally indicative of iron deficiency anemia. Scurvy, or ascorbic acid deficiency, should be evaluated as a potential cause of low ferritin.

Serum Iron. This is not a reliable test for iron deficiency anemia because it has a diurnal pattern with a peak in the morning and a trough in the evening. As with serum ferritin, it can be elevated by many other conditions. The concentration is usually low in iron deficiency anemia.

TABLE 49-8 Laboratory Measurements of Iron Status

Storage iron depletion
Bone marrow iron stain (decreased)
Serum ferritin (decreased)
Serum transferrin (increased)
Transferrin receptor (increased)
Serum iron (decreased)*
Iron deficiency erythropoiesis
Transferrin saturation (decreased)
Total iron-binding capacity (increased)
Free erythrocyte protoporphyrin (increased)
Zinc protoporphyrin (increased)
Red cell mean corpuscular volume (decreased)
Red cell mean corpuscular hemoglobin (decreased)
Red cell distribution width (increased)
Reticulocyte heme (decreased)
Iron deficiency anemia
Hemoglobin (decreased)
Therapeutic trial with increase in hemoglobin concentration

*See text.

However, even a single dose of iron within the 24 hours prior to the test can cause a transient elevation in the serum iron level, thus possibly masking an underlying iron deficiency anemia.[139]

Total Iron-Binding Capacity. Most circulating iron is bound to a plasma protein called transferrin. Total iron-binding capacity (TIBC) is a measure of the total transferrin. As the serum iron decreases, the TIBC increases, and the ratio of these variables in iron deficiency anemia is less than 1:6.[162]

Transferrin Saturation. This value is the ratio of serum iron to TIBC multiplied by 100 to yield a percentage. It represents the percentage of transferrin that is saturated with iron. A low percentage is suggestive of iron deficiency.

Transferrin Receptor. This receptor is bound to transferrin in circulation and is indicative of the concentration of the cellular transferrin receptor. Because receptor synthesis increases with iron deficiency but not with anemia of chronic disease, it may prove to be a more sensitive indicator of iron deficiency.[163] It is also elevated in the presence of ineffective erythropoiesis and sideroblastic anemias. This must be taken into account and evaluated appropriately.

Erythrocyte Protoporphyrin. Under normal circumstances, iron combines with protoporphryin in the red blood cell to form heme, a reaction catalyzed by the enzyme ferrochelatase. In iron deficiency anemia, there is an elevation in erythrocyte protoporphyrin (EP), usually > 35 μg/dl,[164] because there is less iron for heme production. Lead poisoning, which often causes a higher level of EP than iron deficiency, does so by inhibiting ferrochelatase. Inflammatory, infectious, and/or malignant processes also can raise the EP level.[139]

Zinc Protoporphyrin. In iron deficiency and lead poisoning, zinc protoporphyrin is formed instead of EP because zinc fills the iron pocket in the protoporphyrin molecule. This is a sensitive, inexpensive test that will show an elevation in iron deficiency even before anemia is present.[165] When iron stores are sufficient, the ratio of iron-to-zinc incorporation into protoporphyrin is 30,000 to 1.[166] Alone this test does not differentiate between iron deficiency and lead poisoning, so further tests must be done. The issue is complicated because iron deficiency increases the absorption of lead so that in many situations, the two disturbances exist together. A lead level and a therapeutic trial of oral iron therapy may be necessary to sort things out.

Reticulocyte Heme. Reticulocyte hemoglobin content measurement by automated flow cytometry assesses the iron status of red blood cells when they are released from the bone marrow as reticulocytes.[167] It can be used to detect early iron deficiency and has been found to be the strongest predictor of iron deficiency when compared with other commonly used laboratory parameters.[168]

Bone Marrow Biopsy. If the usual tests are equivocal or there are confounding factors making the diagnosis of iron deficiency difficult, such as infection or inflammation, the bone marrow iron stores can be assessed. Staining the specimen with Prussian blue and counterstaining with safranin O helps to show the characteristic paucity of ferritin and hemosiderin, the final breakdown product of iron and ferritin.[127] Normally, 10 to 20% of red cell precursors in the marrow contain iron granules; however, in iron deficiency, few, if any, will be present.[169]

Therapy If iron deficiency is diagnosed or suspected based on some or all of the laboratory tests discussed above, treatment with iron should begin immediately. In most circumstances, oral iron supplementation is used because it is inexpensive and easily absorbed. The dose of iron for infants and children is 4 to 6 mg/kg of elemental iron, depending on the severity of the anemia, divided into two to three doses per day. For adolescents, the dose is 100 to 300 mg of elemental iron per day.[170] Traditionally, three-times-daily dosing has been used, but recent research has demonstrated that once-daily dosing results in similar treatment of anemia,[171] and once- or twice-weekly dosing results in similar improvement in hemoglobin but not ferritin.[172] Further work in this area is ongoing in an attempt to reduce side effects, simplify treatment, and improve compliance.

Ferrous iron is more easily absorbed than ferric iron; thus, the usual treatment for infants and children is ferrous sulfate. Premature infants are frequently vitamin E deficient owing to decreased intake, decreased stores, and poor absorption of vitamin E. Because iron therapy inhibits absorption of vitamin E, this deficiency must be corrected before iron therapy is started.[173] The absorption of iron on an empty stomach is about twice that of a full stomach; therefore, it is recommended that the dose be given about an hour prior to a meal.

The duration of treatment is 2 to 4 months after the hemoglobin has returned to a level normal for age in order to replenish the iron stores.[118] If these stores are not replenished because iron therapy is discontinued too soon, a rapid recurrence of iron deficiency anemia may result. Thus, the importance of completing the full recommended course of treatment must be emphasized to the parents or caretakers of the affected child and to the affected child who is old enough to understand.

Response to treatment is initially evident by a reticulocytosis peaking in 5 to 10 days from the onset of treat-

ment. During the first week of therapy, the hemoglobin rises about 0.25 to 4 g/dL/day and then slows to about 0.1 g/dL/day.[170] It is important to follow up no more than a month later to see if there is improvement because if there is no change in that period of time on an adequate dose and compliance is not an issue, further studies must be done to determine the underlying problem.[118] Failure of oral iron therapy can be the result of impaired absorption, incorrect diagnosis, ongoing blood loss greater than hemoglobin generation, inadequate dose, ineffective iron preparation, superimposed malignancy or inflammatory disease, or, most commonly, simple noncompliance. Compliance can be an issue because of the taste of iron, gastrointestinal distress, or concern of parents that the drops will stain the infant's teeth. These problems can be dealt with by giving the iron with a small amount of food or liquid, preferably something that will enhance the absorption, and by giving the drops in the back of the mouth. If noncompliance is suspected but denied, the stool can be examined. In the presence of iron supplements, it should be black. The stool can also be tested specifically for iron if necessary.

Parenteral iron therapy has greater side effects and therefore is reserved for only specific circumstances. These include true intolerance to oral iron (extremely rare), severe gastrointestinal disease that prevents absorption and may be exacerbated by oral iron therapy, chronic bleeding, or repeated noncompliance.[174,175] The dose is calculated to correct the anemia and replenish the iron stores. The formula is:

$$\frac{\text{Normal Hgb} - \text{Initial Hgb} \times \text{blood volume} \times 3.4 \times 1.5 = \text{mg iron}}{100}$$

The normal hemoglobin (Hgb) should be based on the age. Blood volume is approximately 80 mL/kg of body weight. The value 3.4 converts the grams of hemoglobin to milligrams of iron, and the factor 1.5 provides a little extra iron to supply the iron stores.[174,175]

The side effects of this therapy must be considered before starting. The most significant, although rare (< 1%), is anaphylaxis. Therefore, whenever this treatment is used, a test dose must first be given, and if there is no sign of reaction 5 minutes after the test dose, the therapeutic dose may be started. Epinephrine should be kept at the bedside, as well as resuscitation equipment. Less severe side effects are hypotension and flushing (2%), phlebitis (10%), and a delayed rash with or without arthritis (20%).[174,175] Most often, this is given intravenously; however, if there is extravasation or if it is given through the very painful intramuscular route, the iron can stain the skin, and this stain takes a long time to resolve.

In extreme iron deficiency anemia with a very low hemoglobin and/or cardiovascular instability, a packed red blood cell transfusion is given first to stabilize the patient. This is usually followed by oral iron therapy. In this situation, the transfusion is given slowly, at 5 cc/kg over 4 hours to start. Depending on how much more blood is necessary to increase the hemoglobin to the desired level, the rest of the transfusion can be broken into aliquots and given slowly or at the usual rate for a transfusion.[170]

Copper Deficiency

Copper is present in a number of metalloproteins. Among the cuproenzymes are cytochrome-*c* oxidase, dopamine-β-hydroxylase, urate oxidase, tyrosine and lysyl oxidase, ascorbic acid oxidase, and superoxide dismutase (erythrocuprein). More than 90% of the copper in the blood is carried bound to ceruloplasmin, an α_2-globulin with ferroxidase activity.

Copper appears to be required for the absorption and use of iron. It has been proposed that copper, in the form of ferroxidases, converts and maintains iron in the Fe^{3+} state for its transfer by transferrin.[176]

Copper deficiency has been described in malnourished children[177] and in both infants[178] and adults[179] receiving parenteral alimentation. Copper deficiency in humans is characterized by (1) a microcytic anemia that is unresponsive to iron therapy, (2) hypoferremia, (3) neutropenia, and usually (4) the presence of vacuolated erythroid precursors in the marrow. In infants and young children with copper deficiency, radiologic abnormalities are generally present. These abnormalities include osteoporosis, flaring of the anterior ribs with spontaneous rib fractures, cupping and flaring of long bone metaphyses with spur formation and submetaphyseal fractures, and epiphyseal separation. These radiologic changes have frequently been misinterpreted as signs of scurvy.

The diagnosis of copper deficiency can be established by the demonstration of a low serum ceruloplasmin or serum copper level. Adequate normal values for the first 2 to 3 months have not been well defined and are normally lower than those observed later in life. Despite these limitations, a serum copper level of less than 40 μg/dL or a ceruloplasmin value of less than 15 mg/dL after 1 or 2 months of age can be regarded as evidence of copper deficiency. In later infancy, childhood, and adulthood, serum copper values should normally exceed 70 μg/dL.

Preterm infants are at risk owing to their lower hepatic copper stores, which largely accumulate in the third trimester.[180] Low serum copper values may be observed in hypoproteinemic states, such as exudative enteropathies and nephrosis, as well as in Wilson's disease. In these circumstances, a diagnosis of copper deficiency cannot be established by serum measurements alone but instead requires analysis of liver copper content or clinical response after a therapeutic trial of copper supplementation.

The anemia does not respond to iron but is quickly corrected by administration of copper. Therapy in a dose of 0.2 mg/kg of body weight will cause a prompt reticulocytosis and rise in the leukocyte count. This can be given as a 10% solution of copper sulfate ($CuSO_4 \cdot 5\ H_2O$), which contains about 25 mg of copper/mL.

The daily requirement of copper is 0.1 to 1 mg for infants and 1.0 to 5.0 mg for children and adolescents. Copper intake in infants is usually low because breast milk contains only 0.2 to 0.4 mg copper per liter and infant formulas are generally fortified to 0.4 to 0.6 mg/L; however, copper defi-

ciency is rarely seen in healthy term infants. Older infants and children tend to have increased copper intake as cereals and other foods provide more copper than milk.[180]

SUMMARY

This chapter describes how deficiencies of specific nutrients such as iron, copper, vitamin B_{12}, folate, and vitamins A, C, and E can produce anemia. Although a deficiency of iron is the most common nutritional cause of anemia, it is important to recognize that multiple nutrient deficiencies may be present, and correction of a single deficiency alone will not necessarily correct the anemia. Careful examination of a routine hemogram can suggest the likely underlying nutrient deficiency and can certainly help direct initial diagnostic procedures. Anemia is a well-recognized major world health problem, leading to low birth weight and premature delivery, poor educational performance in childhood, lost work productivity, and decreased quality of life. Early recognition, diagnosis of specific nutrient deficiencies, and provision of effective therapy are immediate medical goals, whereas effective nutrient supplementation of at-risk populations is an important long-range public health goal.

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CHAPTER 50

FUNCTION AND NATURE OF THE COMPONENTS IN THE ORAL CAVITY

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The position of the oral cavity at the entrance to the gastrointestinal tract requires that it perform functions that need diverse tissues and specialized structures. The foods and other items that children eat and drink vary widely in their particle size and texture, degree of hardness, pH, and other chemical stimuli, as well as wide ranges of temperature. These different characteristics produce stresses on the oral components that must be moderated before swallowing. In the mouth, food items must be subdivided by chewing and simultaneously diluted and buffered with saliva until the bolus is suitable to swallow and pass on to the esophagus and lower areas of the gastrointestinal tract. The amount and composition of saliva secreted on each occasion are in response to the whole experience of eating—from the initial seeing, smelling, and anticipating to the tasting, chewing, and swallowing.[1,2] Especially in young children, many undesirable materials are taken into the mouth, which contribute various kinds of microorganisms and/or other dangerous entities.

The temperature and humidity of the oral cavity, as well as the frequent presence of all required nutrients for cellular growth and multiplication in food and drink, result in the mouth being an ideal incubator for many types of microorganisms from birth onward. An important source of the infant's flora is the primary caregiver.[3] There is evidence of matrilineal transmission of mutans streptococci in very early childhood. Strong correlations between salivary mutans streptococci counts in mothers and their children have been reported. Maternal salivary levels of mutans streptococci infection may influence infection rates of mutans streptococci in their children at ages 6 to 18 months and at 4 to 5 years. Salivary concentrations of 10^5 colony forming units mutans streptococci per milliliter of maternal saliva were associated with a 52% infection rate in their children compared with only a 6% infection rate when the maternal saliva concentration was 10^3 or below.[4,5] The presence of caries in the mother and siblings increases risks for the child, but the most consistent predictor of risk of caries (dental decay) in children is past caries experience.[6] Nutrients and the foods that provide them have numerous relationships to the oral tissues and structures, and these relationships vary depending on the nature of the tissue or structure itself. Some relationships differ from those elsewhere in the body. For example, sugars, when metabolized throughout the body, are wholesome sources of energy for the cells' many and varied functions. However, in contrast to this vital systemic relationship, the sugars have an undesirable local effect in the mouth. On the surfaces of dental enamel, sugars support the metabolism of microorganisms in dental plaque with the production of acid.

In the life history of the soft tissues, a transition occurs at birth as a result of the new, stressful exposure of their outer surfaces to microorganisms and food, meanwhile still being nourished systemically. A much more striking transition occurs for the teeth, especially the enamel surfaces, at the time of their eruption into the oral cavity. Prior to eruption, the external surfaces of enamel are surrounded by the enamel cap, including the enamel-forming cells of ectodermal origin, the ameloblasts; the inner surface of the dentin is covered by the layer of odontoblasts, the dentin-forming cells, which are embryonically of mesodermal origin. Both enamel and dentin throughout their formation and mineralization are related fully to the systemic environment. At eruption, the enamel cap is ruptured, and the outer surfaces of enamel become exposed to the oral milieu of saliva, microorganisms, and food. The odontoblastic layer remains intact in contact with the capillaries of the pulp and continues to metabolize slowly with the centripetal formation of secondary dentin at the expense of the connective tissue in the pulp. The latter process accelerates when toxic metabolites from a deep carious lesion in the dentin trigger a protective response with more rapid production of secondary dentin.

Structure of Enamel

Enamel and dentin are characteristically different from other tissues in the body. When fully mature, enamel contains only about 1% organic material and 2% water. Its tiny organic component consists of proteins chemically similar

to the keratins of skin and is dispersed throughout the inorganic crystals as a network of extremely delicate and intricate fibrils.[7] The rest of enamel is the complex calcium-phosphorus salt hydroxyapatite, which varies somewhat in its composition, depending on the concentrations of anions and cations in the extracellular fluids at the time it crystallizes in the embryonic organic matrix. The hydroxyapatite in enamel has more perfectly formed crystals than those in dentin and bone. After its eruption, enamel contains no cells and is cut off from systemic influences other than through saliva, which bathes it continuously throughout life. Elements in saliva exchange with those on the outer surface of the enamel, especially in the period shortly after eruption.[8] Owing to its acellular nature, enamel has no ability to heal or remodel, with the exception that remineralization of early (precaries) surface lesions with the incorporation of calcium and phosphorus from saliva can occur under suitable conditions.[9,10]

Structure of Dentin

Dentin contains about 20% protein of the collagen family comparable to bone. About 70% of dentin is hydroxyapatite. Although dentin continues to form centripetally at a slow rate, like enamel, it is unable to remodel or repair itself as it does not contain anything comparable to the haversian system of bone. Any developmental errors in the formation of enamel and dentin remain throughout life as chemical or histologic artifacts in the kymographic record.

NUTRITIONAL STUDIES ON THE ORAL TISSUES AND STRUCTURES

Soft Tissues

The soft tissues, mucosa, gingiva, tongue, and taste buds, are especially susceptible to local stresses. Their metabolic activity is high. Oral mucosal cells in rats, for example, are replaced in 3 to 5 days by rapid cell division in the basal layer and sloughing of the surface cells; in contrast, the turnover rate in cheek skin is about 10 days.[11] This high metabolic activity accounts for the rapid healing of injuries to soft tissues within the mouth. However, the high metabolic activity of oral tissues results in a high susceptibility to nutritional deficiencies as adequate nutrients must be available to support the rapid cell multiplication and replacement.

In the early decades of nutrition as a discipline, deficiencies were often recognized first as clinical entities because of manifestations in the oral cavity; scurvy (vitamin C) and pellagra (niacin) are the prime examples.[12] The ease of oral examination for abnormalities with minimal violation of the subject's privacy also contributed to early recognition of nutritional deficiencies that affected oral components.

The increased understanding of nutrition and the attention to preventive nutrition, including legally required fortification of foods, such as niacin for the prevention of pellagra, have led to the almost total elimination of such nutritional deficiencies in children of the industrialized nations. However, in the developing nations of the third world, especially in times of famine, such deficiencies still occur.

Mineralized Tissues

In early experimental studies with rats, severe deficiencies of vitamin A caused abnormalities in the ameloblasts, which led to hypoplastic enamel.[13] Severe vitamin C deficiency in guinea pigs, which, unlike rats, require preformed vitamin C in their diets, produced a syndrome in which the odontoblasts produced much less dentin.[14] As a result, the erupting teeth were thin and fragile. Acute deficiencies in rats and dogs of vitamin D or calcium or grossly abnormal calcium-to-phosphorus ratios resulted in inadequate mineralization and hypoplasia of the teeth.[15,16] Little evidence exists to suggest that moderate deficiencies of these nutrients are of clinical significance in children in industrialized countries, although we still see cases of vitamin D–resistant ricketts. In severely malnourished children in developing countries, a linear enamel hypoplasia (natal line) has been described in the anterior teeth of the primary dentition (Figure 50-1), which is much less frequent or absent in better nourished children in the same communities.[17,18] The poorly mineralized ring around the teeth in this syndrome was being formed about the time the children were born and was highly susceptible to dental caries. All children at birth had low serum vitamin A levels.

Low protein intake during the reproductive cycle of white rat dams resulted in delayed eruption of the molars of their offspring. Their teeth were smaller and more susceptible to tooth decay than those of the offspring of

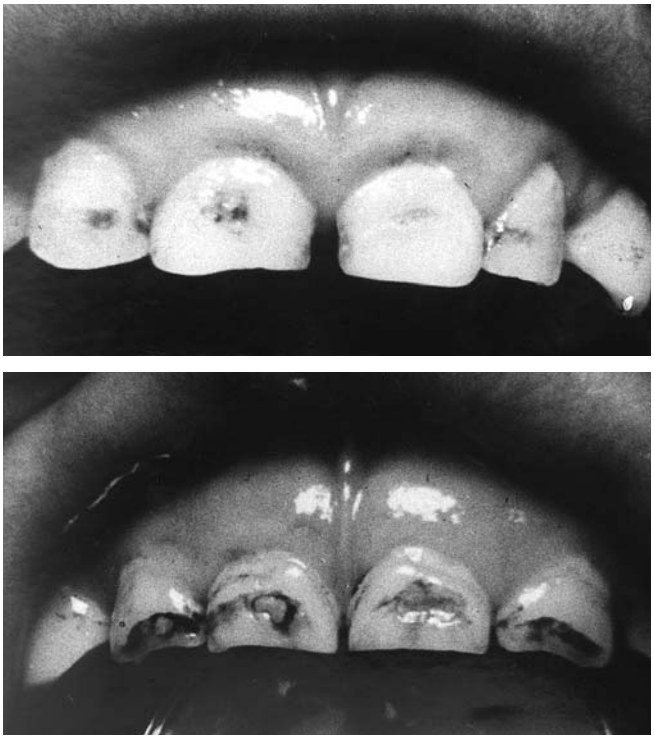

FIGURE 50-1 Photographs of linear hypoplasia of the anterior teeth of Guatemalan children. These hypoplastic areas are prone to develop dental caries. Reproduced with permission from Sweeney EA et al.[17,18]

closely related females provided with adequate protein.[19] The increased caries susceptibility in the deprived rats may be attributable to structural abnormalities in the salivary glands produced by the protein deficiency.[20]

Alvarez conducted two cross-sectional and one longitudinal study among Peruvian children in whom malnutrition in early life was prevalent.[21] He studied the influence of malnutrition on the time of tooth eruption and of deciduous tooth exfoliation and the susceptibility of both deciduous and permanent teeth to dental caries. As in the earlier studies with rodents, tooth eruption was delayed significantly among malnourished children. Because rodents have only a single dentition, exfoliation could not be studied in the laboratory. Among the malnourished Peruvian children, their deciduous teeth exfoliated appreciably later than those in better-nourished children in the same communities. When the length of time that the deciduous teeth were exposed to the oral environment was considered, instead of the traditional method of considering only the chronologic age of the children, the deciduous teeth of malnourished children were observed to have a higher incidence of caries than those of the better-nourished children. Even a single episode of moderate malnutrition before 1 year of age also resulted in a higher incidence of dental caries of the permanent incisors and first molars, which were being formed and were starting to mineralize during that interval. The increased incidence of dental caries among these children again paralleled the rodent studies conducted three decades earlier. Alvarez suggested that this observation may result from imperfect formation of dental enamel early in life.

Several studies, in animals and humans, have evaluated the effect of nutrition and nutrients on the growth and development of oral structures. The conclusion of many studies is that adequate nutrition is essential from the earliest periods of development. Further, a firm diet enhances proper growth and development compared with a soft diet. Specifically, the effect of diet consistency has been shown to affect growth of the mandible and maxilla and proper tooth eruption. Ongoing research on the harmful effects of nutrition on oral growth indicates that excess vitamin A can be a potent teratogen that may contribute to oral defects such as cleft palate. Protective effects of folic acid have been shown in animal studies but not in humans as yet, probably owing to the complexity of other factors also involved.[22]

Adequate amounts of all nutrients should be provided throughout the long periods of tooth formation in children to ensure their normal development, that is, from the last trimester of pregnancy through 16 years of age.

DISEASES OF THE ORAL CAVITY

The two principal diseases of the oral cavity are dental caries (cavities, carious lesions) and periodontal disease (destruction of the tissues that support the teeth in the jaws). Although the latter is the chief cause of tooth loss in adults, juvenile periodontitis occurs infrequently in children, is much more localized than in adults, and may be associated with an immunologic defect in some children. Both diseases are of multifactorial origin, are chronic in nature, and progress slowly and intermittently. Nutrition is not known to have a relationship to juvenile periodontitis except possibly through dietary influences on the dental plaque.

Etiology of Dental Caries

A carious lesion results from an interaction between the carbohydrates in food, especially the sugars, with cariogenic microorganisms in the dental plaque on tooth surfaces and the tooth surface in the presence of saliva; the gross anatomy of the tooth, the composition of the enamel and dentin, and the quantity and quality of saliva all vary in ways that influence the rate of progression of tooth decay. The most serious adverse influence on the ability of the teeth to be maintained in the oral cavity is any reduction in the flow of saliva owing to salivary disease, radiation, or drug use that modifies the ability of the salivary glands to function.[23,24]

Under certain circumstances, the acidic metabolic products of the microorganisms on the tooth surfaces from sugars reduce the pH of plaque sufficiently to demineralize enamel and, later, the dentin progressively until a carious lesion (dental decay) is produced. The epidemiologist commonly speaks of this type of disease production as the relationship of the agent (microorganism[s]), host (the tooth and the person in which it functions), and environment (the components in the milieu around the tooth and the home and community in which the individual lives) (Figure 51–2).[25] All three parameters must simultaneously be in a caries-producing mode for carious lesions to be initiated and progress to become visually detectable. Periodontal disease also results from the interaction of food, the microorganisms in the crevices between the teeth and the gingiva, and the tissues in the area.

Agent The microorganisms producing carious lesions are able to colonize the surfaces of the teeth and/or the pits

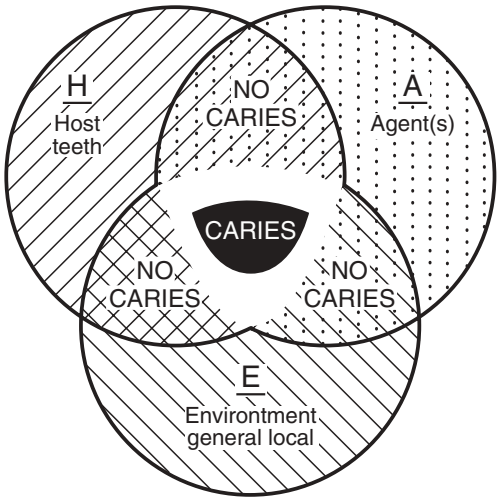

FIGURE 50-2 Diagrammatic illustration of the three major parameters simultaneously required for the initiation and progression of carious lesions. Reproduced with permission from Keyes AH and Jordan HV.[25]

and fissures of the biting surfaces.[26] These microbiota are able to produce sufficiently acidic environments (pH around 5) on the tooth surfaces when metabolizing actively to demineralize enamel and later dentin. They must be able to continue to metabolize actively at these low pH values as the lesion progresses deeper into the tooth. The primary sources of energy required by these organisms are the sugars. *Streptococcus mutans* is of special interest because it produces mutans, a polysaccharide of glucose, which enables it to adhere to smooth surfaces and to build up colonies in dental plaque. The nature of plaque is such that the microbial metabolites are produced in close proximity to enamel with restricted access to buffering saliva. In the human mouth, plaque contains numerous species of microorganisms with acid-producing capabilities. The complex nature of the oral milieu makes it virtually impossible to fully apply Koch's principles for identification of a specific causative organism. Probably more than one species is involved in most situations, but especially as lesions progress more deeply into the tooth with the need to metabolize in a strongly acidic environment.

Host Evidence of genetic determinants of caries resistance is limited in humans, yet a variety of subtle indications of genetic influences have been reported. Early suggestions that large differences in caries experience between national groups were genetically determined have been largely discredited. The caries prevalence in industrialized nations tended to be routinely higher than in developing countries; however, as the dietary customs of the high-caries industrialized nations were adopted in developing countries with increased sugar consumption and more frequent eating, their low-caries experience has been increasing. Meanwhile, in the last 20 years, dental caries prevalence in the industrialized nations has been decreasing significantly.[27]

Comparison of the dental caries experience of twins indicated that identical twins had more similar caries experiences than fraternal twins.[28] This may not be a truly genetic influence as such environmental experiences as food preferences, frequency of eating, and tooth brushing techniques may be more similar for identical than for fraternal twins. Similarities in dental caries for twins reared separately were considered to be about 50% attributable to genetic influences.[29]

Numerous trials have been conducted to develop animal strains of divergent caries resistance. Superficially, differences attributable to heredity seemed to be produced. However, when so-called resistant strains were heavily challenged early in life with cariogenic microorganisms, carious lesions developed readily, although not always as extensively as in the seemingly more susceptible strains.

Mandel suggested three avenues through which genetic influences may be mediated: (1) salivary components that buffer plaque acids elevating the pH and influencing the bacterial ecology of plaque, (2) immunologic and nonimmunologic constituents of oral fluids that have the capacity to alter the ability of cariogenic bacteria to attach to enamel, and (3) protein-bound lipids on the surfaces of teeth that may alter the permeability to acids produced in plaque.[30]

Environment The single most important variable in the oral environment is the frequency of consuming foods containing sugars that adhere to tooth surfaces. The absolute amount of sugars consumed is less important than the frequency of eating. In the 1930s and 1940s, numerous studies were conducted on the relation of frequency of eating to caries experience (Figure 50-3).[31] Almost invariably, the conclusion was that caries experience increased as frequency of food consumption, especially of between-meal snacks, increased. More recently, this type of trial has been less frequent and the above relationship has not been as readily demonstrable. Since the earlier studies, food habits have changed dramatically. At that time, most food was prepared and eaten at home, and the amount of sugar used was controlled by the homemaker. Between-meal snacks were usually candy and cookies. Today, relatively little food is prepared at home; many items are commercially prepared, with the amount of sugar controlled industrially on the basis of the amount needed for "best" taste. In addition, a much higher percentage of meals is consumed away from the home. Snack consumption is much more frequent, and less dependence is placed on three main meals a day.

The amount of sugar available per capita in a country is a reasonable index of the prevalence of dental caries among its children (Figure 50-4).[32] The information supporting the pivotal role of sugars in the etiology of dental caries

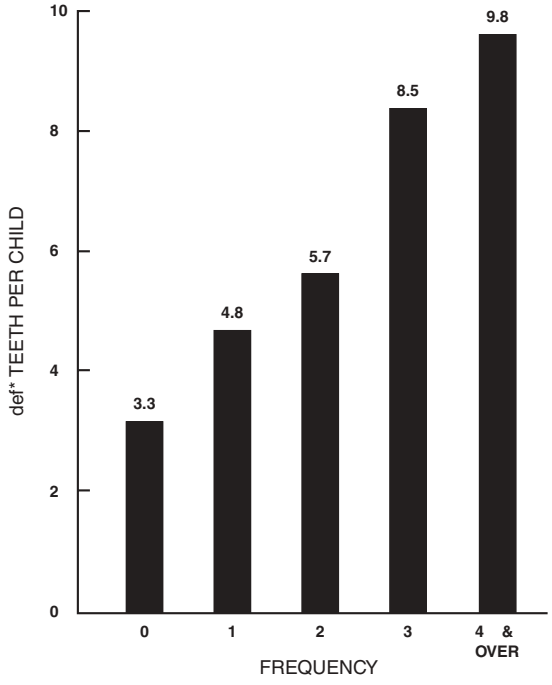

FIGURE 50-3 This bar graph compares the number of decayed, missing, and filled deciduous teeth with the frequency of between-meal eating in preschool children in Tennessee. Reproduced with permission from Weis RL and Trithart AH.[31]

was considered by 1977 to be sufficiently conclusive that Horowitz stated that in human dental experimentation,

> the control group should not be asked to engage in any practice that may have a harmful effect on the dentition or its surrounding tissues. For example, subjects in a control group should not be given or asked to use chewing gum sweetened with sucrose, nor should they be asked to use sucrose rinses or other agents to produce decalcification of tooth enamel or initiate carious lesions, unless the investigators are certain that they can completely "reverse" the defects.[33]

Mandel stated that little disagreement exists that differences in amount, form, and frequency of readily fermentable carbohydrates can affect the rate of caries attack, but considerable variation between children exists when intake appears to be generally comparable.[30]

Foods are complex mixtures of many chemicals. As yet, it has not been possible to devise a series of animal trials and evaluations in the human oral cavity that dependably estimate the caries-producing value of a specific food.[34] Some food items that contain relatively little sugar but substantial amounts of starch are more capable of producing caries lesions than expected; others containing high amounts of sugar are less capable of supporting the caries process than expected.

A special case of rampant dental caries limited to the maxillary anterior deciduous teeth and posterior molars has become known as early childhood caries. This problem occurs in young children who are put to bed at night or for rests during the day with a bottle of formula or sweetened juice. When they go to sleep, salivary secretion decreases drastically, and the fermentable carbohydrates in the milk or juice are not diluted or washed away but are readily available to the microorganisms on tooth surfaces.[35] It is believed that the tongue affords protection to the mandibular anterior teeth so that they are pathognomonically not affected. Excessive on-demand breast-feeding is also capable of causing the same problem. The sugar, lactose, in human milk is clearly able to support the caries process.

Pediatricians and pediatric dentists on a preventive basis need to urge mothers of young infants to follow feeding practices in which excessive exposure to sweetened fluids and breast milk does not occur. When early childhood caries is already present, appropriate dietary corrections need to be made by less frequent feeding and the use of fewer sweet snacks of all kinds. Appropriate professional dental care is needed, probably including topical fluoride applications, such as a fluoride varnish, coupled with strong oral hygiene procedures at home.[36] The latter will

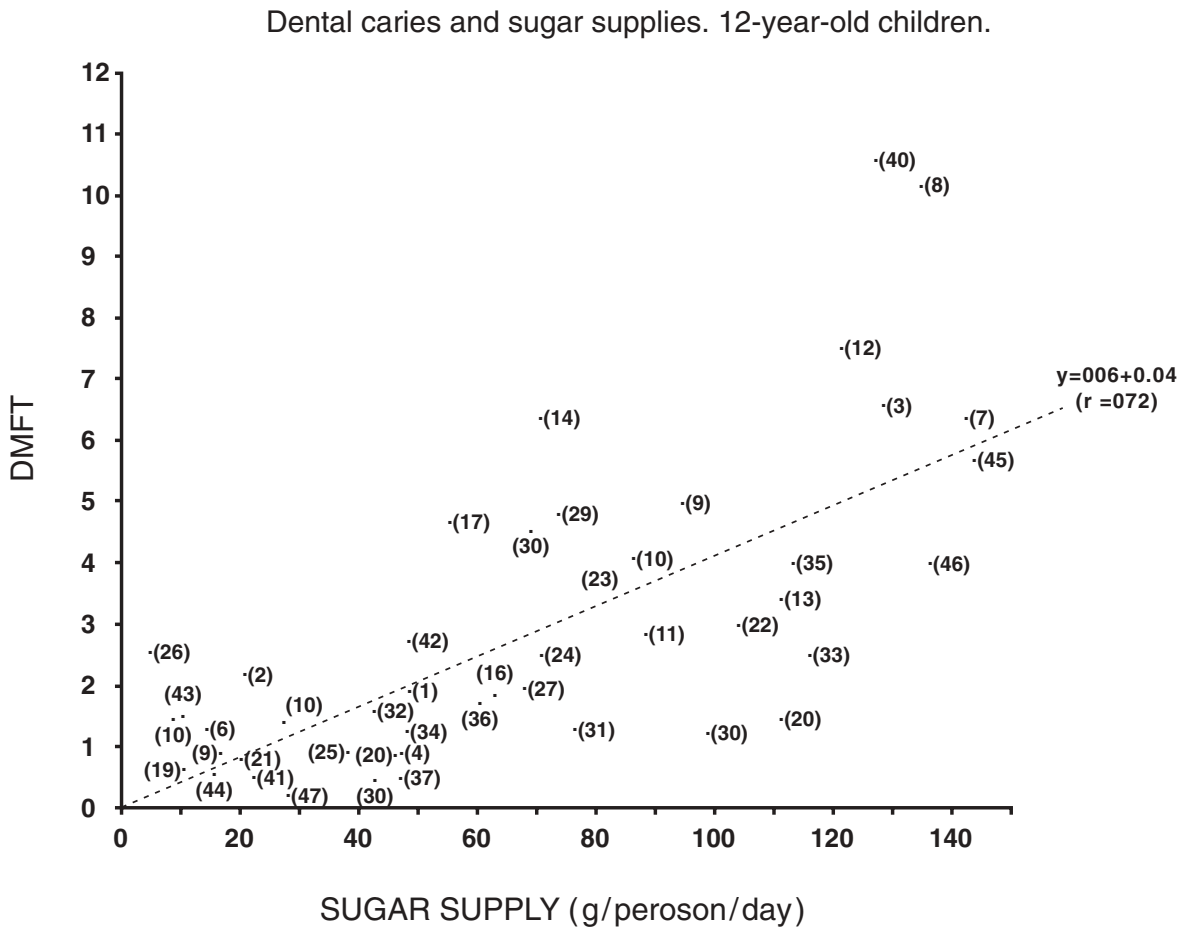

FIGURE 50-4 This graph represents a comparison of the number of decayed, missing, and filled permanent teeth with the sugar supply in grams per person per day for 47 countries. Reproduced with permission from Sreebny LM.[32])

include the parent's brushing of the infant's teeth with fluoridated toothpaste. Care is needed so that excess fluoride is not swallowed.

The importance of maintaining the deciduous teeth is not to be underestimated. They are needed as "space maintainers" as the jaws grow in order that there will be adequate room for eruption of the permanent teeth. Increased likelihood of orthodontic problems accompanies the early loss of deciduous teeth. High levels of untreated caries in the deciduous teeth provide reservoirs of cariogenic microorganisms from which the permanent teeth become quickly infected when they erupt into the oral cavity.

Reduced Ability of Polyols to Support Caries Measurement of the pH of dental plaque in vivo with tiny, sensitive electrodes has become a convenient means of evaluating how various solutions and foods in the oral cavity affect the metabolism in the dental plaque in proximity to the tooth surface. In 1944, Stephan reported on a sharp depression in the pH of dental plaque after a glucose rinse was swished around the mouth.[37] This depression from the resting value with a pH around 6.6 to 7.0 (the range observed in saliva) to 5.0 or less within minutes after the start of the glucose rinse lasted for a few minutes and then slowly returned to the resting value. Plots of results from this kind of evaluation have become known as Stephen curves (Figure 50-5).[37,38] The consensus from the Stephen curve concerning the relation of plaque pH to caries production is shown in Table 50-1.

Both the equipment and the procedures for intraoral tests have been refined and are used widely today. For example, certain varieties of cheese eaten shortly after a sugar rinse or a sweet food prevent the rapid pH drop in dental plaque (Figure 50-6).[38] Likewise, chewing a gum sweetened with a polyol, sorbitol or xylitol, does not result in a pH decrease, whereas chewing a gum sweetened with sucrose causes the typical caries-producing decrease (Figure 50-7).

TABLE 50-1 Relation of Plaque pH to Caries Production

Plaque pH	*Potential for Caries Initiation and Development*
Above 6.0	Safe area; low solubility of enamel; calcium and phosphorous adequate to saturate environment
6.0–5.5	Doubtful or very slow progression
Below 5.5	Danger area; high solubility of enamel; calcium and phosphorous inadequate to saturate environment

Adapted from Stephen RM and Edgar WM.[37,38]

Oral microorganisms have greatly limited abilities to metabolize the polyols, xylitol (5 carbon), sorbitol, and mannitol.[39,40] The effect of sugar substitutes on changes in caries rates has been evaluated in several observational studies as well as clinical trials, with results consistently demonstrating a protective effect of xylitol on caries incidence. Sorbitol was also shown to decrease caries rates compared with controls; however, the reductions in caries rates were greatest when xylitol was the sugar substitute. Some limitations of these studies include a lack of radiographs in caries diagnosis, high loss to follow-up, potential confounding, and bias owing to the nature of long-term community intervention studies. The criteria for causality—consistency, strength association, biologic plausibility, temporal sequence, and dose-response relationship—should be considered. First, these studies are remarkably consistent both in terms of the magnitude of the effect observed as well as the consistent demonstration that xylitol was superior to sorbitol in decreasing the risk of dental caries. Second, the relative risks observed are considered strong (0.19–0.4). It is biologically plausible that xylitol can reduce dental caries because the pH of plaque is lowered with xylitol compared with sucrose. Fourth, a dose-response trend was observed in the two studies that evaluated different concentrations of xylitol,

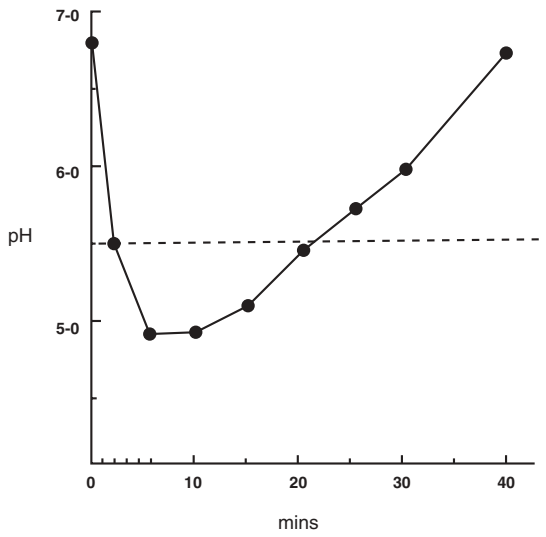

FIGURE 50-5 The typical Stephen curve showing the precipitous decrease in pH measured in vivo in dental plaque after a glucose rinse and the slower return to the resting pH. Adapted from Stephen RM and Edgar WM.[37,38]

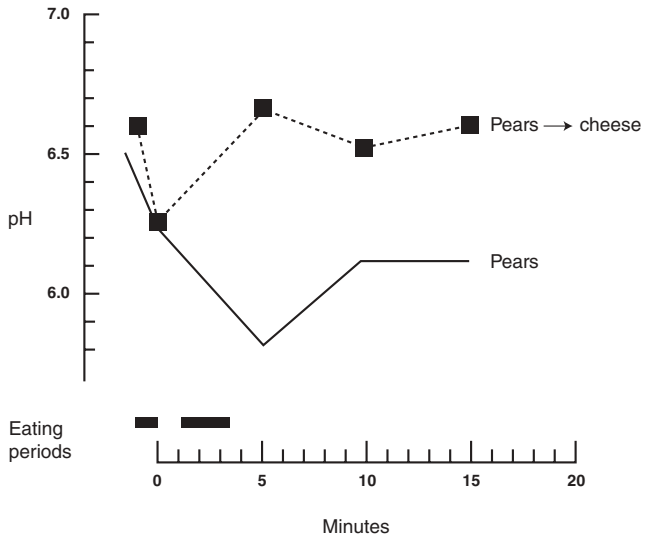

FIGURE 50-6 An example of the sharp pH decrease after eating a portion of sweetened pears and the moderating influence of eating cheese immediately after the same portion of pears. Reproduced with permission from Edgar WM.[38]

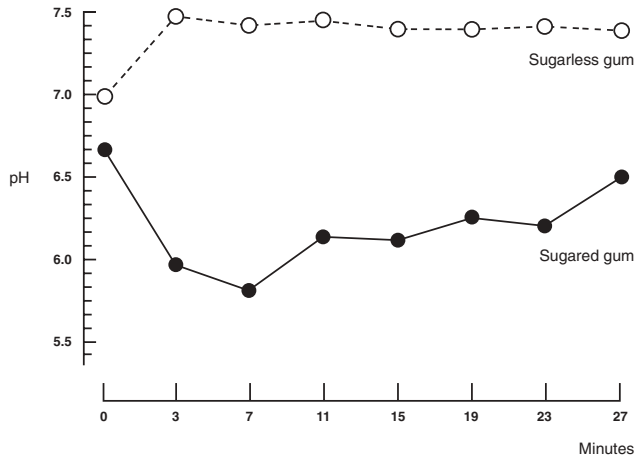

FIGURE 50-7 A comparison of the Stephen curve after chewing sucrose-sweetened gum with the pH curve after chewing gum sweetened with a noncariogenic polyol. Reproduced with permission from Edgar WM.[38]

with the greatest effect observed in the subjects using the strongest xylitol preparations. The evidence to date suggests a strong caries-protective effect of xylitol.[41]

In vivo pH testing has been used extensively in Switzerland, not only in basic research but also in the estimation of the potential of a specific product to cause dental caries when used excessively. When a product has been evaluated by approved methods for in vivo testing and is found not to cause an excessive decrease in pH, the Swiss Health Authority grants permission to identify the product as "zahnfreundlich" (friendly or safe for the teeth) and imprint a distinctive logo on the label (Figure 50-8).[42] This procedure has not been adopted elsewhere because of the inability to find a consensus that this procedure is adequate for the intended purpose.

FLUORIDES AND HUMAN HEALTH

Because fluoride has relationships to dental caries through both the host and the environment, a separate section for fluoride discussion is appropriate. Fluoride ion from any salt of the highly reactive halogen fluorine occurs ubiquitously in water supplies, soils, and foods. Fluoride is also present in all body fluids and tissues, even when the amount of fluoride ingested is low. Probably no nutrient demonstrates more clearly the physiologic spectrum from the influence of an insufficient intake, through normal to toxic levels of ingestion.

Toxicity of Excess Fluoride: Mottled Enamel

Toxic manifestations of excess fluoride ingestion were observed before recognition of its benefits, unlike other nutrients, for which the effects of deficiencies were described first. In 1901, Eager, a physician in the US Public Health Service stationed in Naples, Italy, described an esthetically disfiguring problem of dental enamel in otherwise healthy adults.[43] Their enamel was variously mottled with brown stains; he attributed the problem to local geologic conditions. In striking contrast, he recognized that the enamel of teeth in young children in the area was normal, which he postulated might be attributable to a recent change known to have occurred in the water supply.

Subsequently, descriptions of mottled enamel were reported from numerous parts of the world in humans as well as in domestic animals.[44] Evidence became increasingly clear in humans that this esthetically disfiguring problem was caused by some agent in community or home water supplies. In animals, the problem sometimes was caused by their water supplies and in other situations was related to rock phosphate supplements added to their feeds as a source of calcium and phosphorus.

By 1931, reports from several widely separated laboratories established that the mottled enamel in humans and experimental animals was attributable to excess ingestion of fluoride from drinking water that contained more than 1.5 ppm fluoride, that is, 1.5 mg/L of water.[45–47] At this point, the popular name, mottled enamel, was superseded by the scientific descriptor, chronic endemic dental fluorosis.

This abnormality was determined to result from some as yet undefined altered relationship(s) in the deposition of crystals of hydroxyapatite in the organic matrix formed by ameloblasts, the enamel-forming cell of ectodermal origin. This developmental interrelationship is apparently the most sensitive process to excess fluoride in the extracellular fluids of any in the body. Higher intake (20 mg) of fluoride per day in industrial exposure causes abnormal calcification in the spine and, after 20 years, serious crippling fluorosis.[48]

Classification System for Mottled Enamel

Dean developed a classification system to describe the various visual levels of enamel pathology and a weighting system to provide a community fluorosis index.[49] He used the terms (1) questionable—slight aberrations from the normal glossy translucency of enamel, which the examiner could not be certain was pathologic (weight = 0.5); (2) very mild—small, dull, paper-white areas scattered irregularly over the tooth surface but covering less than 25% of its area (1.0); (3) mild—more extensive white opacities but less than 50% of the area involved (2.0); (4) moderate—all surfaces affected with marked wear on the chewing surface accompanied by brown stains (3.0); and (5) severe—all surfaces affected with marked hypoplasia, discrete or confluent pitting, and widespread brown stains

FIGURE 50-8 The "safe for teeth" logo approved for use on the label of an approved product in Switzerland. Reproduced with permission from Guggenheim B.[42]

(4.0). The community fluorosis index was calculated by combining the weight for each child with the frequency of occurrence of each grade in the child population. A community fluorosis index over 0.5 was considered undesirable, indicating the need to reduce the water fluoride level.

As shown in Figure 50-9, mottled enamel does not become a problem until in excess of 1.5 ppm fluoride in drinking water was ingested during tooth development.[50] However, water concentrations beyond this amount caused increasingly severe fluorosis and increasing frequency. As a public health measure, excessively high fluoride amounts must be reduced or a new lower fluoride water supply found. It must be emphasized that mottled enamel cannot result from consuming excessively high amounts of fluoride after the teeth are formed because this abnormality is completely of developmental origin.

Dental Benefits of Naturally Available Fluorides

One of the earliest observers of enamel fluorosis in this country, McKay, in Colorado Springs, where the water supply was later shown to contain 2.0 ppm fluoride, reported that teeth with mottled enamel did not seem to have an increased susceptibility to dental caries despite the surface irregularities.[51] In the late 1920s and 1930s, several small studies suggested that fluorosis appeared to be associated with reduced dental caries experience.

A combination of the need to know the permissible upper limit of fluoride in drinking water plus the increasing concern about the generally high incidence of dental caries among American children led to many extensive epidemiologic surveys among children. Numerous increasingly large surveys in the 1930s and 1940s indicated the strong correlation between fluoride ingestion during tooth development and tooth decay. For example, Dean and colleagues reported on data for 7,257 12- to 14-year-old children in 21 cities in four states.[52,53] Figure 50-10 indicates the convincing relationship between fluorides during development and dental caries experience. They also considered other factors that might be related—composition of diet, hours of sunshine, and hardness of the water—and concluded that none could explain the naturally available fluoride–dental caries relationship.

Dental Benefits of Water Fluoridation

By 1945, the dental benefits of fluoride in communal water supplies had been demonstrated to the satisfaction of almost all investigators and many health-related professional organizations. The possibility of pathology elsewhere in the human body or of increased susceptibility to other diseases had been thoroughly studied, with negative results with one exception, the crippling fluorosis described above, which has never been observed at the optimal level for caries reduction.

Hence, in 1945, three clinical trials were initiated to adjust the fluoride concentration of community water supplies to an optimal level, with the expectation that 10 years would be needed for demonstration of the benefits. Grand Rapids, Michigan, was selected as one trial community, with Muskegon, Michigan, to serve as the unfluoridated control city and Aurora, Illinois, as a natural fluoride city. A second study was initiated in Newburgh, New York, with nearby Kingston as the unfluoridated control. The third community was Brantford, Ontario, with Sarnia, Ontario, as the unfluoridated control and Stratford, a nearby community with an optimal fluoride level naturally present. The data soon demonstrated that the results from water fluoridated in the distribution system duplicated those observed where fluoride was naturally present, with caries reductions from 50 to 60% in permanent teeth (Figure 50-11).[53–57] The benefits in teeth developed during the study began to show up sufficiently rapidly that Muskegon dropped out as the control community for Grand Rapids before the 10-year test period ended and initiated its own water fluoridation program. In addition, some unexpected reductions in caries initiation were observed among the

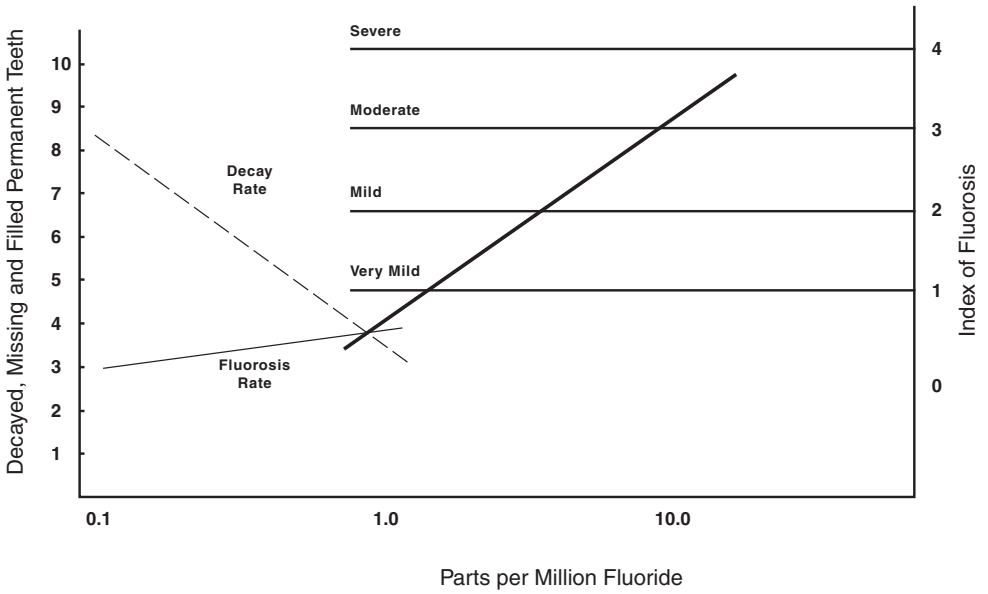

FIGURE 50-9 Relation between decayed, missing, and filled permanent teeth (*broken line*), severity of dental fluorosis (*solid line*), and fluoride concentration in the public water supply, with the latter on a logarithmic scale. Reproduced with permission from Hodge HC and Smith FA.[50]

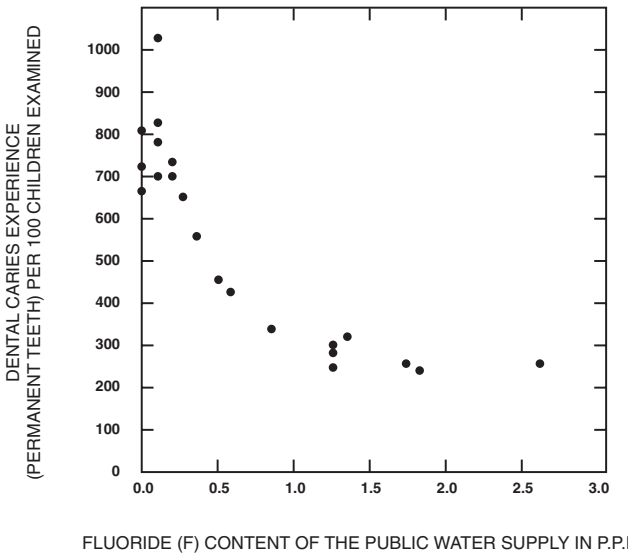

FIGURE 50-10 Relationship between the fluoride content naturally available in public water supplies and the number of decayed, missing, and filled permanent teeth per 100 children 12 to 14 years old. Reproduced with permission from Dean HT et al.[52,53]

teenage population in teeth formed before fluoridation was begun; this observation suggested that an oral environmental influence was occurring in addition to the expected systemic influence on developing teeth. As in communities with naturally available fluoride, the greatest benefit was for the smooth surfaces of the anterior teeth and the least for the carious lesions that develop in the developmental pits and fissures on the grinding surfaces of the posterior teeth. No evidence of esthetically disfiguring mottling was observed in these trials.

Fluoridation of water supplies has been widely adopted in the United States as a valuable and inexpensive public health measure. The Fluoridation Census in 1992 reported that 134.7 million individuals on communal water supplies in 8,572 communities received water fluoridated in the water processing system; in addition, 10.0 million individuals lived in 1,924 communities where the water contained at least 0.7 ppm fluoride naturally.[58] The total percentage of the population benefiting from fluoride in the water in the United States was 62.1.

Metabolism of Fluorides

The varying evidence of mottled enamel within the child population of any community in both natural fluoride areas and areas where fluoridation is practiced has been the subject of much interest since the first evidence of the fluoride relationships. Some variation undoubtedly occurs in the amount of water consumed by individual children; the amounts of canned fish with bones and the use of tea, the only foods with substantial amounts of fluoride, constitute additional variables.

Fluorides from soluble salts are readily absorbed from the gastrointestinal tract.[59] In the presence of high concentrations of cations that produce much less soluble salts of fluoride, its absorption is reduced. When much less soluble sources of fluoride are ingested, absorption of fluoride is also reduced.

The kidneys are the major route for fluoride removal from the body, which is characterized by variable degrees of tubular resorption. A range in resorption has been

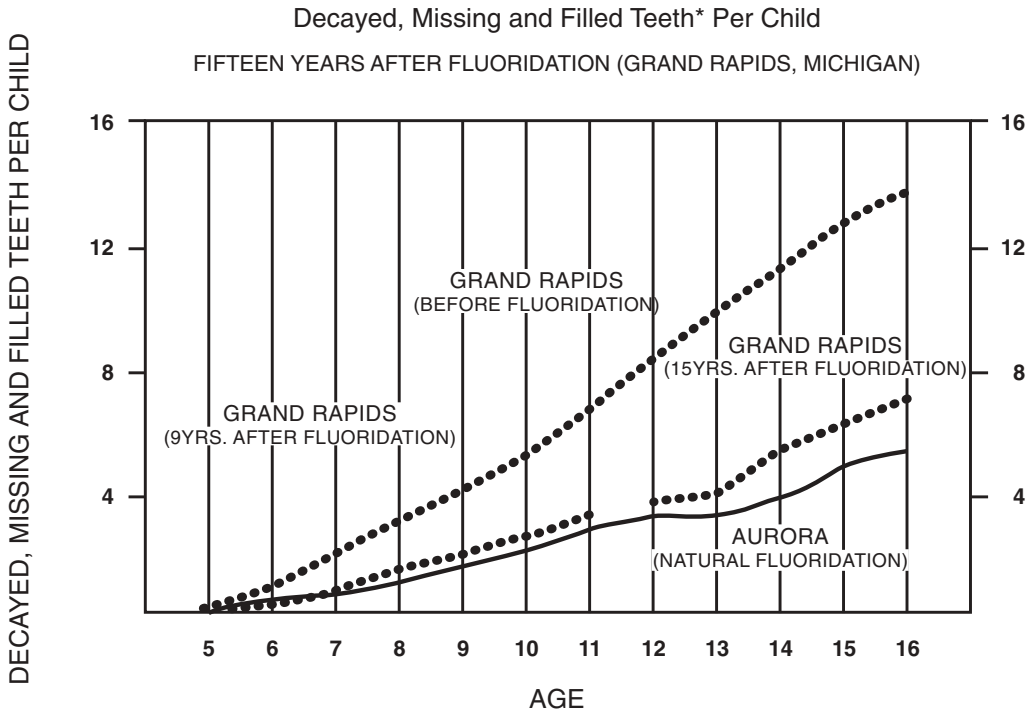

FIGURE 50-11 The benefits of fluoridation of the communal water supply in Grand Rapids, Michigan, are shown for the deciduous teeth after 9 years and for the permanent teeth after 15 years. The inclusion of the data for Aurora, Illinois, where the water naturally contains an adequate comparison of how similar the benefits are between natural fluoride and fluoride introduced at the water treatment facility. Reproduced with permission from Arnold FA et al.[54–57]

reported in humans; in four studies, the average resorption of fluoride after filtration into the tubules varied from 23 to 38%.[60] In general, fluoride clearance tended to increase with increased urinary flow rate. Urinary pH also influenced fluoride excretion. In rats with a urinary pH less than 5.6 induced by administration of ammonium chloride, urinary excretion was less than 5% of the amount filtered; alkaline pH as high as 8.0, induced by administration of sodium bicarbonate, resulted in fluoride excretion approaching 70%. Various factors can chronically alter the acid-base status and affect fluoride relationships. The composition of the diet is normally the major determinant of acid-base balance and urinary pH. In addition, various metabolic and respiratory disorders, level of physical activity, and altitude of residence contribute to acid-base status.

The combination of slightly different levels of fluoride ingestion by children with the above factors, which modify excretion in the urine, is probably adequate to explain the different degrees of mottled enamel in children within the same community.

Dental Benefits of Fluoride Tablets, Toothpastes, and Oral Rinses

Tablets or drops are recommended for children when fluoride is not available in the public water supply or when the water supply is from an individual well.[61] Fluoride analysis of the water in use needs to be made to be certain that it is too low to be beneficial. The levels recommended by the American Academy of Pediatric Dentistry for different ages and levels of fluoride in the water supply are shown in Table 50-2.[62] Fluoride supplementation is especially important for breast-fed infants irrespective of the fluoride level of the local water supply. The amount of fluoride secretion in human milk is low even when the local water supply contains an adequate fluoride level. Because young children are prone to swallow toothpaste, use of fluoridated toothpaste (usually containing 1,000 ppm fluoride, ie, 1 mg F per gram) contributes to the level of fluoride ingested. Therefore, it must be used sparingly; the size of a pea on the brush is adequate.

Fluoride toothpaste is an important part of the preventive approach for all children. Investigations have shown that fluoridated toothpastes and oral rinses, as well as application of concentrated fluoride solutions to enamel surfaces in the dental office or clinic, demonstrate substantial ability to prevent dental caries even in areas where the water is fluoridated.

The extent to which the various uses of fluorides contribute to the dental health of the United States is demonstrated by a statement by Harold Varmus, Nobel laureate and director of the National Institutes of Health, at a Senate Appropriations Subcommittee Hearing on March 17, 1994.[63] In response to Senator Harkin's question, "Does medical research contribute to long-term cost savings?" Varmus stated that his favorite example of the benefits of research concerned the use of fluorides to prevent dental caries, which alone saves the taxpayer several billion dollars per year.

TABLE 50-2 Dietary Fluoride Concentration in the Water Supply

	Fluoride Concentration in the Water Supply		
Age of Child	*Less than 0.3 ppm F*	*0.3–0.6 ppm F*	*More than 0.6 ppm F*
Birth–6 mo	0	0	0
6 mo–3 yr	0.25 mg	0	0
3–6 yr	0.50 mg	0.25 mg	0
6 yr up to at least 16 yr	1.0 mg	0.50 mg	0

Adapted from Pediatr Dent.[62]
The possibility of mild fluorosis has been reported with the above regimen, but no consensus has been reached about reducing these levels. Pediatricians and dentists may want to halve the above levels for children considered to have a low caries risk.

Mechanisms of Action of Fluorides

When the dental benefits of fluoride were first observed, systemic mechanisms of action were sought. The degree of crystallinity of hydroxyapatite in enamel increased as its fluoride concentration increased. Acid solubility of hydroxyapatite decreased as its fluoride concentration increased. Enamel surfaces had particularly high fluoride concentrations.[64]

Saliva contains about 0.019 ppm fluoride (1 μmol/L), about one-fiftieth of the concentration in communal water fluoridated at 1 ppm.[65] Even this low concentration appears to be important in the maintenance of the integrity of the tooth surface and in the remineralization of precarious lesions in the enamel. The mechanisms of action of fluoride in caries inhibition include the following: (1) the enhancement of remineralization during the repeated cycles of demineralization/remineralization in the early stages of the caries process, (2) the inhibition of glycolysis by which sugar is metabolized by bacteria to produce acid, and (3) pre-eruptive fluoride exerts some degree of caries inhibition; it acts by incorporation into the developing enamel hydroxyapatite crystal, thus reducing enamel solubility.[66]

Treatment of Carious Lesions

Because a visually detectable carious lesion is rarely self-limiting, it continues to progress until the pulp is infected, with the probable loss of the tooth, unless specific action is taken to interrupt the progress of the lesion. Decayed enamel and dentin must be removed and replaced with an inert material that is able to resist the forces of mastication and the influences of the oral milieu.

Pit and fissure sealants have been demonstrated to be effective in the primary prevention of caries, and their effectiveness remains strong as long as the sealants are maintained.[6] Sealants are intended to protect caries-susceptible tooth surfaces, which are benefited least by fluoride. They should be placed as soon as possible after the tooth erupts and isolation to prevent moisture contamination during placement can be achieved.

Identification of early carious lesions and treatment with preventive resin restorations have moved dentistry into a new era. This very conservative treatment allows for

the removal of just the small pit and fissure lesion and subsequent restoration with esthetic composite resin to which a sealant can be applied. By removing only the carious enamel and dentin, the preventive resin technique provides a restoration with a minimum of tooth reduction while ensuring the prevention of future caries in other pits and fissures through sealant placement.[67]

Amalgam is the least expensive restorative material to purchase and insert. The new high-copper amalgams are expected to last over 30 years. Questions have been raised in a few publications about the safety of amalgams because of their gradual release of mercury vapor. The media picked up this concern and exaggerated the problem with regard to both its severity and its frequency. Berglund estimated that 1.7 μg of mercury vapor was inhaled from 12 amalgam fillings in a 24-hour period.[68] He noted that the World Health Organization threshold limit value for mercury vapor in the workplace is 100 times greater than this amount.

Osborne stated that allergies to amalgam have been reported in the literature infrequently but that it is speculative as to which component(s) of amalgam (mercury, silver, tin, or copper) is causative.[69] Owing to their frequent handling of amalgam, dentists and their staffs are exposed to more mercury than any patient. Even though the profession urges great care in amalgam handling and ventilation of dental offices, guidelines that are followed by most dentists, dentists still accumulate a greater body burden of mercury than do nondentists. However, dentists have 2½ years longer life expectancies than the population in general, including physicians. Dentists and their staffs do not have elevated levels of spontaneous abortions, and their children do not have a higher incidence of birth defects.[70]

SUMMARY AND RECOMMENDATIONS

Typical of all areas of the body, the mouth and each of its components require a nutritionally well-balanced diet containing adequate amounts of all essential nutrients throughout development and maintenance.

Attention must be drawn to one special requirement for the adequate development and maintenance of the teeth throughout their entire life histories, namely, a source of fluoride. The easiest and least expensive way to provide fluoride is through a communal water supply containing 1.0 ppm fluoride that is present naturally or is added in the local water treatment plant. If, for any reason, water fluoridation is not possible, a proprietary source of fluoride in tablets or drops should be used. However, it is imperative that the diet should not be supplemented if the water already contains 0.7 ppm or more fluoride; an undesirable level of mottling is likely to occur with fluoride from two sources.

Consumption of sticky snacks containing sugars should be kept to a minimum and be replaced whenever possible by such noncariogenic snacks as fresh fruits and vegetables, cheese, or nuts. Candy and gum sweetened with a polyol are good substitutes for products sweetened with sugar.

Good oral hygiene habits need to be followed at least once a day using a small amount of fluoridated toothpaste. Use of a fluoride oral rinse or varnish is appropriate, especially when the child has a high degree of susceptibility and when there is a problem of reduced manual dexterity.

Visits to a dentist regularly are essential to detect and treat early lesions. Usually, every 6 months is sufficient, but when the child is especially susceptible, more frequent visits are important, as suggested by the dentist. Preventive procedures, such as topical fluoride applications to the tooth surfaces and the use of sealants to flow into and fill the susceptible pits and fissures on the occlusal surfaces of the posterior teeth, are to be encouraged.

Children who have had radiation of the head or neck or chemotherapy may have a reduced salivary flow, which is probably the most serious deleterious influence on caries initiation and progression. Special attention to frequent and careful oral hygiene and frequent use of oral fluoride rinses are imperative.

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CHAPTER 51.1

ADOLESCENCE: HEALTHY AND DISORDERED EATING

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Adolescence consists of a period of rapid and often dramatic changes in the teen's physical, cognitive, and emotional states. The pubertal growth spurt, surpassed only by the growth rate in the first 2 years of life,[1] forces each teen to deal with changing body habitus, with resultant shifts in body image. Simultaneously, each teen must deal with the development of primary and secondary sexual characteristics, alterations in mood, and differentiation of cognitive ability.[2,3] Because the onset and speed of these changes can vary considerably, adolescents can be particularly sensitive about their appearance.[4] Many teens attempt to gain control or a sense of mastery over their changing bodies and environment through changes in dietary habits or behaviors.[5–7] Others may engage in exercise for a variety of reasons, ranging from recreation to fitness to use as a means of weight control.[8] Nutrition during this period of rapid growth can be critical for adolescents in ensuring a healthy progression through puberty and achievement of full height, optimal bone density, and, for girls, initiation/continuation of normal menstrual cycles.

Adolescent diets have been shown to contain inadequate amounts of calcium, iron, and other essential nutrients.[9] Teens also may ingest protein, total fats, saturated fats, and cholesterol in higher than recommended doses.[10] Young athletes with higher energy demands may also consume nutrients that are inadequate to ensure growth and development. Moreover, aberrant eating patterns can have their antecedents prior to or early in adolescence, at which point, eating disorders can emerge.[11] A fine line often exists between pursuit of fitness and "healthy" exercising and the more obsessive hyperexercising seen in many teens with eating disorders. This chapter addresses the nutritional concerns of the healthy adolescent as well as the specific dietary concerns for those patients with eating disorders. Topics to be covered include the diagnostic criteria for anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified and a brief overview of the medical complications associated with these conditions. The role of exercise will also be addressed, including the issues of amenorrhea and osteopenia in the adolescent athlete with and without an eating disorder. Strategies for nutritional intervention in the office setting will be provided with the goal of prevention, early identification, and treatment of adolescents at risk for an eating disorder or experiencing the consequences of nutritional insufficiency.

GUIDELINES FOR THE DIETARY NEEDS OF THE HEALTHY ADOLESCENT

Adolescent dietary needs differ from the needs of younger children in the amount of required calcium, iron, most vitamins and minerals, and calories. The calorie and protein needs of adolescents are influenced by several factors, including gender, age, degree of maturation, and level of activity. The main nutritional goal is for the adolescent to ingest optimal nutrients in a balanced way to promote growth and health. Sometimes this nutritional goal is not achieved owing to adolescent eating practices, lifestyle, behaviors, and, in some cases, inadequate food and income.

Recommended daily caloric and nutrient requirements by age are seen in Appendix Table A-8. To look at energy needs in a different way, many dietitians and clinicians use calories and protein per unit height instead of per unit weight as this method takes into account growth better than would a calculation based on weight.[12,13] For instance, if an adolescent girl with anorexia nervosa had her caloric needs estimated by weight, we might underestimate her needs; conversely, an obese adolescent might overestimate caloric needs if using kcal/kg body weight as the basis for determining energy needs. The Recommended Dietary Allowances (RDAs) categorized the calorie and protein needs by chronologic age, without taking into account height. Table 51.1-1 shows the comparison between estimated calories based on weight versus height. A concrete example might be the calculation of energy needs for a 15-year-old girl at a weight of 50 kg (110 pounds) and a height of 160 cm. Based on weight, her calorie needs would be 50 kg × 40 kcal/kg = 2,000 kcal. Protein needs based on weight would be 50 kg × 0.08 g/cm = 40 g of protein. Based on height, the calcula-

tions change to 160 cm × 13.5 kcal/cm = 2,160 kcal, and for protein, 160 cm × .27 g/cm = 43.2 g protein per day.

The use of the kcal/cm provides a quick formula by which to calculate daily needs. For a longer method that takes into account weight, height, and age, basal energy expenditure can be used. The basal metabolic rate (BMR), estimated by the resting energy expenditure (REE), represents the minimum amount of energy needed by the body at rest in the fasting state; measuring REE is usually expensive and inconvenient for the office setting. Estimations of the standard REE for an individual prove more useful for the health care provider and can be calculated from the Harris Benedict equation[14]:

$$\text{For females, REE} = 665 + (9.6 \times \text{wt in kg}) + (1.7 \times \text{ht in cm}) - (4.7 \times \text{age in years})$$

$$\text{For males, REE} = 66 + (13.7 \times \text{wt in kg}) + (5 \times \text{ht in cm}) - (6.8 \times \text{age in years})$$

Above REE, energy requirements are also determined by activity level and the need for weight gain above basal requirements. Correction factors for activity levels and various disease states are seen in Appendix Table A-12.[15–18] Total energy requirements are estimated by multiplying REE by the activity and stress correction factors. The Mayo Clinic Nomogram can also be used to calculate total energy expenditure from surface area, age, and sex.[19]

Adolescents have high intakes of protein, total and saturated fat, and cholesterol. The intake of fat in a typical adolescent diet is around 33%, which is higher than the amount recommended by the American Heart Association (30% calories from fat). In general, adolescents consume more fat than recommended, and their food intakes are deficient in important vitamins and minerals such as calcium and iron.[20–24] A subset of adolescents are overly concerned about their weight and their appearance.[25] Many are dissatisfied with their weight, especially girls who want to lose weight and boys who are underweight and want to be heavier, with more muscle mass. Many adolescents follow unsafe practices to control their weight and to lose weight. Such practices included the use of diet pills, laxatives, vomiting, diuretics, fasting, and strict diets that can compromise the health and growth of the adolescent.[26] In our health-conscious society, the norm for this subset of teens may be a low-fat diet. These teens, along with their mothers and/or families, may falsely assume that "low fat" should mean "no fat." Actually, a low-fat diet for a child, teen, or young adult needs to include a minimum of 30 to 50 g of fat per day. In terms of calories, the ideal balance for the average teen should be as follows:

Regular diet:	*Low-fat diet:*
50–55% carbohydrate	50–55% carbohydrate
15–20% protein	15–20% protein
30% fat	20–25% fat

So, a teen consuming a 2,100-calorie diet might require 70 g of fat (30% calories), 105 g of protein (20%), and 263 g of carbohydrate (50%). Fluid requirements can be calculated in terms of body weight, using the following formula:

Body weight	*Maintenance fluid needs per day*
1–10 kg	100 mL/kg
11–20 kg	1,000 mL + 50 mL/kg for each kg > 10 kg
Above 20 kg	1,500 mL + 20 mL/kg for each kg > 20 kg

Thus, an adolescent weighing 50 kg (110 pounds) needs around 1,500 mL + (30 kg × 20 mL/kg) = 2,100 mL fluid per day or the equivalent of 8.4 cups (8 oz/cup).

The adolescent athlete may ingest a higher carbohydrate-containing diet. However, if eating properly, the lower percentage of fat intake still meets the basic needs of 30 to 50 g/day because overall calorie intake for the elite athlete is presumably higher. Thus, the nutritionally restricting athlete may run into problems of not meeting basic energy, protein, or dietary fat needs, although sheer percentages may meet an 80 to 15 to 5% distribution. General guidelines for adolescent athletes can be found in Table 51.1-2.

During the pubertal growth spurt, the adolescent acquires 15% of adult height, 50% of adult weight, and 40% of adult total-body mineral content.[27] Over half of the adult bone calcium is normally deposited during adolescence, with bone calcium content reaching a maximum by age 30.[28] During this time, the daily intake of elemental calcium must be above a threshold level to meet the daily demands and add new calcium to bone, in other words, creating a positive calcium balance. Currently, the RDA for calcium in teenagers 12 to 18 years of age is 1,200 mg/day. Recent studies have suggested that this amount is insufficient to meet the needs of rapidly growing teens.[29,30] In a calcium balance study, Matkovic and Ilich found that the minimum daily intake of elemental calcium required by adolescents to reach the threshold level is 1,480 mg/day, significantly above the RDA of 1,200 mg/day. The authors recommended a daily intake of 1,600 mg/day to mineralize new bone without depleting current skeletal reserves in growing teens.[31] It is noteworthy that most healthy teenagers fail to meet the RDA of 1,200 mg/day,[32] and patients with eating disorders have been shown to ingest insufficient calcium. In teens with anorexia nervosa, intakes have ranged from 300 mg/day to 1,100 mg/day, with most in the range of 500 to 600 mg/day.[33–36]

To create a positive calcium balance, many teens with eating disorders will require calcium supplementation. Sev-

TABLE 51.1-1 Adolescent Nutritional Requirements: Comparison of Recommended Calorie and Protein Needs for Adolescents

		Calories		*Protein*	
	Age	*kcal/kg*	*kcal/cm*	*g/kg*	*g/cm*
Males	11–14	55	15.9	1.0	0.29
15–18	45	17.1	0.90	0.34	
19–24	40	16.4	0.80	0.33	
Females	11–14	47	14.0	1.0	0.29
15–18	40	13.5	0.80	0.27	
19–24	38	13.4	0.80	0.28	

Adapted from Subcommittee on the Tenth Edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council.[159]

TABLE 51.1-2 Guidelines for Adolescent Athletes

General recommendations
- Adolescent athletes need between 6 and 10 g of carbohydrate per kg of body weight per day.
- Food intake should emphasize the consumption of complex carbohydrates and moderate amounts of fat.
- Fat intake should be kept at 30% of calories from fat.
- Protein recommendations for endurance athletes are 1.2 to 1.4 g/kg body weight. For strength-trained athletes, the protein requirements may increase to 1.6 to 1.7 g/kg body weight per day. The increase in protein intake can be easily met through diet without the use of supplements.
- Fluids: Water is the best alternative for fluid. Diluted fruit and sports drinks are acceptable.
- Vitamins and mineral supplements are not recommended unless the adolescent is not consuming adequate amounts of food. Protein and amino acid supplements are not recommended.
- Vegetarian athletes may be at risk for low-calorie, protein, and micronutrients intake.
- There is no need to use vitamins/mineral supplements, amino acids, or protein mixtures.
- There is no scientific evidence to support the notion that supplements improve athletic performance. Supplements should be recommended only to athletes with poor nutrient intake.
- Adolescent athletes and nonathletes are at risk for iron deficiency and low intakes of calcium. Food intake should emphasize the consumption of those two nutrients.
- Adolescent athletes need adequate calories especially at the time of high-intensity training to support growth and to avoid muscle mass losses and menstrual dysfunction.

Before exercise
- Adolescents should eat a light meal about 3 hours prior to competition.
- Fluids: Adolescent athletes should drink between 14 and 22 oz of fluid 2 hours before exercise.
- Adolescent athletes should not eat sweet foods or drinks before participation in sports.
- A snack or meal before exercise should be high in carbohydrate, low in fat, moderate in protein, and low in fiber.

During exercise
- The most important goal when the athlete is doing exercise is to replace fluid losses and provide between 30 to 60 g of carbohydrate per hour, especially for endurance events that last over an hour.
- Fluids: 6 to 12 oz should be consumed every 15 to 20 minutes, depending on tolerance.

After exercise
- After exercise, the goal is to provide adequate fluids, energy, and carbohydrates.
- Provide a carbohydrate intake of 1.5 g/kg of body weight during the first 30 minutes and again every 2 hours for 4 to 6 hours.
- Fluids: After exercise, the athlete needs to drink between 16 and 24 oz of fluid for every pound of weight loss during exercise.
- After a strenuous competition, athletes should consume a mixed meal with adequate amounts of carbohydrate, protein, and fats.

Adapted from Nutrition and athletic performance: position of the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine. J Am Diet Assoc 2000;100:1543–56.

eral acceptable forms are available, as outlined in Table 51.1-3. Calcium supplements vary in their ability to be absorbed. To test the quality of a particular supplement, the tablet can be placed in a glass of vinegar. If the tablet has not dissolved after 10 to 30 minutes, it is not an easily absorbed source of calcium.[37] To maximize absorption, clinicians should instruct their patients to take calcium carbonate supplements at mealtime as the presence of food in the stomach increases acid levels, helping with absorption. Although calcium carbonate supplements contain the highest percentage of elemental calcium, they may also cause constipation or flatulence. Calcium citrate supplements can be taken at any time, making them easier for patients on a busy schedule. Calcium phosphate can be found in calcium-fortified orange juice, soy milk, and rice milk. Nonchewable supplements should be taken with water to help them dissolve. Absorption is better when a patient ingests no more than 500 mg of calcium at a time. Women's multivitamins with calcium may contain up to 450 mg of calcium, whereas a typical multivitamin may contain no calcium. Other helpful hints include having patients avoid taking calcium with high-fiber meals as fiber reduces the amount of calcium the body can use; avoid preparations with bone meal, dolomite, and oyster shell as they may contain contaminants or toxic ingredients; and avoid taking iron and calcium supplements simultaneously as they may interfere with each other's absorption. The calcium content of some foods and drinks is seen in Table 51.1-4.

EATING DISORDERS: DEFINITIONS

Described as the "relentless pursuit of thinness,"[38] anorexia nervosa is characterized by extreme weight loss, distorted body image, and a morbid fear of obesity.[39,40] Diagnostic criteria have evolved over time, with the latest proposed revision outlined in Table 51.1-5. This table includes definitions for anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified. Of note, in the criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*),[41] anorexia nervosa can involve either weight loss leading to maintenance of body weight less than 85% of that expected or a failure to gain the expected amount of weight during a period of growth, leading to a body weight of less than 85% of that expected. In other words, a teen with a distorted body image who gains in height but maintains a given weight can cross weight centiles during that period of growth, alerting the astute clinician to a potential problem even before other symptoms have become apparent.

Typically, the adolescent who is either overweight or dissatisfied with current body image moves from a moderate effort to lose weight to an intense preoccupation with weight loss and eating; eventually, food-related activities interfere with socialization and family activities. School performance is often affected last, if at all. Restrictive anorexic adolescents are often characterized as obsessive-compulsive, perfectionistic, introverted, and emotionally inhibited.[42,43]

Bulimia nervosa, derived from the Greek root meaning "ox hunger,"[44] is characterized by the binge eating behavior, in which one "eats like a bull." Typically, bulimia nervosa begins in a teen who has been trying to control his or her weight with little success; he or she discovers, either spontaneously, from a friend or family member, or from the media, that self-induced vomiting, laxatives, or diet pills can control weight.[40] Binges may develop subsequently

TABLE 51.1-3 Available Calcium Supplements

Product	*Type of Calcium*	*Manufacturer*	*Elemental Calcium per Tablet (mg)*
Calcet	Calcium lactate, calcium gluconate, calcium carbonate	Mission Pharmacal	153
Calcet Triple Calcium + Vitamin D	Calcium lactate, calcium gluconate, calcium carbonate	Mission Pharmacal	300
Caltrate 600 Plus	Calcium carbonate	Lederle Laboratories	600
Caltrate 600 + Vitamin D	Calcium carbonate	Lederle Laboratories	600
Citracal	Calcium citrate	Mission Pharmacal	200
Citracal + Vitamin D	Calcium citrate	Mission Pharmacal	315
Citracal Liquitabs	Calcium citrate	Mission Pharmacal	500
One a Day for Women multivitamin	Calcium carbonate	Bayer	450
OsCal 500 chewable tablets	Calcium carbonate	Marion Laboratories	500
OsCal 500 + Vitamin D	Calcium carbonate	Marion Laboratories	500
Rolaids	Calcium carbonate	Warner-Lambert	220
Rolaids—extra strength	Calcium carbonate	Warner-Lambert	271
Titralac—extra strength	Calcium carbonate	3M	300
TUMS	Calcium carbonate	Smith Kline Beecham	200
TUMS—extra strength	Calcium carbonate	Smith Kline Beecham	300
TUMS 500	Calcium carbonate	Smith Kline Beecham	500
Viactiv*	Calcium carbonate	McNeil Nutritionals	500

*Do not use if patient has lactose intolerance.

and can involve the ingestion of up to 20,000 calories in a 1- to 2-hour period, with resultant abdominal discomfort, distress, or fatigue.[45] For other patients, a "binge" might consist of the same amount a healthy person would consider normal. In the patient with an eating disorder, this volume triggers an inordinant amount of guilt or negative feelings. Binges usually end with compensatory behavior, such as self-induced vomiting, exercise, and abuse of laxatives or diuretics. Other binges end with an exhausted food supply or interruption by family or friends. These patients often display other impulsive behaviors, including stealing, overspending, substance abuse, self-mutilation, and promiscuity.[46] A history of sexual abuse has also been reported in 20 to 50% of patients with bulimia nervosa.[47]

The teen with anorexia nervosa whose actions and thoughts appear to be egosyntonic or consistent with her inner self feels justified in her behaviors and is extremely resistant to therapy. This intrapsychic state depends on a severe level of cognitive denial and disappears when the denial is successfully challenged. In contrast to the adolescent with anorexia nervosa, the bulimic teen's thoughts and actions are egodystonic, causing her to have feelings of guilt, loss of control, and acute distress. Adolescents with bulimia are more likely to seek help, whereas adolescents with anorexia nervosa are often dragged in by concerned family or friends. However, changing the behavior can be just as difficult in a bulimic patient as in a patient with anorexia nervosa.

TABLE 51.1-4 Comparison of Calcium Content in Various Foods

Food	*Serving*	*Calcium per Serving (mg)*
Milk	1 cup	300
American cheese	1 oz	174
Cottage cheese	½ cup	77
Tofu	½ cup	434
Ice cream	½ cup	88
Yogurt	1 cup	345–415
Frozen yogurt	½ cup	104
Broccoli (cooked)	½ cup	89
Orange juice fortified with calcium	1 cup (8 oz)	300

EPIDEMIOLOGY

Incidence rates for anorexia nervosa have increased steadily from 1975 to 1991 in teens ages 10 to 19 years, although rates in adults have remained relatively constant.[48–50] The prevalence has been most recently estimated to be 0.5 to 3% of adolescent and young adult women, with an increasingly larger number of "healthy" girls expressing worrisome eating attitudes and weight concerns.[39,51–54] The classic image of the overachieving, "perfect little girl" from the upper middle class family is also being challenged, with more eating disorders seen in males (up to 5 to 10% of all cases) and in teens with a variety of backgrounds, ethnicities, and psychological profiles.[51,54–57] Eating disorders have been found in increasing numbers in Japan, China, and other countries.[58–60] In the United States, eating disorders are on the rise in minority groups such as Hispanics and native Americans.[61]

Anorexia nervosa continues to have two peaks of onset, one in early adolescence (ages 11 to 14 years) and a second peak in late adolescence (17 to 19 years),[39,62] whereas bulimia nervosa tends to begin in late adolescence with a teen of normal or high weight. The prevalence of bulimia nervosa has been estimated to be 1 to 19% using *DSM-IV* criteria.[46,48,51,63,64] Studies of female high school and college students have found symptoms of bulimia in 4.5% and 18%, respectively.[65,66] Higher rates of anxiety (43%), chemical dependency disorders (49%), bipolar disorders (12%), and personality disorders or personality trait disturbances

TABLE 51.1-5 Diagnostic Criteria for Anorexia Nervosa, Bulimia Nervosa, and Eating Disorder Not Otherwise Specified

Anorexia nervosa
- Intense fear of becoming fat or gaining weight, even when underweight
- Refusal to maintain body weight at or above a minimally normal weight for age and height (eg, weight loss leading to maintenance of body weight < 85% of that expected or failure to gain weight during a period of growth leading to body weight < 85% of weight expected)
- Disturbed body image, undue influence of weight or shape on self-evaluation, or denial of the seriousness of the current low body weight
- Amenorrhea or absence of at least 3 consecutive menstrual periods for those postmenarchal (also considered amenorrheic if periods inducible only after estrogen therapy)

Types
- Restricting = no regular binges or purges (self-induced vomiting or use of laxatives or diuretics)
- Binge eating/purging = regularly binges or purges in patient who also meets the above criteria for anorexia nervosa

Bulimia nervosa
- Recurrent episodes of binge eating, characterized by
  - Eating a substantially larger amount of food in a discrete period of time (eg, in 2 hr) than would be eaten by most people in similar circumstances during that same time period
  - A sense of lack of control over eating during the binge
- Recurrent inappropriate compensatory behavior in order to prevent weight gain, eg, self-induced vomiting, use of laxatives, diuretics, fasting, or hyperexercising
- Binges or inappropriate compensatory behaviors occurring, on average, at least twice weekly for at least 3 mo
- Self-evaluation unduly influenced by body shape or weight
- The disturbance does not occur exclusively during periods of anorexia nervosa

Types
- Purging = regularly engages in self-induced vomiting or use of laxatives/diuretics
- Nonpurging = uses other inappropriate compensatory behaviors, eg, fasting, hyperexercising, without regular use of vomiting or medicines to purge

Eating disorder not otherwise specified (those that do not meet criteria for anorexia nervosa or bulimia nervosa by DSM-IV*)*
- All criteria for anorexia nervosa except has regular menses
- All criteria for anorexia nervosa except weight still in normal range
- All criteria for bulimia nervosa except binges < twice/week or < 3 mo
- A patient with normal body weight who regularly engages in inappropriate compensatory behavior after eating small amounts of food (eg, self-induced vomiting after eating 2 cookies)
- A patient who repeatedly chews and spits out large amounts of food without swallowing
- Binge eating disorder: recurrent binges without the compensatory behaviors associated with bulimia nervosa

Adapted from the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington (DC): American Psychiatric Association; 1994.

(50 to 75%) have also been found in patients with bulimia nervosa.[46,67–71] Another series found that 50% of patients with anorexia nervosa and 30% of patients with bulimia nervosa met criteria for major depression.[72]

Many adolescents may show unhealthful eating behaviors even without evidence of a full-blown eating disorder. Adolescents and young adults who are required to reduce their food intake or follow a strict diet owing to a disease state are at high risk for developing an eating disorder.[73] In a study of 4,746 public middle school and high school students in Minnesota, healthful weight control behaviors were used by the majority of teens to control weight (85% adolescent girls, 70% adolescent boys).[74] These behaviors included cutting down on high-fat items and sweets, increasing fruits and vegetables, and exercise. Unhealthful weight control practices included fasting, restricting, using a food substitute (powder or special drink), skipping meals, and smoking more cigarettes; these behaviors were used by 57% of adolescent girls and 33% of adolescent boys. Extreme weight control behaviors, defined as use of diet pills, laxatives, diuretics, or vomiting to control weight, were used by 12% of the girls and 5% of the boys. The authors found that a high percentage of average-weight girls perceived themselves as overweight, desired to weigh less, and expressed body dissatisfaction.[74] Their data also found that obese adolescents recognized that they were overweight, with most reporting some steps taken to lose weight. Thus, prevention of both obesity and eating disorders may lie less in recognizing who is overweight and a superficial review of desirable weight control behaviors; rather, interventions may be more effective if more time is spent in building skills in how to engage in healthful weight control behaviors successfully.[74] Further strategies for eating disorder nutritional management are discussed in more detail later in this chapter.

In a study in Cleveland, Ohio, 1,268 urban, suburban, and rural high school students were given questionnaires asking about dieting and purging behavior.[5] Laxatives and diuretics were used more frequently by black girls than by white girls (10% versus 3% for laxatives, 5% versus 2% for diuretics). Vomiting was used more commonly by white girls, with 8% vomiting monthly compared with only 1% of black girls. It should be noted that 40% of the boys reported dieting, with similar dieting and purging behaviors between black and white boys. A survey of 36,320 Minnesota public school students in grades 7 through 12 revealed chronic dieting reported by 12.1% of the girls and 2.1% of the boys, with significantly greater numbers of girls dieting as they progressed from junior high through high school. Chronic dieters were more likely to report use of laxatives, ipecac, diuretics, self-induced vomiting, and other maladaptive behaviors.[7] Thus, clinicians should be alerted to the possibility that an adolescent who has reported chronic dieting may be developing an eating disorder.

Some male runners with compulsive exercise patterns have been shown to have bizarre preoccupations with food, concern about weight with strict monitoring of intake, and a high achievement orientation.[75] Such behaviors may indicate the presence of an eating disorder in the male athlete. In a group of 93 elite women runners, 13% had been diagnosed previously with anorexia nervosa, 25% displayed binge eating, 9% binged and purged, and 34% had atypical eating practices.[76] Among college athletes who often engage in highly intense competition, abnormal dietary patterns are prevalent. Self-induced vomiting has been reported in 14%, laxative abuse in 16%, routine use of diet pills in 25%, and at least one unhealthful eating habit in 32% overall.[77] A study of female college gymnasts

showed that 62% reported unhealthful eating behaviors, with two-thirds told by their coaches that they were too heavy.[78] Athletes whose coaches had commented on their weights were more likely to engage in unhealthful dietary practices. Athletes should be questioned by their clinicians about body image, weight concerns, menstrual patterns, and eating behaviors.

NUTRITIONAL ASSESSMENT OF THE TEEN WITH AN EATING DISORDER

A careful history and physical examination can reveal much information about the chronicity of the teen's illness, abnormal eating behaviors, and potential strategies for management. The clinician can start the history taking session by asking the parent and the teen individually why he or she is being seen. This information can be most helpful in revealing hidden agendas or different perceptions of parents and their teenagers. Ideally, the parent and teen each should be given time alone with the provider to promote a sense of individualized caring and listening to each one's needs. Confidentiality should be established immediately, with the explicitly stated caveat that the provider will break confidentiality if the situation is life-threatening or extremely dangerous. The clinician should ask the teen what is the most he or she has ever weighed and when. What is the least weight remembered and when? What is the current weight? For girls, at what age did periods start? When was her last period? Are menses regular, with or without cramps, and how long do they last? Has flow or duration changed? If periods have ceased, at what weight was she when she had her last period? Eating disorders can be associated with both primary and secondary amenorrhea. It is helpful to elicit the age of menarche and regularity of periods of the mother and the teen's female siblings.

The clinician should also ask questions about body image and self-esteem. For instance, does the teen feel underweight, overweight, or just right? At what weight would the teen like to be? Does he or she have any "trouble spots" or areas on the body that cause the teen particular discomfort or concern? With a reticent teen, the clinician might change the phrasing to state that most people have certain parts of their body that they would like to change and then ask the teen if he or she has any "trouble areas." Asking the teen how hard he or she struggles to lose or maintain weight simultaneously gives information on the effort placed in the abnormal eating behaviors and acknowledges the difficulty and stress the teen may feel over weight issues.

The clinician should specifically ask how the teen controls weight. Does the teen vomit to lose weight and, if so, using what methods (finger, toothbrush, or other tool)? A teen who can vomit at will without use of a finger or other item has probably been practicing this behavior frequently or for a long time. Does the teen use diet pills? Diuretics? Laxatives? If so, what kinds, how many per day, and how often? How often does the teen have bowel movements? Are they loose or formed? Any diarrhea or constipation? How much caffeine does he or she consume daily? The amount and kinds of fluids consumed also are important. Use of over-the-counter and illicit drugs, cigarettes, and alcohol should also be assessed.

The provider should determine the amount of time spent in exercise, what kinds of exercise and level of competition, and duration of involvement in a sport. Exercise can serve as another means of purging behavior. When women with eating disorders exercise, they tend to do so compulsively.[79] Many women pursue abnormally low body weights to participate in ballet, to compete in sports such as track or gymnastics, or to pursue a career in modeling.[80] Menstrual disorders have been associated with eating disorders in gymnasts, runners, ballet dancers, and models.[81] The amount of distress or any physical symptoms caused by missing a workout should also be assessed. The clinician should also ask the patient and family members whether the teen performs other "anxious" repetitive movements, such as pacing or foot tapping.

In obtaining a dietary history, the clinician can ask about the frequency and location of meals and snacks and about the quantity of food consumed. If she states that she eats a bagel for breakfast, ask how many bites she can manage; in this way, the provider acknowledges his or her awareness of the difficulty in consuming foods. Does the teen usually skip breakfast? Lunch? Dinner? Can the teen comfortably eat food prepared outside the home, for example, at school, restaurants, or friends' houses? Is he or she comfortable eating in front of friends and family? At home, who prepares the food, and are meals eaten alone or with other family members? How many nights a week is there a family dinner? Does he or she ever binge or "pig out?" What constitutes a binge? The provider and the patient may have different concepts about the definition of a binge, so explicit descriptions of the last binge can be helpful. How long does a binge last? Are they planned? What are the rituals around the bingeing?

The clinician should ask if the teen has any "taboo" foods or foods that she simply cannot or will not eat. Certain foods may be deemed "safe," whereas others are "unsafe"; for example, cake and cookies may be assiduously avoided, whereas many patients will eat muffins.[82] Other patients may be sophisticated label readers and eliminate all hidden fats, believing that if less fat is good, then none is better. Foods may be classified as absolutely good or bad, often with episodes of "magical thinking." Extreme examples include avoidance of all fat grams as they will automatically produce body fat, fear of talking about food on the telephone lest the calories move through the telephone and deposit themselves on the patient's body, or assumptions that restaurants or companies prepare foods in the most caloric way possible. Some patients may refuse to look in a particular mirror in the house because of the belief that the mirror literally added pounds to the teen's hips and buttocks. Such extreme delusional thinking often resolves with refeeding,[83] but many of the associated eating behaviors can be difficult to change. Families may note unusual use of utensils in eating or ritualistic behaviors, such as cutting food into minuscule pieces or chewing each bite multiple times.

Strict avoidance of fat grams, red meat, or other items can alert the clinician to potential nutritional insufficiencies while simultaneously painting a picture of how rigid the teen's diet currently may be. Many teens begin their eating disorder with a gradual switch to "healthful eating," often heralded by the weight-conscious family as a positive sign. For instance, the teen may cut out red meat, then move to lacto-ovovegetarianism, and then shift to be a "vegan," one who abstains from consumption of meat, fish, fowl, dairy products, and eggs.[84] Although a vegetarian diet can be healthful, the adolescent may use this diet as a means to restrict further, especially in the context of a nonvegetarian family who may be accepting of this seemingly healthful change and not realize the extent of the abnormal eating.

Another method for assessing daily intake is by 24-hour recall. Although this technique has achieved some popularity owing to its ease of use, its validity has been questioned.[85,86] Teens with eating disorders may exaggerate or minimize the amounts and types of food consumed, depending on whether they are restricting or bingeing. Having a parent in the room during this part of the interview may serve as a "reality check," with the body language and parents' interruptions "correcting" the teen's potential misrepresentation of amounts. Also, the meals of the teen's previous day may not be "typical," with a change in intake solely in anticipation of "reporting" to the health care provider. The main point of the 24-hour recall lies in distinguishing the types and amounts of foods consumed, including dairy products, fruits and vegetables, sources of fat and protein, and any junk foods. Patients with anorexia nervosa in particular should not be encouraged to count calories excessively as they may eat even less when attention is given to caloric contents, quantity, and quality of foods ingested.

For teens with disordered eating, a 3-day food record or a daily food journal can be a useful tool, not only during the dietitian's initial assessment but also to monitor the changes being made during recovery. Specific instructions on how to complete the food record can help improve accuracy of the information. The teen should be given advice on how to quantify food using standard measuring tools (eg, tablespoons or cups rather than "mouthfuls"). Patients with obsessive-compulsive tendencies may benefit from a more generalized approach to journaling and changing behavior patterns, helping them get away from strict calorie or fat gram counting, weighing, and measuring. In contrast, patients with bulimia nervosa can use the information obtained from the food record to identify foods or situations that trigger a binge (see Table 51.1-6). Attention can be placed on the emotional state during a binge, timing, or other pertinent aspects. For instance, if a teen always binges on arrival home after school, the clinician can suggest filling the time with more structured activities so that the teen does not automatically enter the kitchen at that time. Such simple interventions can sometimes provide a new behavioral pattern for a teen who is otherwise "stuck." Asking what the teen has tried, if anything, to avoid bingeing can also guide the clinician toward potentially useful interventions. The clinician should determine how the binge typically ends and whether they engage in compensatory behaviors after a binge. For purgers, the ability to postpone vomiting for even an hour may be a positive first step. Those patients who vomit should be advised to rinse their mouths with water with baking soda or mouthwash in lieu of brushing teeth after vomiting to minimize the impact of acid on the tooth enamel.

The clinician should also ask about more general symptoms. This review of systems should include questions about the level of energy or fatigue, change in mood, depression, and suicidal ideation. Tolerance to cold, irritability, and changes in skin should also be assessed. Level of school and family functioning should also be determined; patients with anorexia nervosa may slowly isolate themselves from peers and family, and all teens with eating disorders may show an extreme narrowing of interest.

TABLE 51.1-6 Sample Food Journal

Name Date

Time	*Place*	*Description of Food*	*Amount*	*Time Spent Eating*	*Hunger Level*	*Fullness Level*	*Exercise*	*Purge*	*Binge*	*Laxative*	*Thoughts*	*Mood*

Scale: 1 = hungry, 5 = comfortable, 10 = uncomfortably full.

Major losses or changes in the family structure can also trigger the onset of an eating disorder.

In the office setting, weights should be obtained in a hospital gown after voiding. Clinicians should be on the alert for weight manipulation during office visits, ranging from simple water loading for weight elevation to hiding of weights or other objects beneath the hospital gown or in various orifices. Many providers weigh patients backwards on the scale, especially if a patient will use a number on the scale to restrict further. A dipstick urinalysis can help assess specific gravity, with a value of 1.005 or less indicating water loading intentionally or perhaps a misguided view on fluid requirements. Urinalysis can also illuminate ketosis, proteinuria, and dehydration. Dehydration may result in an accelerated heart rate, masking a sinus bradycardia. Relevant findings on the physical examination of a patient with an eating disorder are listed in Table 51.1-7.

MEDICAL COMPLICATIONS OF EATING DISORDERS

Despite substantial malnourishment, adolescents with eating disorders may have remarkably few physiologic abnormalities at the time of presentation and in follow-up.[40] Medical complications of the eating disorder can be caused directly or indirectly by three processes: (1) caloric restriction, (2) purging behaviors, and (3) binges. Almost every organ system of the body can be affected by these behaviors.[87–90] Pure restrictors can have a different constellation of complications from those found in patients who purge; binges put the patient at risk for a separate set of problems. To clarify the myriad complications, the following sections divide the problems into those caused by caloric restriction, those caused by purging behaviors, and those related to bingeing.

Medical Complications of Caloric Restriction

The most serious sequelae of a prolonged starvation state include risk of sudden cardiac death, risk of arrhythmias, and myocardial wasting. In anorexia nervosa, thinning of the left ventricle and decreased cardiac chamber size have been reported,[91,92] along with the associated decreased blood pressure and reduced cardiac output.[39] The teen may complain of cold hands and feet, caused by diminished peripheral circulation owing to increased peripheral vascular tone in the face of decreased cardiac output.[93]

Sinus bradycardia, sinus arrhythmia, and hypotension can be seen as protective mechanisms or adaptations to a

TABLE 51.1-7 Physical Findings in Teens with Eating Disorders

Finding	*Cause*
Mouth	
Dental caries	Bingeing on sugar-containing foods
Enamel erosions on lingual and occlusal surfaces	Chronic vomiting
Dry mouth	Anxiety, decreased salivary output
Scratches on posterior pharynx or palate	Use of toothbrush, finger, or other object for vomiting
Skin	
Lanugo	Extreme weight loss (primitive response to warm body)
Russell's sign (calluses on the knuckle)	Use of finger for vomiting
Dry, cold, scaly skin	Decreased basal metabolic rate
Orange skin	Hypercarotenemia
Brittle hair and nails	Relative hypothyroidism
Petechiae	Thrombocytopenia from extreme malnutrition, on face from vomiting with Valsalva
Pedal or pretibial edema	Withdrawal from laxatives or diuretics; rapid refeeding
Sallow, loose, or sagging skin	Loss of subcutaneous fat
Callus formation or pressure sores	Pressure from sitting or exercising excessively
Eyes	
Conjunctival hemorrhage	Vomiting with Valsalva
Cheeks	
Parotid enlargement	Chronic vomiting
Cardiac	
Hypotension by pulse or blood pressure, bradycardia	Myocardial wasting, malnutrition
Breasts	
Atrophic tissue	Loss of subcutaneous tissue
Abdomen	
Scaphoid	Loss of subcutaneous tissue
Palpable loops of stool	Slowed gastrointestinal motility; constipation
Genitalia	
Dry, atrophic vagina	Hypoestrogenemia
Extremities	
Cold hands and feet; acrocyanosis	Poor circulation
Muscle wasting	Malnutrition
Other	
Loose-fitting clothes	To hide cachexia

state of malnutrition, occurring gradually over time; by themselves, these changes are not thought to be life-threatening.[94] In contrast, direct myocardial impairment can occur more quickly and can be lethal; examples include primary cardiovascular abnormalities such as prolonged corrected QT interval, ventricular dysrhythmias, and reduced myocardial contractility. Thus, the low heart rate of patients with anorexia nervosa is primarily a problem in association with a primary cardiovascular abnormality or electrolyte imbalance predisposing to arrhythmia. However, bradycardia, hypotension, and hypothermia are appropriately used as cues indicating medical compromise and the need for intervention. Varying heart rates (less than 40 to 60 beats per minute) have been used as a criterion for admission in various programs.[44,46,95,96] Gradual refeeding and bed rest under close observation remain the appropriate therapy for profound asymptomatic sinus bradycardia, with the cardiac abnormalities reversible when the teen returns to a more normal weight.[94] Rapid refeeding has been associated with congestive heart failure, probably caused by the large increase in afterload in patients with cardiac wasting.[97] Refeeding can also result in hypophosphatemia, caused by the combination of depletion of total-body phosphorus stores during catabolic starvation and increased cellular influx of phosphorus during anabolic refeeding.[98,99] This extracellular hypophosphatemia is often treated with 500 mg, orally twice a day, of a phosphorus replacement product such as Nutraphos (250 mg phosphorus, 164 mg sodium phosphate, 278 mg potassium phosphate; Willen), in a dose of two capsules orally twice a day, to provide the RDA of 1,000 mg phosphorus per day during acute refeeding.

Many patients develop a pattern consistent with the "euthyroid sick syndrome." Peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) is decreased, with a high or high-normal level of reverse T_3.[39,100] It is most likely that the decrease in T_3 represents another adaptive response to starvation by helping to reduce the metabolic rate in the face of decreased energy stores. Suggestive symptoms include bradycardia, cold intolerance, dry skin, coarse hair, slowed relaxation of reflexes, and hypercarotenemia.[39] Teens with anorexia nervosa should not be given thyroid hormone solely on the basis of a low T_4 level.[93]

As with other starved patients, growth hormone and cortisol levels are the only hormones typically above normal in anorexia nervosa.[93] Elevated levels of growth hormone probably reflect the associated decrease in insulin-like growth factor I, which normally inhibits growth hormone secretion at the level of the hypothalamus and the pituitary.[39] With refeeding, growth hormone levels fall to normal within a few days. Hypercortisolemia has been postulated as a cause of the osteopenia associated with eating disorders.[33]

Hematologic changes include pancytopenia, neutropenia without an apparent increased susceptibility to infection, and a normochromic or hypochromic anemia.[40] The bone marrow tends to be hypocellular.[39] Although many patients who have eliminated red meat from their diets may also have iron deficiency anemia, the anemia associated with their malnourished state often resolves with refeeding.

Gastrointestinal manifestations include delayed gastric emptying and slowed motility, with patients often describing feelings of early satiety, bloating, postprandial discomfort, and constipation.[89,90,101] Abnormal liver function tests may reflect fatty infiltration of the liver and usually normalize with weight gain. Teens with anorexia nervosa may also have transient hypercholesterolemia, also reversible with weight gain; in general, checking cholesterol levels in these teens should be avoided as they tend to use an elevated level as an excuse to restrict their daily fat intake further.

An elevated blood urea nitrogen level can also be observed, reflecting dehydration and a decreased glomerular filtration rate.[40] Starvation can also cause total-body sodium and potassium depletion, with 25% of patients with anorexia nervosa found to have peripheral edema with refeeding; it is most likely that this effect is caused by increased renal sensitivity to aldosterone and the action of increased insulin secretion on the renal tubules.[40] A minority of patients may have impaired or erratic release of vasopressin in response to osmotic challenge.[102] These patients may note mild polyuria. Remarkably, almost all patients who lose weight solely by caloric restriction tend to have normal electrolyte levels, even in the face of severe malnutrition.[51] The exception occurs in adolescents who restrict fluid to lower the weight and develop severe dehydration and in adolescents who load water to manipulate the weight prior to a visit to a health care provider and present with significant hyponatremia.

Amenorrhea, hypoestrogenism, and osteopenia occur commonly in girls with low weight as well as in patients with bulimia (see Chapter 51.3, "Adolescents: Bone Disease").

Medical Complications from Purging and Bingeing

Chronic, self-induced vomiting has been associated with hypokalemic, hypochloremic, metabolic alkalosis.[51,103,104] Loss of hydrogen, chloride, and water from gastric fluid results in chloride and volume depletion, triggering a secondary hyperaldosteronism. Consequently, tubular reabsorption of sodium and excretion of potassium increase. The loss of hydrogen ions, both from tubular excretion and from gastric fluid, further causes an exchange of hydrogen and potassium at the cellular level, with worsening hypokalemia. Sodium levels tend to be low or normal but can also be high. It is unclear why some teens who report vomiting over 20 times per day can have remarkably normal electrolytes, whereas those vomiting only three or four times per week can have values that are markedly abnormal.

Hypokalemia can also cause fatal or life-threatening arrhythmias. In a series of 37 patients with anorexia nervosa, 24% had prolonged corrected QT, with each case except one associated with hypokalemia, hypomagnesemia, or medications.[105] Adults with a protracted course of anorexia nervosa may be at greater risk for fatal arrhythmia.[106] Teens who use ipecac to purge are also at risk for irreversible myocardial damage as well as a diffuse myositis secondary to emetine toxicity.[40] If the myopathy is detected at an early stage, it may be reversible.[107] Diuretic abuse can also result in electrolyte abnormalities through tubular excretion of potassium and hydrogen; it has also

been associated with low levels of calcium, magnesium, and zinc in patients with eating disorders.[93,108] Laxative abuse causes loss of fluid and electrolytes in the stool. Those patients who combine vomiting with laxative and diuretic use are most at risk for severe electrolyte imbalances. Significant peripheral edema with accompanying fluid and electrolyte shifts can occur in patients who abruptly stop taking laxatives and diuretics, as might occur on admission to an inpatient unit.[51]

Vomiting can also cause parotid enlargement and a characteristic pattern of dental enamel erosion (perimolysis) on the lingual and occlusal surfaces of the incisors from repeated contact with gastric acid.[89,93] Patients may note thermal hypersensitivity when dental erosion has occurred. Bingeing on foods with high sugar content can also cause an increase in dental caries. Elevated amylase levels have also been found and are probably salivary in origin.[109] Vomiting in a state of decreased consciousness, as would occur in a patient using alcohol or drugs, may result in aspiration pneumonia.

Binge eating can cause acute gastric dilatation and even rupture.[110,111] A few patients who binge and vomit have also developed Mallory-Weiss tears and esophageal rupture.[109]

AMENORRHEA AND OSTEOPENIA

Recently, attention has been focused on the "female athlete triad," consisting of amenorrhea, osteopenia, and the presence of an eating disorder.[112] Amenorrhea, one of the cardinal signs of eating disorders, can also be seen in certain athletes, especially those participating in competitive sports that emphasize endurance and/or a slender physique with minimal body fat.[113–119] Binge-purging has also been shown to be a risk factor for secondary amenorrhea, with an odds ratio of 4.17.[120] In eating disorders and in long-distance runners, amenorrhea has been associated with hypothalamic dysfunction, weight loss, decreased body fat, excessive exercise, and stress.[121,122] Typically occurring after a 10 to 15% loss of body weight, amenorrhea can also precede weight loss in 50 to 75% of patients with eating disorders.[113,123,124] The basic mechanism appears to be an alteration in the regulation of gonadotropin-releasing hormone secretion by the hypothalamus, with changes in the dopaminergic and opioid systems found in patients with anorexia nervosa and in athletes.[113] Heavy training (over 18 hours per week) starting before and continuing throughout puberty has been shown to alter growth rate and to reduce growth potential in adolescent gymnasts. The proposed mechanisms include prolonged inhibition of the hypothalamic-pituitary-gonadal axis by exercise combined with the metabolic effects of dieting.[125]

"Athletic amenorrhea" can result in a hypoestrogenic state associated with decreased bone density in adults and delayed or interrupted puberty with decreased bone density in teens.[126,127] The osteopenia occurring with prolonged loss of menses has been associated with increased risk of stress fractures in both athletes and patients with eating disorders.[116,127] The risk factors for osteopenia in athletes and eating disorder patients can be seen as a negative net balance between bone resorption and formation.[127] Increased bone loss through resorption occurs with hypoestrogenism (amenorrhea) and hypercortisolemia (chronic stress). Decreased bone formation occurs with glucocorticoid excess and with inadequate calcium and protein intake. Excess glucocorticoids decrease calcium absorption from the gut and inhibit bone formation through direct, receptor-mediated osteoblast effects.[128,129] Acquisition of bone mineral normally continues through the second decade, with peak bone mass reached only in late adolescence or early adulthood.[130,131] Approximately 40 to 60% of bone mass is acquired during the pubertal growth spurt, occurring in females between the ages of 11 and 13 years; evidence suggests that as much as 5% may be acquired during the third decade.[34] This latter figure gains importance in that an extra 5% can account for a significant decrease in fracture risk.[34] Net gains are positively correlated with physical activity, weight, and calcium and protein intake and negatively associated with age.[34]

Osteopenia has been associated with amenorrhea of even a relatively short duration. Bachrach and colleagues found that 12 of 18 teens with anorexia nervosa had osteopenia, with half of this group having been diagnosed within the previous year.[130] The authors postulate that either osteopenia occurs relatively quickly or each patient had unrecognized illness for a longer period of time. Age at onset and duration of anorexia nervosa correlated significantly with bone density, whereas activity level, duration of amenorrhea, and calcium intake did not show a significant relationship with bone density. In contrast, Rigotti and colleagues found that exercise offered some protection against bone loss in anorexia nervosa.[35] Neither calcium supplementation nor vigorous exercise will protect against osteopenia in teens with severely abnormal eating behaviors.

Therapy for osteopenia and amenorrhea in athletes and patients with eating disorders has not been adequately studied. Estrogen replacement therapy can prove problematic for some teens with eating disorders and for athletes who are concerned about potential weight gain or the development of secondary sexual characteristics. Moreover, in teens who have not achieved final height and show significant pubertal delay, estrogen doses high enough to prevent osteopenia may cause accelerated fusion of the epiphyses, compromising final adult height.[130,132] Although estrogen may have an independent effect on bone mass in adolescents,[133] preliminary data suggest that hormonal replacement therapy alone may be insufficient to overcome the detrimental effect of low weight for height on bone density.[134] Weight gain with associated re-establishment of normal estrogenization appears to be the best means of increasing peak bone mass in teens with eating disorders, with increased bone mineral density seen even before the return of menses.[133,135]

Several noninvasive methods are available and have been used to assess bone density, analyzing either trabecular or cortical bone. Best measured in the vertebral spine, trabecular bone consists of plates traversing the internal cavities of the skeleton. Found in the distal radius and other areas, cortical bone forms the outer layer of the

skeleton.[113] Both cortical and trabecular bone mass increase during the pubertal growth spurt. In anorexia nervosa, trabecular bone appears to be most severely affected, with a relative sparing of cortical bone; this discrepancy is probably attributable to the more rapid turnover of trabecular bone, with resultant increased sensitivity to the metabolic changes caused by starvation or stress.[33,127,130] Single-photon absorptiometry, used in Rigotti and colleagues' study,[35] measures only cortical bone, whereas quantitative computed tomography of the spine exclusively measures trabecular bone. This latter method involves 75 times the radiation exposure of absorptiometry and thus has been used primarily in research studies.[136] Dual-photon absorptiometry, or dual-energy x-ray absorptiometry (DXA), measures trabecular bone of the axial skeleton (eg, the lumbar vertebrae or femur). DXA is currently the method of choice in assessing bone density in adolescents because of its precision, accuracy, and minimal dose of radiation.[113]

Several questions remain with respect to the triad of eating disorders, amenorrhea, and osteopenia. First, who should be studied with dual-energy absorptiometry or another methodology? For those with significant osteopenia, who should be treated and with what? Many centers consider obtaining bone density assessments of teens with eating disorders who have had amenorrhea for 6 to 12 months. The information can then be used as an impetus for weight gain and/or for improved compliance with calcium supplementation.

The decision for hormonal (estrogen/progestin) replacement should be made on an individual basis, taking into account potential final height and bone age. Bachrach and colleagues found that recovered anorexics displayed persistent osteopenia, suggesting that deficits in bone density acquired during adolescence may not be completely reversible.[133] The burden, then, should be placed on early detection of eating disorders, initiation of efforts to promote weight gain at the onset, calcium supplementation to ensure intake of 1,200 to 1,600 mg orally per day,[27] and consideration of hormonal replacement or other interventions after 6 to 12 months of hypoestrogenic amenorrhea.

FORMING A NUTRITIONAL PLAN

Treatment of eating disorders should involve a team approach, including a primary care provider to address medical concerns, a therapist, a registered dietitian, and often a family therapist or social worker.[44,90,96] Nutritional intervention is an essential part of treatment. The extreme thought disorder often accompanying severe malnutrition will not change with therapy alone; the initial step must ensure adequate nutrition before any therapy will be effective or even tolerated.[83]

In performing the anthropometric assessment, the clinician needs to determine if the patient weighs less than 85% of the weight expected for her age and height (ideal body weight [IBW]). The body mass index (BMI) is calculated as the weight in kilograms divided by the height in squared centimeters. In adults, a BMI less than 17.5 raises the suspicion of anorexia nervosa.[137] The newer growth charts now help track the BMI and can be found through the Centers for Disease Control and Prevention Web site (<www.cdc.gov/growthcharts.2000>). Adolescents with a BMI less than the 10th percentile are considered to be underweight; a BMI less than the 5% may indicate a higher risk for anorexia nervosa. The clinician should also consider the patient's weight history, body build (muscle versus fat), and stage of development when using the BMI.[55,56,137] The IBW initially can also be determined by using the 10th percentile weight for height (Appendix Tables A-1 and A-2) or, more commonly, the Frisch table at the 10th percentile (Table 51.1-8).[138] The latter table establishes a minimum weight for patients with both primary and secondary amenorrhea. The clinician should make clear to the patient that menses will not necessarily resume the moment the teen achieves the target weight; otherwise, the teen may inch herself up to that weight and not budge an ounce above it. The health care provider should emphasize a weight range, above which menses are most likely to return, remembering that the weight will probably be at or near that weight at which periods ceased.

Several other methods can be used to determine IBW for patients over 18 years of age. The 1959 Metropolitan Life Charts provide estimations for weight by age, sex, and appropriate frame size. The Hamwi formula provides a simple means of calculating desirable body weight.[139] For women of medium frame, allow 100 pounds for the first 5 feet and then add 5 pounds for every inch above. For example, a women who is 5 feet and 3 inches would have a Hamwi desired weight of 100 + (3 × 5) = 115 pounds (range 112–118 pounds given to the patient). For women of a large frame, add 10%, and for those with a small frame, subtract 10%. In men, the medium frame starting point is 106 pounds, with 6 pounds added per inch.

Overall goals for nutritional management should be spelled out clearly to the teen and family at the start of therapy. The dietitian may be viewed with some fear and mistrust by the adolescent initially[140]; the teen should be reassured that the dietitian hears and understands his or her concerns and will work with the teen to ease the transition back to health.[141] Recognition of the extreme variability between individual patients' diets and identification of the specific diet pattern exhibited by a particular teenager can have practical implications for planning individualized treatment.[142] Proceeding too quickly with nutritional changes may trigger anxiety and cause the patient to become more resistant to therapy.[143] The primary care provider, nutritionist, therapist, and other members of the care team must work together to allay these fears and to stabilize the patient medically and psychologically.

A food plan, developed collaboratively with the teen, will support the gradual transition to a normalized eating pattern. Initially, a daily intake of as little as 1,200 calories may be appropriate to prevent postprandial discomfort after prolonged starvation. Otherwise, a 1,500-calorie diet should be adequate to start, with calories added in 200 to 300 kcal increments to produce a rate of weight gain of 0.2 kg per day (⅓ pound) if hospitalized or ½ to 2 pounds per week in the outpatient setting.[89,90,144]

TABLE 51.1-8 Minimal Weight for Particular Height Associated with the Onset or Restoration of Menstrual Cycles

Height		Menarche or Primary Amenorrhea (13–15 yr)			Secondary Amenorrhea (16–18 yr)		
		Minimal Weight (10th Percentile)		Average Weight (50th Percentile)	Minimal Weight (10th Percentile)		Average Weight (50th Percentile)
inches	*cm*	*lb*	*kg*	*kg*	*lb*	*kg*	*kg*
53.1	135	66.7	30.3	34.9	74.6	33.9	38.9
53.9	137	68.6	31.2	36.0	76.8	34.9	40.1
54.7	139	70.6	32.1	37.0	79.0	35.9	41.2
55.5	141	72.6	33.0	38.0	81.2	36.9	42.4
56.3	143	74.4	33.8	39.0	81.4	37.9	43.5
57.1	145	76.3	34.7	40.1	85.6	38.9	44.7
57.9	147	78.3	35.6	41.1	87.8	39.9	45.8
58.7	149	80.3	36.5	42.1	90.0	40.9	47.0
59.4	151	82.2	37.4	43.1	92.2	41.9	48.1
60.2	152	84.3	38.3	44.2	94.4	42.9	49.3
61.0	155	86.2	39.2	45.2	96.6	43.9	50.4
61.8	157	88.2	40.1	46.2	98.8	44.9	51.5
62.6	159	90.2	41.0	47.2	101.0	45.9	52.7
63.4	161	92.2	41.9	48.3	103.2	46.9	53.8
64.2	163	93.9	42.7	49.3	105.4	47.9	55.0
65.0	165	95.9	43.6	50.3	107.6	48.9	56.1
65.7	167	97.9	44.5	51.4	109.8	49.9	57.3
66.5	169	99.9	45.4	52.4	112.0	50.9	58.4
67.8	171	101.9	46.3	53.4	114.0	51.8	59.6
68.1	173	103.8	47.2	54.4	116.2	52.8	60.7
68.9	175	105.8	48.1	55.5	118.4	53.8	61.8
69.7	177	107.3	49.0	56.5	120.6	54.8	63.0
70.3	179	109.6	49.8	57.5	122.8	55.8	64.1
71.3	181	111.8	50.8	58.5	125.2	56.9	65.3

Adapted from Frisch RE and McArthur JW.[138]

Liquid supplements (Ensure, Boost, Resource, or other brands) may be used as needed in patients who initially cannot tolerate the addition of solid foods. If a teen has a 1,500 calorie a day meal plan and can manage only 750 calories as solid food initially, three cans of a supplement (250 calories each) could be substituted.

Nasogastric tube feedings and peripheral alimentation carry increased medical and psychological risks; their use should be limited to those patients unable to consume sufficient calories orally who need urgent or acute stabilization.[145,146] A protocol for inpatient nutritional stabilization is outlined in Table 51.1-9.

Metabolic rate or caloric demands may increase quickly in the refeeding anorexia nervosa patient. In one study, during several stages of anorexia nervosa, when weight remained stable, restricting anorexic patients needed to consume a greater number of calories than patients with bulimic anorexia nervosa.[147] Differences in activity did not account for these findings, and bulimic anorexic patients were found to have similar or greater activity than the restricting group. As patients transition from a hypometabolic state to a hypermetabolic state during refeeding, daily caloric intake may need to be increased to as high as 3,500 to 4,000 calories.

The clinician should establish safe ranges for intake of both macronutrients and micronutrients. RDAs for various nutrients are found in Appendix Table A-8. Protein should constitute 20% of total calories, with minimum intake equal to the RDA in g/kg of IBW. Carbohydrates should account for 50 to 55% of total calories, and the clinician can encourage intake of fluids and water-insoluble fiber to treat the constipation that often accompanies refeeding.[82] Many patients with anorexia nervosa eat a relatively large quantity of fruits and vegetables; fiber in other forms, such as whole-wheat breads, cereal, or other grains, should be recommended. The last 20 to 30% of calories should come from ingestion of fat to provide sources of essential fatty acids; in teens ingesting few or no fat grams initially, the nutritionist can use a starting goal of 15% fat intake. This latter dietary change is often the most traumatic for the teen and should occur with a gradual, sequential reintroduction of the patient to "normal" eating. Expanded food selections should be encouraged, but the addition of a multivitamin mineral supplement providing 100% of the RDA for most micronutrients will help ensure an adequate nutrient intake. Iron-containing preparations may aggravate constipation,[82] but the clinician can counter this effect with use of sufficient fiber.

An easy way to communicate these calorie and nutrient requirements is through the use of a food plan. Food plans offer structure and help eliminate the binge, purge, and restrict patterns common to teens with eating disorders. Food plans allow the teen to eat mechanically until he or she is able reliably to recognize hunger and satiety signals.

It is important for the teen to be comfortable eating a wide variety of foods without any fear, guilt, or anxiety. "Forbidden" foods should be gradually reintroduced into the diet. With the help of a parent, creating a list of foods liked and disliked prior to the onset of the eating disorder can help determine whether a food is now avoided out of fear or is one that has always been disliked. It is useful to

TABLE 51.1-9 Nutritional Treatment for the Patient with an Eating Disorder during an Inpatient Admission

I. Initial caloric and protein requirement
   a. Calorie intake at 1,500 kcal per day (females), 1,750 kcal per day (males), until assessed by nutritionist
   b. Maintenance calorie range for weight gain on a long-term basis is determined by adding 500–1,000 kcal to the initial estimated caloric requirement. In some cases, higher calorie levels are necessary.
   c. Minimum protein intake range is per RDA for age based on minimum weight goal and ideal body weight.
   d. Micronutrient supplementation (daily multivitamin)
   e. Nutraphos, 500 mg orally twice a day for 5 d
   f. Maintenance fluid requirements

II. Nutrition monitoring
   a. Daily weight in a hospital gown after voiding: expect 0.2 kg/d weight gain
   b. Adequate caloric provision, with 30 min bed rest after each meal
   c. Increase calories by 250 calories until steady weight gain is achieved.
   d. Supplements: if < 0.2 kg gain after 2 d in hospital, 250-calorie supplements are given, starting with two supplements initially, to be treated as medicine (non-negotiable). Each day that weight goal is not met, an additional can is added.

III. Patient education

RDA = Recommended Dietary Allowance.

then develop a hierarchy of identified fear foods and begin reintroducing the least "scariest" foods first.

Vegetarianism is an easy way to justify the elimination of meats, which are often feared because of their fat content. Adherence to a vegetarian diet, if begun with the onset of the eating disorder, should be discouraged during the recovery process to facilitate an adequate nutrient intake and promote comfort with eating a wide variety of foods.

The refeeding process can cause discomfort with bloating, flatulence, constipation, or diarrhea. The dietitian or clinician should remind teens that these symptoms, although bothersome, will gradually resolve as their body adjusts to the changes they are making. Bloating and gas can be reduced by limiting gas-producing foods. Constipation can be corrected by consuming adequate calories and fluids, as well as more soluble fiber found in whole grains.

There are several dietary modifications to consider when refeeding teens with anorexia nervosa. Limiting raw high-fiber foods and consuming only a moderate amount of fat help promote gastric emptying. Eating foods cold or at room temperature helps reduce the feeling of fullness. Choosing to eat smaller, more frequent meals will reduce bloating. Restricting the use of caffeine, gum, sugar substitutes, and diet beverages will improve the teen's ability to recognize hunger and satiety. Calorie and fat gram counting should be discouraged, and access to scales should be limited or prohibited. Social eating should be encouraged, and time limits should be placed on mealtimes to prevent the teen from being at the table all day.

Interventions for teens with bulimia nervosa should focus on creating feelings of satiety and implementing a structured eating behavior pattern. Selecting hot or warm foods with adequate amounts of fat enhances feelings of satiety. Buying foods in single servings whenever possible and avoiding "trigger" foods initially will help control the urge to binge. Eating meals and snacks sitting down and selecting foods that require the use of utensils will slow down the rate of eating and increase satiety. Skipping meals, eating on the run, and eating secretly should be discouraged. Binge purge behaviors should be stabilized before assisting an overweight teen with weight loss. Other helpful hints can be found in Table 51.1-10.

Attention can be placed on the emotional state during a binge, when and where it occurs, and how hungry the teen is at the time. For instance, if a teen always binges on arrival home after school, the clinician can help identify triggers and explore possible solutions with the teen. If boredom is the trigger, filling the time with more structured activities will be helpful. Effective strategies also include disrupting the automatic behavior chain by entering through a different door and changing the order of activities, for example, checking electronic mail or calling a friend before snacking. Deciding on a snack in advance, encouraging the teen to put leftovers away after assembling the food, sitting down at a predetermined location, and eating without distraction (eg, never in front of a television or computer) will help prevent a binge. If a teen arrives home overly hungry, it makes eating a moderate amount of food nearly impossible. Therefore, encouraging an adequate intake of calories at breakfast and lunch is important in preventing binge eating after school.

For teens with secondary amenorrhea, resumption of menses often occurs as they improve fat intake toward a range of 40 to 60 g per day, although, anecdotally, menses may resume at lower intakes. Hence, if an adolescent girl has regained weight to that weight at which periods had ceased but remains amenorrheic, one intervention could be to increase fat grams to 40 to 60 g of fat per day, a task difficult for many of these patients.

In addition to the above guidelines and concerns, adolescent athletes may also have specific nutritional issues. For instance, much mythology exists about the pre-event meal and the pros and cons of carbohydrate loading. Short-term, high-intensity activities, such as sprinting, diving, or high jump, rely on anaerobic fuel sources. Longer-term activities of lesser intensity, such as long-distance running or cross-country skiing, require aerobic energy sources.[149] Activities

TABLE 51.1-10 Guidelines for Adolescents with Eating Disorders

Individualize treatment
Avoid discussing numbers such as weight and calories
Encourage variety of foods
Slowly incorporate unsafe foods
Avoid fat gram and/or calorie counting
Limit meal time to 20–30 min per meal
Encourage small frequent feedings
Avoid gas-producing foods
Avoid diet beverages, sugar substitutes, gum, and caffeine
If patient is not eating fat, start with 15% calories from fat
Use multivitamin supplement with calcium
Provide concrete ideas to facilitate changes in eating behavior patterns

such as tennis, basketball, and soccer use both. A high-carbohydrate diet promotes muscle glycogen storage, which, over time, can enhance endurance. Caloric requirements may be as high as 2,400 to 4,500 calories daily in the high school or college athlete,[8] whereas skilled competitive cyclists riding 19 hours a day may need as many as 9,500 to 14,000 calories per day.[150] The metabolism of additional carbohydrates may also increase requirements of thiamin, riboflavin, and niacin, but a well-balanced diet should supply sufficient amounts of these nutrients. Large doses of vitamins and minerals will not enhance muscle mass or performance.

A strong emphasis on competition can make young athletes vulnerable to nutrition misinformation and unsafe practices thought to enhance performance. During prolonged, strenuous exercise, carbohydrate supplementation has been shown to improve performance.[151] However, carbohydrate ingested prior to competition has not had an effect on performance and, in past years, has even been considered detrimental.[149] One study showed that pre-exercise candy bar consumption does not cause premature fatigue or decreased endurance.[152] In counseling teens on nutrition to optimize performance, emphasis should be placed on a healthful, balanced diet, with adequate calories and fluids to prevent dehydration and electrolyte imbalances. Carbohydrates should be ingested within 2 hours after prolonged, strenuous exercise and preferably within about 20 minutes because glycogen synthesis rates are 50% higher than at 2 to 4 hours after exercise.[151] Complex carbohydrates are preferred as they facilitate faster gastric emptying when ingested in high concentrations, they are associated with less gastrointestinal stress than found with simple sugars, and they contain fiber, vitamins, and minerals.[153–155]

In sports such as wrestling and lightweight crew, the clinician should use the preparticipation physical as an opportunity to educate and intervene in any unhealthful eating practices detected at that time. Wrestlers have been shown to use profuse sweating, diuretics and laxatives, and spitting into a cup to keep from swallowing saliva as added water weight.[156] Tcheng and Tipton have recommended a desired minimum range of 7 to 10% fat for wrestlers; the athlete should not be allowed to compete below the weight recommended by the physician.[157] The athlete should be asked about desired weight goals, dieting practices, and training activities, with nutritional guidance and appropriate interventions occurring before, during, and after the season as needed.

Teens who engage in weight lifting and similar activities should be discouraged from use of anabolic steroids or protein supplements. Strenuous physical activity does not increase protein requirements[158]; athletes can easily meet their protein needs by following a balanced diet.[149] The RDA for protein is 0.36 kg protein per pound of body weight for the average adult or adolescent athlete[159]; a total of 0.45 g of protein per pound is recommended for marathoners. Diets that provide more than 0.9 g of protein per pound of body weight have not been shown to increase muscle strength.[160,161] Dehydration in combination with use of protein supplements can compromise kidney function with the added load of nitrogen; with nitrogen excretion, further water is lost.[162]

Strenuous physical activity or intense training has been associated with anemia, which can impair performance. Contributing factors include marginal iron intake, increased iron losses, and increased destruction of erythrocytes with extreme exercise.[163] Screening with a yearly hemoglobin or hematocrit is warranted in teenagers engaging in competitive or strenuous athletics.[164]

CONCLUSION

Adolescents with eating disorders or those who participate in athletics can have specific nutritional needs, most of which can be adequately provided through a healthful, balanced diet. Clinicians and nutritionists can work with patients and families and within the community to target high-risk eating behaviors and to do preventive education. Nutritional education for coaches, parents, and other individuals involved in teens' lives and activities can be provided within the school setting, church, or community. Teens who are deemed to be at high risk can be referred to appropriate centers for further counseling and treatment.

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CHAPTER 51.2

THE ADOLESCENT ATHLETE: PERFORMANCE-ENHANCING DRUGS AND DIETARY SUPPLEMENTS

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Practitioners in pediatric nutrition are often faced with the issue of optimal nutrition in the adolescent athlete. As sports have become more competitive, this issue has become increasingly important to young athletes and their families. In certain instances, young athletes will turn to performance-enhancing drugs and dietary supplements in an effort to improve sports performance. For the health practitioner, knowing how and when to deal with these issues, especially in terms of potentially injurious substances such as anabolic steroids, is of tremendous importance.

Performance-enhancing drugs, also known as ergogenic aids, are designed to give athletes a chemically induced advantage in athletic competition. The thought of pediatric and adolescent athletes using performance-enhancing drugs, once used only on Olympic and professional levels, was previously inconceivable. As the nature of youth sports has changed, the need to win at all costs has created an environment that encourages the use of performance-enhancing drugs and dietary supplements in children and teens. Unfortunately, child and adolescent athletes are using ergogenic aids to chemically improve sports performance.

There are few safeguards to discourage children and teens from taking performance-enhancing drugs, whereas Olympic, collegiate, and professional athletes are routinely tested as a means of active discouragement. Because young athletes who use performance-enhancing drugs are often remiss in discussing these issues, knowing how, when, and where to address drug use is essential for pediatricians with athletic patients in their practices. Pediatric and adolescent athletes who take performance-enhancing drugs will rarely discuss these issues with their health care providers unless asked directly and even with direct questioning might be tempted to provide misinformation. The opportunities for meaningful intervention and prevention are few.

Performance-enhancing drug use in children and adolescents is of tremendous concern for both health and social reasons. From a health perspective, the effects of all performance-enhancing substances are not presently known in the pediatric and adolescent age group because none of these products have ever been tested in these groups. Neither short-term nor long-term effects of these products are known, and they are potentially harmful to young users. From a social perspective, the use of chemicals to enhance sports performance is against the very nature of healthful competition that youth sports are meant to encourage.

The effective education of young athletes who might be considering the use of performance-enhancing drugs is of paramount importance. The health practitioner who deals with the young athlete population should take aggressive measures to educate the athletic and parent community about the ill effects of many of the supplements that young athletes are using. This chapter examines the issue of performance-enhancing drugs in the young athlete and provides helpful ideas on how to recognize, counsel, and thoughtfully discourage use in the young athlete.

YOUTH SPORTS: CHANGING NATURE

The past 25 years have witnessed a significant change in the nature of youth sports. In the "old days," sports participation in young athletes was generally considered a pastime, a helpful way to encourage health and fitness in children and teens. Often this type of activity consisted of children playing on neighborhood sports teams, usually in local recreational leagues.

In the past 25 years, however, a youth sports explosion has changed the demographics of the young athlete population. These changes are most visible in three domains: gender, number of competitors, and the nature of competition. Spurred on by Title IX, a federal regulation passed in 1972 that guaranteed an equal ratio of scholarships for men and women at the collegiate level, there has been a substantial increase in the number of female athletes of all ages. Initially this was restricted to the collegiate level, but as the number of available college scholarships for female athletes increased, so did the number of female athletes on all levels. In 1972,

there were approximately 25,000 high-school female athletes; in 2000, there were more than 3 million.[1] Figure 51.2-1 illustrates these trends, including a dramatic increase in female athletes as well as an overall increase in high-school sports participation.

At present, there are more than 30 million children and teens under the age of 18 playing on some form of organized sports teams in the United States.[2] For pediatricians, the increasing number of young athletes has translated into an increase in the amount of sports medicine practiced in the pediatric office. This includes the evaluation of both medical and orthopedic issues related to the young athlete.

As the number and makeup of the young athlete population has grown, the very nature of athletic competition in children and teens has changed as well. The "win at all costs" mentality has become the norm in many youth sports leagues around the United States. Although competition is a favorable aspect of youth sports, excessive competition can have unfavorable manifestations in children and adolescents.

When winning is defined as the only acceptable outcome for athletes, this can encourage them to look for any available means of improving athletic performance. When winning is defined as the only goal of athletics, children and teens are most susceptible to using performance-enhancing drugs.

HISTORY OF PERFORMANCE-ENHANCING DRUG USE IN SPORTS

The issue of performance-enhancing drugs in sports is not a new phenomenon. In 300 BC, two competitors were barred from the first Olympiad in Greece because of illegal ingestion of animal protein.[3] As the technology and the science of performance-enhancing substances have improved over the past 2,000 years, so have the methods that athletes use to chemically improve sports performance.

Initially, professional and Olympic athletes used performance-enhancing substances primarily because they had the most to gain in terms of wealth and fame from athletic success. A survey published in *Sports Illustrated* in 1996 asked US Olympic athletes the question, "If you could take an undetectable performance-enhancing substance, win every competition for 5 years, and then die, would you?" More than 50% said "yes."[4] As performance-enhancing substances became more available, use was popularized in college athletics. More recently, high-school and junior-high athletes have admitted to taking performance-enhancing substances. Two studies have shown the user rate of anabolic steroids in the high-school athlete population to be approximately 10%.[5,6] A study published in 1998 found a 3.5% user rate for anabolic steroids in the junior-high population.[7] Clearly, the issue of performance-enhancing drugs, once confined to elite athletes, has trickled down to the youth sports world.

MAJOR CATEGORIES OF PERFORMANCE-ENHANCING SUBSTANCES

There are many categories of performance-enhancing drugs and dietary supplements. This section concentrates on several of the major categories of products used by adolescent athletes.

Anabolic Steroids

Anabolic steroid use is a major health risk to the adolescent athlete. As previously mentioned, the user rate of anabolic steroids in the male high-school athletic population is approximately 10%. Anabolic steroids were invented in the 1950s and use was popularized in the 1970s, mainly in Olympic and professional athletes.[8] Anabolic steroids are available in several forms, including oral, injectable, and topical. The most popular forms of these products include nandralone and methandrostenolone (Dianabol).

The biochemical basis for anabolic steroid effectiveness rests in the increased levels of testosterone that these products produce. Unlike pure testosterone, which causes a degree of secondary sexual characteristic growth, such as deepening voice and facial hair, roughly equivalent to anabolic effect on muscle, anabolic steroids are chemically altered testosterone derivatives that emphasize anabolic growth.[9] Anabolic steroids that have been developed thus far can only preferentially encourage anabolic effect but cannot totally isolate muscle and bone growth. Therefore,

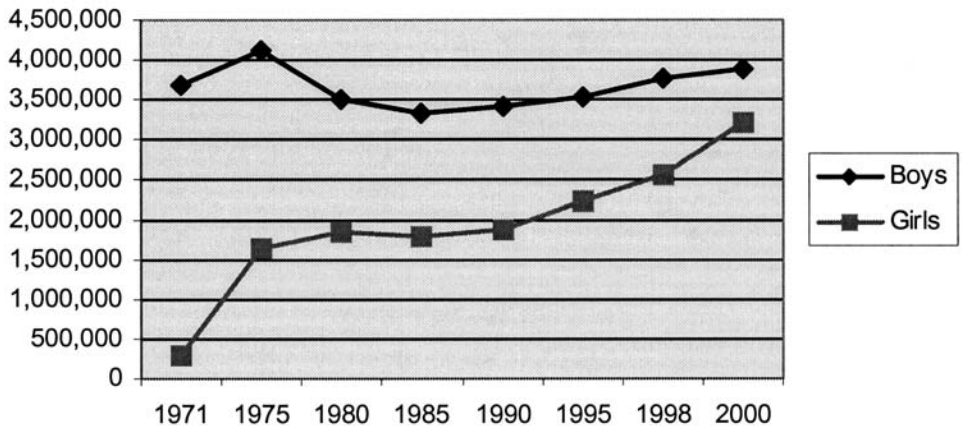

FIGURE 51.2-1 High-school sports participants, 1972–2000. Adapted from the National Federation of Youth Sports.[1]

users of anabolic steroids will show significant increase in muscle mass but will also show signs of secondary sexual characteristic development. The major effects of anabolic steroids are listed below.

- Increased muscle mass
- Hirsutism
- Deepened voice
- Acne
- Psychological lability ("testosterone rage")
- Increased risk of hepatic cancer
- Increased risk of cardiovascular disease
- Increased ratio of low-density lipoprotein to high-density lipoprotein
- Impotence

Physician Intervention Young athletes, both boys and girls, are using anabolic steroids. The active discouragement of anabolic steroid use is the responsibility of every health professional who encounters this issue. A helpful principle for the pediatrician to remember is that cases are rarely isolated. If one athlete on a team is implicated, chances are that teammates are aware of the problem and might also be using these drugs.

The keys to successful intervention in anabolic steroid use include a careful review of known side effects of these dangerous drugs and a discussion with the athletic director of the school where the athlete is participating. When the athletic department is involved in the active discouragement of use, there is generally much more success in addressing the problem.

A final point with regard to discouragement is the need to recognize that these products work. Anabolic steroids have been proven to increase muscle mass, so discouragement in the "just say no" model is generally ineffective.[10] Using an honest approach, admitting to the athlete that anabolic steroids do work but that the health risks are significant is the most effective method of discouragement.

Diuretics

Use of diuretics, including furosemide and hydrochlorothiazide, has been popularized primarily in wrestling, where rapid weight-loss practices—losing 5 to 10 pounds over several days to meet criteria for a certain weight class—have been a significant cause of concern. The exact user rates are not known, but the known side effects of diuretic use include rapid weight loss owing to diuresis and significant electrolyte abnormalities. In some episodes, these electrolyte abnormalities have led to fatal cardiac arrhythmia.[11]

The setting of wrestlers struggling to "make weight" is the most common scenario for the use of diuretics in sports. As is the case with anabolic steroids, these drug-use outbreaks generally occur in groups. Therefore, if a case of diuretic abuse is discovered, discussion with both the patient and the athletic community is required. Furthermore, a discussion with the athletic director at the local school is important to explain the dangers of unsafe weight-loss practices. The American Academy of Pediatrics has a helpful position statement on healthful weight-control practices in young athletes that can assist the pediatrician in providing guidelines for this discussion.[12]

The hallmark signs of diuretic abuse include excessive urination, rapid weight loss over a short period of time, and syncope owing to orthostatic hypotension. Unfortunately, cases of diuretic abuse are often discovered when the situation has become serious enough to draw a complication to medical attention. It is best to address the issues of safe weight loss with wresting teams before the season begins rather than wait for complications to occur.

Dietary Supplements

Dietary supplements are performance-enhancing substances that have become popular with pediatric and adolescent athletes for two main reasons. First, they are readily available and can be purchased in most health-food stores and over the Internet. Second, they are marketed as "safe and natural" ways to improve sports performance. With the Proxmire amendment of 1993, jurisdiction over the use of nutritional supplements was removed from the US Food and Drug Administration (FDA).[13] The nutritional supplement market has since exploded, with advertising campaigns targeted at young athletes. These campaigns have included professional athletes endorsing these products through direct campaigns, clothing, and commercials. Much like cigarette advertising campaigns of the early 1960s and 1970s, in which cigarette use was encouraged to promote health, vitality, and vigor, nutritional supplements have been promoted to the general population today with scant attention to scientific research or safety.

Despite protestations to the contrary, often from companies or scientists who produce these compounds, none of the nutritional supplements has ever been shown to be safe and/or effective in pediatric or adolescent subjects. Nutritional supplement use in young athletes is a significant health concern. There have been several cases in which supplements that were perceived to be "safe and natural" were found to be dangerous. The most recent case involved ma huang, a nutritional supplement that was very popular until 2000, when it was found to be the causative factor in 23 cases of death or permanent disability in a study performed over a 2-year period in California.[14] In addition, because the FDA does not regulate these products, there is no guarantee that the compounds listed on the bottle are the exact contents of the pills or tablets inside.

There are hundreds of nutritional supplements, and more are developed each year. None of these products are approved for use in pediatric or adolescent subjects. The next section discusses two popular products, creatine and androstenedione.

Creatine

Creatine remains the most popular nutritional supplement in young athletes, with sales of more than $400 million (US) yearly.[15] A recent study of 1,103 children and adolescents in grades 6 to 12 found that 5.6% of student athletes were using creatine, with a stated goal of improving sports performance in 75% of cases. In this study, users were

found at all grade levels, including sixth- and seventh-grade students.[16]

Creatine is a naturally occurring compound and is synthesized by the liver, kidneys, and pancreas. Creatine is also found in chicken, meat, and fish. The total daily requirement for creatine is 2 g.[17] When creatine loading, athletes routinely take three to four times the recommended daily amount. Creatine is thought to increase muscle strength in short bursts of activity in some athletes.[17] Thus far, there have been two reported cases of renal failure linked to creatine use, but the wider concern about unknown side effects in the future is a more significant cause for concern.[18,19] Because of the lack of any scientific data that support safety, the American College of Sports Medicine does not recommend creatine use in any adolescent under the age of 18 years.[20] Therefore, the pediatrician should discourage creatine use in any adolescent patient and should document in the medical record if this advice is given.

Androstenedione

Androstenedione, otherwise known as andro, is a "natural" supplement that was popularized in 1998 when professional baseball player Mark McGwire used the product to enhance strength during his home-run record-setting year. Androstenedione is a testosterone precursor, a step on the biosynthetic pathway of testosterone. In 1999, in the aftermath of the McGwire home-run controversy, Major League Baseball commissioned a study of the effects of androstenedione on serum testosterone concentrations. This study found that in doses greater than 300 mg/day, androstenedione was capable of raising serum testosterone levels.[21] The implications of this study are significant, particularly for the pediatric and adolescent user.

Androstenedione is a steroid precursor that raises the level of testosterone, a side effect that can have potentially significant complications, particularly for the preadolescent male and the postadolescent female. The preadolescent boy with exogenous amounts of testosterone added to his baseline testosterone level will begin puberty prematurely, thus effectively reducing adult height through premature physeal closure. In addition, concern about long-term testosterone production is also important for the prepubescent boy. The postadolescent female who uses this product exposes herself to increased amounts of androgen and can develop undesirable side effects, such as hirsutism and acne. Although androstenedione might produce increased amounts of skeletal muscle mass, the risks for children and adolescents are significant, and its use should be discouraged.

THOUGHTFUL DISCOURAGEMENT, THE KEY TO PREVENTION

Effective discouragement of the use of performance-enhancing drug and dietary supplements requires a well-founded argument to convince most adolescents to change their habits. For that reason, the best approach, *thoughtful discouragement*, requires the physician to give both pertinent advice to counsel the teen athlete against these potentially harmful products and healthful alternatives to drug use to help achieve improved strength and sports performance.

The first part of the solution to the issue of performance-enhancing drug use in pediatric and adolescent patients is recognition. Most adolescent athletes are remiss in admitting use of these substances to their pediatricians and will offer this information only when asked. This is most easily and naturally accomplished during the preparticipation examination with the addition of a simple question, "Are you using any substance to improve your sports performance?" This often leads to a broader discussion with the athlete and his or her family.

Once recognition of the problem is accomplished, the next step is educational. A well-known sports adage says, "The best defense is a good offense." This point is especially true concerning the prevention of performance-enhancing drug use in young athletes. As has been mentioned, the increasingly competitive climate of youth sports encourages the use of performance-enhancing drugs. Unlike at higher levels, where athletes are routinely tested for performance-enhancing drug use, the most effective means of discouragement in the adolescent athlete population is aggressive intervention with education, on both the personal and global levels. There has been recent discussion about the possibility of instituting drug testing in the adolescent athlete community as a means of discouraging use of performance-enhancing drugs. Although this might serve as a minor deterrent, the main approach to effective discouragement is education of the parent and athletic communities.

When faced with a young athlete who asks about performance-enhancing drugs in the office, discussing the most recent research and case reports on the side effects of these products, with mention of the lack of any significant information regarding product safety, is helpful. On a more general level, the pediatrician can make a significant difference by speaking to the athletic director or local school administrator and recommending that the school, and coaches, adopt a policy against use of any type of performance-enhancing product.

In the spectrum of performance-enhancing drugs, the pediatrician faced with an athlete who is using nutritional supplements such as creatine or androstenedione is placed in an especially difficult position. These compounds are perceived as safe and natural, and product use is sometimes encouraged by various factions, including coaches, trainers, or fellow athletes. The effective discouragement of use in the adolescent athlete is often difficult. Encouraging patients who are taking performance-enhancing drugs, and particularly nutritional supplements, to seek consultation with a sports nutritionist who is well versed in pediatric sports nutrition can encourage healthful caloric intake to maximize muscle growth.

Finally, recognizing that athletes who are taking performance-enhancing drugs are doing so to improve strength and sports performance, pediatricians need to provide an alternative to drug use for children and adolescents. Rather than using discouragement alone—the "just say no" approach—it is essential to offer a healthful alter-

native for increasing muscle strength. This lies in the form of pediatric strength training. Endorsed by organizations such as the American Academy of Pediatrics and the American College of Sports Medicine, strength training in children as young as 8 years is a safe and effective method of increasing baseline strength and improving athletic performance.[22] The program should be supervised and needs to emphasize repetition rather than maximum weight lifting, but the results can be tremendously gratifying for children and teens and can include a baseline strength increase of 30 to 40%.[23]

CONCLUSION

The use of performance-enhancing drugs in young athletes is an issue that is important for pediatricians and nutritionists to address with their athletic patients. This is particularly important in today's youth sports climate because increasing competitiveness encourages the use of performance-enhancing drugs to help athletes gain an advantage. Recognition of performance-enhancing drug use is most effectively accomplished during the preparticipation examination. Once the issue of performance-enhancing drug use is identified, thoughtful discouragement is the most effective method of intervention. This involves a combination of individual and local education and the encouragement of alternative methods of increasing baseline strength, such as strength training. If these steps are taken, pediatricians can make a significant difference in the health and safety of the young athlete and can better serve their athletic adolescent patients.

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CHAPTER 51.3

ADOLESCENCE: BONE DISEASE

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Adolescence is a critical period for lifetime bone health. Evidence has accumulated that an individual's peak bone mass (PBM), which is the strongest predictor of his or her future risk of osteoporosis, is reached by early adulthood. At least half of all adult mineralized calcium is laid down during the adolescent years, with the most rapid bone accretion occurring in late childhood and early adolescence.[1,2] Any condition that impairs this process may create a deficit in bone mass that will have permanent ramifications for future risk of osteoporosis, which afflicted over 10 million Americans and cost more than $15 billion in direct medical expenditures just for fracture care in 2001.[3]

Unfortunately, there are several disease states, each related to nutritional deficits, that can inhibit bone accretion at this crucial time, including rickets, anorexia nervosa (AN), the "female athlete triad," inflammatory bowel disease (IBD), celiac disease, and cystic fibrosis (CF). In this section, these conditions are discussed in detail. Adolescence itself may also prevent maximal PBM attainment as the dietary habits of many modern teenagers do not optimize calcium and vitamin D intake.

NORMAL BONE PHYSIOLOGY AND DEVELOPMENT

Bones are the fundamental units of the skeletal system, providing an adaptable frame that supports and protects the major organ systems of the body while allowing for locomotion. Because of its role in calcium and phosphate homeostasis, bone can also be considered an organ system. The skeletal system is the reservoir for the calcium used in essential mechanisms ranging from the regulation of cardiac electrical activity, contraction of muscles, and varied inter- and intracellular messaging systems. Each bone, housing lymphoid and myeloid precursor cells within the marrow, is also an organ unto itself. Finally, these organs are composed of a unique tissue substance that is once again called "bone."

Types of Bone

Bone, as a tissue, takes on two forms in normal health: cortical (dense) and trabecular (cancellous or spongy) bone. Cortical bone, which makes up 80% of the skeletal bone mass, is found in the diaphysis (shaft) of long bones such as the femur, as well as the "walls" of almost all other bones, including the vertebrae. It provides strength against tensile, torsional, and shear forces. The remaining 20% of bone mass consists of trabecular bone, found in the metaphyses (ends) of long bones and the entire bodies of the vertebrae. It is well suited to resist compressive forces. Because of its high surface area-to-volume ratio, trabecular bone occupies greater than 20% of the volume of the skeletal system and has approximately eight times the metabolic activity of cortical bone.[4] Owing to its higher metabolic availability, trabecular bone is more significantly affected by disease states.

Histology: The Building Blocks of Bone

Regardless of its structure or ultrastructure, on a microscopic level, bone consists of thin layers, or lamellae, of a mineralized protein matrix. This mature lamellar bone is 70% (by dry weight) mineral, predominantly calcium and phosphate in the form of hydroxyapatite crystals [$Ca_{10}(PO_4)_6(OH)_2$] and a less pure, carbonate-rich analogue called bone apatite, which is more soluble and thus more available for metabolic activity. The remaining 30% of the mass is an organic substance called osteoid, primarily protein in the form of type I collagen. Cellular elements, which produce all of the metabolic activity of bone, make up only 2% of the osteoid.

Osteoblasts are bone-forming cells derived from fixed-tissue osteoprogenitor cells. Osteoblasts synthesize osteoid on the surface of already mature lamellar bone, periosteum, or endosteum. They then regulate the process of mineralization of the collagen matrix through the actions of bone-specific alkaline phosphatase (BSAP), which is different from the alkaline phosphatase produced in the liver and can be distinguished from it by special assays.

Once the osteoid matrix has mineralized, it is considered bone. The osteoblasts, which are synchronized in such a way as to create the parallel lamellae, become trapped inside small caverns called lacunae and mature into osteocytes that communicate via long processes with each other to direct mineral homeostasis.

Osteoclasts are multinucleated cells from the marrow monocyte-macrophage cell line. Producing lysosomal enzymes such as acid phosphatase, osteoclasts break down the mineralized bone matrix, mobilizing calcium and phosphorus for participation in homeostasis, in a process called bone resorption.

Growth and Remodeling: Bone Cycle

Bone is a dynamic tissue. Growth in long bones occurs at the physes (growth plates) and apophyses (secondary centers of

ossification) by a process known as enchondral ossification in which osteoblasts lay down bone on a cartilaginous framework that is ultimately resorbed by osteoclasts. Even after skeletal maturity, osteoblasts respond to structural stresses in bone by laying down new matrix. Osteoclasts concomitantly resorb areas of bone under less stress. Thus, bone is constantly remodeling. At times of growth, bone formation by osteoblasts is greater than resorption by osteoclasts. With disuse, osteoclasts outpace osteoblasts and bone mass decreases. Otherwise, osteoblasts and osteoclasts are tightly "coupled" to keep formation and resorption equally balanced in what is known as "the bone cycle."[5]

Importance of Adolescence

Bones grow at different rates throughout the skeleton. The extremities (appendicular skeleton) have largely completed growth by the time of the pubertal growth spurt (peak height velocity [PHV]). Increases in estrogen and testosterone during puberty result in growth of the trunk and spine (axial skeleton). These increases in vertebral bone size are accompanied by dramatic increases in bone mineral density (BMD) in cross-sectional studies.[6,7] This trabecular bone reaches its peak BMD by age 20 to 30 years but steadily declines thereafter.[8] Alarmingly, one animal model showed that calcium restriction in adolescence resulted in a decreased bone volume throughout life, even after restoration to recommended calcium intake in young adulthood.[9]

Adolescence is an essential time for significant bone accretion. Over half of adult bone calcium is laid down during the teenage years.[1] Maximal rates of bone mineral accretion follow PHV by 6 to 12 months.[10–12] As a consequence, at the time of PHV (Tanner pubertal stage II–III in girls, Tanner stage III–IV in boys), teenagers have reached approximately 90% of their adult height but have acquired only 60% of their adult total-body mineral content, resulting in relatively less mineralized bone.[11] In North America, these pubertal stages are reached by age 11 to 14 in girls and 13 to 17 in boys. Studies by Thientz and colleagues are consistent, showing that girls' BMD may plateau by age 16 (or 2 years postmenarche) and boys' BMD by age 20.[2] This is a much earlier window of opportunity than was previously suspected. In fact, 95 to 100% of PBM may be attained by the end of adolescence.[13,14]

Factors Affecting Bone Health

Genetics Intrinsic factors dominate the determination of bone density (Figure 51.3-1). Males have a higher bone mass than females at nearly all ages.[8] Black children demonstrate an approximately 10% higher BMD by dual-energy x-ray absorptiometry (DXA) than do children of other ethnicities,[15] even after correcting for bone size.[14] An interesting finding among black and white girls was that their spinal BMD was similar until puberty, at which point the black girls had an increase of 34%, whereas the white girls improved only 11%.[16] Family history of osteoporosis in postmenopausal women predicts lower BMD for their daughters,[17] and both elderly men and women have an increased risk of osteoporosis when other family members have been affected.[18] In all, 60 to 80% of the variance in PBM is attributed to heritable factors.[8] Polymorphisms in the genes encoding receptors for vitamin D,[19] estrogen, type I collagen,[20] insulin-like growth factor I (IGF-I), transforming growth factor β, and interleukin-6 (IL-6) are being studied,[21] but none have been able, singly or in combination, to account for more than a small percentage of this variance in PBM.

Hormonal Status A normal hormonal milieu is essential to attain and maintain normal bone formation. Early menarche and regular menses are strong predictors of increased bone mass in women,[22] demonstrating the importance of estrogen. Among adolescent girls, an estimate of estrogen exposure was positively correlated with spine BMD.[8] Estrogen deficiency may also slow growth in axial bone size when it occurs during adolescence, a time when truncal growth typically accelerates.[23–25]

Androgens exert independent and positive effects on PBM.[26] Men with a history of delayed puberty[27] or documented low serum androgen levels[28] have been shown to have decreased BMD. Testosterone replacement over 18 months normalized BMD rapidly in a study of men with

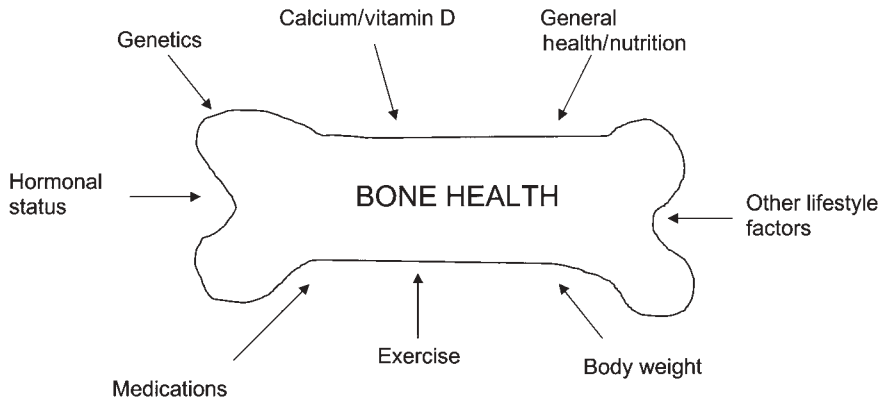

FIGURE 51.3-1 Factors affecting bone health. Reproduced with permission from Loud KJ, Gordon CM.[169]

acquired hypogonadism.[28] Patients with androgen insensitivity have a mutation in the androgen receptor, with consequent impaired androgen action, such that there is resistance to even elevated androgen levels. Previous reports have shown that affected individuals have decreased bone mineralization.[29–31] Even after administration of estrogen replacement therapy (ERT) in these individuals, BMD did not significantly increase, again highlighting the importance of androgens in bone physiology.[29] Women with androgen excess also have been shown to have a higher BMD.[32,33]

Children and adults with childhood-onset growth hormone (GH) deficiency have lower BMD than controls.[34,35] Studies have shown that patients on adequate replacement doses of GH have increased BMD compared with GH-deficient patients,[36,37] although young adults who had received GH replacement during childhood but who discontinued the medication at the completion of linear growth demonstrated decreased spine and hip BMD in long-term follow-up.[8] The actions of GH are likely mediated by IGF-I, an anabolic factor that stimulates osteoblast function directly.

Exercise Patients with impaired activity owing to central nervous system or neuromuscular disease develop disuse osteoporosis.[38] Several studies now suggest that individuals engaged more intensely in weight-bearing activities have higher measured BMD than less active controls.[39–43] Even among women with amenorrhea, those who are more athletic have higher bone density.[44] Unfortunately, swimmers do not consistently reap this benefit as their activity is largely weightless, highlighting the importance of weight-bearing activities.[45] The increases in BMD are site specific; for example, runners and ballet dancers have higher proximal femur (hip) BMD than controls, whereas gymnasts have higher measured radial (arm) BMD.[46] These gains in BMD persist years after these athletes have retired from sports.[47–49] Intervention trials have not consistently duplicated these findings but have been hampered by the relatively small sample sizes and the short duration of these studies.[50]

General Nutrition and Health In addition to participating in weight-bearing exercise, individuals must maintain appropriate weight. At most weights, there is a direct relationship between body mass index (BMI) and BMD, with underweight individuals at increased risk for lower BMD.[51] Adolescent girls with low weight owing to AN have decreased BMD, as discussed below. Excessive BMI may also have a deleterious effect on BMD. A case-control study of boys found that those with distal forearm fractures had an increased prevalence of obesity (BMI > 85th percentile for age) and a lower BMD than age-matched controls.[52] These associations were hypothesized to be attributable to the increased adiposity of the overweight boys.[52]

The carbohydrate, fat, and protein macronutrients are essential to provide the building blocks for growth and attainment of appropriate BMI to maximize BMD. These nutrients also provide energy for the muscle contractions that mechanically load bone, thereby stimulating bone formation. In addition, lipids are substrates for the synthesis of prostaglandins, which are cytokines that may play an essential role in regulating bone metabolism.[53] Proteins are particularly important as the fundamental elements of muscle tissue, as well as the predominant components of osteoid, the unmineralized precursor to bone. In one study, protein intake and bone mass gains were positively correlated in children, possibly mediated by IGF-I production,[54] although ongoing research continues in this area.

Other nutrients with putative, but not studied, influences on bone density include magnesium, phosphorus, copper, manganese, zinc, and vitamins C and K. Approximately 60% of the body's magnesium and 85% of the phosphorus are in bone. Magnesium may decrease the brittleness of bone by modulating the size of hydroxyapatite crystals. The other minerals and vitamins are important cofactors in the synthesis, folding, and cross-linking of the proteins found in bone, including collagen, elastin, and osteocalcin.[53]

Medical conditions that impair bone density are shown in Table 51.3-1. Many of these act by causing malnutrition, with concomitant decreases in BMI and absorption of important nutrients. Some are described in detail later in this section. Tobacco (by decreasing osteoblast function)

TABLE 51.3-1 Conditions Predisposing to Osteoporosis in Children and Adolescents

Chronic illnesses Mechanisms = malnutrition, cytokines, endocrinopathies, medication effects, decreased activity	Inflammatory bowel disease (Crohn's disease, ulcerative colitis), celiac disease, asthma, chronic renal failure
Organ transplantation Mechanisms = malnutrition, cytokines, immunosuppression, endocrinopathies, medication effects, decreased activity	Bone marrow, heart, lung, kidney, pancreas, liver
Endocrine abnormalities	Genetic sex hormone deficiency, Turner's syndrome, acquired sex hormone deficiency, anorexia nervosa, exercise-induced amenorrhea, premature ovarian failure, irradiation, chemotherapy, other endocrine abnormalities, Cushing's syndrome, hyperparathyroidism, hyperthyroidism, growth hormone deficiency, hyperprolactinemia, diabetes mellitus
Medications	Corticosteroids, anticonvulsants, cyclosporine A, lithium, gonadotropin-releasing hormone agonists, heparin, methotrexate
Family history	Osteoporosis, frequent fractures
Female athlete triad Definition = disordered eating, amenorrhea, and osteoporosis	Any female athlete, but particularly those in activities that emphasize lean physique
Prolonged immobilization	

and excessive alcohol use increase the risk of lower BMD in young women, although these factors have not been thoroughly studied in younger adolescents.[55]

Calcium and Vitamin D As described above, bone is a calcified tissue that derives its compressive strength from its calcium-phosphate crystal structure and, in turn, serves as the body's vast reservoir of calcium. Enormous gains are made in total skeletal calcium over childhood and adolescent development, from approximately 25 g at birth to 900 (females) to 1,200 g (males) at skeletal maturity.[10,12] It follows that calcium is an essential nutrient for skeletal as well as general health. Dairy products are an important source of dietary calcium, providing approximately 75% of the calcium in a typical North American diet.[53] Epidemiologic data suggest that osteoporosis is more prevalent in regions where dairy intake is low and that milk consumption in childhood and adolescence correlates with postmenopausal BMD.[56–59] There is some evidence that calcium is a necessary, but not sufficient, element for bone accretion. In one study, women consuming greater than 1,000 mg of calcium daily made no significant gains in their BMD if they did not concomitantly increase their activity patterns.[60]

Vitamin D is the important partner of calcium in dairy products. The active form of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], is necessary for normal mineralization of bone. In addition to being absorbed though the gut, vitamin D is also synthesized endogenously in the skin under the influence of ultraviolet sunlight. It is converted to 25-hydroxyvitamin D [25(OH)D] in the liver and then to 1,25$(OH)_2$D in the kidney. Activated 1,25$(OH)_2$D facilitates absorption of calcium and phosphate from the duodenum and jejunum, as well as reabsorption of calcium from the renal tubules. At high levels in the serum, it can stimulate osteoclasts to resorb bone, but this action is mediated via receptors on osteoblasts.[61]

Vitamin D deficiency has been clearly linked to fractures in postmenopausal and osteoporotic women.[62,63] Plasma 25(OH)D levels, the most sensitive clinical index of vitamin D status, are positively correlated with BMD in middle-aged and elderly women.[64,65] Even serum 25(OH)D levels in a range suggesting subclinical vitamin D deficiency are associated with a reduced bone mass.[63] Seasonal variation of vitamin D metabolites, with high summer/fall and low winter values, has been established in adults and is generally more pronounced in northern latitudes, where there is reduced cutaneous production of vitamin D for up to 6 months of the year.[66–72] Some, but not all, studies have indicated a similar seasonal difference in BMD.[73–76,77] In postmenopausal women with low intakes of vitamin D, BMD significantly decreases in winter, which can be prevented by vitamin D supplementation.[76]

The effects of calcium and vitamin D are difficult to separate. When calcium intake is sufficient, non–vitamin D–dependent passive absorption predominates. However, in the face of low calcium intake, vitamin D–dependent active transport becomes the major route for calcium absorption. Thus, the effect of vitamin D deficiency on calcium bioavailability is critical when it coexists in the setting of low dietary calcium intake.[78,79] Fortunately, such a deficit can be easily treated, and the incidence of fractures possibly decreased, with combined vitamin D and calcium supplementation.[80–83]

NUTRITIONAL INFLUENCES ON BONE ACCRETION IN ADOLESCENCE

CALCIUM

Although calcium intake would be a seemingly obvious factor promoting increased BMD, the literature is not uniform. In growing children, the influence of calcium availability on gains in bone density has been demonstrated. Dietary calcium is one of the most significant predictors of bone mass in cross-sectional studies of children and adolescents.[84–86] Controlled supplementation trials in healthy children and adolescents, including twin studies, have generally shown increased gains in BMD in at least some subgroups of those supplemented with calcium, milk extract, or dairy products.[87–94] However, the response to calcium varied among studies with respect to skeletal site, pretreatment calcium consumption, pubertal stage, and genetic factors.[50] There is also uncertainty in how well the gains are maintained after supplementation is discontinued as only one of the studies demonstrated persistence of the increase more than 1 year later.[95] This is an area of ongoing study, but the available data on potential benefits justify endorsement of the recommended daily intakes, for adolescents, in the range of 1,300 mg of elemental calcium (Table 51.3-2).

VITAMIN D

In a study of hospitalized adults, Thomas and colleagues reported that 57% of the men and women screened were vitamin D deficient on serum testing.[96] Research in Scandinavia has shown that dietary intake of vitamin D in children, even when combined with vitamin stores from the

TABLE 51.3-2 Dietary Intake Recommendations for Adolescents in the United States

	1994 NIH	1997 NAS
Calcium AI* (mg/d)		
Age		
11–18 yr	1,200–1,500	
9–13 yr		1,300
14–18 yr		1,300
19–50 yr	1,000	1,000
Magnesium RDA (mg/d)		
Males		410
Females		360
Phosphorus RDA (mg/d)		
All ages		1,250
Vitamin D AI (IU/d)		
All ages		400

Adapted from Weaver CM et al[53] and the Committee on Nutrition, American Academy of Pediatrics.[168]

*AI: Adequate Intake: used if sufficient scientific evidence is not available to derive a Recommended Daily Allowance (RDA).

summer, is not sufficient to sustain healthy vitamin D levels during the winter.[97,98] The prevalence of vitamin D deficiency among otherwise healthy American adolescents is currently unknown. A concern is that vitamin D deficiency can result in an increase in the bone remodeling rate, which could impair bone density achievement during skeletal growth.[99]

Dietary vitamin D intake of some of the patients identified as deficient in the Thomas and colleagues study exceeded the Recommended Daily Allowance (RDA), and many had no apparent risk factors for vitamin D deficiency. To address this issue, investigations are ongoing into the mechanisms of vitamin D action. One such area is the role of the vitamin D receptor gene in calcium absorption and bone mass accretion. One study noted a significantly lower spinal BMD in girls with a homozygous recessive (BB) genotype at one restriction site when compared with heterozygous (Bb) or dominant (bb) genotypes.[100] Thus, alleles for this receptor may influence an individual's response to calcium intake and other environmental factors.

Disturbances in Adolescent Nutrition with Implications for Bone Health

General Nutrition It should be remembered that rates of gastrointestinal calcium absorption and urinary excretion significantly influence the bioavailability of calcium. Foods high in oxalic acid such as spinach, beans, sweet potatoes, and rhubarb, which are not typically major components of the average teenager's diet, may inhibit calcium absorption.[53] Otherwise, calcium absorption is relatively high and excretion relatively low in adolescents when compared with adults. The typical adolescent's high-salt diet may negate this advantage, however, as each gram of urinary sodium excretion obligates a loss of 26 mg of urinary calcium.[101,102]

Dairy Intake A survey in the United States showed that although adolescents overwhelmingly (> 90%) believed that calcium is healthy and important for bones, few (19%) were aware of the RDA for calcium and even fewer (10%) knew how to meet this goal with dairy products.[103] It is not surprising, therefore, that less than 16% of adolescent girls in the United States meet the Dietary Reference Intake (DRI) of calcium of 1,300 mg/day.[104–106] The mean calcium intake for girls aged 9 to 13 years is approximately 890 mg/day, or 69% of DRI; this value drops to approximately 710 mg/day, or 55% of DRI, in 14- to 18-year-old girls.[53] Similarly, mean magnesium intake is approximately 93% and 60% of the RDA for the respective age groups, probably largely owing to lack of dairy consumption.[53]

Carbonated Beverages Wyshak and Frisch have shown that consumption of carbonated beverages, particularly cola (phosphoric acid–containing) drinks,[107] in teenaged girls may be associated with increased risk of bone fractures.[108] The association was not found to hold for teenaged boys.[107] The pathophysiology is not completely understood but is felt to be attributable, in large part, to the substitution of carbonated beverages for milk. Cola drinks may be particularly implicated because they create a high phosphoric acid load, which both chelates calcium and may increase parathyroid hormone (PTH) secretion. High intake of calcium was protective in the study,[107] but it is noted that between 1970 and 1997 in the United States, per capita consumption of carbonated beverages increased by 118% at the same time consumption of milk declined by 23%.[109]

BONE DISEASES

Osteomalacia

Rickets, or vitamin D–deficient osteomalacia, is a classic example of the detrimental effect of malnutrition on bone and continues to be a problematic condition for growing children in North America and worldwide. Evidence is beginning to accumulate that vitamin D deficiency may be prevalent among American adolescents and young adults, particularly those who live in northern latitudes.

Low levels of $1,25(OH)_2D$ lead to low levels of serum calcium, which stimulates PTH secretion. Under the stimulus of PTH, osteoclasts increase the rate of bone resorption to maintain calcium homeostasis. Osteoblasts respond to the increased osteoclast activity by increasing osteoid formation. Owing to the relative lack of calcium and phosphate, this osteoid is poorly mineralized. As a consequence, vitamin D deficiency impacts negatively not only on trabecular bone, which is more hormonally responsive and more commonly affected by such deficiencies, but also on cortical bone.

In addition to poor dietary intake, vitamin D deficiency can be caused by inadequate exposure to sunlight. Anticonvulsants cause increased hepatic breakdown of vitamin D. Patients with renal disease may have decreased activation of 25(OH)D to $1,25(OH)_2D$, in addition to increased tubular losses of calcium and phosphate. Use of aluminum-containing antacids impairs phosphate absorption. Other gastrointestinal conditions also impair absorption of vitamin D, calcium, and phosphate, as will be described.

Clinical manifestations of rickets in skeletally immature children include flaring of the metaphyses and growth retardation. In skeletally mature adolescents and adults, findings are more subtle, including bone pain, susceptibility to fracture, and pseudofracture. Serum levels of 25(OH)D are a reliable measure of total vitamin D stores. However, the desirable level for 25(OH)D, including what constitutes the threshold stimulus for rises in PTH, is a subject of debate.[78,83,98] Recent data by Haden and colleagues showed that PTH levels start to increase at a 25(OH)D level of 25 ng/mL, higher than the threshold of 12 to 15 ng/mL previously established for vitamin D deficiency.[110] Treatment consists of ensuring adequate dietary intake of vitamin D, with supplementation as necessary. A commonly prescribed replacement dose for adolescents and young adults with rickets is ergocalciferol (vitamin D), 2,000 IU by mouth once daily. Parenteral weekly dosing of 50,000 IU intramuscularly is also used but must be undertaken cautiously, with assurance of

adequate calcium intake and appropriate monitoring of vitamin D and PTH levels.

Osteoporosis

Definitions In contrast to *osteomalacia*, which refers to a condition in which the bone matrix is poorly mineralized regardless of the actual mass of bone tissue produced, *osteoporosis* is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.[111] A related term, *osteopenia*, is used to describe a significant reduction in bone mass for age and sex. In each of these conditions, the osteoid is mineralized normally to form calcified bone, but there is less of it and its structural arrangement is abnormal.

Diagnosis Adult osteoporosis is defined by the World Health Organization (WHO) as a BMD below 2.5 standard deviations from the mean peak BMD attained for gender (ie, *t*-score < –2.5) as measured by DXA. Osteopenia is the term reserved for BMD with a *t*-score between –1.0 and –2.5.[112] Using these definitions, DXA scanning has become the gold standard for diagnosing abnormalities in bone tissue in adults. Unfortunately, these WHO definitions currently exist only for postmenopausal women and are not available for children and adolescents.

Dual-Energy X-Ray Absorptiometry DXA uses x-rays of two differing photon energies passing through the body to a sensitive detector. The beams are attenuated differentially depending on the tissues through which they pass. A computer then calculates body composition, bone mineral content (BMC), and BMD based on the attenuation. DXA scanners report BMC in grams of mineralized calcium and BMD in grams per area of bone region in squared centimeters (g/cm^2). Advantages of DXA scanning include relatively rapid scanning times (approximately 5 minutes for each scan), low levels of radiation exposure (one-tenth the radiation of a chest radiograph), and precision in the range of 1%. For these reasons, DXA can be used in children, with reliable normative data available consistently by 8 years of age, with some databases including children as young as 4 years.[113]

Limitations of DXA for Adolescents The major limitation of DXA is that it uses a two-dimensional technique to quantify a three-dimensional structure. Density is, by definition, a measure of mass per unit volume. The BMD reported by DXA scanners is areal, or per unit area in g/cm^2. The significance of this calculation is more than academic as the mechanical properties of bone are dependent on its architecture and geometry, as well as its composition. Good mathematical models have been developed to calculate approximate volumetric BMDs known as bone mineral apparent densities in g/cm^3, although their prognostic value is not well established.[114]

These limitations of DXA are more significant in adolescents. First, not all DXA scanners are equipped with the proper software to evaluate pediatric body composition and, therefore, BMD. Even comparing a single adolescent with himself or herself on a single machine with reliable pediatric software is subject to flaws. Presumably, one could measure serial DXA scans over time to assess the effect of a disease state or treatment on BMD. Unfortunately, the growth of the child complicates interpretation. To illustrate, consider quantifying the density of a tree trunk by measuring the shadow cast by the tree in the sun. After 1 year of growth, the tree trunk casts a wider (and perhaps darker) shadow, but it may be no denser than it was previously. Using DXA, the "shadow" or areal BMD (aBMD) of this tree would be reported as greater than it was the previous year. The same phenomenon occurs when measuring a growing child's bones. The opposite phenomenon, that of a growing child's measured aBMD remaining constant, should therefore appear ominous to the clinician. Unfortunately, limitations on the actual scores reported for BMD do not allow the clinician to quantify the degree of risk. Fortunately, bone grows stronger as it increases in diameter, even at the same BMD.[115]

As mentioned, interpreting even reliable values for BMD is challenging. The *t* (or standard deviation) score, which compares an individual adult's BMD to the mean peak BMD (or PBM) attained by young adults of the same gender, provides a valid estimate of the risk of fracture for that adult. The z-score compares an individual's BMD to the mean BMD (in standard deviation units) for his or her age and gender, which is useful to grade patients with respect to their peers but has no prognostic significance. Reliable pediatric databases report *t*- and z-scores, but the *t*-scores are not informative as most children and adolescents have not reached their peak young adult BMD. Uniform definitions of osteoporosis or osteopenia based on z-scores do not yet exist. Furthermore, as bone mass accretion is strongly influenced by Tanner stage, which does not directly correlate with chronologic age, comparing BMDs based on age alone may be problematic. Finally, most databases include predominantly or exclusively white populations, which makes the interpretation of BMD data more difficult for patients of different ethnic groups.[113]

Other Imaging Techniques Quantitative computed tomography is a technique of bone densitometry that can generate measures of bone volume and thus a more accurate volumetric BMD. Pediatric algorithms are available, but the increased time required and significantly increased radiation doses limit its use in this age group. A newer technology, quantitative ultrasonography, shows promise as it has no associated radiation exposure and has been validated in Israeli and Korean adolescents with reasonable precision.

Serum Markers Bone turnover markers are used infrequently in the assessment of metabolic bone disease, primarily for research purposes, to gauge the relative contributions of bone formation versus bone resorption in the bone remodeling cycle. Some endocrinologists also use them to monitor treatment response. Serum alkaline phosphatase levels, particularly BSAP, reflect osteoblast func-

tion, as does serum osteocalcin, an osteoblast-specific product. Serum tartrate-resistant acid phosphatase is an osteoclast equivalent for BSAP, whereas collagen type I cross-linked N-telopeptide (NTx), which, as a breakdown product of bone, reflects osteoclast activity and can be measured in the urine. Adult studies have shown these markers to be inferior to bone densitometry for diagnosing osteoporosis and monitoring skeletal health, and pediatric reference ranges are limited as growth, puberty, and diurnal cycling cause wide variation in these values.

NUTRITIONAL DISEASE STATES ASSOCIATED WITH OSTEOPOROSIS

Anorexia Nervosa

Patients with AN are at risk for profound deficits in BMD that are often irreversible, even with a return to appropriate weight. Previous research has shown that patients with chronic AN have a sevenfold increased incidence of fractures and are at increased risk for developing early osteoporosis.[116–120] Because the incidence of anorexia increases during the years of attainment of PBM, the lifelong impact on skeletal health in maturity is particularly concerning. The mechanisms of this bone loss are certainly related to decreased dietary intake of calcium, vitamin D, and other macronutrients. Women with AN also develop hypothalamic amenorrhea, which results in low circulating levels of estrogen.

It is hypothesized that estrogen helps regulate bone mass by impairing osteoblast-mediated bone resorption. Oral contraceptive (OCP) use by young women with AN was shown in a retrospective cross-sectional study to be associated with a higher BMD.[121] In a small pilot study of women with AN and hypothalamic amenorrhea, ERT resulted in increases in BMD.[122] Unfortunately, ERT alone has not consistently been shown in other controlled studies to be able to reverse the bone loss in patients with AN, with the possible exception of those most profoundly affected (below 70% of ideal body weight).[123] Despite the fact that its effects on bone accretion have been disappointing, ERT remains one of the standard therapies used to help maintain skeletal health in patients with AN,[124] along with psychological support. Ultimately, nutritional rehabilitation and weight restoration are necessary to return menstrual function, circulating estrogen levels, and bone formation to normalcy. Even prior to attainment of menstrual regularity, however, bone density increases with weight gain in adolescent girls with AN.[125]

It has been suggested that bone formation is more profoundly decreased than resorption is increased in patients with AN.[118] This "uncoupling" of the normal bone cycle has led investigators to address both sides of the formation-resorption dyad.[120,126–128] Serum levels of IGF-I have been found to be decreased in patients with AN.[128] Short-term randomized controlled trials of IGF-I administration showed significant increases in bone formation in patients with AN, with greatest improvement in those also given OCPs, arguing for a synergistic effect between ERT and IGF-I.[129,130] Unfortunately, use of this agent in children and adolescents may be limited owing to its availability only as an intravenous or subcutaneous preparation. Longitudinal data are also awaited to determine long-term efficacy.

Nutritional Supplements: Dehydroepiandrosterone Like IGF-I, levels of the adrenal steroid dehydroepiandrosterone (DHEA) are low in patients with AN.[131–133] DHEA is positively correlated with BMD in adults and parallels the pattern of bone accretion in that secretion of DHEA peaks during the same adolescent years as bone mass acquisition accelerates.[131,134–141] DHEA is thought to increase levels of IGF-I, thereby increasing bone formation by stimulating osteoblasts, and also decreases mediators of osteoclast-mediated resorption.

Recent studies of administration of short-term oral DHEA, which is currently sold as a nutritional supplement, in adolescent girls with AN have shown that this agent is well tolerated. The adolescents who were given DHEA showed significant decreases in concentration of NTx, a marker of bone resorption, and increases in osteocalcin, a marker of formation.[142] The effect of DHEA on BMD in these patients is still under study. Because it is unregulated by the US Food and Drug Administration, DHEA is widely available, but it is potentially unsafe, depending on the preparation and dosing. For both of these reasons, DHEA cannot be recommended at this time as a therapy for patients with bone loss secondary to AN.

The Female Athlete Athletic participation has become increasingly common among adolescent girls since the enactment of Title IX of the Educational Amendments Act in 1972, which required women's intercollegiate athletic offerings to be proportional to their representation in the student body. As noted previously, an active lifestyle has the potential for improved skeletal health. Unfortunately, some female athletes may develop patterns of unhealthful eating, irregular menstrual cycles, and an ensuing state of low estrogen levels, which can undo the beneficial effects of exercise on bone density.[143] In 1992, 20 years after Title IX, the American College of Sports Medicine coined the term "female athlete triad" to define this interrelatedness of disordered eating, amenorrhea, and osteoporosis in certain female athletes.[144,145] Owing to its relatively recent definition, the prevalence of the entire female athlete triad has not been well established. Studies have shown, however, that 3.4 to 66% of female athletes have experienced amenorrhea compared with only 2 to 5% in the general population, and 15 to 62% of female college athletes demonstrate disordered eating compared with a 5 to 10% prevalence of eating disorders in the general population.[146–150]

Complete epidemiologic characterization of the female athlete triad may prove elusive as most athletic women with menstrual irregularities do not meet the criteria for osteoporosis or frank eating disorders. Some of these women even consume adequate calories, leading some clinicians to use the term "athletic amenorrhea," believing it is caused by the stress of exercise. Loucks and colleagues have disputed this concept, showing that low energy availability, defined as a failure to match food intake directly to

exercise energy expenditure, not stress of exercise, alters luteinizing hormone (LH) pulse frequency and amplitude.[151] These disturbances in LH pulsatility can cause amenorrhea or more subtle menstrual dysfunction, including irregular, anovulatory, and short luteal phase cycles, all of which can cause a relative estrogen deficiency and increased bone resorption. Work with elite gymnasts and runners has shown that even within-day, hourly energy deficits cause changes in body composition, with greater amplitude and frequency variations in energy balance correlating with increased body fat percentage.[152] The authors suggest that these wide swings also predispose to menstrual dysfunction.[152]

An alternative but complementary hypothesis is that cognitive dietary restraint, defined as the intention to limit food intake to control body weight, regardless of actual food limitation, is associated with higher levels of cortisol, which, in turn, impairs bone mass accretion by directly decreasing osteoblast activity and indirectly increasing osteoclast activity. In studies by McLean and colleagues, exercising women with high dietary restraint measures by questionnaire had similar BMI and menstrual cycle length to those with low restraint but higher urinary cortisol excretion[153] and lower total-body BMC.[154] In either case, it is important to counsel adolescent female athletes to maintain positive energy balance throughout the day with frequent appropriate pre-, post- and between-exercise meals.

Celiac Disease

Celiac disease is a disorder of nutrient absorption in the small intestine that affects as many as 1 in 250 people of European descent. In susceptible individuals, an immunologic reaction to gluten (a protein found in wheat, barley, and rye) leads to a chronic enteropathy of the proximal intestine. Low BMD is a common complication of celiac disease, caused by general malnutrition secondary to anorexia (reduced dietary intake) and impaired absorption of nutrients, especially calcium and vitamin D,[155] among other etiologies.

A gluten-free diet (GFD) is the mainstay of treatment for celiac disease, decreasing intestinal manifestations and improving BMD in adults and, in short-term trials, children. A recent long-term longitudinal study in children and adolescents showed that spinal BMD in patients with celiac disease was significantly lower than in controls at the time of diagnosis. After long-term GFD treatment (4 years), patients had regained BMC and BMD to levels similar to controls, with significant "catch-up" gains made in the first year of GFD treatment. Of note, the effects were most pronounced in the subgroup most compliant with GFD.[155]

Inflammatory Bowel Disease

Like patients with celiac disease, adolescents with IBD are at risk for low BMD. Patients with Crohn's disease (CD) have a higher incidence of osteopenia than those with ulcerative colitis (UC),[156] likely related to the more widespread distribution of intestinal inflammation in the former versus the latter diagnosis. In addition to malabsorption of calcium, phosphate, and vitamin D, these patients have generalized malnutrition. They may also have delayed puberty, leading to inadequate levels of estrogen and/or testosterone to promote adequate bone accretion. High concentrations of circulating inflammatory cytokines IL-1β, tumor necrosis factor α, and IL-6 that occur in IBD may have direct stimulating effects on osteoclasts, increasing bone resorption. Finally, extensive mucosal disease or surgical resection of the small bowel, particularly the terminal ileum, seen in CD further impairs calcium and vitamin D absorption.

The magnitude of corticosteroid use is the single greatest predictor of osteopenia in patients with both UC and CD.[157] Steroids directly decrease bone formation by inhibiting osteoblast activity. Indirectly, corticosteroids decrease the secretion of estrogen and testosterone, which are necessary for bone accretion, as well as decrease the absorption of calcium in the gut and reabsorption of calcium in the kidneys.

These adverse effects of corticosteroids are a concern for other patients with systemic steroid-dependent diseases such as juvenile rheumatoid arthritis (JRA) and collagen vascular diseases and solid organ transplant recipients. A recent study has shown a dose-related loss of BMD at the hip in premenopausal adult women using inhaled glucocorticoids for treatment of their asthma.[158] Although there is a similar concern for children and adolescents, it is largely speculative as the studies in these age groups are few and have not shown significant differences in BMD between patients on inhaled corticosteroids and controls.

Cystic Fibrosis

Patients with CF are at increased risk for significant bone disease. A review of the literature from 1988 to 1998 has shown relative BMD decreases for patients with CF, with measured z-scores ranging from –0.31 to –2.14 in studies with varying age populations and densitometry methods. This decrease in BMD translates into measurable increases in fracture rates and kyphosis (compression of the thoracic vertebrae) in CF patients aged 6 years and older.[159]

Once again, the pathophysiology of bone loss in these patients is felt to be multifactorial, with malabsorption of calcium and vitamin D, general malnutrition, inflammatory cytokines, and systemic corticosteroid use all playing roles. Vitamin D is a fat-soluble vitamin that relies on pancreatic enzymes for optimal absorption and reabsorption via enterohepatic circulation. Patients with CF have been shown to have a high prevalence of vitamin D deficiency, even after exogenous supplementation.[159] CF patients additionally have decreased levels of IGF-I and growth impairment, with height deficits as great as one standard deviation when compared with controls, which impairs maximal bone mineral accretion and may warrant GH replacement.[159,160] Pubertal delay and hypogonadism ensue, even in adulthood, leading to deficits in the estrogen and testosterone necessary to optimize the bone cycle. The decreased levels of IGF-I may also have direct deleterious effects on bone density. An additional

consideration in CF can be a lack of exercise tolerance in patients owing to their respiratory disease. Because bones require mechanical loading for remodeling, lack of weight-bearing activity further hinders normal bone mineral acquisition.

EVALUATION AND MANAGEMENT

The conditions described above are only a few of those that predispose children and adolescents to osteoporosis (see Table 51.3-1). The wide variety of conditions that impair skeletal health necessitates a high index of suspicion and heightened level of concern for bone health on the part of the pediatric health care or nutrition practitioner. The limitations of DXA scanning in pediatric populations detailed earlier have delayed its widespread use. Therefore, there is little evidence on which to make general recommendations as to when and how frequently specific groups of children should have bone density measurement by DXA. Standard practice in the authors' clinic is to perform DXA scans on girls and young women with AN after 6 months of hypothalamic amenorrhea. It is reasonable to perform a baseline DXA scan at the time of diagnosis on patients, age 8 years and older, with celiac disease, IBD, JRA, and CF. Bone density measurement is also recommended for patients with multiple fractures, regardless of etiology, pathologic or atraumatic fractures, and stress fractures. A higher level of suspicion should also be raised in any patient with a strong family history of osteoporosis or with long-term use of systemic corticosteroids. DXA scans should then be repeated over time, but not more frequently than annually in clinical practice as the changes noted over a shorter period are unlikely to be significant.

Patients found to have subnormal BMD on DXA scanning should have a screening evaluation of calcium homeostasis in addition to any clinically indicated laboratory assessments of their underlying medical conditions. A panel including serum calcium, phosphorus, magnesium, 25(OH)D, PTH, and thyroid-stimulating hormone, as well as a urinary spot calcium-to-creatinine ratio (normal < 0.2), would be sufficient. Any abnormalities, or BMD z-scores < –2.5, warrant referral to a provider (eg, an endocrinologist) experienced in calcium metabolism and skeletal health.

MANAGEMENT

Management of bone disease in patients with the chronic illnesses described consists primarily of optimizing nutritional status, particularly with respect to calcium and vitamin D, and ensuring a normal hormonal milieu, with exogenous replacement of estrogen, testosterone, and GH, as warranted. GFDs have already been mentioned for patients with celiac disease. Systemic corticosteroids should be used judiciously but should not be withheld if that would jeopardize management of the underlying disease process. As with many decisions in clinical medicine, potential risks and benefits must be balanced for each individual case.

The uses of DHEA and IGF-I in patients with AN have already been discussed. The positive effects of each on bone formation may make them attractive candidates for use in other diseases, particularly IGF-I for CF. However, long-term improvements in BMD, as well as solutions to the limitations mentioned above (nonstandard preparations for DHEA, parenteral administration for IGF-I), will need to be demonstrated before widespread use can be recommended.

Another class of agents being explored in several clinical trials of patients with AN and some of the other subgroups mentioned above is the bisphosphonates. These investigations have been prompted by the successful use of the bisphosphonate pamidronate in children with osteogenesis imperfecta,[161] as well as increasing experience with the bisphosphonate alendronate in postmenopausal women with osteoporosis. Bisphosphonates are potent and irreversible inhibitors of bone resorption that become incorporated permanently into the mineralized bone matrix. Until the introduction of alendronate, an oral preparation, bisphosphonates were limited by the same considerations as IGF-I. Alendronate may cause significant esophageal erosions, which can be mitigated by the recent development of once-weekly dosing. Concerns still exist around use of bisphosphonates in pediatrics, especially with respect to possible inhibition of primary remodeling of growing bone, increased risk of osteomalacia, long half-life in bone (> 10 years), and unknown effects on the growing fetus. Additionally, despite increases in BMD, there is concern that bone matrix, intercalated with bisphosphonate, may not provide normal mechanical strength. Therefore, although there is great promise to translate their established benefits in the elderly to younger patients, at the present time, these agents should not be used outside of research studies, with the possible exception of use by experienced and skilled providers for patients with diseases causing severe osteopenia or osteoporosis.

Finally, early recognition of the conditions that predispose to osteopenia and early identification of patients at risk are essential to the prevention of bone loss in adolescents with chronic illnesses, which may be the most effective way to manage bone disease in these patients.

PREVENTION

In addition to managing the skeletal complications of chronic illnesses, one of the most important goals of adolescent nutrition is the potential prevention of osteoporosis by maximizing skeletal health in otherwise healthy teenagers. It is essential to ascertain family history of osteoporosis, especially early-onset osteoporosis, or frequent fractures. Dietary sources of calcium and vitamin D should be assessed and inadequacies addressed. Recommended age-appropriate daily calcium, magnesium, phosphorus, and vitamin D intake guidelines have been developed in the United States by the National Institutes of Health and National Academy of Sciences (see Table 51.3-2) and should be endorsed.[106] Metabolic studies of calcium retention in adolescent girls showed such large

variation, however, that it might be necessary to individualize calcium requirements based on postmenarcheal age.[162,163] Others have argued that gender and physical activity should also modify recommendations for optimal calcium intake.[164]

The consensus recommendation for vitamin D intake is also subject to modification. The efficiency of conversion of 25(OH)D in the kidney increases during puberty, suggesting that requirements for vitamin D in adolescents are no higher than in adults.[165] But, as mentioned above, the prevalence of subclinical vitamin D deficiency in adolescents (or adults) is not known. Higher 25(OH)D levels than previously believed may be needed to protect against secondary hyperparathyroidism. Both of these questions are the subject of current research. In the meantime, it is recommended that adolescents consume 400 IU of vitamin D daily.

The success shown by a single supplementation trial in maintaining increases in BMD several years after discontinuation of concentrated milk protein as the primary calcium source may suggest the superiority of milk over other sources,[95] but further study is necessary to confirm this finding. Adolescent girls may need to be reassured that consuming dairy products instead of calcium supplements will not increase their weight or percent body fat, as shown in a 4-year longitudinal study.[166] Some examples of dietary sources of calcium and vitamin D are listed in Table 51.3-3. For those who cannot or will not consume adequate dairy products, calcium supplements are a suitable alternative (see Table 51.3-3). Despite concerns to the contrary, chronic consumption of high levels of calcium has not been shown to impair absorption of such essential nutrients as iron, magnesium, and zinc as long as the intake is held below 2.5 g (2,500 mg) daily.[53,167]

CONCLUSIONS

The growing body of literature highlighted in this section should alert clinicians in all disciplines to the adverse effects of chronic illnesses and inadequate nutrition on the skeletal health of adolescents. Most clinicians should find the solutions less obscure, however, as the promotion of skeletal health is ultimately no more than the promotion of good general health, including recommending balanced general nutrition, moderate weight-bearing exercise, and avoidance of alcohol and tobacco for all adolescents. The challenge is in helping teenagers modify their behaviors to meet these goals.

TABLE 51.3-3 Examples of Dietary Sources of Calcium

Food	*Calcium*	*Serving Size*
Milk	300	8 oz
Low-fat yogurt	300–415	8 oz
Calcium-fortified orange juice	300	8 oz
Cheddar cheese	300	1.5 oz
Cooked broccoli	35	½ cup

Adapted from Steelman J and Zeitler P.[8]

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CHAPTER 52

FAILURE TO THRIVE: MALNUTRITION IN THE PEDIATRIC OUTPATIENT SETTING

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HISTORY, BACKGROUND, AND DEFINITION OF TERMS

Pediatricians have described malnourished children with the words "failure to thrive" since at least the nineteenth century.[1] There continues to be a notable lack of progress regarding a valid and reliable definition of the term.[2] A review of general pediatric and pediatric nutrition textbooks failed to find a consensus definition, with various anthropometric and nonquantitative descriptive terms being employed.[3] Vinton and Dietz have rightly suggested that the term is a mere euphemism for undernutrition.[4]

Indeed, the child termed "failed to thrive" in the office of a pediatrician in industrialized countries would more likely (and more accurately) be described in developing countries as malnourished or suffering from protein-energy malnutrition.[5] The continued use of vague terminology such as failure to thrive limits the ability to scientifically study the nutritional status of a population and is likely symptomatic of the medical profession's unwillingness or inability to recognize and treat nutritional disorders among their patients.

Nonetheless, if only owing to the strength of historical precedent, the term failure to thrive will continue to be used to describe infants and young children with malnutrition. It is therefore recommended that quantitative criteria be specifically employed as well. Commonly used criteria include (1) a child whose weight (or weight for height) is more than 2 SD below the mean for sex and age and/or (2) a child whose weight curve has crossed more than 2 percentile lines on the Centers for Disease Control and Prevention (CDC) growth charts after having achieved a previously stable pattern.

Alternative wordings of the first criterion include "less than the 3rd percentile" or "a weight-for-age (or weight for height) z score (or standard deviation score) less than –2.0." z-scores are calculated by the following formula:

$$\text{z-score} = \frac{\text{actual weight} - \text{median weight}}{\text{standard deviation}}$$

where standard deviation is the age- and sex-specific standard deviation of weight and median weight is the median value for age and sex. It should be noted that expressing anthropometric measures in terms of z-scores is recommended by the World Health Organization (WHO), especially when describing groups of subjects.[6] Z-scores allow more precision in describing anthropometric status than does the customary placement "near" or "below" a certain percentile curve. For example, the phrase "below the 3rd percentile" does not distinguish between a child just below this point (whose z-score may be –2.1) from one with severe growth faltering (whose z-score may be –3.5 or lower) (Figure 52-1). Similarly, 3% of normal children will weigh less than the 3rd percentile, but a z-score significantly lower than –2.0 clearly indicates a growth problem. The CDC has established computer programs that calculate anthropometric data such as weight for height for age and weight for height; these are expressed as percentiles, z-scores, and percentage of the median without making recourse to plotting points by hand.[7] Software for palm-based computers is also available.

The second criterion is a more functional definition of growth failure that takes into account the fact that weight loss or even lack of normal growth during infancy and childhood is abnormal. Thus, these patients should not await the attainment of the low anthropometric scores noted above before appropriate evaluation and treatment are instituted. What constitutes a "stable pattern" can be difficult to define, although Edwards and colleagues addressed this issue by defining the true percentile as the maximum achieved between 4 and 8 weeks of age because weight at this point was found to correlate more strongly with weight at age 12 months than did birth weight.[8] They proposed a functional definition of failure to thrive as "a child whose weight deviates downwards across two or more major centiles from the maximum centile achieved at 4 to 8 weeks for a period of a month or more."

Anthropometric assessment of nutritional status can also be categorized to help determine chronicity of nutritional deprivation. The simple use of a weight-for-age cut-

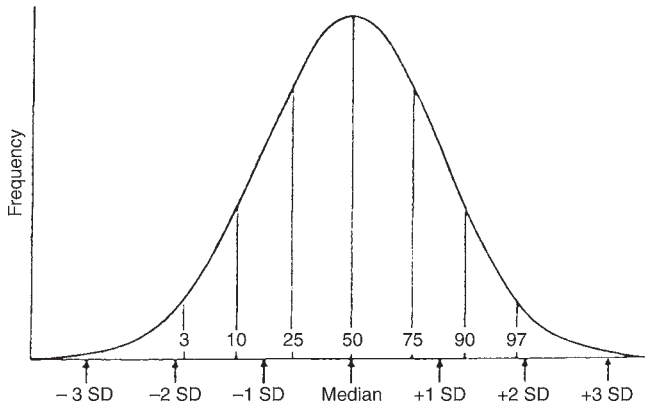

FIGURE 52-1 Comparison of percentiles versus standard deviation or z-scores. Two SDs below (or above) the mean corresponds to the 3rd (or 97th) percentile. Adapted from Jeliffe DB et al.[15]

off to define malnutrition is obviously nonspecific because patients included can be either well proportioned and just constitutionally small or truly of low weight. A classic distinction between acute malnutrition ("wasting" or low weight for height) and chronic malnutrition ("stunting" or low height for age) was proposed by Waterlow and has been widely adopted.[9] Table 52-1 recounts this classification scheme, in which percentage of the median is calculated by the following formula:

$$\% \text{ median} = \frac{\text{actual weight} \times 100}{\text{median weight}}$$

where median weight is the median value for age and sex.

An important caution should be noted when a subject's height faltering is used to call attention to nutritional status. Clearly, genetic and constitutional causes of short stature need to be ruled out before implicating chronic malnutrition as the cause of poor height growth. Elicitation of family history and interpretation of growth parameters in light of midparental height and parental growth patterns can be helpful in this regard. In addition, strict adherence to standard growth curves should not be expected. Smith and colleagues underlined the fact that the National Center for Health Statistics (NCHS) standard curves are mathematical averages based on large numbers of children (ie, cross-sectional curves) and not growth lines along which individual children should be expected to grow (ie, longitudinal).[10] They also demonstrated that infants manifest a growth rate at birth that is predominantly determined by maternal factors. They then shift to one that is increasingly determined by their genetic background. Thirty percent of healthy, full-term, white infants crossed one percentile line and 23% crossed two lines as they moved from birth to age 2 years. Children whose birth lengths were near the 10th percentile but whose subsequent lengths were closer to the 50th percentile tended to catch up at an average of 11.5 months; those born near the 90th percentile and moving down to the 50th percentile did so at an average age of 13 months (Figure 52-2). Karlberg and colleagues analyzed the length curves of healthy children in the first 3 years of life.[11] Children were found to have nonlinear decelerations in their growth rates starting during infancy. During the second year of life, the variation in the growth rate was found to increase, with greater gains in linear growth during the spring/summer than autumn/winter. During the third year, the growth pattern stabilized. Thus, fluctuations in length percentiles are a normal phenomenon in infant growth and, especially in the face of normal weight gain, should not prompt evaluation for nutritional disease. Horner and colleagues have demonstrated that a more significant decline in the linear growth rate occurs in children with constitutional short stature.[12] This fall in the growth rate generally first became apparent in the first 6 to 9 months of life and was greatest during the first 2 years. These children fell more than 2 SD below the mean for height by 3 years of age. Subsequently, their growth rate was the same as that of normal children but below and parallel to the 3rd percentile.

Alternative or supplemental anthropometric criteria for failure to thrive have been proposed, including decreased weight velocity, low triceps skinfold (TSF) values, and midarm circumference (MAC). For example, data have been published on incremental gains in the length and weight of the infants enrolled in the Iowa and Fels studies.[13] Measurement and interpretation of skinfold thickness and growth velocity have the disadvantage of requiring special equipment and/or graphically represented standards and may not add specificity or sensitivity to the screening criteria noted above. Depleted fat stores and slowed growth velocity are often concomitant findings in the patient with malnutrition, and their presence or absence can be noted on detailed clinical evaluation. In some settings, for example, in refugee camps or in famine situations, a quick assessment of nutritional status is provided by the MAC because this value is relatively independent of patient age and correlates well with risk of death, especially when adjusted for height.[14] However, for standard screening purposes in most US settings, the anthropometric measurements of weight, height, and age are usually sufficient.

Certainly, any diagnosis of malnutrition requires accurate measurements of weight, length, head circumference, and age. Infants' lengths should be measured supine on a length board until age 2 years, after which time they should be measured upright. Infants and children should

TABLE 52-1 Waterlow Criteria for Categorizing Type and Chronicity of Malnutrition

Type of Malnutrition	*Acute (Weight for Height) (% of Median)*	*Chronic (Height for Age) (% of Median)*
Normal	> 90	> 95
Mild	80–90	90–95
Moderate	70–80	85–90
Severe	< 70	< 85

Abnormalities of weight for height are termed "wasting" and those of height for age are called "stunting." Adapted from Waterlow JC.[9]

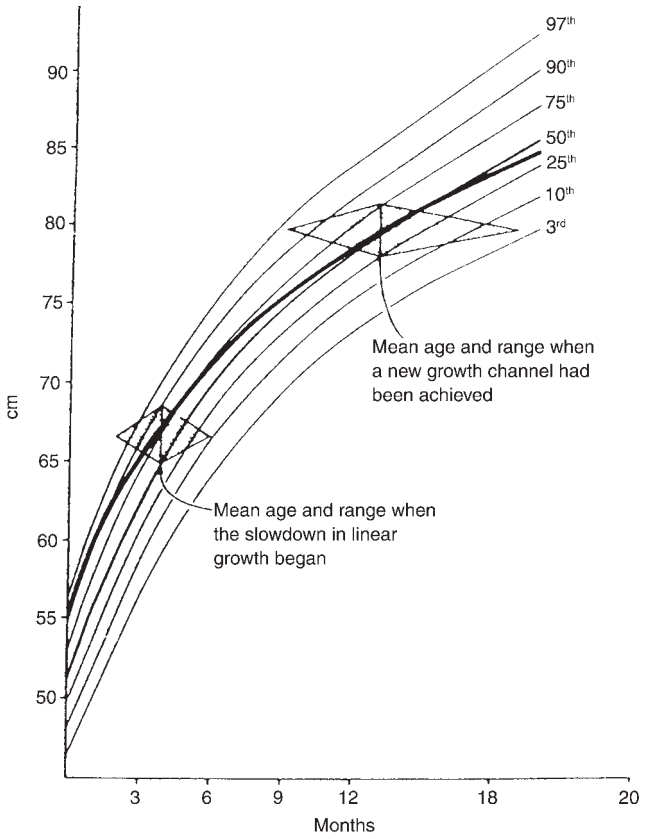

FIGURE 52-2 Mean linear growth curve of 16 healthy infants who crossed percentile lines during infancy. Whereas at birth they were at the 90th percentile, by age 2 years, they had reached the 40th percentile. This shift generally occured between 3 and 13 months. Adapted from Waterlow JC.[9]

be weighed with minimal clothing on scales accurate to at least 100 g. If possible, one person in the office should be designated as solely responsible for weighing and measuring patients. Detailed summaries of anthropometric techniques have been published elsewhere.[15]

These measurements should be plotted on appropriate graphs (see Appendix). When plotting infants with a history of premature birth, their chronologic age should be corrected by gestational age until 24 months for weight, 40 months for length, and 18 months for head circumference.[16]

The NCHS standards have previously been recommended and used worldwide since 1978 by the WHO regardless of racial or ethnic origin.[17,18] In 2000, the CDC developed new standards for infants from birth to 36 months and for children from 2 to 20 years of age.[19] These standards are now recommended for use in the United States. The new growth charts were developed to address some of the concerns raised about the 1977 NCHS curves.[19] The new CDC curves are more representative of a cross-section of the ethnicity of the children living in the United States. Data from breast-fed infants are also included so that the mix of formula-fed and breast-fed infants is more accurately represented. The distribution of birth weights now more closely matches the national distribution. Statistical methods have been employed to smooth the disjunction between length and height. Finally, the body mass index (BMI) is now available for children from ages 2 to 20 years. On the NCHS charts, weight-for-stature charts are available but stop at age 10 years for girls and 11 years for boys.

A somewhat misleading distinction in the medical literature is still written of concerning organic versus nonorganic failure to thrive (eg, Rosenn and colleagues[20]). The former is that type of malnutrition attributable to an underlying medical condition that has presumably limited the intake, absorption, or use of adequate calories. Nonorganic failure to thrive, in contrast, implies a primary social dysfunction of the family or societal unit whose net result is that the child is not offered adequate calories. Berwick and colleagues reviewed the records of 122 children between the ages 1 and 25 months who were hospitalized for failure to thrive.[21] Thirty-three percent had no specific diagnosis, 32% were felt to have a social or environmental explanation, and 31% were given a specific medical diagnosis. Because the vast majority of childhood undernutrition in the United States is attributable to so-called nonorganic causes, the discussion of therapy will be directed at identifying and rectifying these reasons (see below). It has also been written that a so-called mixed failure to thrive category exists in which both organic and psychosocial factors are responsible or one may result from the other, resulting in the poor nutritional status.[22,23] This is not surprising and reflects the difficulty in any attempt to dichotomize between physiologic and social influences on health in general and nutrition specifically.

EPIDEMIOLOGY

Significant pediatric undernutrition in the United States is often cited to occur in 10% of low-income children.[24] The prevalence of underweight children can range from 1 to 10%, depending on the clinical setting.[25] Unfortunately, the definitions of malnutrition used to support such claims include well-established anthropometric criteria but also terms as inclusive and perhaps biased as "[failure to thrive] noted on the problem list or in the clinic notes."[26] Other factors that can interfere with an accurate survey of failure to thrive infants have been reviewed.[27]

National surveys have been undertaken that provide information on the prevalence of inadequate growth.[25] The National Health and Nutrition Surveys (NHANES I [1971–1974], II [1976–1980], and III [1988–1991]) studied the prevalence of low height for age and weight for height among 2 to 5 year olds. In the 1988–1991 survey, the prevalence was found to be 5.2% and 2.7%, respectively. The Pediatric Nutrition Surveillance System (PedNSS) measured the prevalence of inadequate growth in predominantly less than 5-year-old low-income children who participated in publicly funded nutrition and public health programs. In 1996, the prevalence for low height for age was 5.8% and low weight for height was 2.6% in 2 to 5 year olds. Furthermore, the PedNSS reported in 1996 that infants from birth to 2 months experienced the highest prevalence for both indicators. In this group, 12% had low height for age and 4.1% low weight

for height. Finally, blacks had the highest rates for both of these indicators.

In recent years, pediatric health care providers have encountered growing numbers of international adoptees and the children of new immigrants. Every year, 3 million children ages 0 to 19 years of age immigrate to the United States mainly from Asia, Western Europe, and North Africa.[28] Immigrant children have been found to be deficient for height for age and weight for age.[29] They may also have developmental delays, infectious diseases, a variety of health problems, and psychosocial stressors.[28–30] Fifteen thousand foreign-born children are adopted by American citizens each year.[28] Since 1990, the majority were adopted from China and the countries of the former Soviet Union.[28] Among the children adopted from China, z-scores were ≤ –2 SD in 39% for height, 18% for weight, and 24% for head circumference.[30] Developmental delays, both global and in specific areas, were common, as were infestations, infections, and chronic medical conditions.[30]

TABLE 52-2 Risk Factors for the Development of Failure to Thrive

Infant characteristics
Any chronic medical condition resulting in
Inadequate intake (eg, swallowing dysfunction, central nervous system depression, or any condition resulting in anorexia)
Increased metabolic rate (eg, bronchopulmonary dysplasia, congenital heart disease, fevers)
Maldigestion or malabsorption (eg, AIDS, cystic fibrosis, short gut, inflammatory bowel disease, celiac disease)
Premature birth (especially intrauterine growth retardation)
Developmental delay
Congenital anomalies
Intrauterine toxin exposure (eg, alcohol)
Plumbism and/or anemia
Family characteristics
Poverty
Unusual health and nutrition beliefs
Social isolation
Disordered feeding techniques
Substance abuse or other psychopathology (including Munchausen syndrome by proxy)
Violence or abuse

MEDICAL RISK FACTORS FOR MALNUTRITION

There are many well-known medical and psychosocial risk factors for the development of failure to thrive (Table 52-2), which can generally be viewed as relating to the infant or to the family. Almost all chronic medical conditions in a child can lead to poor weight gain by a variety of factors.[31] These include decreased caloric intake (anorexia, food withholding, altered mental status), increased caloric requirements (fever, infections), and/or inefficient use of ingested calories (maldigestion, malabsorption, and metabolic disorders). The nutritional implications of hospitalization for the treatment of medical or surgical conditions are almost uniformly detrimental, and the nutritional status of hospitalized pediatric patients is poor (see Chapter 11, "International Nutrition").[32] Nutritional recommendations for specific disease states are found elsewhere in this textbook.

An important medical risk factor for undernutrition in childhood is premature birth. Growth data are available for low birth weight preterm infants (see Appendix).[33–36] Recently, growth curves for the use with hospitalized very low birth weight growth curves have been developed.[37] Standard growth curves should be used once the infant has achieved a gestational age of 40 weeks. As noted above, correction for prematurity should be done when plotting an infant's anthropometric measurements on the CDC growth curves to correctly assess growth. Even with correction for gestational age, however, Casey and colleagues have shown that patients who were both low birth weight and premature have smaller mean lengths, weights, and head circumferences than their term counterparts in the first 3 years of life.[34,35] The lower the birth weight, the greater the depression of the mean.

Having plotted growth parameters, the clinician should keep in mind the myriad potential complications of prematurity that can lead to malnutrition, including chronic lung disease, necrotizing enterocolitis and intestinal resection, developmental delay, retinopathy of prematurity, and other sensorineural abnormalities. In addition, behavioral abnormalities of some premature infants (including irritability and oral aversion) can predispose to poor postnatal growth.

The infant who is small for gestational age is a special case because prenatal factors may have already exerted a deleterious effect on somatic growth. The reasons for in utero growth failure include both genetic problems (such as chromosomal aberrations), environmental influences (such as maternal smoking, malnutrition, or exposure to drugs or other toxins), and infection. Infants with symmetric growth retardation (in which weight, height, and head circumference are equivalently depressed) are less likely to respond to nutritional supplementation with catch-up growth. Conversely, asymmetrically growth-retarded infants (whose weight is disproportionately low) have more truly suffered in utero malnutrition and can therefore be expected to achieve better growth after birth.[38] Strauss and Dietz have observed that many infants who are labeled intrauterine growth retarded (IUGR) often have mothers and non-IUGR siblings who are smaller and lighter and come from families in which there is an increased prevalence of IUGR infants.[39] They concluded that some of these infants may be genetically small, which may limit their catch-up growth.

A prospective case-control study of premature infants has identified some risk factors for poor weight gain after hospital discharge among this population.[40] Among 914 infants with birth weights ≤ 2,500 g, 19.7% were diagnosed with failure to thrive at some point in the first 3 years of life. Multivariate analysis revealed that among infants with growth failure, significantly more had birth weights less than 1,500 g, were small for gestational age, had an abnormal neurologic examination at 40 weeks gestational age, or had a mother whose height was less than 5 feet

2.5 inches. Interestingly, infants born to mothers who were college graduates or who were living with the infant's father had a higher risk of developing failure to thrive than those without these characteristics. Family income, prenatal care, and maternal race were found not to be significant factors.

The child with neurologic disease is also at special risk for poor growth. Children with cerebral palsy are especially at risk for abnormalities of growth and nutritional status (see Chapter 34).[41–44] Many children with developmental delay are short for their age, and although stunting owing to chronic malnutrition is a possible cause, genetic programming owing to the underlying condition and/or altered neuroendocrine axis can also be an etiology. In addition, children with developmental delay may suffer from swallowing dysfunction, gastroesophageal reflux, constipation, and other gastrointestinal diseases that, in addition to their underlying neurologic dysfunction, may alter their caloric intake. Children with hypertonia and movement disorders can have excessive energy expenditure, which may be an additional factor contributing to poor growth. Conversely, children with cerebral palsy often have limited physical activity and therefore lower energy requirements than similarly aged children, thereby placing them at risk for obesity.

Anthropometric evaluation of children with spastic cerebral palsy can be difficult owing to contractures or scoliosis, and interpretation of growth should be done in light of the growth potential of any known diagnosis or syndrome. Because of these difficulties in correctly measuring and interpreting linear growth, emphasis should instead be placed on obtaining adequate weight for height as a measure of good nutrition. However, weight for height in cerebral palsy patients may underestimate their degree of malnutrition.[41] Stallings and Spender and their colleagues have found that linear growth in children with quadriplegic, hemiplegic, and diplegic cerebral palsy can be assessed by the measurement of upper arm and lower leg lengths.[42,45] Growth curves are available for these parameters.[45] In children with quadriplegic cerebral palsy, upper arm length and lower leg length were found to correlate with TSF and MAC.[42] Samson-Fang and Stevenson have recommended the use of TSF for the nutritional screening of children with cerebral palsy.[41] A TSF less than the 10th percentile indicates the need to more fully assess a child's nutritional status, growth, and overall health.

Table 52-3 lists suggested energy requirements in developmentally delayed children based on calorie per centimeter of height because experience has shown that estimating needs by Recommended Dietary Allowance (RDA) and weight often leads to excessive energy intake in this population. The role of malnutrition in infancy in contributing to the development of the central nervous system is addressed in Chapter 21, "Nutrition and Brain Development."

Children born with congenital anomalies are also at nutritional risk. For example, infants born with cleft lips and/or palates may have significant oral-motor dysfunction requiring special nipples and feeding instructions. Some of these infants may require feedings by nasogastric tube or gastrostomy. The occurrence of some congenital anomalies may represent part of a genetic syndrome of which intrauterine growth retardation, poor growth, or short stature is a component. If available, syndrome-specific growth curves should be used. As with the developmentally delayed child, weight for height is a useful anthropometric assessment of nutritional status in these patients. TSF and MAC may also be helpful in these children.

Lead intoxication is a medical risk for poor growth.[46] High blood lead levels probably correlate with poor nutrition based on the fact that a high-fat, low-iron diet promotes lead absorption from the intestine. What is less clear is to what extent the anorexia and other behavioral problems seen with iron deficiency and/or lead poisoning are contributing factors to malnutrition.

PSYCHOSOCIAL RISK FACTORS

Many factors that predispose to poor growth in the United States are not attributable solely to medical characteristics of the child but may be social or behavioral in origin. Feeding-related behavioral disorders are not uncommon in children with poor growth.[47–51] These behavioral difficulties may extend beyond mealtimes.[50] These children are perceived as having more difficult temperamental characteristics and are rated by their parents as being more negative, irregular, dependent, and unstoppable.[49] There may be a temperamental mismatch between the child and mother.[48] Chatoor and colleagues described the diagnostic criteria of the infantile anorexic, a severe eating disorder that arises in the toddler years.[49] Some behaviors may have a medical basis or have had roots in prior medical problems suffered by the child leading to food aversion[47,48,52] or the perception that the child is vulnerable or fragile.[50] Maternal developmental delay, learning disorders, anxiety, psychiatric disease, substance abuse, and difficulties with maternal attachment all may impact the feeding and nurturing of a child as well.[48,49,51] Indeed, an extensive literature has

TABLE 52-3 Estimated Energy Needs for Developmentally Delayed Children

Condition	*Daily Caloric Recommendation*
Ambulatory, ages 5 to 12 yr	13.9 kcal/cm height
Nonambulatory, ages 5 to 12 yr	11.1 kcal/cm height
Cerebral palsy with decreased levels of activity	10 kcal/cm height
Cerebral palsy with normal or increased levels of activity	15 kcal/cm height
Athetoid cerebral palsy, adolescence	Up to 6,000 kcal
Down syndrome, boys ages 5 to 12	16.1 kcal/cm height
Down syndrome, girls ages 5 to 12	14.3 kcal/cm height
Myelomeningocele	Approximately 50% of RDA for age after infancy; may need as little as 7 kcal/cm height

Adapted from Pemberton CM, Moxness KE, German MJ, Nelson JK, Gastineau CF, editors. Mayo Clinic diet manual. Philadelphia: BC Decker Inc; 1988.
RDA = Recommended Dietary Allowance.

arisen around the transactional model of failure to thrive,[16] which emphasizes the interrelationships between medical, behavioral, and developmental characteristics of the infant on the one hand and the familial, psychosocial, and economic environment of the child's caretakers on the other. Such a multifactorial approach to the problem of poor growth has direct implications for treatment modalities, as discussed below.

Of all of the social risk factors, poverty is the most pervasive among children seen for growth failure.[53] Frank and Zeisel stated that 13% of their patients are homeless and noted that inadequate medical care can exacerbate the tendency of acute illnesses to lead to poor growth.[24] The degree to which federal food aid to poor families in the United States helps improve the nutritional status of this population is controversial.[54]

Other psychosocial risk factors for failure to thrive include the health and nutrition beliefs and concerns of the family, including a fear of obesity or cardiovascular disease.[55] Such concerns can lead to suboptimal caloric intake or a diet low in fat, resulting in poor growth. Also in this category are infants who are exclusively breast-fed for longer than is recommended because breast milk as the sole source of nutrition is inadequate for optimal growth after 6 to 8 months.[56] It should be noted that although growth failure in the neonatal period owing to breast milk insufficiency can be serious, failure to thrive in the older breast-fed infant is more likely attributable to underlying medical problems.[57,58] There have also been reports of severe malnutrition caused by the inappropriate use of health food beverages. Carvalho and colleagues reported two cases of children who developed severe nutritional deficiencies caused by the consumption of health food beverages.[59] One received a soy-based beverage and was placed on a strict vegan diet as a result of the dietary practices of the parents. Another was reported who received a rice beverage because of perceived milk intolerance. Concern about food allergies is widespread, with one-quarter of American households altering their dietary intake based on the perception that one or more household members suffer from food allergies.[60,61] These concerns can lead to the unnecessary restriction of a child's diet.[61]

Another dietary practice that can lead to poor nutrition, especially in toddlers, is excessive intake of fruit juices. In addition to the role some juices can play in the etiology of chronic diarrhea, it appears that juices can displace more calorically dense items from the diet.[62,63] Reduction of juice intake was recently shown to be associated with improved weight gain in a series of eight children who were referred for evaluation of growth failure.[64]

Parenting skills (especially feeding skills), life stresses, and social isolation are also factors that can contribute to growth failure. Most studies examining the role of stress and other social factors in pediatric malnutrition have been retrospective and therefore unable to say whether stress preceded or was caused by the infant's nutritional status. Altemeier and colleagues performed a prospective, case-control study among mothers at risk for having children with poor growth by performing prenatal interviews and monitoring subsequent growth.[65] They found that a combined measure of life stress of the parents correlated significantly with subsequent failure to thrive, as did maternal characteristics such as frequent separations, arguments, and reconciliations with the child's father. Self-reported drug and alcohol use, self-image, and attitude toward pregnancy were not correlated with infant growth. Of note, mothers whose children grew poorly reported unhappy childhoods and being subjected to physical abuse more often than did mothers whose children grew normally. In one series, 66% of mothers of infants with growth failure reported having been abused as children themselves compared with 26% of controls from a similar socioeconomic group.[66] The children of immigrants and international adoptees may experience unique stressors, including those related to relocating to a new country, language barriers, having spent extended periods in orphanages, or having witnessed war and other atrocities.[28–30]

Unfortunately, the theme of abuse and violence runs throughout much of the lives of children who grow poorly. Indeed, frank childhood neglect (or the maternal deprivation syndrome) was first hypothesized to be the etiology of many cases of growth failure, as implied by past uses of the term failure to thrive.[67] Food withholding has also been reported to occur in some cases of growth failure.[68] A case series of children diagnosed with Munchausen syndrome by proxy indicated that 29% had been diagnosed with failure to thrive, and 17% of their siblings had had either nonaccidental injury, neglect, inappropriate medication administration, or failure to thrive.[69] These reports all underscore the fact that infants with growth failure may represent a flag for serious social and psychological problems in the family.

APPROACH TO THE PATIENT WITH FAILURE TO THRIVE

Evaluation of a child with growth failure should begin (and often end) with a thorough history and physical examination because the diagnostic benefits of additional laboratory tests are minimal.[21,70] Because so-called nonorganic growth failure is by far the most prevalent type seen by US primary care physicians, simple but noninvasive efforts should be made to screen for possible underlying medical problems. The identification of psychosocial issues that may be afflicting the family should be done concurrently. Because many children with poor growth suffer from behavioral and developmental problems as well as social and economic disadvantages, a multidisciplinary approach has been advocated as an effective method of diagnosis and therapy.[71–73] The use of home visits in conjunction with a multidisciplinary growth and nutrition clinic may provide further benefit.[74] Evaluation by a social worker, behavioral specialist, and/or psychologist will obviously supplement the primary medical and nutritional evaluation. Translators are often essential to allow for adequate communication with immigrant families.

In the medical assessment, important historical points to consider (Table 52-4) include maternal history (espe-

cially use of drugs, possible congenital infections, maternal nutrition, and health during pregnancy), labor, delivery, and neonatal events. Altemeier and colleagues showed that although postpartum complications of the mother did not predict subsequent failure to thrive, unresolved health questions at nursery discharge (eg, bilirubin levels) and difficulty feeding in the neonatal period were associated with later growth problems.[65]

The child's general medical history should also be explored, especially with regard to intercurrent illnesses, medication use, and immunization history. Acute infections can embarrass nutritional status by the increased metabolic demands of fever and stress response, as well as by reducing caloric intake through anorexia. At the same time, a history of recurrent or unusual infections should increase the clinician's suspicion for the presence of an immunodeficiency, including acquired immune deficiency syndrome (AIDS). A developmental history should be obtained. Any suggestion of oromotor or feeding difficulties should also be sought. Assessment by an interdisciplinary feeding team may be helpful and effective.[52]

The growth history should be reviewed by careful plotting of past growth points on the CDC curves. Specific growth curves exist for a number of syndromes, and these should be used in those instances once the diagnosis has been established (see Appendix).[75–77] Dietary history should include a qualitative assessment of feeding behavior and organization of the household at mealtimes, as well as a quantitative measure of caloric intake. Intake data are most easily obtained by 24-hour food recall, but a more reliable and valid assessment is a record of food consumed over 3 to 5 days.[78] Calculation of intake with respect to the US RDAs for age can then be performed and the need for dietary supplementation of micro- and/or macronutrients determined. The child's activity level, feeding history, juice and soda intake, perceived food allergies, and presence of dietary restrictions should be assessed. Culturally based food preferences and feeding practices should also be ascertained.

Family history should include the growth parameters of siblings as well as the stature and growth patterns of parents. The average of maternal and paternal heights can be calculated to derive a midparental height using the following formula:

$$\frac{\text{maternal + paternal heights}}{2} \quad \begin{array}{l} +\ 5\text{ cm if a boy} \\ -\ 5\text{ cm if a girl} \end{array}$$

Comparison with published values can then be done to predict adult stature.[79]

A social history that documents the caretaker's economic status is crucial to help guide diagnostic and therapeutic efforts. Elicitation of the social risk factors outlined above should be performed, as well as the parent's perception of the child's nutritional status. The family's ability to afford, store, and prepare food should also be determined.

A home visit performed by an appropriately trained professional may be helpful. The child and family can be evaluated in a more natural setting, aiding the assessment of the child's environment and mealtimes and allowing for the modeling of behaviors. These visits can even be extended to the child's other significant caregivers (eg, other family members, day care, or preschool). Another method that may be helpful is to ask the child's primary caretaker to videotape the child eating a meal. This tape can then be reviewed with the family, with specific advice offered according to the feeding and caretaker behaviors noted on the tape.

Screening for organic disease should also include a thorough review of systems. Questions regarding gastrointestinal function (dysphagia, vomiting, abdominal pain, bloating,

TABLE 52-4 Historical Evaluation of Infants and Children with Growth Failure

Prenatal
General obstetric history
Recurrent miscarriages
Was the pregnancy planned?
Use of medications, drugs, or cigarettes
Labor, delivery, and neonatal events
Neonatal asphyxia or Apgar scores
Prematurity
Small for gestational age
Birth weight and length
Congenital malformations or infections
Maternal bonding at birth
Length of hospitalization
Breast-feeding support
Feeding difficulties as neonate
Medical history of child
Regular physician
Immunizations
Development
Medical or surgical illnesses
Frequent infections
Growth history
Plot previous points
Nutrition history
Feeding behavior and environment
Perceived sensitivities or allergies to foods
Quantitative assessment of intake (3-day diet record, 24-hour food recall)
Family history
Maternal and paternal height and weight
Growth of other siblings
Gastrointestinal and other systemic diseases
Social history
Age and occupation of parents
Who feeds the child?
Life stresses (loss of job, divorce, death in family)
Social and economic supports (WIC, AFDC)
Perception of growth failure as a problem
History of violence or abuse by or of caretaker
Review of systems/clues to organic disease
Anorexia
Change in mental status
Dysphagia
Stooling pattern and consistency
Vomiting or gastroesophageal reflux
Recurrent fevers
Dysuria, urinary frequency
Activity level, ability to keep up with peers

AFDC = Aid to Families and Dependent Children; WIC = Special Supplemental Nutrition Program for Women, Infants and Children.

diarrhea, etc) are especially important. The presence of fevers or other metabolic stresses should be assessed.

The physical examination of a child with malnutrition should be comprehensive, and findings therein can implicate both organic and socioeconomic causes of growth failure. The importance of accurate anthropometric measurements has already been stressed. Indeed, the pattern of growth failure itself is often indicative of whether genetic or environmental factors are to blame; genetically small children often maintain normal weight for height; have proportionately low weights, lengths, and head circumferences; and can grow parallel to but lower than the 5th percentile curve. Alternatively, children with caloric deprivation or malabsorption fall off their weight curves first, followed by length, followed by head circumference. They will therefore acutely show a deficit of weight for length and then more chronically a deficit of height for age. Figure 52-3 illustrates characteristic linear growth curves for children with intrinsic shortness, constitutional growth delay, and attenuated growth (as might be seen with caloric deprivation or gastrointestinal disease).

A critical aspect of the physical examination is an assessment of caregiver–child interaction, such as physical proximity, verbalization toward each other, and eye contact. Evidence of child neglect should be sought by paying attention to general hygiene, oral health, and the presence of diaper dermatitis. The possibility of organic disease can be evaluated by examination of all major organ systems. Table 52-5 gives a summary of possible findings on physical examination in children with growth failure, which should prompt further evaluation for underlying medical problems.

Unfortunately, the extensive differential diagnosis that can be engendered by the consideration of a child with poor growth (which Tunnessen compared to the index of any pediatric textbook[80]) can lead to excessive diagnostic testing. Sills's landmark study in 1978 succinctly showed the lack of utility of many laboratory tests in children with poor growth, especially given the psychosocial etiology of most cases.[70] In 185 children less than 3 years old admitted for evaluation of failure to thrive, only 36 of 2,607 laboratory tests performed (1.4%) were helpful in making a diagnosis, and all of these 36 positive results were suspected on clinical grounds. Berwick and colleagues also demonstrated the importance of a thorough history and examination over extensive testing.[21] Thus, a good history and physical examination are effective screening tools for the presence of organic disease, and laboratory testing should be minimized. Some basic screening tests may include complete blood count, blood urea nitrogen, albumin, erythrocyte sedimentation rate, lead concentration, and urinalysis. By no means is it necessary for all patients undergoing evaluation to be so tested. However, the diagnostic yield of screening tests of immigrant children and international adoptees with undernutrition is higher.[28–30,81,82] Current recommendations for the health care and screening of immigrant children and international adoptees are covered elsewhere.[28,29]

Another diagnostic tool often employed has been admission to hospital and evaluation of growth under supervision.[83] It is hoped that the combination of the provision of adequate calories and extraction from an unfavorable environment may lead to a rapid weight gain in patients with so-called nonorganic failure to thrive, whereas children with medical reasons for their poor nutritional status will be correctly identified. Unfortunately, once a child is hospitalized, the tendency to perform diagnostic tests often increases, which may, in turn, interfere with feeding the child (multiple consultants, tests requiring nil by mouth status, etc). As noted before, the average acute care hospital can also be described as a poor environment for adequate nutrition. Berwick and colleagues pointed out that weight gain or loss in the hospital did not distinguish between organic and psychosocial causes of poor growth, and it is unclear whether children with poor growth owing to social or environmental reasons will actually grow better when admitted than those with organic disease.[21]

TREATMENT OF GROWTH FAILURE

The treatment of malnutrition in children is obviously determined by the etiology of any underlying pathology, be it biologic, psychiatric, or economic. Rarely, simple dietary advice regarding correct formula preparation may be all that is needed to ensure adequate caloric intake. Much more likely is the need for a long-term treatment and follow-up plan, involving nutritional advice, behavioral modification, and social work intervention. As noted above, the multidisciplinary team approach to management has advantages and may even result in better nutritional outcomes for patients.[70,72–74]

Obviously, if a heretofore unsuspected medical illness is diagnosed, treatment of this underlying problem should proceed. However, nutritional aspects of the medical illness should not be ignored, given the well-recognized propensity of poorly nourished individuals to suffer more complications and higher mortality rates with many disease processes.[84] The relationships between nutritional status and specific disease states are explored in Section IV of this text.

Alternatively, if medical and nutritional assessments indicate that inadequacy of caloric intake is the etiology of the poor growth, primary nutritional therapy should be the treatment of choice. The pace and aggressiveness of nutritional repletion should be dictated by the degree of malnutrition, with mild cases most suitable for outpatient management.[85]

It has been recommended that to achieve adequate catch-up growth, calories be increased in proportion to the weight deficit. A general guideline for caloric requirements for infants with poor growth is

$$\text{kcal per kg required} = \text{RDA for age (kcal/kg)} \times \frac{\text{ideal weight for height}}{\text{actual weight}}$$

where ideal weight for height is the median weight for the patient's height (as read from the NCHS weight for height curves).

For example, a 3-month-old boy with a weight of 3.6 kg and length of 57 cm has the following anthropometric measures: weight-for-age z-score, –2.50; height-for-age z-score,

–1.55; and weight-for-height z-score, –2.11. In addition, assessment via the Waterlow classification shows that he is suffering from moderate acute malnutrition (weight for height = 74% of the median) and mild chronic malnutrition (height for age = 93% of the median). Because his RDA for calories is 108 kcal/kg/day and his ideal weight for length is 4.8 kg, his estimated caloric requirement for catch-up growth is (108 × 4.8)/3.6 = 144 cal/kg/d. Similarly, because his RDA for protein is 2.2 g/kg/day, his protein requirement for catch-up growth is closer to (2.2 × 4.8)/3.6 = 2.9 g/kg/day.

In mild malnutrition, therapy should center on ways to increase oral caloric intake in an outpatient setting. Com-

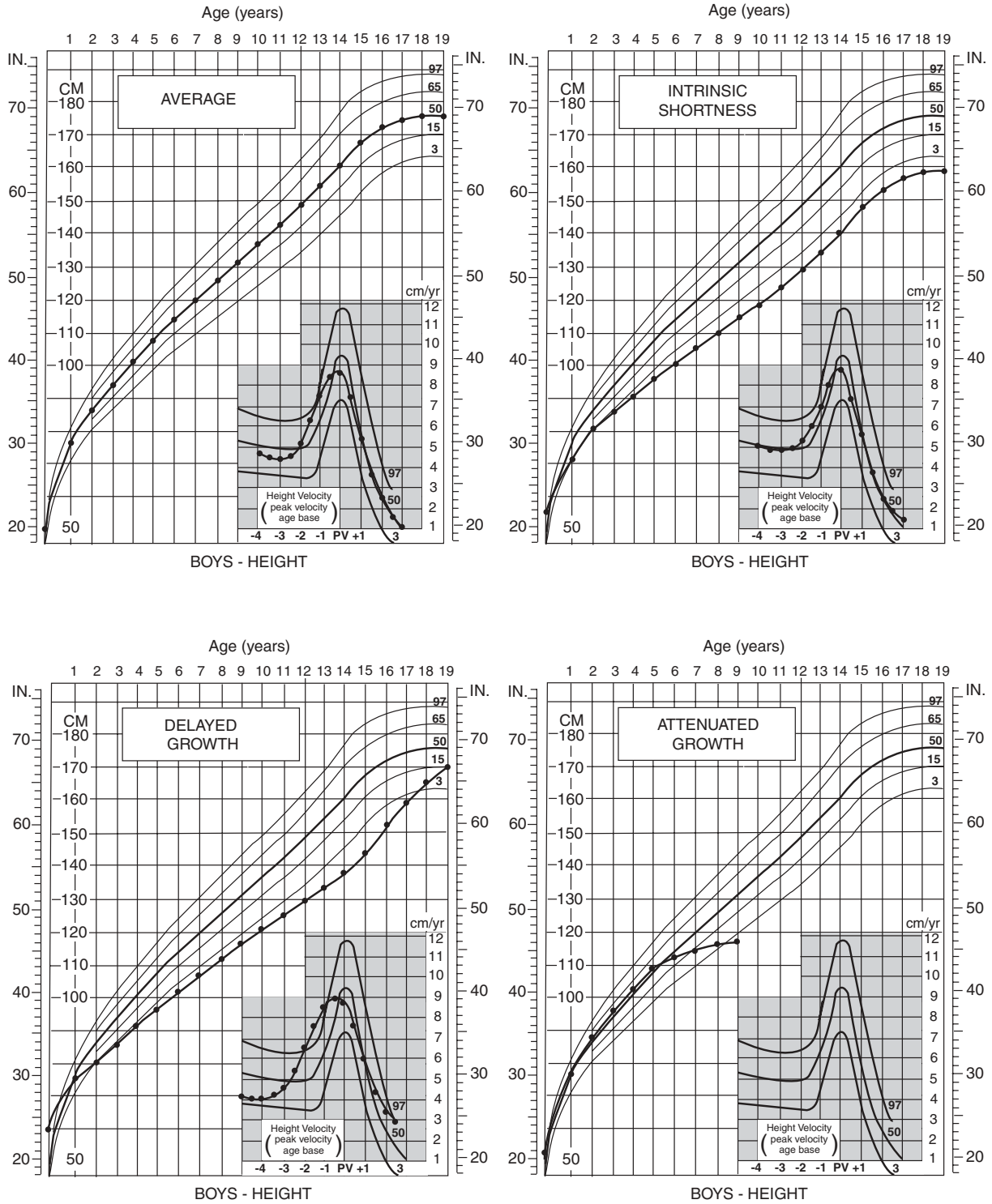

FIGURE 52-3 Linear growth curves (and height velocity curves, *insets*) of four different patterns of growth: average, intrinsic shortness, delayed growth, and attenuated growth. The last pattern is more characteristic of malnutrition. Adapted from Schaff-Blass E, Burstein S, Rosenfield RL. Advances in diagnosis and treatment of short stature, with special reference to the role of growth hormone. J Pediatr 1984;104:801–13.

TABLE 52-5 Physical Examination of Infants and Children with Growth Failure

	Abnormality	*Considerations*
Vital signs	Hypotension	Adrenal or thyroid insufficiency
	Hypertension	Renal disease
	Tachypnea/tachycardia	Increased metabolic demands
Skin	Pallor	Anemia
	Poor hygiene	Neglect
	Eccyhmoses	Abuse
	Candidiasis	Immunodeficiency
	Eczema	Allergic disease
	Erythema nodusom	Ulcerative colitis, vasculitis
HEENT	Hair loss	Stress
	Chronic otitis media	Immunodeficiency, structural orofacial defect
	Cataracts	Congenital infections, galactosemia
	Papilledema	Increased intracranial pressure
	Uveitis	Vasculitis
	Aphthous stomatitis	Crohn's disease
	Delayed tooth eruption	Delayed bone age
	Milk bottle caries	Neglect
	Thyroid enlargement	Thyroid disease
Chest	Wheezes	Cystic fibrosis, asthma
Cardiovascular	Murmur	Congenital malformations
Abdomen	Distention, hyperactive bowel sounds	Malabsorption
	Hepatosplenomegaly	Liver disease, glycogen storage, tumor
Genitourinary	Anomalies	Associated endocrinopathies
	Diaper rashes	Diarrhea, neglect
Rectum	Fistulae	Crohn's disease
	Empty ampulla	Hirschprung's disease
Extremities	Edema	Hypoalbuminemia
	Loss of muscle mass	Chronic malnutrition
	Clubbing	Chronic lung disease
Nervous system	Abnormal deep tendon reflexes	Cerebral palsy
	Developmental delay	Altered caloric intake or requirements
	Cranial nerve palsy	Dysphagia
Behavior and temperament	Uncooperative	Difficult to feed

Adapted from Collins J, Mezey AP. Failure to thrive. In: Shelov SP, Mezey AP, Edelman CM, Barnett HL, editors. Primary care pediatrics. Norwalk (CT): Appleton-Century-Crofts; 1984. p. 327–9.
HEENT = head, eyes, ears, nose, and throat.

monly, dietary supplementation with high-calorie foods and food additives is recommended to increase macronutrient intake. Infants may respond well to increasing the caloric density of their formula. For toddlers and children, the use of oils, sour cream, heavy cream, butter, peanut butter, and cheese as dietary additives is helpful. It may be necessary to work within the framework of the traditional food preferences and feeding practices of immigrant families and adoptees. For micronutrients, routine supplementation with a zinc- and iron-containing multivitamin is probably prudent, with the need for further iron therapy determined by laboratory values.

For some children, inpatient evaluation and treatment should be considered. Indications for hospital admission include (1) anthropometric evidence of acute or severe malnutrition, (2) evidence of child abuse or neglect, (3) significant dehydration, (4) significant mental illness in or substance abuse by the caretaker, (5) failure of outpatient management to achieve weight gain, and (6) a medical disorder requiring inpatient treatment or surgery.

A common error among hospitalized patients with growth failure is to underestimate their caloric requirements for growth because these can be quite high. Children recovering from severe malnutrition may gain weight safely on caloric intakes as high as 170 kcal/kg/day and protein intakes of 4 to 5 g/kg/day.[86] It should be noted that such extremes in caloric requirements are unusual in the average patient admitted for growth failure in the United States. It is also important to note that any calculations used to judge caloric requirements are merely estimates and that the sufficiency of any diet is proven by the occurrence of subsequent weight and, eventually, height gain. These parameters should be measured and charted graphically to allow assessment of the dietary intervention.

In addition to nutritional therapy, social evaluation to assess family dynamics and economic situation (eg, eligibility for state and federal assistance) should be performed. As mentioned above, visits to the home or other settings where the child receives care by a nurse or other appropriate personnel can also be enlightening in this regard. Regular outpatient and/or home visits should occur to document adequate weight gain and compliance with dietary management and to address any ongoing behavioral issues.

Behavioral modification should center on improving feeding techniques, removing conflict or struggles from mealtimes, reducing between-meal snacking or "grazing," and eliminating television and other distractions during mealtimes. Caregivers are encouraged to establish an eating routine with specific times, as well as a consistent setting and place for meals. It is also recommended that the duration of meals be limited to 30 minutes. Table 52-6 recounts a helpful schema in which three developmental stages of feeding disorders are described, with typical features of affected infants and caretakers. As noted, the approach to therapy will largely be determined by the type of feeding disorder and age of the patient.

PROGNOSIS

The ultimate growth potential of a child with growth failure is determined by a variety of factors, including genetic potential, the timing of malnutrition (intrauterine versus neonatal versus later infancy), and the severity of malnutrition (weight alone affected versus weight, height, and head circumference). The presence of underlying medical problems and their ability to be successfully managed are also important variables. Some premature infants fail to catch up

TABLE 52-6 Classification of Feeding Disorders in Infants and Children with Growth Failure

Disorder Type	*Age of Onset*	*Associated Medical Conditions*	*Features of Infants*	*Features of Caretakers*	*Treatment*
Homeostasis	0–2 mo	Limited experience with oral feeds (eg, respiratory distress)	Excitable; irritable; passive	Anxious; depressed; over- or under-stimulates infant	Pacifier during nasogastric feeds; occupational therapy re: suck and swallow
Attachment	2–6 mo	Prolonged hospitalization or separation from mother; developmental delay	Sad; hypervigilant; arches or resists when picked up	Detached; depressed; holds infant loosely	Emotional nurturance; developmental stimulation; education of caretaker re: needs of infant
Individuation or separation	6 mo–3 yr	Any condition that limits or restricts food intake (eg, diabetes, celiac)	Refuses food; defiant; plays with food	Frustrated; doesn't allow infant to self-feed	Regularly scheduled mealtimes; separate mealtimes from playtimes; encourage self-feeding

Adapted from Chatoor I, Dickson L, Schaefer S, Egan J. A developmental classification of feeding disorders associated with failure to thrive: diagnosis and treatment. In: Drotar D, editor. New directions in failure to thrive: implications for research and practice. New York: Plenum Press; 1985. p. 235–58.

normally. For instance, Kitchen and colleagues showed that in a cohort of children whose birth weights had been less than 1,500 g and who had weights or heights less than the 10th percentile at age 2 years, half were still less than the 10th percentile at age 8 years.[87] Casey and colleagues have shown that low birth weight premature infants demonstrated little catch-up growth in the first 3 years of life.[34,35] However, more recent studies have demonstrated that these children may demonstrate catch-up growth through childhood and even into adolescence, ultimately achieving predicted genetic height.[88,89] Another recent study compared adolescents born with an extremely low birth weight (ELBW, < 1,000 g) without significant neurodevelopmental disability with a matched group who had a normal birth weight.[90] It was found that those who were ELBW attained growth parameters within 2 SD of the mean, although they had smaller heights, weights, and head circumferences than their normal birth weight peers. The effect was most marked for those who were ELBW and small for gestational age. There were no significant differences in sexual maturation.

Long-term data on the growth of full-term children with a history of growth failure have been limited. In one cohort of 40 children who had been admitted for malnutrition, 17 (42.5%) had weights or heights below the 3rd percentile on follow-up after a mean of 3.4 years.[91] In another series of 30 children diagnosed before age 2 years, mean weights were 15% lower and mean heights were 5% lower than a control group in years 3 through 6 of life.[26] The interpretation of these types of studies is made difficult by biases introduced by patient selection and follow-up rate because patients requiring admission obviously represent a more severely affected spectrum of disease. Thus, not all children referred for growth failure are expected to suffer long-term growth problems.

The relationship between malnutrition in early infancy and subsequent intellectual and behavioral performance should also be commented on. As alluded to above and as further developed in Chapter 21, the human neurologic system continues to develop and grow postnatally, making environmental influences early in life crucial in any effort to achieve genetic potential. Studies from developing countries have clearly shown that children who were admitted early in life with protein-energy malnutrition had subsequently lower intellectual performance on standardized tests. Many of these studies, however, have been confounded by social and economic factors, which may also bear on ultimate intellectual function.

To help clarify the role of malnutrition per se in the genesis of developmental and intellectual delay, a classic study assessed the intellectual, motor, and social functioning of 41 patients who had suffered malnutrition in infancy.[92] Many of these patients had a history of cystic fibrosis, and none of the families had socioeconomic deprivation. Although controls scored higher than their previously malnourished siblings on intelligence testing at 2 to 5 years, this difference was not seen at later ages. Tests of motor development and social maturity were also similar between the two groups. Other more recent studies have supported the concept that appropriate psychosocial stimulation is important for cognitive development both early and later in the child's life.[93,94] How the generally milder degree of malnutrition seen in US children with growth failure impacts on subsequent cognitive, behavior, and emotional development is less clear.

PREVENTION

Because, in the United States, most causes of poor growth stem from or are complicated by social and economic adversity, amelioration of these conditions is the ultimate path to improved nutritional status of children. In the meantime, clinicians caring for these children should have an increased awareness of the medical and psychosocial factors that may predispose to growth failure, should classify such patients along the anthropometric guidelines mentioned above, and should recognize the benefits of multidisciplinary approach to difficult management situations.

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CHAPTER 53

PROTEIN-ENERGY MALNUTRITION IN THE HOSPITALIZED PATIENT

Susan Baker, MD, PhD

Growth depends on a constant supply of essential nutrients in sufficient amounts and proportions. Failure to thrive occurs when growth fails as a result of inadequate nutrition. Inadequate nutrition can be caused by inadequate intake, increased losses, or increased requirements. Often a complex relationship exists between the nutrient needs of a child and the ability of the environment in which the child lives to provide the needed nutrients, whether or not in increased amounts relative to normal. Nowhere is this interaction more dramatic than in the hospital setting. In the hospital, children are physically sick and are in a stressful environment where fear, loneliness, a sense of abandonment, loss of control, and pain contribute to the physical factors that increase the demand for nutrients. Yet many diseases are associated with anorexia. Nutritional status has an impact on general health, healing after trauma or surgical procedures, risk of developing infections, clearing infections, and the pharmacokinetics of drugs. These are important factors in treating patients, especially children, who require hospitalization.

Whether it is possible or even desirable for critically ill children to grow may be debated. Although many of the nuances of nutrition support remain to be clearly demonstrated, starvation is undesirable and leads to malnutrition, with associated comorbidities. It seems reasonable that careful attention to nutritional status, disease state, and the nutritional requirements of hospitalized children could improve outcomes during a hospital stay.

Table 53-1 summarizes the many factors that affect nutritional status and hence whether children thrive or fail to thrive when hospitalized.

NUTRITIONAL STATUS ON ADMISSION

The nutritional status on admission to the hospital is an important factor in whether a child thrives in the hospital. Children whose nutritional status is poor or places them at nutritional risk may have deficits that must be repleted before growth can commence.[1–5] These deficits may be long-standing and profound, such as osteopenia caused by malabsorption, and their repletion may not be feasable during a single hospitalization. Or the deficits may be of short duration and easily reversed, such as acute weight loss associated with infectious diarrhea in an otherwise healthy child. The nutritional status on admission to hospital is an important aspect of the patient assessment and sets the baseline for nutrition planning. Recognizing this, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires a focus on the provision of appropriate nutrition care in a timely manner.[6] JCAHO defines nutrition care for the hospitalized patient as consisting of the following process: (1) screening, assessing, and reassessing nutrition needs; (2) developing a plan for nutrition therapy; (3) prescribing or ordering food and other nutrients; (4) preparing and distributing or administering food and other nutrients; and (5) monitoring patient response to nutrition care.

The nutrition screen is generally conducted within 48 hours of hospitalization and determines the patient's need for a comprehensive nutrition assessment. Table 53-2 is an example of a nutrition screen. A nurse or diet technician can administer the nutrition screen. For patients who are determined to be at risk, that is, the probability exists that malnutrition is present or will develop, a full assessment and prescription for nutrition therapy are done by a

TABLE 53-1 Factors That Affect Nutritional Status in Hospitalized Children

Nutritional status on admission
Presence of a chronic disease
Acute medical condition
Infection
Trauma
Surgery
Diagnostic tests
Treatments
Drugs
Hospital environment
Staffing
Child

dietitian. For the screening tool identified in Table 53-2, a dietitian evaluates all children who have a BISON (Buffalo Integrated Scoring of Nutritional Status) score greater than 3, inappropriate growth velocity, presence of one of the chronic diseases listed in the table, or a serum albumin of 3.0 g/dL or less. Many children who enter the hospital enter in a poor nutritional state, often with a concurrent chronic disease. For example, between January 1, 2002, and June 30, 2002, 24% (range 15–32%) of the children admitted to the Children's Hospital of Buffalo were determined to be at risk by the nutritional screen. A dietitian then evaluates the at-risk children, a nutrition care plan is developed, and this plan is reassessed on a periodic basis during the hospitalization. The reassessment considers the appropriateness of the nutrition plan in light of disease progression or resolution, treatments, and diagnostic studies. This requirement by JCAHO appears to be a step forward in preventing the development or worsening of malnutrition during hospitalization. To date, however, no assessments of the nutritional status of children in the hospital have been performed and compared with data obtained prior to the implementation of the nutrition screen.

MALNUTRITION IN HOSPITALIZED PATIENTS

Surveys of hospitalized pediatric patients document that the prevalence of malnutrition ranges from 20 to 40%. Using anthropometric measurements, serum albumin levels, and lymphocyte counts when available, Merritt and Suskind demonstrated that one-third of all children older than 3 months in a large referral center exhibited evidence of acute malnutrition by Waterlow's criteria.[7–9] Half of these had second- or third-degree malnutrition; 55% exhibited chronic malnutrition. In addition, 9% of the patients had lymphocyte counts of less than 1.5×10^9/L and 6% less than 1.0×10^9/L. Of the 15 recorded serum albumins, 8% of the surveyed patients, 5 showed results of less than 3.5 g/dL. On a single day in 1992, Hendricks and colleagues resurveyed the Boston Children's Hospital patients, recording weight, height, serum albumin, and total lymphocyte counts.[10] They found the prevalence of acute malnutrition based on weight for height to be 24.5%, with 1.3% of the children demonstrating severe, 5.8% moderate, and 17.4% mild malnutrition. The prevalence of chronic malnutrition based on height for age was 27.2%, with 5.1% of the children demonstrating severe, 7.7% moderate, and 14.5% mild malnutrition. Fifty-four percent of the children had a serum albumin level recorded, and of those, 24% had a serum albumin level less than 3.0 g/dL. Sixty-six percent of the surveyed children had a lymphocyte count recorded, and of those children, 34.8% had a total lymphocyte count less than 1.5×10^9/L. The observations between 1979 and 1992 at the same institution show improved monitoring; 50% of the children had a serum albumin recorded in 1992 compared with 8% in 1979, and the prevalence of acute and chronic malnutrition was statistically less in 1992. For clinical purposes, however, the incidence of acute and chronic malnutrition remains high in children hospitalized at the same medical center.

In another large referral center, Cooper and colleagues studied 198 children with an age range of 0 to 22 years.[11] Anthropometric assessments were performed, and the degree of malnutrition was defined using McLaren and Read's criteria.[12,13] The overall prevalence of acute malnutrition was 54%, with 40% moderately to severely malnourished. If all infants less than 3 months of age were selected, the prevalence of acute malnutrition was 63%. Among infants requiring acute intensive care, 100% of all premature infants were malnourished, whereas 62% of term infants were malnourished. Among infants requiring chronic intensive care, 92% of premature infants and 43% of term infants were malnourished. Even infants requiring routine care were malnourished. Among the surgical population, 31% of children admitted for burns or trauma suffered from acute malnutrition, 39% of those admitted for elective procedures were acutely malnourished, and 64% of those admitted for acute but complex operative procedures were acutely malnourished. Data from two additional studies obtained on children on admission to the hospital show that the prevalence of malnutrition ranged from 15 to 32% and represented the nutritional status of children before hospitalization.[14,15] No attempt was made to correlate the presence of a chronic disease with nutritional status. Parsons and colleagues' study reassessed children after 14 days of hospitalization.[14] Only 12 of the patients who were initially studied remained in the hospital. Those patients, however, showed a significant decrease in triceps skinfold thickness, indicating that adequate nutrition was not being supplied. Biochemical values were also quantitated in this group of patients. Measurements of significance were low serum phosphorus and serum calcium concentrations in children more than 2 years old and low erythrocyte folate levels.

There is no information about hospitalized children and the effect that malnutrition has on the type and frequency of complications, length of hospital stay, or other adverse outcomes. But the serious consequences of malnutrition on adult hospitalized patients, beginning in 1935 with Studley's landmark study, are well documented.[16] Most recently, Naber and colleagues showed that patients who were malnourished on admission developed more complications during their hospital stay.[17] Patients who were more severely malnourished were more at risk than were less malnourished patients. Of interest, this study showed that confounding factors such as age, underlying disease, or severity of disease had an effect on the risk of complications developing in malnourished patients, and when these confounding factors were taken into consideration, the risk of complications decreased, although it remained high relative to nonmalnourished patients.

It is well established that primary malnutrition, that is, malnutrition caused by inadequate food intake and not associated with a disease process or surgical procedure, is associated with an increased mortality.[18–22] When coupled with an infectious process, which frequently occurs in malnourished children,[24] the risk of dying is increased further. Thus, it is likely that malnutrition has an adverse effect on children who are sick and malnourished.

TABLE 53-2 Sample Pediatric Nutrition Screen

Date_____ Time_____

Admission diagnosis _____

Feeding regimen prior to admission _____

Current diet order _____

Food allergies/intolerances _____

Admission Weight _____ kg _____ % Weight/Height _____%

Height _____ cm _____ % BMI _____ BMI _____%

HC _____ cm _____ % Birth weight _____

Weight change? [ ] Yes [ ] No If "yes," quantify _____

Acute or chronic condition affecting nutritional status (see below) _____

BISONS Complete for ages < 4 yr

	0 Points	*1 Point*	*2 Points*	
Weight for age	> 10th %	5–10th %	< 5th %	_____
Height for age	> 10th %	5–10th %	< 5th %	_____
Weight for height	> 10th %	5-10th %	< 5th %	_____
% Weight loss	None	< 5th %	≥ 5th %	_____
Crossing percentiles	None	1 curve	≥ 2 curves	_____
Add 1 point for chronic condition affecting nutritional status				_____
			BISON total score	_____

Nutrition education

Instruction needed [ ] Yes [ ] No
Goal for instruction
Plan/interventions
[ ] Routine care. Visit at mealtime. Follow-up in ____ days.
[ ] Diet technician's recommendations _____

[ ] Refer to dietitian for further assessment/recommendations.

Signature/Title_____

Acute or chronic medical conditions to be included in BISON Score

Acute medical conditions
[ ] Burns ≥ 10% body surface area
[ ] Gastroenteritis (emesis and/or diarrhea ≥ 2 days)
[ ] Pancreatitis
[ ] Other

Chronic medical conditions
[ ] Anorexia/bulimia
[ ] Celiac disease
[ ] Cystic fibrosis
[ ] Diabetes mellitus
[ ] Failure to thrive or malnutrition as a diagnosis
[ ] Food allergy/intolerance
[ ] Food aversion/refusal
[ ] HIV/AIDS
[ ] Inflammatory bowel disease
[ ] Inborn error of metabolism
[ ] Mechanical ventilation
[ ] Neoplastic disease
[ ] Oropharyngeal motor dysfunction
[ ] Renal disease
[ ] Serum albumin < 3.0 g/dL
[ ] Parenteral nutrition
[ ] Tube feeding
[ ] Other

AIDS = acquired immune deficiency syndrome; BISON = Buffalo Integrated Scoring of Nutritional Status; HC = head circumference; HIV = human immunodeficiency virus.

The costs that can be directly or indirectly ascribed to malnutrition in hospitalized children are unknown. Studies on adult hospitalized patients, as summarized by Tucker and Miguel and Smith and Smith,[25,26] show an increased length of stay and increased hospital charges for patients who are malnourished or at risk of becoming malnourished. These costs can be significant and when applied to the Children's Hospital at the Medical University of South Carolina amounted to $1.5 million annually in 1995 dollars.

DISEASES

A child who has a chronic disease that requires increased nutrient intake or is associated with decreased intake or increased losses on a long-term basis can enter the hospital with nutritional deficits that will likely require repletion before growth can occur. In addition to the repletion of deficits, any ongoing increased requirement will need to be met and ongoing losses replaced. It may be difficult or impossible to accomplish this during a hospitalization, especially because most hospitalizations are necessarily short. Children who are healthy but have experienced acute trauma, an elective procedure, or an acute illness present a less serious, but still important, requirement for attention to nutrition.

The actual ingestion of foods can be a problem for children with facial, oral, pharyngeal, or esophageal problems.[27–31] Central control of ingestion, mastication, and swallowing can interfere with the ability to take in enough nutrients, as can generalized muscular weakness or spasticity. Delays in the normal progression of feeding skills can occur, especially in children who have manifestations of delays in other skills.[32,33] Children who have been sick and required invasive procedures around their mouth, such as suctioning, nasogastric tubes, or endotracheal tubes, may become intolerant of oral stimulation and find feeding to be an aversive situation. Some children who have heart disease with a high oxygen requirement may simply tire before completing a feed or may have a limited ability to suck owing to anoxia or breathlessness.[34,35]

Vomiting, associated with reflux,[36] increased intracranial pressure, chemotherapy,[37] super mesenteric artery syndrome,[38,39] or volitional vomiting in older children, contributes to nutritional deficits. Disease of the gastrointestinal tract such as undiagnosed gluten-sensitive enteropathy, food allergy, inflammatory bowel disease, pseudo-obstruction, and even partial bowel obstruction can be chronic and result in inadequate nutrient retention. Loss of nutrients can also occur with rumination and cyclic vomiting. Acute causes of vomiting, such as obstruction or infections, are usually resolved in a short time and do not lead to chronic nutrient losses.

Nutrient losses also occur with diarrhea, malabsorption,[40] or protein-losing enteropathy.[41] The causes of malabsorption are many and generally involve one or more of three organs: the small bowel, the pancreas, and the liver. Any interference with the optimum functions of these organs can result in maldigestion and inadequate nutrient absorption. Problems of digestion and absorption are intrinsic to the organ itself, such as pancreatic insufficiency, cholestasis, or enteropathy. They are often long-standing and can have a severe impact on nutritional status.

Anorexia is a common occurrence in illness. Acute infections and injury are associated with the proliferation and release of inflammatory mediators such as cytokines, tumor necrosis factor, interleukins, and glucocorticoids.[42–47] These mediators are associated with anorexia, net protein breakdown, and liver anabolism. At the time of the initial infection or injury, muscle proteolysis may serve a beneficial function as a rapid source of amino acids for gluconeogenesis and liver synthesis of acute-phase reactants. Chang and Bistrian recently reviewed current understanding of the metabolic effects of individual mediators.[48] Cachexia and wasting syndromes occur in patients with a variety of serious illnesses. It is postulated that endogenous mediators of inflammation play a pivotal role in cachexia. Although the mechanisms of mediator action, interaction among mediators, and the interaction of mediators with tissues such as skeletal muscle, nervous tissue, and liver are unknown, it is likely that the endogenous mediators cause anorexia and ultimately the weight loss, low albumin, anorexia, and poor wound healing associated with severe chronic illness. Specific mediators proposed as agents in this process include tissue necrosis factor-α, interleukin-1 and -6, and interferon-γ. Currently, there are no anti-inflammatory treatments such as inhibitors, antibodies, competitive receptor binding proteins, or antisense molecules that have been shown to overcome the cachexia of chronic illness.[49] It is likely that nutrition support that is appropriately applied to critically ill patients can be beneficial in reversing protein loss and preventing the development of malnutrition. Cachexia caused by inflammation of chronic disease, however, has not been so readily reversed.

HOSPITAL-CENTERED PRACTICES THAT LEAD TO FAILURE TO THRIVE

General hospital practices, despite the best intentions, can hinder the provision of nutrition to ill children. For example, during times of financial crisis or nursing shortages, limited nursing staff may be available, the staff may be required to rotate among wards frequently, or temporary help who are not oriented to children may be employed. Knowledge of how long a child has been nil per os for diagnostic tests or treatments may be lost among the staff. Also, late food trays, incorrect formulas, child refusal to eat, and catering to specific child likes and dislikes may not be noted unless a calorie count is maintained.

DIAGNOSTIC TESTS

To understand disease and design effective treatments, diagnostic tests are required. For many of these tests, a child must not consume food for several hours prior to the test. Often scheduled tests are delayed, cancelled, or repeated, so the time a child cannot eat may be longer than anticipated. Diagnostic tests may be of considerable dura-

tion, during which time the child cannot eat. If a child requires several diagnostic tests over several days, the cumulative food intake can be very low.

TREATMENTS

Some diseases, such as a gastrointestinal obstruction, require that a child not consume food. When disease, surgery, or trauma makes it impossible to provide nutrition via the gastrointestinal tract, parenteral nutrition is an option. The use of parenteral nutrition, however, has declined over the past generation as the importance of the modulation of nutrients by the gastrointestinal tract became better understood, techniques to deliver nutrients were refined, and formulas were developed and improved to provide nutrients for different metabolic conditions. Other diseases, such as infectious diarrhea, do not routinely require food restriction, but it is not uncommon for "bowel rest," clear liquids, or other food restrictions to be inappropriately prescribed. For example, children with diarrhea are often made nil per os, given clear liquids, and then progress to a BRAT diet,[50–53] despite practice guidelines[54] and literature[55–59] that demonstrate the importance of emphasizing continued nutrition over the number or consistency of stools.

Children who have experienced significant trauma, have undergone surgery, or require care in an intensive care unit have specific nutrition needs that are best managed by a nutrition support service where dedicated nutrition professionals can frequently assess the nutritional status of the child and respond to the child's needs. Most often enteral or parenteral support is required. See Chapter 56, "Enteral Nutrition," and Chapter 57, "Parenteral Nutrition."

MEDICATIONS

A complicated interaction exists between medications and nutritional status. The relevance of this interaction to hospitalized children may be minimal or significant. The liver, gastrointestinal tract, and kidney are the organs primarily involved in drug metabolism.

Drug pharmacokinetics can be influenced by the route of drug administration; the absorptive anatomy and function of the gastrointestinal tract; the quantity of transport molecules; the ability of the liver to oxidize, reduce, and conjugate drugs; renal function; and the length of time the drugs are required. Drugs can alter nutritional status by inducing anorexia, changing the anatomy or absorptive physiology of the gastrointestinal tract, or altering liver and renal function. Specific nutrient deficiencies as well as general malnourished states can have differential effects on drug metabolism.

Drug metabolism in mildly to moderately malnourished children is not well studied. If drug metabolism is altered in mild or moderate malnutrition, the significance of the alteration is unknown. Although it is likely that mild to moderate malnutrition has important effects on some drugs, the effects may not be a serious concern for drugs that have a wide margin of safety. For drugs with a narrow therapeutic index, such as antineoplastic drugs, mild to moderate malnutrition may have important effects on their toxicity. Similarly, drugs that may be used repeatedly and for extended periods of time, such as acetaminophen, may present a cumulative risk for toxicity at a lower level than in well-nourished children.

Drugs affect the nutritional status of children. Many drugs, especially antineoplastic drugs, can cause anorexia, nausea, vomiting, and painful gastrointestinal disorders such as mucositis, diarrhea, and abdominal pain. Children receiving these drugs necessarily eat less and potentially have increased nutrient losses. These drug effects can contribute to the development or worsening of poor nutritional states and can be a cause of failure to thrive in themselves. Also, drugs can alter the absorptive capacity of the gastrointestinal tract by inducing achlorhydria, reducing pancreatic function, causing cholestasis, and damaging the absorptive surface of the small bowel. Through binding to transport proteins and direct effects on liver and renal function, drugs can alter nutritional status. Conversely, nutritional status can affect drug metabolism. Any nutrition-caused alteration in the gastrointestinal tract, such as vomiting, bacterial overgrowth, decreased motility, or altered absorptive surface area, can adversely affect drug absorption.[60] Transport proteins, such as albumin, may be low in malnourished states. For drugs that have a large fraction bound to proteins, an increase in plasma-free drug fraction may cause variation in response or toxicity.[61]

The hepatic CYP450 superfamily of enzymes oxidizes drugs. The expression of enzymes in this superfamily varies among individuals and is affected by nutritional status. Markers of hepatic oxidative metabolism, such as antipyrine and acetanilide,[62–64] show increased half-life and decreased clearance of the marker, suggesting that malnutrition decreases hepatic oxidative metabolism. Similarly, using such markers as chloramphenicol,[65] acetaminophen,[65] isoniazid,[66] and sulfadiazine,[65] conjugation of drugs was shown to be decreased in malnourished states. The impairment can result in decreased clearance and increased elimination half-life of some drugs. This altered

TABLE 54-3 Nutritional Status and Drug Metabolism

Decreased intake
Vomiting
Anorexia
Painful mucosal lesions
Increased losses
Vomiting
Diarrhea
Decreased absorption
Altered small bowel anatomy
Decreased binding proteins
Decreased solubulization
Decreased gastric acid
Bacterial overgrowth
Altered metabolism
Decreased transport proteins
Decreased liver biotransformation
Oxidation
Conjugation
Reduction
Altered renal excretion

metabolism could lead to greater drug exposure and may influence drug toxicity or efficacy. See Chapter 14, "Drug Therapy and the Role of Nutrition," for further discussion.

CHILD-CENTERED FACTORS

Even if there are no impediments to a child receiving good nutrition during a hospitalization, there are many reasons why a child may not consume enough food. The child may be frightened and anxious, may need to exert control, or may exhibit oppositional behavior. Age-related eating behaviors or strong food dislikes, needing a special chair or plate, or disruption of the child's feeding schedule may contribute to inadequate intake. Careful attention to child-centered needs, such as provided by a child life program, pediatric trained nurses and physicians, and, when necessary, child psychologists, can help children overcome these issues.

SUMMARY

Many factors conspire to make the provision of adequate nutrition to hospitalized children difficult. These factors include the child's environment, the child's state of health, diagnostic and treatment requirements, and the child's developmental stage and mind-set. The importance of nutrition to hospitalized children is recognized, and efforts to overcome the many difficulties inherent in providing nutrition to sick children are ongoing.

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CHAPTER 54

EVALUATION AND MANAGEMENT OF OBESITY

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Worldwide, nutrition-related problems are increasing at an alarming rate. Trends in morbidity and mortality are shifting away from infectious diseases to nutrition-related diseases. By the end of the twentieth century, the cycle of poverty and undernutrition has worsened in some countries, whereas that of overnutrition has reached epidemic levels.[1,2] The notion of "nutrition transition" has been developed to describe the unique dietary and nutritional changes that accompany economic and sociodemographic changes in the world.[3,4] Currently, the prevalence of overnutrition and related complications is such that it is considered the most important nutritional problem globally.

DEFINITION

Any definition of obesity is useful only if it predicts medical disability or complications. Because most medical complications of obesity are associated with body fat and not muscle mass, measures of obesity represent an attempt to estimate the adipose compartment. Furthermore, most definitions of obesity represent an attempt to identify those individuals who are at risk for developing medical problems because of excess body fat.

At present, there is no precise clinically practical method to measure body fat in children and adolescents. Methods used to define obesity generally measure under- or overweight, not lean or fat. Therefore, an athlete with increased muscle mass may be classified as overweight but may not have excess body fat. Conversely, a child with an endocrine disorder that results in muscle wasting and excessive body fat may be classified as not overweight but may have an unhealthy proportion of fat tissue. Thus, measures that rely on body weight are imperfect, but they are inexpensive and practical for use in the clinical setting and in epidemiologic studies.

A variety of methods have been developed for measuring the adipose compartment directly. They include underwater weight measurements, dual-energy x-ray absorptiometry, magnetic resonance imaging, computed tomography, and stable isotope methods. These methods have recently been reviewed elsewhere[5,6] and are important for studies requiring accurate measures of adiposity but are generally too cumbersome or expensive for routine clinical use. Skinfold thickness measurements can be performed easily in a clinical setting but are imprecise. Bioelectric impedance analysis may be a reasonable compromise as it is considerably less expensive than the other direct measures of adiposity mentioned above but provides a measure of body fat with a level of accuracy that is generally acceptable for clinical and public health purposes as long as appropriate standards are available.[5,7]

Traditionally, in the United States, obesity has been defined as weight for height above the 90th percentile on the National Center for Health Statistics (NCHS) growth charts or excess weight above 120% of the median for weight given the child's age, height, and gender. More recently, body mass index (BMI), defined as the weight of the child in kilograms divided by the height in meters squared (kg/m^2), has been established as a useful standard measure of adiposity. Although BMI does not directly measure body fat, it is typically used to evaluate adiposity in adults and has been recognized as a useful predictor of adiposity in children and adolescents, which, in turn, also predicts risks for present or future medical complications of obesity.[8] BMI in children is not only correlated with other predictors of body fat but also with blood pressure,[9,10] lipid levels,[11,12] and insulin levels.[13]

Typically, BMI is not constant during childhood and adolescence and differs by gender (see BMI charts in the Appendix). Therefore, researchers who study changes in BMI should account for age and gender or for standard deviations of BMI (BMI z-scores). As reviewed elsewhere, BMI also depends on pubertal stage, reflecting disproportionate gains in fat-free compared with fat mass.[14] In addition, there is some evidence that BMI varies with ethnicity.[15] Therefore, in addition to age and gender, pubertal stage and ethnicity should be taken into account in studies involving BMI.

In 2000, the Centers for Disease Control and Prevention (CDC) established new growth charts using data from the NCHS in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. These growth charts do not include data from the past decade because of the sharp rise in BMI during that period. Recognizing that the BMI of children and adolescents tends to predict obesity and related complications in adulthood, the CDC has also suggested specific nomenclature for the pediatric age group: subjects above the 85th percentile are

considered "at risk for overweight" and those above the 95th percentile are considered "overweight." Use of the term "overweight" rather than "obese" reflects the fact that the weight status of the adolescent may still improve before he or she reaches adulthood; thus, the overweight adolescent may not face the medical risks conferred by the term "obesity" in adulthood.

Most industrialized countries and countries in economic transition are experiencing a trend toward increasing obesity but at different rates, so creating definitions appropriate for international use is challenging but important. Following suggestions from the European Childhood Obesity Group and the practices of the NCHS, an International Obesity Task Force (IOTF) agreed on standard cutoff points to identify degrees of overweight among children and adolescents in both developed and developing countries. The IOTF has compiled data from six large data sets in various countries, allowing for more relevant international comparisons.[16] These data provide age- and gender-specific cutoff points for children aged 2 to 18 years. The 85th percentile on the IOTF standard charts, defining children and adolescents "at risk for overweight," also corresponds to a BMI of 25 kg/m^2 by age 18, the adult definition of "overweight." The 95th percentile on the standard chart, defining children and adolescents as "overweight," corresponds to about 30 kg/m^2 by age 18 years, the standard adult definition of "obesity."

EPIDEMIOLOGY

Relevance and Significance

Presently, one in five children in the United States is at risk for overweight, and 14% of children and adolescents in the United States are overweight (above the 85th and 95th percentiles for age and gender, respectively, based on the new CDC standards). Since the 1960s, the prevalence of obesity has tripled. Similar but more gradual trends are seen worldwide. Determining the specific causes of this rapid increase in rates of obesity is clearly essential, yet remarkably complex. Both genetic and environmental factors have been shown to contribute significantly to this problem. In general, genetic factors explain a large part of the variation of body weight within a given population in a common environment, whereas environmental factors tend to explain changes in obesity over time in that population. The study of Pima Indians provides an important example of the interaction between environmental and genetic factors.[17] The Pima Indians who live in the Southwestern United States are predisposed to obesity and diabetes, and these traits assort in patterns, indicating genetic inheritance. The genetically similar Pima living as subsistence farmers in Mexico are substantially less obese. Genetic factors clearly explain a large part of the obesity among Pima Indians in this country, whereas environmental factors explain the dramatic difference in rates of obesity between the two Pima populations.

Epidemiologists have used cohort studies and case-control designs to determine which environmental factors may contribute to obesity. Such studies have pointed to dietary trends, sedentary lifestyle, decreases in structured physical activity, psychosocial stressors, and cultural trends as likely contributors to the obesity epidemic.[3] A number of dietary factors have been proposed to play important roles. These include the easy availability, high caloric content, and strong marketing techniques of the fast-food industry, as well as general trends toward consumption of foods that are highly processed and contain high carbohydrates and/or total calories (including sugary beverages) and decreased consumption of fiber and low-density foods. Other factors include decreases in structured physical activity, particularly for children, as well as decreasing lifestyle activity (occupations and transportation require less movement than in the past) and increasing sedentary activities (particularly television viewing and computer use). However, it is important to note that, to date, no single factor among these has been shown to play a pivotal role in the increasing prevalence of obesity.

Obesity and Related Complications

A large body of evidence supports an association between obesity and important risk factors for cardiac disease and type 2 diabetes. Hyperinsulinemia, dyslipidemia, obesity, and hypertension often cluster together and are termed the "metabolic syndrome," "syndrome X," or "insulin resistance syndrome."[18,19] More recently, these findings have also been shown to be closely associated with nonalcoholic fatty liver disease, such that fatty infiltration of the liver is now often considered part of the metabolic syndrome.

The mechanisms underlying the association between these endocrine abnormalities and disease affecting diverse organ systems are the subject of ongoing research. There is support for the concept that an increased ratio of visceral to subcutaneous adipose tissue, perhaps acting through adipocyte-derived hormones such as resistin and leptin and through substrates such as circulating fats, leads to insulin resistance and high circulating levels of insulin.[20,21] Many adults with obesity display all of the elements of the metabolic syndrome, but there are some striking exceptions, even among those with severe obesity. For example, a multicenter study using clamp techniques in a group of obese adults showed that 26% of participants aged 18 to 85 years with a BMI > 25 kg/m^2 and 60% of those with a BMI > 35 kg/m^2 were insulin resistant. The frequency of hyperinsulinemia was 41% in participants with a BMI > 25 kg/m^2 and 77% in participants with a BMI > 35 kg/m^2.[22]

Similar clustering patterns have been found in children. Studies in children have shown a relationship among fasting insulin and lipids,[23–25] blood pressure,[25–28] weight,[29] and BMI.[30–32] As in adults, body fat distribution is also correlated with cardiovascular risk factors.[33,34] Berenson and colleagues showed that blood pressure, lipid levels, and BMI were positively correlated with aortic and coronary atherosclerosis at autopsy in both children and adults (2–34 years), suggesting that the metabolic syndrome starts before adulthood.[35] Using data from the Bogalusa study of cardiovascular risk factors,[36,37] Tershakovec and colleagues showed that the expression of the hypercholesterolemia in children precedes the expression of increased

body fat and that insulin and blood pressure subsequently rise as the children grow older and body fat increases.

Although there are many similarities between the findings of the metabolic syndrome in children and adults, it is important to recognize that children have a different hormonal milieu than adults, especially during puberty. All children become more insulin resistant at the time of puberty compared with either before or after puberty.[38] Increased body fat and BMI correlate strongly with fasting insulin levels and insulin resistance and have been proposed as potential mediators of the pubertal changes in insulin resistance.[39–42] However, insulin resistance can also occur during puberty in the absence of changes in BMI, coinciding with a period of rapid growth during puberty.[40] Interestingly, insulin resistance appears to oppose further weight gain in adults but may not have the same effect in children. Adults with lower insulin levels are more likely to gain weight, whereas higher insulin levels in children may predict weight gain, at least in studies either adjusted for obesity[42] or in populations in which obesity is rare.[43] However, in one study of obese children, childhood insulin resistance decreased the risk of obesity in adulthood,[44] suggesting that the difference in findings may depend on the weight class of the population studied.

In addition to hyperinsulinemia associated with the metabolic syndrome, frank type 2 diabetes is becoming increasingly common in children. The Third National Health and Nutrition Examination Survey (NHANES III) estimated a prevalence rate of 0.13% for type 2 diabetes and 1.76% for impaired glucose tolerance among a representative sample of US adolescents. Obesity increases the risk for diabetes substantially: in a study of obese adolescents, 4% had silent type 2 diabetes and 25% had impaired glucose tolerance.[45] The prevalence of type 2 diabetes is particularly high in children in people of non-European origins.[46] It has been estimated to be 3.6% among adolescent North American Indians[47] and 5.9% among Pima Indian adolescents.[48] In Ohio, type 2 diabetes accounted for 33% of all cases of diabetes among black and white adolescents, representing a 10-fold increase in the incidence of type 2 diabetes this past decade in Cincinnati.[49] Risk factors for type 2 diabetes include obesity, family history of diabetes, female gender, acanthosis nigricans, and nonwhite ethnicity.

Other consequences of obesity seen in childhood are sleep apnea, nonalcoholic steatohepatitis, cholelithiasis, pseudotumor cerebri, gastroesophageal reflux disease, polycystic ovary disease, and orthopedic problems, including Blount disease and slipped capital femoral epiphysis (Table 54-1). In addition to these complications, obesity in adults is associated with debilitating or life-threatening degenerative problems (axial arthritis and cardiovascular and cerebrovascular disease),[50,51] as well as with increased risk of certain neoplasias (breast, ovarian, prostate, and colon cancers).[52]

Tracking

"Tracking" describes the risk for a disease state persisting over time. In the case of obesity, there is a moderate risk of childhood obesity persisting into adulthood, and that risk increases if the child stays overweight as he/she grows older (Figure 54-1). Moreover, the child's risk for having obesity in adulthood also depends on the weight status of the parents. Whitaker and colleagues showed that the rate of obesity in adulthood ranged from 8% for children aged 1 and 2 years old without obese parents to 79% for adolescents aged 10 to 14 years old with at least one obese parent.[53] Before 3 years of age, the primary predictor of obesity in adulthood was the parents' obesity status, and the child's obesity status was not an important indicator of the risk of adult obesity. By contrast, after 7 years of age, the child's own obesity status became the more important predictor of his/her risk for adult obesity.

Obesity in childhood thus confers a higher risk of obesity in adulthood. Moreover, adults who were obese in childhood have a greater risk of morbidity and mortality, independent of their BMI in adulthood, family history of cardiovascular diseases or cancer, and smoking.[54,55] In the Harvard Growth Study, overweight adolescents were shown to have an increased risk for developing obesity-related medical problems in adulthood, including cardiovascular disease and diabetes, compared with adults with more recent onset of obesity. Furthermore, overweight boys had an increased risk of coronary heart disease, atherosclerotic cerebrovascular disease, colorectal cancer, and death from all causes.[54] Likewise, Sinaiko and colleagues showed that weight gain during childhood and adolescence predicts cardiovascular risk in young adults.[26]

Heritable Factors

Studies of twins and adoptees provide useful estimates of the role of heritable factors in determining an individual's body weight (see Bouchard's 1997 summary of relevant papers on heritability).[56] Adoption studies tend to generate the lowest heritability estimates (30%), whereas twin studies provide the highest heritability estimates (70%). The variability in these estimates of heritability depends in part on definitions of obesity: more severe obesity tends to have a greater heritability factor than lesser variations in BMI.[57] Such analyses are consistent with the "thrifty genotype hypothesis,"[58] in which genes predisposing to energy conservation were preserved as a survival characteristic in former times of famine but become a liability in environments with plentiful food and low required physical activity.[57] Possible mechanisms through which genetic polymorphisms can translate to differences in body weight regulation are discussed below.

Imprinting

Several decades ago, Hales and Barker showed that poor fetal and infant growth is associated with an increased risk for type 2 diabetes and other elements of the metabolic syndrome and proposed that poor nutrition early in life imprints permanent changes in glucose and insulin metabolism.[59] This concept of "fetal programming," also known as the "Barker hypothesis," has now been supported by numerous studies in other populations. It has also been extended to include the possibility that postgestational

TABLE 54-1 Prevalence of Diseases Associated with Obesity in Children

Disease	*Prevalence*	*Study Population*
Endocrine		
Type 2 diabetes	0.13%	Community, 10–19 years old; *n* = 2,867[175]
Fasting blood sugar > 110 mg/dL	1.76%	
Impaired glucose tolerance	21–25%	Obesity clinic, 4–18 years old; *n* = 167[45]
Polycystic ovaries	45% of oligomenorrheic girls, 9% of girls with regular menses	Community, all ninth grade girls (*n* = 2,249)[176]
Gastrointestinal		
Gallstones	0.6%	Pediatric inpatients[150]
Fatty liver (elevated aminotransferases)	10%	Community, obese, 12–18 yr (*n* = 332)[177]
Fatty liver (elevated aminotransferases)	20%	Obesity clinic, 2–18 yr (*n* = 72)[178]
Gastroesophageal reflux disease	22%	Community, 14–17 yr (*n* = 449)[179]
Constipation	25%	Obesity clinic, 2–18 yr (*n* = 80)[180]
Encopresis	15%	
Orthopedic		
Slipped central femoral epiphysis	0.01% (50–60% of patients are obese)	Community[181]
Blount disease	Prevalence not well established	
Respiratory		
Sleep apnea	1.6% (4.5-fold higher risk if obese)	Community; children[182]
Sleep apnea	5%	Obesity clinic[183]
Asthma	8.9% nonobese, 14.9% obese	Community[184]

influences can participate to create a "thrifty phenotype."[60] For example, a study of adults in Finland showed that the development of type 2 diabetes mellitus was associated with low birth weight followed by accelerated gain in height and weight during childhood and with high maternal BMI.[61] Similarly, a study of adults in England showed that accelerated weight gain in early childhood added to the effect of low birth weight on the risk of high blood pressure in adulthood.[62] Indeed, populations in transition from conditions of low to high nutrition may be at the greatest risk for such obesity-related complications because of the combination of fetal undernutrition and childhood overnutrition.[63]

Other studies show that the effect of birth weight on future risk is directly related to the intrauterine environment rather than to genetics, distinguishing the concept of a "thrifty *phenotype*" from that of the "thrifty *genotype*." In a study of the effects of wartime famine in Holland, infants exposed to famine in utero had higher rates of obesity and diabetes in adulthood compared with a genetically similar cohort not exposed to famine, and this effect was largely independent of birth weight.[64] Furthermore, the timing of the famine exposure during gestation appeared to have important effects as fetuses exposed to famine during the first trimester of gestation were more severely affected than those exposed later in gestation. The mechanisms underlying the observed associations, including the contributions of maternal hyperglycemia, insulinemia, and postnatal growth to the development of later complications, are an important subject for future studies.

BIOLOGY

Regulation of Body Weight

Both animals and humans have a strong tendency to maintain a stable body weight over time, owing to a close but sometimes imperfect matching of energy intake with energy expenditure. Animal studies in which energy

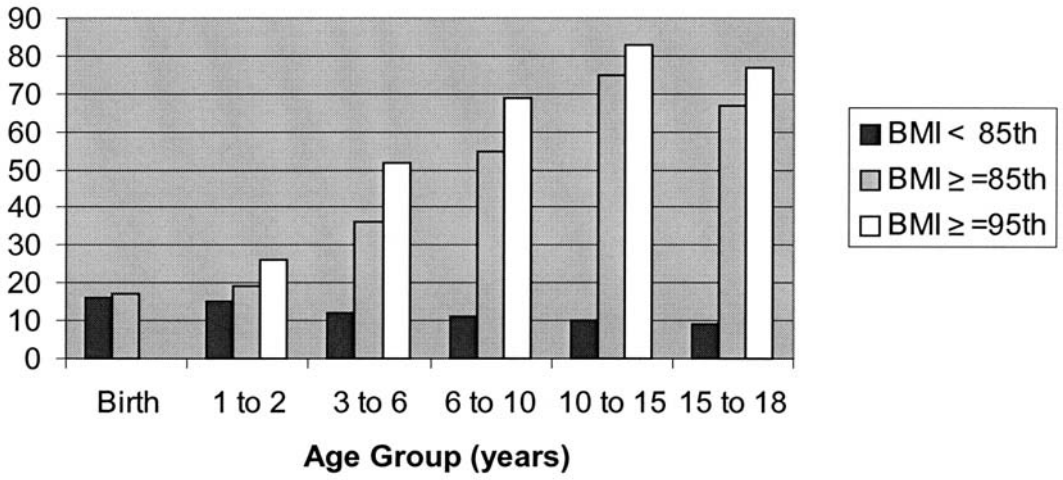

FIGURE 54-1 Percentage of children who will become obese adults. Adapted from Whitaker WC et al.[53] BMI = body mass index.

intake is manipulated reveal powerful influences from homeostatic mechanisms defending body weight. Similarly, the poor long-term results of weight reduction therapies in humans (about 95% of adults regain all weight after dieting) suggest that there are mechanisms that defend a highly individualized "set point" for body weight. When an individual has a heritable or acquired susceptibility to positive energy balance, superimposed on these native homeostatic mechanisms, he or she has a tendency to become obese.

Animal models of obesity have been invaluable in establishing an understanding of the complex mechanisms regulating body weight. Our growing understanding of these pathways is likely to lead to better-targeted interventions, both pharmacologic and behavioral. This is an area of vigorous ongoing research; the major elements of the pathways as we currently understand them are outlined below.

Afferent Pathways Circulating insulin, which reflects recent nutrient intake and metabolic demands, is an important regulator of nutrient partitioning in peripheral tissues and also communicates to centers regulating appetite in the brain. Peptides (such as cholecystokinin) secreted by the gastrointestinal tract in response to intraluminal nutrients and plasma concentrations of the macronutrients themselves also provide independent signals to the central nervous system, affecting short-term appetite and satiety.[65] For a discussion of the role of these nutrients as molecular signaling agents, see Chapter 23, "Energy and Substrate Regulation of Obesity."

Ghrelin is a peptide secreted by the stomach that is an important short-term mediator of appetite. Its name is derived from its ability to stimulate growth hormone release from the pituitary, but it also stimulates appetite through specific receptors in the ventromedial hypothalamus. Ghrelin is released from the stomach during periods of fasting and is suppressed by nutrient administration.[66] The specific stimulants of ghrelin release are not clear, but volumetric stretching of the stomach wall has no effect. A recent report shows that ghrelin is suppressed in humans who lose weight after gastric bypass surgery but not in the setting of weight loss through caloric restriction.[67] These findings suggest that ghrelin may be the mechanism for the appetite-suppressing effect and high success rates of gastric weight loss surgery.

Leptin is an important regulator of body fat, first identified in 1994 through studies of the leptin-deficient obese mouse.[68] It is produced primarily in adipose tissue and provides feedback to specific receptors in the ventromedial hypothalamus, an important center for regulation of appetite and energy expenditure. The leptin signal decreases appetite, increases both voluntary and resting energy expenditure, permits fertility,[69] and even activates central "reward" pathways that may, in turn, affect appetitive behavior.[70] The leptin-deficient animal or human therefore has hyperphagia and decreased thermogenesis and physical activity, all of which are reversible by leptin administration.

The central mechanisms through which leptin exerts these diverse effects have been partly elucidated through studies in other animal models. Animals with defects in the leptin receptor (the diabetes mouse and Zucker rat) predictably have phenotypes indistinguishable from leptin deficiency itself.

Central Nervous System The leptin signal activates a network of regulatory neuropeptides in the central nervous system. The anatomy of this network is the subject of ongoing research, but many important elements have been described. Some of the neuropeptides are orexigenic (favoring energy intake); others are anorexigenic (inhibiting energy intake). In general, leptin-generated signals tend to inhibit the orexigenic peptides and to stimulate the anorexigenic peptides, thus decreasing appetite. The network also participates in leptin's effects on the reproductive system and energy expenditure (Figure 54-2).

The melanocortin pathway is among the most important links downstream of leptin. Leptin appears to directly increase expression of pro-opiomelanocortin (POMC), which is cleaved by prohormone convertase to α-melanocyte-stimulating hormone (α-MSH),[71] as well as β-endorphin. α-MSH, in turn, stimulates the melanocortin-4 receptor (MC4-R),[72] a potent inhibitory influence on the lateral hypothalamus. Meanwhile, leptin also directly inhibits the expression of agouti-related protein, which opposes α-MSH action at the melanocortin receptors. The melanocortin pathway appears to be a particularly important regulator of body weight homeostasis because it exhibits less redundancy than other leptin-related pathways (eg, neuropeptide Y); an interruption in the melanocortin pathway can produce severe obesity, as seen in the agouti mouse.

Leptin also decreases appetite through melanocortin-independent pathways. It inhibits the expression of the orexigenic agent neuropeptide Y while increasing expression of cocaine- and amphetamine-related transcript (CART). In addition to decreasing appetite, CART has actions on the paraventricular nucleus of the hypothalamus and spinal sympathetic preganglionic neurons, where it affects energy expenditure via the autonomic nervous system (see Figure 54-2).[73]

Efferent Pathways This leptin-responsive network of neuropeptides in the hypothalamus acts on effector pathways in the cerebral cortex, pituitary-adrenal axis, and autonomic nervous system. Most signals regulating appetite and satiety meet in the nucleus tractus solitarius in the medulla, where they are further modulated by afferent signals from the autonomic nervous system. The pituitary-adrenal axis mediates leptin's effects on fertility and likely also affects energy expenditure. Indeed, adrenalectomy prevents the development of obesity in most animal models.[74]

Efferent signals to regulate energy expenditure are integrated in the locus ceruleus, from which the sympathetic nervous system stimulates lipolysis in white adipose tissue and mediates processes that facilitate voluntary energy expenditure and heat generation. Genetically engineered

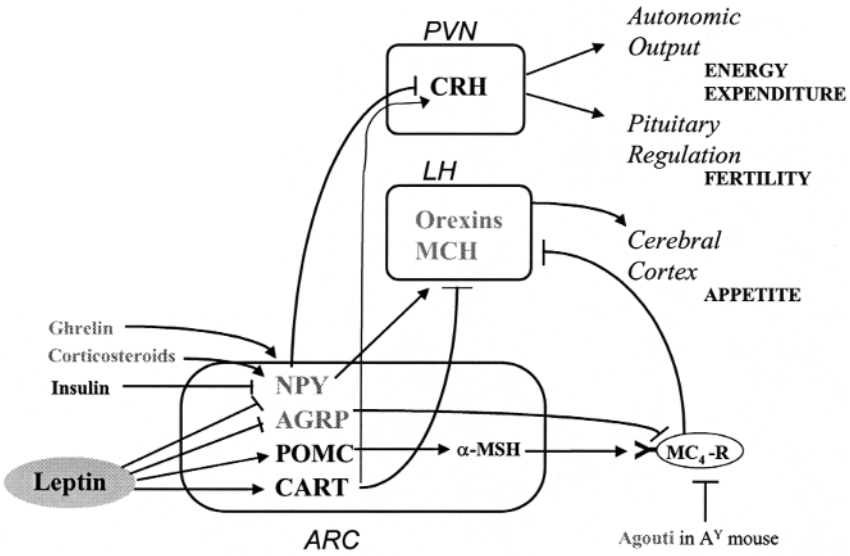

FIGURE 54-2 Central nervous system pathways regulating appetite and energy metabolism. Leptin positively regulates proopiomelanocortin (POMC) while negatively regulating agouti-related protein (AGRP)-releasing neurons in the arcuate nucleus (ARC) of the hypothalamus. POMC is a precursor of α-melanocyte-stimulating hormone (α-MSH), which is an antagonist at the MC4 receptor (MC4-R). AGRP and agouti protein are antagonists at MC4-R. The MC4-R pathway negatively regulates appetite, perhaps acting through appetite-stimulating neuropeptides in the lateral hypothalamus (LH), including melanin-concentrating hormone (MCH) and the orexins. Meanwhile, leptin has some actions that are independent of the POMC pathway, including negatively regulating neuropeptide Y (NPY), itself a potent appetite stimulant. Ghrelin also appears to act to stimulate appetite through the NPY pathway.[185] NPY also influences autonomic and pituitary output through the paraventricular nuclues (PVN), acting in part through corticotropin-releasing hormone (CRH).

animal models have clarified some elements of these effector pathways. Animals in which uncoupling protein in brown adipose tissue is knocked out have increased body fat and decreased thermogenic response to food.[75] A knockout of the β-3 adrenergic receptor has a similar phenotype, suggesting that these elements of the sympathetic nervous system are involved in increasing energy expenditure to match energy intake.[76] Parasympathetic efferent signals through the vagus nerve increase insulin secretion in the pancreatic beta cells and may be a mechanism for the hyperinsulinemia in some groups of obese people.[20]

In addition to these autonomic processes, energy expenditure has a "voluntary" component (5 to 50% of total energy expenditure, depending on the level of exercise)[77] and a component of "fidgeting," or nonexercise activity thermogenesis (NEAT). NEAT has been proposed as a genetically determined system of protection from obesity and may also be mediated by the sympathetic nervous system.[78]

Genetics of Obesity

Exploration of the genetic determinants of body weight can be done in several ways, each offering different insight and limitations. Candidate gene approaches focus on specific genes and pathways that prior studies have shown are likely to be important in producing a phenotype. Each of the neurohormones described above, as well as their receptors and the enzymes responsible for processing, can be considered a candidate gene with potential importance in the regulation of body weight. Association studies use a case-control design to assess the association between variations in genotype and obesity phenotype. This technique lends itself to testing of several polymorphisms in candidate genes within a population; however, it is also prone to substantial false-positive and false-negative results, depending on sample size. Such studies therefore are most reliable if similar gene associations can be demonstrated in several different populations. Linkage studies rely on genome-wide scans of large populations to assess the strength of the association between variations in a genomic locus and the phenotype. This technique does not rely on a priori assumptions about the biologic significance of a particular gene and is therefore important in identifying new areas for inquiry. However, it also has relatively low sensitivity and can easily overlook linkages that are common contributors to less extreme phenotypes (eg, common genes predisposing to moderate degrees of obesity). A complete list of published linkages to obesity phenotypes is summarized yearly.[79]

Any of the genes encoding a component of the mechanism for regulating body weight homeostasis, including those mentioned above, could be considered a "candidate gene" for a predisposition or resistance to obesity. Specific mutations in a few of these genes have been shown to cause obesity in rare kindreds. Mutations with strong effects were found in the leptin gene,[80] the leptin receptor gene,[81] the *POMC* gene,[82] the prohormone convertase gene (*PCSK1*),[83] and the MC4-R.[84] The latter is the most common gene in which specific mutations cause obesity, but it is still very rare (27 mutations in 68 individuals published by 2001).[85]

Association studies have analyzed many other candidate genes from the afferent and efferent pathways mentioned above in genetically similar populations (siblings, twins, or kindreds). By 2001, polymorphisms linked to

58 candidate genes had been shown to have some association with obesity phenotypes,[85] including ghrelin,[86] peroxisome proliferation–activated receptor gamma,[87] uncoupling proteins,[88] and the β-3 adrenoreceptor genes.[89]

Linkage studies in large populations have identified many chromosomal loci with associations to a variety of obesity-related phenotypes, including BMI, leptin levels, fat distribution, and hyperlipidemia. Thirty-three such loci have been identified as of the 2001 gene map update,[85] some of which appear to represent the chromosomal regions of previously identified candidate genes such as the leptin or MC4-Rs. For many other regions or quantitative trait loci, the biologic mechanisms for the apparent linkage with obesity phenotypes remain unclear.

A number of human genetic syndromes displaying mendelian patterns of transmission and whose phenotype includes obesity have been identified and catalogued in the Online Mendelian Inheritance in Man (OMIM) database.[90] Twenty-five of these syndromes have been mapped to one or more chromosomal locations. The most common syndrome with severe obesity is Prader-Willi syndrome (short stature, hyperphagia, hypogonadotropic hypogonadism, cognitive defecits), mapped to chromosome 15q 11-13, a region containing several candidate genes for which a mechanistic explanation for the Prader-Willi phenotype is being sought.[85] The Bardet-Biedl syndrome requires a mutation at one of six loci plus an additional mutation in a second locus[91] and includes polydactyly and retinopathy. Alström syndrome (obesity, retinopathy and deafness, no cognitive deficits)[92] and Cohen syndrome (hypotonia, retinopathy, and cognitive deficits)[93] have been mapped to one location each, but no obvious candidate genes have been identified.[85] Each of these syndromes has characteristic findings, as outlined in Table 54-2 and in the OMIM database,[90] and can usually be distinguished from common obesity by a careful medical history and physical examination.

EVALUATION

Medical Assessment

The initial step for the assessment of the overweight child is to exclude potential associated syndromes or endocrinopathies and to diagnose possible associated complications, as summarized in Table 54-1. Several syndromes associated with obesity should be considered, including the mendelian syndromes mentioned above. Obesity may also accompany the more common, easily recognizable syndromes of trisomy 21 and Turner. In most cases, these syndromes can be distinguished on the basis of their unique features (listed in Table 54-2 and in some excellent recent reviews,[94–96]) and specific laboratory testing is valuable for confirmation but not for screening. The assessment of medical conditions related to overweight (see Table 54-1) has also been summarized elsewhere.[97]

The value of screening laboratory testing has been debated[98] but can be useful to establish whether there is dyslipidemia, steatohepatitis, or evidence of glucose intolerance, particularly as specific treatments for some of these disorders are increasingly considered.[99,100] Blood testing should be done in a fasting state if practicable. Thyroid-stimulating hormone, hemoglobin A_{1C}, total cholesterol, very-low-density lipoprotein, low-density lipoprotein, high-density lipoprotein, aspartate aminotransferase, and alanine aminotransferase (ALT) have been recommended to screen for possible hypothyroidism, diabetes, dyslipidemia, and steatohepatitis, respectively. Fasting glucose and insulin levels will provide information on carbohydrate metabolism and insulin resistance and may predict a

TABLE 54-2 Characteristics of the Major Syndromes Associated with Obesity

Syndrome	*Cognitive Deficit*	*Obesity*	*Features*
Albright's[96]	Mild	Variable (general), early onset	Neuroendocrine anomalies, normal or short, skin hyperpigmentation/vitiligo, polydactyly, bone fibrous dysplasia, precocious puberty
Alström[186]	None	Moderate (central), onset age 2–5 yr	Retinitis pigmentosa, deafness, neuroendocrine anomalies, normal or short stature, normal or hypogonadism
Bardet-Biedl[95]	Moderate	Moderate (central), onset age 1–2 yr	Normal or short stature, hypotonia, compulsive behavior, retinitis, heart anomalies, polydactyly, renal dysfunction, hypogonadism
Carpenter[187]	Mild	Central	Acrocephaly, polydactyly, syndactyly, short stature, flat nasal bridge, high arched palate, heart anomalies, hypogonadism
Cohen[94]	Mild	Variable (central), midchildhood	Short or tall stature, hypotonia, microcephaly, retinochoroidal dystrophy, short philtrum, low hairline, heart anomalies, normal or hypogonadism
POMC mutation[82] (autosomal dominant)	None	Early onset	Red hair, ACTH deficiency, hyperphagia
Prader-Willi[188]	Mild to moderate	Moderate to severe (generalized), onset 1–3 yr	Short stature, hypotonia, almond-shaped eyes, V-shaped mouth, neuroendocrine anomalies, compulsive behavior, high arched palate, hypogonadism

ACTH = adrenocorticotropic hormone; POMC = pro-opiomelanocortin.

risk for diabetes. Specific guidelines to screen for type 2 diabetes in overweight children have been developed (Table 54-3) but are also controversial because of the large number of adolescents fitting the screening criteria (currently about 2.5 million in the United States) and the relatively low yield of the suggested screening tests.[101] Serum levels of vitamin E have been shown to be low in about 30% of obese children but return to the normal range with multivitamin supplements, so empiric treatment, rather than specific blood testing, is probably appropriate.

Further laboratory testing may be useful in selected cases but can be expensive, and some tests are not readily available. Sleep studies can and should be performed if there are strong clinical symptoms of sleep apnea, and radiographic evaluation is necessary when slipped capital femoral epiphysis or Blount disease is suspected. Indirect calorimetry can be used to predict the energy deficit necessary for weight loss.[102] This might be especially useful when poor compliance or an eating disorder is suspected and at times may be useful to provide concrete caloric goals to support dietary changes. Bone age may be helpful in supporting the diagnosis of an endocrinopathy. Consultations with specialists in sleep disorders, neurology, otorhinolaryngology, pulmonology/allergy, endocrinology, genetics, ophthalmology, and surgery may be necessary to manage specific complications. Involvement of specialists in nutrition, physical therapy, behavior therapy or psychology, psychiatry, and social work can be valuable in forming specific treatment plans.

The medical history should include assessment of concomitant medical diseases for their potential to contribute to weight gain (such as a history of significant head trauma or hypothalamic dysfunction) and to identify barriers to treatment (factors limiting mobility or ability to be physically active). A variety of drugs used for the treatment of psychiatric disease, epilepsy, diabetes, and migraines are associated with weight gain. Identifying these as a likely trigger of weight gain may prompt consideration of alternate drugs (Table 54-4).

TABLE 54-3 American Diabetes Association Guidelines for the Assessment of Type 2 Diabetes in Children with Overweight or Obesity

Children and adolescents should undergo specific testing for diabetes if they are:

Overweight, as defined by
- BMI > 85th percentile for age and sex, or
- Weight for height > 85th percentile, or
- Weight > 120% of ideal (50th percentile) for height, and

Have at least two of the following risk factors:
- A family history of type 2 diabetes in first- and second-degree relatives
- Belong to one of the following specific race/ethnic group
  - American Indians
  - African Americans
  - Hispanic Americans
  - Asians/South Pacific Islanders
- One or more of the following signs of insulin resistance or conditions associated with insulin resistance
  - Acanthosis nigricans
  - Hypertension
  - Dyslipidemia
  - Polycystic ovary syndrome
- Testing should consist of either
  - Fasting plasma glucose (8-hour fast), or
  - Oral glucose tolerance test (blood glucose level 2 hr post challenge)
- Further study is called for to determine the predictive value of Hgb A_{1C} and fasting insulin levels in determining risks for type 2 diabetes in children.

Adapted from American Diabetes Association.[49]

Nutritional Assessment

Nutritional evaluation should include, at a minimum, anthropometric measurements and a history of the onset of obesity, as well as of weight loss attempts. Periods of adiposity rebound and potential triggers for excess weight gain should be identified. Family history of obesity and related medical problems should be evaluated to help establish the genetic factors underlying the weight disorder and of the potential future medical risks. Assessing dietary intake by recalled food frequency helps to identify diet composition but, in most cases, does not provide a good estimate of energy intake as under-reporting of food intake by obese subjects is well described.[103] In particular, estimating the proportion of each macronutrient and fiber in the diet may help identify targets for dietary change if the diet is particularly skewed toward fat- or energy-dense foods. In addition, the diet recall may be useful to assess the diet for deficiencies in micronutrients, particularly calcium and vitamins A and E, betacarotene, folic acid, and other B vitamins; excessive energy intake does not always mean adequate intake of micronutrients.

To establish possible areas for intervention, the amount and type of dairy products, fruits, vegetables, and legumes should be evaluated, and particular attention should be given to the consumption of sugary beverages, including juices and soda. Excessive consumption of sugary beverages has been associated with excess weight gain and increased rate of obesity[104] and is an early target for dietary change. Similarly, the frequency of use of fast-food restaurants and other restaurant meals should be examined as these meals often contain excessive caloric content. The diet history should also determine usual meal patterns, with attention to whether there is regular skipping of meals, binge pattern of eating, and the social context of meals, particularly if there are routine family dinners.

Finally, the potential role of exercise and sedentary behaviors should be evaluated, with particular attention to determining the frequency of television and computer use. Several studies have suggested specific causal effects of television viewing on obesity,[105] and the American Academy of Pediatrics recommends limiting television viewing to 1 or 2 hours per day.[106] Assessment of lifestyle exercise, in the form of outdoor play or regular walking (eg, walking to school), is as important as assessing structured exercise, such as participation in sports programs.

Behavioral Assessment

The psychosocial complications of obesity are often subjective and difficult to measure in a standard fashion but undoubtedly represent one of the greatest burdens of obe-

TABLE 54-4 Selected Drugs Associated with Weight Gain

Drugs with Weight Gain Potential	*Alternatives with Less Potential for Weight Gain*
Atypical antipsychotics[189,190]	
Clozapine ++++ (gain 4–12 kg)	Quetiapine
Olanzapine ++++	Ziprasidone
Risperidone ++	
Mood stabilizers[191,192]	
Divalproex sodium +++	Lamotrigine (weight neutral)
Lithium +++ (10 kg over 6–10 yr)	Adjunctive topiramate (6% of weight lost at 1 yr)
Tricyclic antidepressants[191,193]	
Amitriptyline ++	
Imipramine ++	Desipramine
Nortriptyline	
Monoamine oxidase inhibitors[191,194]	
Phenelzine > isocarboxazid	Tranylcypromine
Selective serotonin reuptake inhibitors[195]	
Paroxetine ++ (3.6% gain at 6 mo; 25% of patients gained more than 7% of body weight)	
Sertraline +	Fluoxetine
Atypical antidepressants[196]	Buproprion (weight loss)
Anticonvulsants[197]	
Valproate +++ 10–60% of patients gain weight; average gain 8–20 kg[198]	Zonisamide Topiramate (weight loss)[199] 50% lose > 5 lb
Carbamazepine ++ 15 kg /3 mo	
Gabapentin ++ (23% gained > 10% of weight)	
Antidiabetic agents	
Insulin +++ (average 4 kg over 10 yr)[200]	Metformin (2–3 kg weight loss over 6 mo)[201]
Thiazolidinediones ++ (2–5 kg gain)[201]	

sity in children and adolescents. In many cases, psychosocial issues are best understood as consequences of the disease, brought on by feelings of discouragement and criticism by family, peers, or self. In other instances, the psychological issues precede or exacerbate the obesity. Regardless of the causality, it is important to acknowledge and assess these behavioral and psychological issues in each individual to best target treatment.

Depressive symptoms,[107,108] anxiety,[109,110] binge-eating disorder,[111–114] decreased self-esteem[115–117] and problems with social interactions[118,119] have generally been found more frequently in obese children and adolescents than in their lean peers. Negative psychosocial outcomes also persist into early adulthood, when obesity is associated with lower educational attainment and household income and lower rates of marriage, independent of baseline education and aptitude.[120,121] Many of these consequences can be attributed to the widespread and culturally entrenched bias against obese individuals in our current society.[121,122]

Optimal assessment of the psychosocial issues contributing to and stemming from obesity in a particular patient has not been established and varies greatly between centers and providers. Whether or not standardized instruments are used, some effort should be made to assess mood, motivation, school and social performance, self-image, and eating attitudes and behaviors. It is also important to assess these issues in parents or close caretakers of the patient as factors such as motivation, mood disorders, and eating disorders in a parent will have a substantial impact on the child's attitudes, behaviors, and ability to respond to treatment.[119] The family's financial resources and level of cognitive stimulation in the household also predict the development of obesity[123] and may also affect the family's ability to respond to treatment. A "stages of change" model may be helpful in establishing the readiness of the patient and family for making lifestyle changes (Table 54-5). If the patient or family is in an early stage of change (precontemplation or contemplation), efforts should be focused on helping them forward into the next stage, perhaps using motivational interviewing techniques.

TREATMENT

Nutritional Therapy

Long-term studies of nutrition and exercise interventions for prevention of pediatric obesity are sparse and generally inconclusive. However, studies with short and moderate lengths of follow-up have shown benefits from a variety of "lifestyle" interventions, including nutritional education (in 3- to 9-year-old school children),[124] exercise, and measures to decrease sedentary activity.[125] All of these interventions have some effects in specific settings, although similar interventions in different settings failed to show an effect.[126–128] These studies are the subject of several recent reviews.[6,129,130] Most such studies target a school-based population and do not include the family in the intervention. The interpretation of such studies is hampered by high attrition rates, lack of standardization in definitions of obesity and treatment techniques, and limited generalizability.

There is better information available about treatment interventions for preadolescents and adolescents with established obesity, but the majority of studies still do not provide long-term data, and many issues, such as optimal macronutrient composition of diets and strategies to change food preference, have not been adequately studied. A few studies have suggested that structured exercise increases weight loss compared to diet alone,[131,132] and treatments focusing on increasing lifestyle exercise and reducing sedentary behaviors have also shown beneficial effects.[133–135] In general, regimens that combine hypocaloric diets with exercise and behavior modification have been particularly effective.[134–136] Epstein and colleagues have shown a medically significant long-term effect of an 8-month family-based behavioral intervention for families with children 6 to 11 years old. The improvement persisted 10 years after the intervention was completed.[137] The design of this study supports the conclusion that the behavioral intervention was a critical component of the success.

Typically, dietary recommendations for adults and children with obesity have consisted of reduction in dietary fat and energy intake as a balanced, hypocaloric diet. Recommendations have been developed by the American Academy of Nutrition as summarized in the *Pediatric Nutrition*

TABLE 54-5 Stages of Change

Precontemplation
Unaware of, denies, or minimizes the problem
Needs: encouragement to re-evaluate current behavior; encouragement of self-exploration, NOT action; provide information, personalizing the risks
Contemplation
Aware of the problem, ambivalent about change
Needs: gentle confrontation, information and rationale for change, clarification of any misinformation
Preparation
Has decided to make change, plans to do so within the next month or is gathering information
Needs: assistance in identifying and overcoming obstacles; assistance to identify social supports; encouragement to take small initial steps
Action
Plan is in progress; attitudinal and behavioral changes have begun
Needs: tools and techniques to implement goals, positive reinforcement; support to deal with obstacles and losses, focusing on long-term benefits
Maintenance/relapse
Action maintained over 6 months (maintenance) or return to old habits (relapse)
Needs: self-monitoring tools for successful maintenance, feedback and encouragement; stress management; use of support systems

Adapted from Prochaska J et al.[202]

handbook[138] and are similar to those supported by other governmental agencies, as described in a recent review by Ikeda and Mitchell.[139] The goal of the intervention is to reach a healthy weight without affecting linear growth. Specific recommendations include limiting beverages and foods with high caloric density and low nutritional value, including sugary beverages, full-fat or low-fat baked goods and candies, and encouraging whole grains, fruits, and vegetables. Simple behavioral measures such as meal planning and label reading during grocery shopping are also generally encouraged to support the implementation of these nutritional guidelines.

The "traffic light diet" provides a structured, balanced, hypocaloric diet in a simple format and has been used effectively for preadolescent[132,137] and preschool children.[140] It uses a simple color-coding scheme to categorize foods into categories for free consumption (low-density foods, green), moderate consumption (moderate-density and protein-containing foods, yellow), and very limited consumption (foods with high caloric density and/or with high sugar or fat content, red). The prescribed caloric content of the diet is generally between 900 and 1,300 kcal daily.

The protein-sparing modified fast diet (PSMF) provides high-quality lean protein while strictly limiting total calories. It has been used to treat severe obesity in a variety of settings, including hospitalized patients and school-based interventions. This diet has been effectively used in settings where short-term weight loss is medically necessary, but there are no data to suggest that it reliably improves obesity in the long term. The principles of this diet are described in Table 54-6 and have been reviewed elsewhere, with sample menus.[141,142] Typically, patients start with a hypocaloric diet for 2 weeks before the PSMF diet is started (1,200 kcal/day); the PSMF diet continues for about 12 weeks (600–800 kcal/day) and is followed by a maintenance diet (balanced, 1,200 kcal/day). Of note, Figueroa-Colon and colleagues reported an 11.2 kg weight loss after 10 weeks of a PSMF diet, substantially more than that achieved by less restrictive measures, but by 15 months follow-up, the weight loss achieved by the two groups was similar.[143]

Although the caloric content of a diet has been shown to relate to treatment success at 1 year,[144] to date, there is little evidence to suggest that alterations in specific macronutrients yield long-term weight reduction. A variety of popular diets have arisen around alterations of specific macronutrients, with or without limitations on total caloric intake. Many of these show good short-term weight loss, but whether these diets achieve long-term effects on obesity is unclear as no adequate long-term studies (with 5 or more years of follow-up) of these diets in representative adult or pediatric populations have been published. Freedman and colleagues reviewed the available evidence of benefits and risk associated with popular diets in adults.[145] Diets that specifically limit fat intake, popularized by Dean Ornish, were the subject of a recent review of studies with 6 to 18 months of follow-up.[146] The authors of that review conclude that fat-restricted diets are no better than calorie-restricted diets in achieving long-term weight loss in overweight or obese people.

Several dietary approaches have focused on limiting carbohydrates, with (as in the "Zone" diet) or without (as in the Atkins diet) restrictions on fat intake. Careful analysis reveals that in the short term, low-carbohydrate diets cause a greater loss of body water than body fat. If the diet is maintained in the long term, it results in the loss of body fat. There are few long-term data regarding the overall efficacy of these low-carbohydrate diets. High-fat, low-carbohydrate diets such as the Atkins diet are nutritionally inadequate and require supplementation of calcium and water-soluble vitamins.[145]

Caution should be used when considering the results of studies such as these that focus on adult populations because there is compelling evidence that at least some "lifestyle" approaches to obesity are substantially more effective in children than they are in adults.[147] Some dietary

TABLE 54-6 Protein-Sparing Modified Fast Diet

High-protein, hypocaloric diet for 12 weeks:
600–800 kcal
Protein 2 g/kg/d (maximum 100 g/d; approximately 50% of calories)
13–20 oz/d lean meat or substitute
Fat approximately 30–40% of calories
Carbohydrate 10–20% calories
As low-starch vegetables, may include one fruit
Ad libitum: tea, bouillion, pickles, spices, mustard
2 L of water per day
Supplements
Multivitamin with minerals
Elemental calcium supplement to meet Recommended Daily Intake
Monitor serum potassium and supplement as needed
Maintenance diet (36 wk)
Balanced macronutrients
1,200 kcals/d

Adapted from Suskind RM et al.[141]

approaches might prove to have long-term results in children even if none can be demonstrated for adults. Diets that include a low glycemic index/load approach or higher consumption of calcium are currently under investigation[104,148] and will require long-term study before any useful conclusions can be drawn. A trial of increasing the fiber content of a hypocaloric diet in children yielded no better short-term results than a hypocaloric diet alone.[149] Medical guidance is important as there are ongoing concerns about medical complications, including dyslipidemias arising from the use of some popular diets and from the use of dietary supplements for weight loss, including in children. As many as 80% of children using unsupervised diets from popular magazines had medical problems resulting from these diets.[139]

As the rates of obesity rise, obese children represent an increasing proportion of hospital inpatients.[150] Whether or not the child is hospitalized for an obesity-related condition such as gallstones, diabetes, sleep apnea, or orthopedic problems, their nutritional needs must be considered. It is particularly important to recognize that the obesity is a chronic problem and will not resolve by attempting weight loss acutely during the inpatient stay. Moreover, acute severe caloric restriction is inappropriate and can lead to metabolic problems, including refeeding syndrome, despite the child's adequate energy stores. Guidelines for nutritional care of the obese adult inpatients have been developed,[151] but this issue has not been examined in children. It may be appropriate to prescribe a modest reduction in caloric intake, guided by indirect calorimetry or by calculations based on adjusted body weights and using a stress factor that is appropriate to the child's condition (see Appendix). The inpatient stay may also present an opportunity for nutritional education and for engaging the patient and family in a therapeutic plan to address the obesity beyond the hospital stay.

Behavior Therapy

As discussed above, some interventions in childhood have demonstrated long-term improvement of obesity with 5[152] or 10 years[137] of follow-up; thus, children appear to have a more consistent and durable response to therapy than adults in the same family[147] or adult populations in general. The importance of including behavior therapy in the treatment of obesity in children has been demonstrated, at least in a family-based setting.[153] Although many interventions use combinations of dietary, exercise, and behavioral interventions, it is notable that the few studies with long-term results have had a rigorous and structured behavioral component.[136]

Commonly used techniques include self-monitoring of food intake and weight, modeling, positive reinforcement (praise), contingency management (certain behaviors are paired with predictable, reinforcing responses), and stimulus control (learning to avoid situations that are cues to overeat). Some studies have tested specific elements of these behavioral techniques. These have shown superiority of family-based over patient-focused treatment,[137] of gradual behavioral treatment (eight sessions over 15 weeks) over rapid behavioral treatment (eight sessions over 4 weeks),[154] of positive reinforcement over restrictive or critical approaches,[135] and of frequent (daily) over less frequent (weekly) positive reinforcement.[155] The value of problem-solving techniques has not been consistently shown.[156,157] Thus, there is ample evidence to support the use of behavioral modification techniques in the treatment and possibly the prevention of obesity in children. Behavior therapy should be thought of as a tool to achieve long-term changes in diet and exercise. By contrast, there are few data to support the use of behavior "micromanaging" techniques such as rate of eating and bite size.

Weight Loss Drugs

Many of the drugs used for the treatment of obesity in adults in the past are characterized by unproven claims, highly variable efficacy, or dangerous side effects. Nonetheless, the incomplete but growing understanding of the mechanisms underlying the homeostatic control of body weight and the increased rigor applied to clinical drug trials hold promise for the development and use of pharmacologic agents to treat this chronic disease. In the short term, drugs can be important for a patient whose medical condition requires acute weight loss. Drugs may also have a role in treating the chronic component of obesity. Modification of the environmental and societal pressures contributing to obesity should always be thought of as an important ultimate goal, but the use of drugs to promote weight loss may keep an individual patient engaged in the "lifestyle" component of treatment and might even change some of the consumer pressures that contribute to our obesity-promoting environment. Thus, pharmacotherapy for obesity is not at odds with lifestyle-changing approaches. As increasingly specific drugs are developed, efficacy and safety improve, and pharmacotherapy may ultimately be an essential tool to treat an otherwise refractory and devastating disease. Whether pharmacologic treatment is cost-effective depends in large part on whether it prevents the medical complications of obesity and associated costs of medical care.

Current options for the pharmacologic treatment of obesity are limited but may have some clinical utility in adults and adolescents. In general, the drugs demonstrate only modest efficacy but minimal side effects. Sibutramine (Meridia) is an appetite suppressant that has been the subject of extensive clinical trials and was approved by the US Food and Drug Administration (FDA) for use in adults with obesity in conjunction with a dietary regimen. It is an inhibitor of both norepinephrine and serotonin reuptake and also weakly inhibits dopamine reuptake. At doses of 10 or 15 mg daily, combined with a reduced calorie diet, modest weight loss is achieved in most patients (loss of 5 to 8% of baseline weight compared with 1 to 4% of weight on placebo),[158–160] but the range of weight loss varies greatly. Weight loss is sustained for most patients as long as the drug is continued (up to 3 years observation periods reported)[161] but generally is regained after the drug is discontinued. Side effects include modest increases in blood pressure (2 mm Hg average) and heart rate, dry mouth, constipation, and insomnia. Most side effects are

transient and lead to discontinuation of the drug in about 5% of patients.[160] Importantly, no evidence of valvular heart disease such as that associated with fenfluramine treatment has been found in rigorous studies. Metabolic abnormalities associated with obesity, including hyperlipidemia and insulin resistance, tend to improve commensurate with weight loss.

Orlistat (Xenical) is the only FDA-approved drug that reduces nutrient absorption. It acts by inhibiting gastrointestinal lipases, reducing fat digestion and absorption. Predictably, its side effects are related to fat malabsorption, consisting of steatorrhea when high-fat meals are taken and decreases in serum levels of fat-soluble vitamins, primarily vitamin D.[157] Daily administration of a multivitamin is therefore recommended. Modest weight loss (3.2% more than placebo)[162] is generally achieved, and sustained use partially prevents weight regain during a second year of treatment.[163] Orlistat and sibutramine are currently approved by the FDA for short-term use (up to 1 year). Long-term studies (up to 5 years) of these drugs in adults are in progress.

A few other drugs have been tested in preliminary phases in children and adolescents. Metformin improves insulin sensitivity and also promotes modest weight loss in adults.[164] By contrast to other antihyperglycemic agents, metformin does not increase insulin secretion but decreases hepatic glucose production and improves insulin sensitivity in both diabetic and nondiabetic adults.[165] Small open-label trials of metformin have suggested that it may be useful in ameliorating psychotropic drug-induced weight gain in children.[166] A small randomized trial of metformin in adolescents with hyperinsulinemia and a family history of diabetes showed improved glucose tolerance and a modest decrease in BMI.[167]

The safety and effectiveness of weight loss drugs in adolescents and children have not been established. Large multicenter randomized placebo-controlled trials of sibutramine and orlistat in adolescents are in progress, as are smaller randomized trials of metformin and ephedrine-caffeine. Careful review of these results will be necessary before pharmacotherapy outside clinical trials can be recommended in adolescents or children.

Based on current literature, the modest weight loss achieved by the use of current available drugs in conjunction with reduced-calorie diets is probably not adequate to treat individuals with severe life-threatening complications of obesity, but the drugs may be useful to boost weight loss, assist weight loss maintenance, and reinforce lifestyle change. Whether phenotypic or genotypic analysis can be used to select for patients who respond relatively well to these agents is a subject for future study.

Phentermine, diethylproprion, phendimetrazine, and benzphetamine are noradrenergic agents with appetite-suppressant effects but are studied and approved for short-term use only (generally 12 weeks or less).[157] The latter two drugs are considered to have some potential for abuse and are listed on Schedule III of the Drug Enforcement Agency. The use of any agent with only short-term goals for weight loss in children and adolescents, particularly one with any potential for abuse, is highly questionable.

Dietary "supplements" or herbal medicines are popular, and consumers spend more than 1 billion dollars on these products annually in the United States. However, they are unregulated and relatively untested. The commonly used herbal supplements are listed in Table 54-7. Supplements that could be used with caution in adults include conjugated linoliec acid, ginseng, chromium, hydroxy citric acid, dehydroepiandrosterone (DHEA), hydroxymethyl butyrate, chitosan, and St. John's wort, but there is little evidence of the effectiveness for these drugs. Substances that have questionable safety and should be discouraged include Ephedra (or ma huang), horsetail, herbal laxatives, and some forms of caffeine and fiber.[168,169] To our knowledge, there are no studies of dietary supplements and weight loss in children, and no supplements for weight loss can be recommended or even considered with caution.

Weight Loss Surgery

Over the past 15 years, surgically induced weight loss has emerged as an important option for adults with severe obesity. In contrast to poor long-term success rates for nonsurgical treatments of obesity, surgical approaches generally produce durable and substantial weight loss. Over 80% of patients lose at least half of their excess body weight during the first year. Weight generally stabilizes 12 to 24 months after surgery, and 10 to 20% of patients regain a significant portion of the lost weight. If a patient maintains weight loss for 5 years, there is an excellent likelihood that the weight loss will persist for at least 14 years.[170] Studies have shown improvement or resolution of many of the medical complications of obesity, including diabetes mellitus, hypercholesterolemia, and obstructive sleep apnea.[171]

The jejunoileal bypass was an early surgical procedure for weight loss and caused global malabsorption. It caused frequent and unacceptable side effects, including intractable diarrhea, nutrient deficiencies, kidney stones, and hepatic failure. The two most common operations performed today are the Roux-en-Y gastric bypass and vertical banded gastroplasty (Figure 54-3), both of which reduce the gastric capacity to restrict caloric intake. In contrast to the jejunoileal bypass, these operations do not cause significant malabsorption, and their safety profile is substantially better. The mechanism through which these operations cause weight loss is not fully understood, although recent studies suggest that it may suppress gastric production of ghrelin, thereby reducing appetite.[67] About 10% of patients have important complications of these procedures, which include anastomotic strictures, incisional hernias, and gallstone formation requiring cholecystectomy. Anastomotic leaks, staple line disruptions, and dumping syndrome can occur but have been reduced to 1 to 2% each by modifications in surgical technique.[172] Although protein-calorie malabsorption is rare, malabsorption of selected micronutrients, particularly iron and vitamin B_{12}, is common and requires postoperative monitoring and treatment.

Gastric restrictive procedures for weight loss are thus an appropriate treatment option for adults with medically significant obesity, but there is still significant uncertainty regarding optimal patient selection. To date, no psycholog-

TABLE 54-7 Dietary Supplements for Weight Loss[167,168,203]

Dietary Supplement	*Other Names*	*Mechanism*	*Effectiveness*	*Safety*
Ephedra alkaloids	Ma huang, norepinephrine	Thermogenic	Yes, only in combination with caffeine	Unsafe (hypertension, palpitation, tachycardia, stroke, seizures, death)
Caffeine	Guarana *(Paullinia cupana)*, Yerba maté *(Ilex paraguayansis)*	Thermogenic	No, when used alone	High doses or combinations may be unsafe (hypertension, tachycardia, nausea, dizziness)
Chromium	Chromium picolinate	≠ Insulin sensitivity	Uncertain	Uncertain
Ginseng	Korean ginseng *(Panax ginseng)*, American ginseng (*Panax quinquefolux*), Siberian ginseng *(Eleutherococcus senticosus)*	≠ Insulin sensitivity, Thermogenic, ≠ Lipolysis	Uncertain	Uncertain; may interfere with anticoagulant effect of warfarin
Fiber	Guar gum, psyllium, flaxseed, glucomannan	Malabsorption ≠ Insulin sensitivity	Unlikely	Generally safe, but some forms may have risk of gastrointestinal obstruction
Hydroxycitric acid	Malabar tamarind *(Garcinia cambogia)*	Ø De novo fatty acid synthesis	Unlikely	Uncertain
Dehydroepiandrosterone (DHEA)	Adrenal steroid hormone	Ø Fat synthesis	Uncertain	Uncertain, metabolites may stimulate breast and prostate tissue
Chitosan	Chitin (crustacean shells)	Blocks dietary fat absorption	Uncertain	Uncertain
Horsetail	*Equisetum* sp	Diuretic	Uncertain	Unsafe (may be K+ wasting)
Senna cascara	*Cassia* sp *Rhamnus pushiana*	Laxatives	Uncertain	Unsafe for treatment of obesity
St. John's wort	"Herbal phen-fen" *Hypericum perforatum*	Antidepressant	Unlikely	Uncertain, phototoxicity; drug interactions with many psychoactive drugs

ical or physiologic factors have been defined that will determine which patients are most likely to suffer weight regain after surgery (approximately 20%) or to suffer medical or psychological complications of surgery. Similarly, there are limited data on the outcomes of weight loss surgery in adolescent patients, but a few series have been published,[173,174] and these suggest that short- and long-term outcomes and complications in adolescents are similar to those seen in adults. Weight loss surgery may therefore be appropriate in selected severely obese adolescents. Given the limited data available on outcomes in this age group, these procedures should probably be limited to patients who have exhausted other management approaches and have significant medical complications of

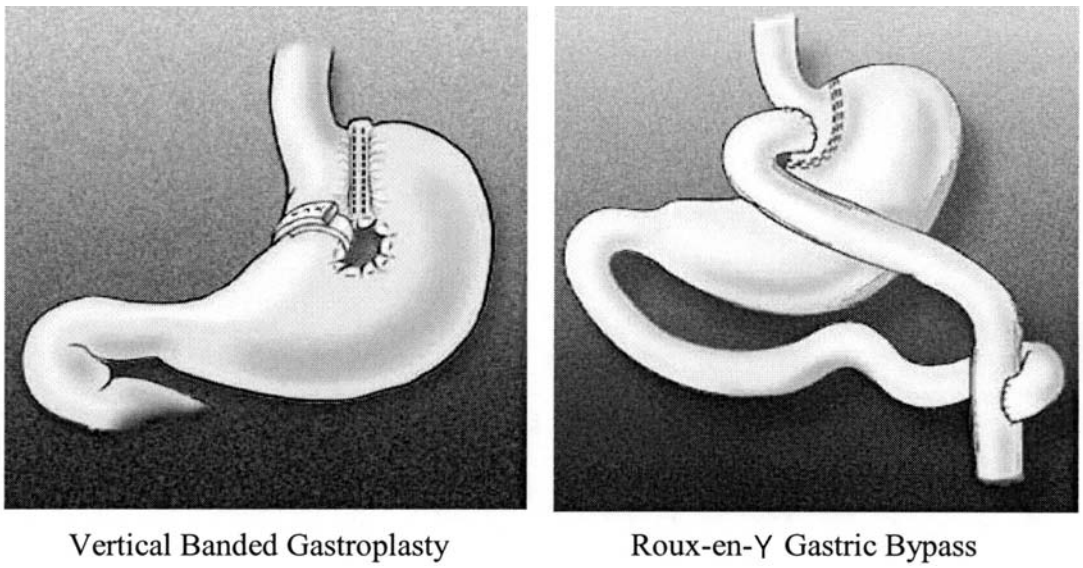

FIGURE 54-3 Gastric restrictive surgery for weight loss.

their obesity. To optimize long-term outcomes, any concomitant psychiatric disorders should be carefully assessed and under good control before surgery, and measures should be taken to ensure long-term follow-up for medical, surgical, and nutritional issues, ideally in the setting of a multidisciplinary obesity treatment center with substantial experience in surgical treatment of obesity.

Future Directions

With the exception of surgery, current treatments for established obesity have disappointing long-term outcomes. However, research is likely to lead to advances in several important arenas. Perhaps most importantly, public recognition of the obesity problem should lead to public education and public programs designed to prevent obesity during childhood. Such population-wide approaches are more likely to be effective than treatment approaches targeting individual patients with resource-intensive and weakly effective therapies. However, the identification of which preventive strategies will be most effective is important before they can be implemented widely. Second, improved understanding of the genetic determinants and neural pathways underling the homeostatic control of body weight is likely to lead to pharmacologic interventions that are more specific and therefore safer and more effective. Third, rigorously scientific and detailed analysis of specific environmental factors contributing to obesity, including issues of diet composition and meal patterns, may lead to more focused dietary and behavioral interventions to treat obesity. Finally, education of the public and health care community to recognize and reverse the commonly held bias against obese individuals should help to minimize the stigma and therefore much of the psychological burden associated with the disease.

USEFUL WEB SITES

Nutrition and Exercise

- An excellent rating guide to other nutrition Web sites, with links: <http://navigator.tufts.edu/>
- A site with nutritional and exercise material: <http://www.brightfutures.org/>
- Promoting Better Health for Young People Through Physical Activity and Sports: <http://www.cdc.gov/nccdphp/dash/presphysactrpt/index.htm>
- Healthy eating and physical activity across the lifespan: helping your child (in English and Spanish): <www.niddk.nih.gov/health/nutrit/nutrit.htm>

Anthropometric Measurements

- New growth charts (2000): <www.cdc.gov/growthcharts>

Nutritional Supplements and Alternative Therapies

- National Institutes of Health: <http://nccam.nih.gov/>
- US Department of Agriculture: http://www.nal.usda.gov/fnic/pubs/bibs/gen/dietsupp.html
- Peer-reviewed journal that analyzes the claims of alternative medicine: <http://www.quackwatch.com/04ConsumerEducation/sram.html>

Genetics

- The Human Obesity Gene Map: <http://www.obesity.chair.ulaval.ca/genes.html>
- Online Mendelian Inheritance in Man (OMIM): <http://www3.ncbi.nlm.nih.gov/omim>

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CHAPTER 55

STANDARD AND SPECIALIZED ENTERAL FORMULAS

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As research and experience over the past century have advanced our knowledge of the nutrient requirements and digestive functions of infants and children in health and illness, enteral formulas have become more sophisticated and diversified to meet their nutritional and metabolic needs. These liquid meals, together with advances in enteral feeding techniques, have contributed to the increased survival and shorter hospitalizations of pediatric patients with severely compromised intestinal function. This chapter reviews the composition of the major groups of available formula feedings for infants and children and discusses their use in general. Breast- and formula feeding of infants and the enteral nutritional support of children with specific chronic illnesses are discussed in other chapters. The composition of these formulas is also listed in detail in Appendix 3, grouped by category and by use.

HISTORICAL BACKGROUND

Human milk was the principal source of nutrition for newborns and infants up to the mid-nineteenth century. Wet nurses provided an alternate source of milk when the mother's milk was not adequate or available. Milk from donkeys, horses, and cows was used as a substitute when human milk was not available. The mortality of bottle-fed infants was 4 to 10 times greater than that of breast-fed infants in the early part of the twentieth century, mainly because of unsanitary methods of preparation and storage of the milks. Innovations toward the end of the nineteenth and beginning of the twentieth century, such as evaporated cow's milk, the rubber nipple, pasteurization, and the introduction of refrigeration into most households in the industrialized world, led to a greater use of formula-feeding, and the practice of wet nursing was gradually replaced by feeding with cow's milk formula.[1,2]

The modification of cow's milk to make its nutrient composition more similar to that of human milk began in a scientific way with the German pediatrician Philip Biedert, who added cream, whey, and sugar to cow's milk to make it suitable for infants. Meigs' Mixture, formulated by the American physician John Meigs, was similar in composition to Biedert's mixture.[3] In addition to changing the quantity of cow's milk constituents, the quality of the protein, fat, and carbohydrate in cow's milk was also a subject of investigation and in some cases changed, as with the acid treatment of casein curds to render them smaller and softer.[4] These early formulas formed the basis for the modern formulas with a defined nutrient composition that are currently fed to human infants.

STANDARD INFANT FORMULAS

In spite of Abraham Jacobi's admonition that "Cow's milk cannot be changed into woman's milk.…The efficiency of all alleged improvements in artificial feeding is liable to be overestimated, and not always received with sound criticism,"[5] modern proprietary formulas intended for infants continue to attempt to simulate human milk. In doing this, however, the nutrient composition has also been adjusted to provide what are currently established as the nutrient requirements of growing infants. The levels of nutrients present in all infant formulas are determined by regulations established by the US Food and Drug Administration (FDA) (Table 55-1) (see Appendix 3).[6] For many nutrients, minimal and maximal amounts are specified. In addition, the Infant Formula Act of 1980 and the amendments of 1986 mandate the quality control standards under which all infant formulas are manufactured. Modifications in nutrient and non-nutrient content are generally based on recommendations from the

TABLE 55-1 Recommended Nutrient Levels for Infant Formulas*

Nutrient	*Minimum*	*Maximum*
Protein (g)	1.8	4.5
Fat (g)	3.3	6.0
% Calories from fat	30	54
Essential fatty acids		
Linoleic acid (mg)	300	—
% Calories from essential fatty acids	2.7	—
Vitamins		
A (IU)	250	750
D (IU)	40	100
K (μg)	4	—
E (IU)	0.7	—
C (ascorbic acid) (mg)	8	—
B_1 (thiamin) (μg)	40	—
B_2 (riboflavin) (μg)	60	—
B_6 (pyridoxine) (μg)	35	—
B_{12} (μg)	0.15	—
Niacin (μg)†	250	—
Folic acid (μg)	4	—
Pantothenic acid (μg)	300	—
Biotin (μg)‡	1.5	—
Choline (mg)‡	7	—
Inositol (mg)‡	4	—
Minerals		
Calcium (mg)	60	—
Phosphorus (mg)	30	—
Magnesium (mg)	6	—
Iron (mg)	0.15	3
Iodine (μg)	5	75
Zinc (mg)	0.5	—
Copper (μg)	60	—
Manganese (μg)	5	—
Sodium (mg)	20	—
Potassium (mg)	80	—
Chloride (mg)	55	—

Adapted from Rules and Regulations.[6]
*Per 100 kcal.
†Includes niacin (nicotinic acid) and niacinamide (nicotinamide).
‡Required only for non–milk-based infant formulas.

scientific and medical communities. These government regulations came about following an epidemic of hypochloremia and alkalosis in infants fed with a chloride-deficient soy formula.[7,8] The potential for error in preparation and contamination of infant formulas before and after marketing continues even in the twenty-first century. Recalls of batches of contaminated powdered infant formulas were made after one infant died of meningitis caused by *Enterobacter sakazakii* in Tennessee and another infant developed botulism from *Clostridium botulinum* type B toxin in the United Kingdom.[9,10]

Cow's Milk–Based Formulas

Standard cow's milk–based formulas are marketed in ready-to-use, concentrated liquid, and powdered forms. All are based on nonfat cow's milk, to which lactose and vegetable oils have been added. These formulas are low in cholesterol because the fat is derived from vegetable sources. In addition, emulsifiers (eg, lecithin) and thickeners (eg, carrageenan) have been added. Their mineral and vitamin content has also been adjusted to suit the needs of human infants.

Cow's milk has a relatively greater amount of casein than does human milk. Experience accumulated over the past 50 years has shown that casein-predominant milks support normal growth in both premature and full-term infants.[11] Casein has served as a standard reference protein by which to measure the biologic value of other proteins such as soybean or egg protein. The measure of the biologic value is the grams of weight that a reference animal gains for each gram of protein fed. Setting casein as 100%, FDA regulations require protein at a minimum level of 1.8 g per 100 kcal of formula. For proteins with a lower biologic value, the formula must contain proportionately more protein. No protein source can be used with a biologic value less than 70% that of casein.

Those formulas that are based on casein have an amino acid and mineral composition that more closely resembles that of cow's milk than human milk. The osmolality and renal solute loads of these standard formulas fall intermediately between human and cow's milk, although these values increase, as do those of the other constituent nutrients, if the formulas are prepared to be more highly concentrated.[12]

Infants who are fed a casein-predominant formula have a different profile of amino acids in their serum after feeding than do those taking human milk, and some have developed metabolic derangements on casein-predominant formulas.[13] For this reason and others, including attempts by manufacturers to simulate human milk, whey-predominant and whey-only formulas have achieved popularity for both premature and full-term infants. By increasing the amount of whey proteins, mainly α-lactalbumin and β-lactoglobulin, the amino acid composition of the formula is altered so that it resembles human milk more than cow's milk. This is particularly so for the sulfated amino acids, cystine, taurine, and methionine. Clinical studies have demonstrated the adequate growth of full-term infants taking these formulas. Serum amino acid profiles of infants fed whey-predominant formulas are different from those fed human or cow's milk, with a higher percentage of branched-chain amino acids and threonine in circulation. However, the significance of this finding is unclear.[14,15]

Just as other minerals and vitamins are present in the formula to prevent nutritional deficiencies, iron is added to the standard formulas to prevent iron deficiency in newborns in the first year of life. Iron supplementation is particularly important for premature or small-for-gestational-age infants, who have reduced iron stores. The amount of iron present in the fortified formulas ranges from approximately 4.7 to 14.5 mg/L in the United States and 4 to 7 mg/L in Europe.[16] The availability of low-iron formulas and parental misperception regarding iron as a cause of infantile constipation or hyperirritability are some of the reasons that could lead to discontinuation or avoidance of the iron-fortified formulas for some infants.[16]

Nucleotides are now being added to many of the standard cow's milk–based formulas based on the presence of nucleotides in human milk and a decreased incidence of diarrheal disease in a few studies of infants fed formulas supplemented with nucleotides.[17,18] Furthermore, nucleotide

supplementation in formula has also increased plasma lipoproteins and enhanced the growth of small-for-gestational-age infants.[19,20] In a study of full-term infants, cow's milk–based formula supplemented with nucleotides enhanced antibody responses to diphtheria and *Hemophilus influenzae* vaccinations, but the antibodies to poliomyelitis and tetanus were unaffected.[21] In preterm infants on formula supplemented with nucleotides, serum IgM and IgA were higher, whereas IgG and lymphocyte subsets were unaffected.[22]

The fatty acid composition of infant formulas is an area of intense investigation. Human milk contains relatively more monounsaturated fatty acids than regular infant formulas do, and also contains long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid and docosahexaenoic acid (DHA). Arachidonic acid and DHA are important structural components of lipid membrane in the brain and retina. Studies have shown enhanced cognitive development and visual acuity in premature infants fed with formulas supplemented with arachidonic acid and DHA.[23,24] Studies in full-term infants, however, have shown mixed results.[25,26] LCPUFAs also influence the maturation of the immune system. The expression of CD45RO (mature phenotype) on CD4+ cells and interleukin-10 production were higher in preterm infants fed human milk and those fed formula supplemented with LCPUFAs compared with those in infants fed formula alone, although it is unclear whether this is a clinically important phenomenon.[27] The supplemented formulas appear to be safe as all studies have shown no significant difference in the growth parameters for infants on supplemented formulas with appropriate ratios of arachidonic acid and DHA.[24–26] Formulas with added arachidonic acid and DHA have been in use in Europe for a number of years and were formally approved for marketing in the United States in early 2002.

Cow's milk–based formulas with lactose are contraindicated for infants with galactosemia, cow's milk allergy, or lactose intolerance. However, a lactose-free cow's milk–based formula with corn syrup solids as the carbohydrate is an appropriate choice for infants with lactose intolerance. Lactose in cow's milk–based formulas was shown to enhance absorption of calcium in full-term infants between 8 and 12 weeks of age.[28] This apparent advantage of lactose-containing formulas over lactose-free formulas in enhancing calcium absorption was not clinically significant, however, at least for healthy full-term infants, because the amount of calcium absorbed in infants on the lactose-free formula was still adequate.

A cow's milk–based formula with added rice starch was specifically marketed for infants with uncomplicated gastroesophageal reflux. Rice cereal is frequently added to thicken the formula in the management of uncomplicated gastroesophageal reflux, although studies with esophageal pH probe have failed to demonstrate any significant decrease in the reflux time in infants fed with formulas thickened with cereal.[29,30] This practice increases the amount of carbohydrate relative to protein in the feeding and could potentially lead to intake of either excessive calories or inadequate protein by the infant. This formula addresses this concern by replacing part of the lactose with rice starch so that the protein-to-calorie ratio remains at 2.5 g per 100 kcal.

Milk feedings formulated specifically for premature and small-for-gestational-age infants are sold in a liquid ready-to-use form for use in hospitals and following discharge. These formulas differ from the standard formulas by attempting to meet the nutritional requirements of rapidly growing low birth weight infants within the limitations of intestinal and renal functions seen in these infants. These formulas have either 20, 22, or 24 kcal per ounce. When prepared at 20 kcal per ounce, they contain more protein than standard formulas do. Fat malabsorption is a common occurrence in the low birth weight infant. Therefore, a high percentage of the fat in most of these formulas is in the form of medium-chain triglycerides (MCTs), which have been shown to reduce steatorrhea, enhance calcium absorption, and improve nitrogen retention in low birth weight infants.[31,32] Carbohydrate is provided as a mixture of lactose, maltodextrins, and glucose polymers. Glucose polymers appear to be well tolerated by premature infants.[33] Finally, the concentration of both calcium and phosphorus in a 2:1 ratio is increased above levels found in standard formulas.

Soy-Based Formulas

The soy protein formulas were introduced for use in infants who are cow's milk intolerant. Although soy formulas are extensively used in cow's milk–allergic children, soy protein is also antigenic. Soybean protein, however, is readily available and is a high-quality protein. Soy protein isolate is supplemented with L-methionine and taurine to balance the amino acid ratio and improve its biologic value.[34] Soy formulas are also supplemented with carnitine, which is found only in animal proteins. Nucleotides are not added to the soy formulas as studies failed to show any obvious immunologic advantages, such as response to vaccines and lymphocyte maturation, in infants on nucleotide-supplemented soy formula.[35,36] The carbohydrates in soy formulas consist of sucrose, corn syrup solids, and/or maltodextrin. These formulas are therefore useful in patients with clinically significant lactose intolerance. Infants with acute diarrhea fed soy formula can have a shorter duration of diarrhea, although for most infants with acute infectious diarrhea, lactose intolerance is not clinically significant.[37,38]

Although earlier studies showed that bone mineralization was reduced in infants fed a soy-based formula compared with infants fed a cow's milk–based formula,[39] more recent studies on soy formulas with improved mineral suspension showed no difference in bone mineralization in full-term infants fed soy and cow's milk–based formulas.[40,41] Bioavailability of phosphorus, zinc, manganese, copper, and iron are reduced by phytic acid and polysaccharides present in the soy protein isolate.[42] Soy formulas are therefore supplemented with zinc and iron. Iron status appears to be equivalent in infants fed soy and cow's milk formulas.[43]

Aluminum has been found in soy formulas at concentrations of 600 to 1,300 ng/mL, compared with concentrations of 4 to 65 ng/mL found in human milk.[44,45] Alu-

minum is the most abundant metal in the earth's crust and is present in many plants. It is present in the formula as a contaminant of calcium salts and the soy protein isolate. Aluminum-induced encephalopathy has been reported in patients with renal disease and those taking aluminum salts as an antacid or as phosphate binders. Aluminum also competes with calcium for absorption and could contribute to the osteopenia seen in infants with compromised renal function.

Soy protein isolate also contains isoflavones with estrogenic activity. Plasma concentrations of the isoflavones in infants fed with soy formulas were two orders of magnitude higher than levels found in infants fed cow's milk formulas or human milk.[46] The high concentrations of isoflavones found in infants fed soy formulas have raised concern regarding the long-term health effects on infants exposed to soy. Although many studies have demonstrated adequate growth for infants fed with soy formulas, so far only one study has reported on the sexual development of infants fed soy-based formulas. It was a retrospective cohort study of young adults who had participated in studies on soy- and cow's milk–based formulas in their infancy. This study found no effect of soy formulas on either growth or sexual maturation of human infants.[47]

Specific indications for soy formulas, in addition to lactose intolerance, include galactosemia and a parental preference for avoiding feeding infants animal products (ie, vegans and those whose religious dietary laws preclude the use of animal-based milks). Patients with fructose intolerance should avoid soy formulas that contain sucrose. There is no benefit from the use of soy formulas to treat common problems in infancy such as gastroesophageal reflux, colic, or constipation unless these are symptoms of cow's milk intolerance. The majority of infants with cow's milk protein intolerance can tolerate soy formula. In two prospective studies, between 10 and 14% of those with cow's milk protein allergy were found to have concomitant soy allergy.[48,49] Infants who have allergic enterocolitis can have a higher risk of having both milk and soy allergy. In a retrospective analysis of 16 patients with food protein–induced enterocolitis syndrome, 7 (42%) were found to have reactions to both cow's milk and soy.[50] This finding remains to be confirmed by prospective studies involving a greater number of subjects.

Weight gain and bone mineralization in preterm infants fed soy formula were less than those in infants fed cow's milk–based formulas.[51,52] Because of this and a concern for aluminum toxicity associated with soy formulas, the American Academy of Pediatrics issued a policy statement that "soy protein–based formulas are not designed or recommended for premature infants who weigh < 1,800 g."[53] For the same obvious reason, soy formulas should also be avoided in patients with renal disease.

Other Non–Cow's Milk Infant Formulas

Goat's milk has frequently been used to feed infants sensitive to cow's milk, although studies show that it is as antigenic as cow's milk. Like almost all mammalian milks (the California sea lion is an exception), lactose is the carbohydrate in goat's milk. Goat's milk is high in essential fatty acids and has a higher percentage of MCTs than does cow's milk; it is low in folate. Because of more useful and effective commercial formula alternatives, its popularity has waned markedly in the United States. Goat's milk remains a significant source of nutrition for infants after weaning in other countries. Infants fed with home preparations of goat's milk are at risk for nutritional deficiencies and infections if the milk is contaminated.

Meat-based formula is yet another alternative for infant feeding free of lactose and cow's milk protein. Its nutritional adequacy for healthy infants has been demonstrated, but experience in infants requiring nutritional rehabilitation is too limited to recommend routine application.

PROTEIN HYDROLYSATE FORMULAS

Protein hydrolysate formulas are intended for patients with disorders associated with compromised enteric digestion, such as short-bowel syndrome, food allergy, autoimmune enteropathy, human immunodeficiency virus–associated enteropathy, cystic fibrosis, pancreatic insufficiency, and hepatobiliary disorders such as biliary atresia. The casein or whey in these formulas is modified by hydrolysis and the addition of free amino acids. The casein hydrolysates are supplemented with L-cystine, L-tyrosine, and L-tryptophan to increase their biologic value to the infant. The major portion of the nitrogen in the formulas is in the form of oligopeptides. Although the hydrolyzed protein peptides are less likely to induce an antigenic response than are whole protein molecules, they are not nonallergenic.[54–56]

A recent study suggests that peptides consisting of five, four, or even three amino acids can still activate T-cell clones in vitro.[57] There is evidence to support the considerably faster rate of intestinal amino acid uptake from solutions containing individual dipeptides, tripeptides, or partially hydrolyzed proteins than from solutions composed solely of free amino acids.[58] Formulas with oligopeptides produce a lower osmolality than a free amino acid–containing formula and therefore could have a theoretic advantage over the amino acid–containing formulas for infants and patients with short-bowel syndrome. With immaturity of the intestine or loss of absorptive surface area, either following bowel resection or as a result of inflammation, all of the disaccharidases, but most commonly lactase, can be diminished.[59] The use of sucrose or glucose polymers (partially hydrolyzed corn starch) would therefore be useful in circumventing the absence of lactase or both lactase and sucrase. Monosaccharides are not used exclusively in any of the prepared formulas because of their high osmolality, which can inhibit gastric emptying and further impair intestinal function.[60,61]

MCTs form a large percentage of the total fat content of these formulas. MCTs can be absorbed across the intestinal mucosa with minimal lipolysis to enter the portal circulation. Because of the enhanced solubility of medium-chain fatty acids in aqueous fluids, absorption of this form of fat can also take place in the absence of bile salts in the intestinal lumen and unstirred layer. None of these formulas con-

tain only MCTs because they would then be devoid of essential fatty acids. MCTs increase the osmolality of formula more than long-chain fatty acids do, and the excessive use of this form of fat can also contribute, in some patients, to excessive losses of stool water.

FREE AMINO ACID FORMULAS

The principal difference between free amino acid formulas and peptide-based formulas is in the protein composition. At present, only one of these formulas is specifically designed for infants under 1 year of age, with an osmolality of 360 mOsm. The lipid component is a mixture of safflower, coconut, and soy oils to provide essential and nonessential fatty acids. The carbohydrate is from corn syrup solids or maltodextrins, which are both derived from corn starch, differing only in the size of glucose polymers. Because free amino acids by themselves are nonimmunogenic, these formulas are most useful for children with multiple food allergies who do not tolerate even the peptide-based formulas.

Several studies have shown that most infants with cow's milk or multiple food allergies are able to grow adequately on amino acid–based formulas.[62,63] However, depending on the manufacturing and purification process, the soy oil can be contaminated by trace amounts of soy protein and could trigger an allergic response in susceptible individuals.[64] Children with severe enteropathy or short-bowel syndrome unable to tolerate protein hydrolysates might benefit from the amino acid–based formulas as an alternative and reduce their dependency on parenteral nutrition.[65]

FOLLOW-UP FORMULAS

Follow-up formulas are defined by the joint FAO/World Health Organization Codex Alimentarium Commission (1988) as "A food intended for use as a liquid part of the weaning diet for the infant from the 6th month on and for young children."[66] Currently, several formulas for this use are marketed in the United States. These formulas are either cow's milk– or soy-based, differing from infant formulas only slightly in nutrient concentrations. Even though follow-up formulas are nutritionally adequate, they have no advantage over a combination of solid foods and standard infant formulas or human milk and could interfere with the normal weaning process. Ideally, the weaning process should take place over a period of several months, effecting a transition to a solid-food diet comprising 30 to 50% of total calories. Solid foods should complement infant formula or breast milk in mineral and vitamin composition.[67] For the great majority of children who are able to make the transition to solid food, there is really no need for these follow-up formulas.

FORMULAS FOR CHILDREN 1 TO 10 YEARS OF AGE

Although the frequency of formula use decreases significantly after the first year of life, many children require continued nutritional support with a liquid formula for a variety of reasons, including inadequate intake, compromised digestion or absorption, or inherited disorders of metabolism. These formulas can be cow's milk–, soy-, peptide-, or amino acid–based. The carbohydrate is usually corn starch-derived glucose polymers and sucrose, and the fats a blend of vegetable oils, such as safflower, soy, canola, and coconut oil, to provide both medium- and long-chain triglycerides. These formulas are different from the infant formulas with higher caloric density and protein concentration. The mineral and vitamin concentrations are intended to support the daily requirements for this age group.

Children who are unable to chew and swallow adequately because of neurologic impairment but who have intact intestinal motility, digestion, and absorption exemplify those with a need for such a liquid enteral formula, often administered via a gastrostomy. Children in the intensive care unit who are unable to eat by mouth because of airway problems can use the enteral formulas in the short term via nasogastric or nasojejunal tube. Historically, both adult and infant formulas have been used with preschool and school-aged children because of a lack of pediatric formulations. If such formulas are "tailored" and use is monitored to meet individual patient needs, they can be used successfully in this age group. However, vitamin and mineral deficiencies or excesses, osmotic diarrhea, and an excess renal solute load are a few of the concerns with the use of adult products in young children. Products specifically manufactured for this age group have made it easier to monitor and to more appropriately recommend products based on individual requirements. Some of the formulas have added soy fiber. Studies in adult patients have shown fewer problems with diarrhea (and constipation) when fiber is added to enteral nutrition.[68,69]

Peptide- and amino acid–based formulas designed for older children are often used for patients with limited digestive and absorptive capacity, such as those with Crohn's disease, pancreatitis, and chemotherapy-induced enteropathy, in addition to those disorders mentioned above. In the case of Crohn's disease (see Chapter 37, "Inflammatory Bowel Disease"), peptide- and amino acid–based formulas have been used successfully to induce and maintain remission. Whereas a meta-analysis of several randomized, controlled trials indicated that enteral nutrition was less effective than steroids in induction of remission in adults with active Crohn's disease,[70] studies in children suggest the opposite.[71,72] Several studies have also demonstrated that enteral nutrition begun early in the course of acute pancreatitis was superior to parenteral nutrition, with fewer septic complications and lower cost.[73–75] Appendix 3 lists both standard and special enteral products for children and adolescents.

Children requiring long-term tube feeding support, without any oral supplementation, should be monitored for the development of macro- and micronutrient deficiencies, such as vitamin B_{12}, zinc, or selenium deficiency, especially in those with chronic disease processes and severe diarrhea. Children with severe developmental delay and mental retardation are also at risk for obesity and osteopenia because of a low resting energy expenditure and inactivity. Because vitamins and trace elements in these

formulas are present in proportion to the calories, provision of supplemental vitamins and minerals might be necessary if the number of calories provided is substantially less than the usual Recommended Dietary Allowance (RDA) for age.[76]

MODULAR FORMULAS

Modular formulas can be either complete or intended as supplements to the diet and can be used to satisfy a particular nutrient requirement or to augment an established feeding regimen (eg, caloric supplementation; see Appendix 3, Tables A-36 and A-37). For example, a carbohydrate-free product containing protein, fat, vitamins, and minerals can be mixed with another carbohydrate source in the treatment of conditions such as fructose intolerance or galactosemia. Carbohydrate-free formulas are also used in a ketogenic diet for infants and young children with intractable seizure disorders. Protein preparations of casein or whey are available separately without lactose or fat. Human milk fortifiers provide a mixture of protein (cow's milk), fat (MCTs), carbohydrate (corn syrup solids), vitamins, and minerals to provide additional nutrients to premature and full-term infants fed with breast milk. Problems can arise with their solubility in various commercial formulas, and they can also cause a significant increase in the osmolality of the new mixture.[77] Additionally, when modular formulas are prepared by supplementing a standard liquid diet with extra carbohydrate or fat, changes in the calorie-to-nitrogen ratio can occur that will not support optimal growth.

In spite of these limitations, when used appropriately, these formulas and additives provide a means of specifically tailoring formulas to meet the nutritional needs of infants and children for whom no standard prepared formula is available. Children with congenital heart disease, renal disease, liver disease, or bronchopulmonary dysplasia are representative of those requiring formulas of increased caloric density because they are often fluid restricted and have increased caloric requirements.

FORMULAS FOR METABOLIC DISORDERS

Liquid feedings are available to support patients with specific inborn errors of metabolism (see Appendix 3, Table A-38). These formulas generally use a mixture of amino acids as the protein source, minus the amino acid(s) that can cause toxicity owing to the particular enzyme deficiency in the disorder (eg, phenylalanine in phenylketonuria). These formulas are also available for different age groups. Some formulas can be used for more than one metabolic disorder. The formula for patients with maple syrup urine disease is free of the branched-chain amino acids leucine, isoleucine, and valine, and it can also be used for patients with hypervalinemia, methylacetoaceticaciduria, isovalericacidemia, hyperleucine-isoleucinemia, and leucine-induced hypoglycemia. Because the missing amino acid(s) are also essential for growth, a certain minimal amount of additional protein containing the missing amino acid(s) needs to be provided in the diet for these patients. For patients with metabolic disorders of fatty acids, such as long-chain and very-long-chain acyl-CoA dehydrogenase deficiencies, a formula with MCTs as the predominant fat source is used.

These patients' metabolic status can be easily deranged by an acute viral infection that affects their oral intake. The mainstay of a "sick-day plan" is provision of adequate calories using a glucose polymer to prevent starvation-induced gluconeogenesis and lipolysis and subsequent accumulation of toxic metabolites.[78] Patients must be monitored closely for clinical and laboratory indices of toxicity and deficiency. These formulas include vitamins and minerals age adjusted to meet the patients' needs. However, one study, based on 3-day diet records, indicated that children with maple syrup urine disease were getting only 21 to 66% of the RDA for selenium.[79] Until further studies have been completed, the long-term efficacy and safety of some of the metabolic formula products remain to be determined.

FORMULAS INTENDED FOR OLDER CHILDREN WITH CHRONIC ILLNESS

Enteral formulas intended for adults can generally be used for children with chronic illness older than 10 years. The osmolality of these formulas varies from 280 to more than 600 mOsm/L. Sucrose is often one of the carbohydrate ingredients, perhaps to make these formulas more palatable. The sources of protein, carbohydrate, and fat are similar to those used for younger children and infants but differ in their concentrations. Fiber is added to many of the formulas. In addition to standard formulas for those chronically dependent on feeding tubes, a number of disease-specific formulas are available (see Appendix 3).

Patients with severe pulmonary compromise can benefit from formulas that provide 40 to 55% of calories from fat, which has a lower respiratory quotient—that is, lower CO_2 production—than carbohydrates do.[80] In contrast, formulas with a high carbohydrate and low fat content are preferred for patients with burn injuries,[81] and patients with renal failure can benefit from formulas with low protein and salt concentrations. Some enteral formulas have increased concentrations of branched-chain amino acids that can be protein sparing or reduce ammonia production in patients with chronic liver failure. Although there are anecdotal reports of success, most studies have failed to show any significant long-term clinical advantages of these formulas compared with those with a conventional amino acid mixture or the use of lactulose in the treatment of acute or chronic hepatic encephalopathy.[82,83]

Formulas for Critically Ill Patients

A number of nutritional substrates can modulate the host response to critical illness, including major trauma. Included among these are zinc, glutamine, arginine, and omega-3 fatty acids. Animal, human, and epidemiologic data suggest that one or more of these nutrients can be beneficial in the treatment of diseases such as acquired immunodeficiency syndrome (AIDS),[84,85] ulcerative colitis,[86] systemic lupus erythematosus,[87] rheumatoid arthritis,[88] major burns,[89,90] and coronary heart disease.[91]

Possible effects include an improvement in nitrogen balance (arginine), normalization or reduction of platelet aggregation (arginine),[92] substrate availability for energy use in rapidly replicating cells such as enterocytes and lymphocytes (glutamine),[93,94] a decrease in the incidence of bacterial translocation (glutamine),[95] and alterations in eicosanoid and cytokine production (omega-3 fatty acids).[96,97] Several randomized, controlled, prospective studies have demonstrated decreased infection rates, improved nitrogen balance, a decrease in length of hospital stay, and decreased cost of care in adult patients on an enteral formula supplemented with glutamine or with added fish oil, arginine, and nucleotides.[98–102] However, none of the studies has shown any difference in mortality in patients as a result of these supplements, and their real benefit in clinical practice remains to be demonstrated both in adults and children.

In addition to the "conditionally essential" nutrients mentioned above, there is also research interest in the potential therapeutic role of cytokines and growth factors found in the whey fraction of cow's milk. Bovine colostrum is currently available as a dietary supplement and has been reported to protect against the nonsteroidal anti-inflammatory drug–induced increase in intestinal permeability.[103] Studies in vitro have demonstrated suppression of T- and B-lymphocyte proliferative responses to mitogens and protection of epithelial cells against chemotherapy drugs by a bovine whey protein concentrate.[104,105] Transforming growth factor β (TGF-β) is present in bovine whey, especially that of colostrum, but it can account for only some of the activities seen with the bovine whey extract or colostrum.[105,106] An enteral formula with bovine TGF-β is available for adult patients with inflammatory bowel disease. Further research will determine whether TGF-β or other factors in bovine whey are useful in the management of patients with severe enteropathies.

In all patients with critical illness on a defined diet, the potential for the development of serious metabolic complications, such as azotemia, hypocalcemia, or hypomagnesemia, is high. Thiamin deficiency has been reported in 10 of 80 critically ill children admitted to the intensive care unit for more than 2 weeks and in four of six patients on chemotherapy.[107] Thus, in spite of their label as "complete" enteral feedings, chemically defined diets can lack essential nutrients, especially trace nutrients. A regular system for monitoring nutritional adequacy, including anthropometric determinations, must be undertaken. Laboratory tests, such as complete blood count, total protein, albumin, ferritin, electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, and phosphorus, require only small volumes of blood, and additional tests, such as zinc, copper, folate, and vitamins B_{12}, A, and E, might also be indicated, depending on the underlying medical condition.

CONCLUSION

Standard infant formulas have evolved significantly since the turn of the twentieth century and now provide some, but not all, of the advantages seen with breast-feeding. There has also been a significant advance in our ability to provide adequate and appropriate nutrition by the enteral route to infants and children who would otherwise have required extended parenteral nutrition support. In spite of the relative ease of enteral feeding, patients must be carefully observed to ensure that they are growing and developing appropriately and that nutritional deficiencies are not developing. Current research efforts will help define the role of nutrients and non-nutritive substances in the diet that will further promote the development and the health of these vulnerable infants and children.

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CHAPTER 56

ENTERAL NUTRITION

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The delivery of food via a tube directly into the gastrointestinal tract has been described since pre-Christian times. In ancient Egypt, and later in Greece, feeds were introduced into the rectum, and in the nineteenth century, rudimentary tubes were used to infuse basic foods such as broths, eggs, milk, and even alcohol into the esophagus and stomach.[1] Despite the increasing sophistication in other areas of medical care over the past century, treatment with enteral nutrition had been slow to develop. However, over the past two decades, enteral nutrition therapy has undergone a renaissance.[2–7] Many patients who previously received parenteral nutrition are now successfully managed with enteral nutrition alone or in combination with parenteral nutrition.[2,3,8,9] This has been made possible by the increasing range of options for gastrointestinal access, improved delivery systems, and advances in enteral nutrition formulas. Home enteral nutrition therapy is now an important adjunct to the management of infants and children with chronic disease or feeding problems.[6]

PRINCIPLES OF ENTERAL NUTRITION

Enteral nutrition therapy has a number of potential advantages over parenteral nutrition in the management of patients requiring nutritional support. The main advantages of enteral nutrition include preservation of gastrointestinal function, cost, manageability, and safety.

Preservation of Gastrointestinal Function

Apart from the oral phase of digestion, enteral nutrition activates the same gastrointestinal responses as the ingestion of normal meals. The presence of intraluminal nutrients stimulates (1) gastrointestinal neuroendocrine function, effecting motility and digestion through the secretion of digestive juices and gastrointestinal hormones, and (2) maintenance of gut mucosal mass, including gut-associated lymphoid tissue (GALT).

Intestinal functional and structural changes occur through local and systemic interaction of nutrients and neuroendocrine peptides, cytokines, and hormones.[10–15] The list of these mediators is constantly growing and includes gastrin; enteroglucagon; peptide YY; interleukin 3, 11, or 15; epidermal growth factor; growth hormone; insulin-like growth factors I and II; glutathione; fiber; short-chain fatty acids; glutamine; triglycerides; dietary nucleotides; and polyamines.[10–15] Monosaccharides and fatty acids can influence the secretion of enteroglucagon and peptide YY and via these mediators effect mucosal growth and decrease intestinal transit time.[16] Carbohydrate, protein, zinc, magnesium, potassium, or manganese deficiency can modify the effect of growth hormone and insulin-like growth factor II.[17–19]

GALT consists of the lamina propria, intraepithelial lymphocytes, immunoglobulin A (IgA), Peyer's patches, and mesenteric nodes and is responsible for processing intestinal antigens.[20] During periods of "bowel rest," such as occur with intravenous feeding and starvation, there is a reduction in gut mass and the functions of GALT are suppressed.[20] This has been associated with a reduction in IgA secretion and increased gut permeability and can result in increased bacterial adherence to the intestinal wall, cellular injury, and bacterial penetration with adverse systemic host responses.[20–22] In contrast to what has been found in animal studies, the correlation between parenteral nutrition and bacterial translocation has not yet been proven in humans.[23] During oral or enteral nutrition therapy, bacterial translocation does not seem to occur, except in association with disturbances in intestinal permeability related to the underlying disease process (eg, short-bowel syndrome) or the chemical composition of the enterally provided substance (eg, blue food dye).[20,24–26]

Cost

Enteral nutrition is estimated to be two- to fourfold less expensive than parenteral nutrition on an inpatient or outpatient basis.[2,3,27–29] In a recent study of home nutrition support, the annual cost per patient (based on US Medicare charges) was $55,193 ± $30,596 (US) for parenteral solutions versus $9,605 ± $9,327 (US) for enteral tube feeding.[4] In addition, the annual cost of hospitalization for a patient receiving parenteral nutrition (0.52 to 1.1 admissions/year/patient) ranged from zero to $140,220/patient, compared with zero to $39,204/patient for patients receiving enteral nutrition (0 to 0.5 admissions/year/patient).[4]

Manageability and Safety

As a result of advances in tube technology, delivery methods, technical skill of health professionals, and better education of parents and caregivers, the administration of enteral nutrition has been associated with improved clinical outcome and safety profiles.[30] Enteral nutrition therapy

is easier and safer to administer than is parenteral nutrition. Not only are the risks of intravenous access avoided, but there is also a wider margin for error for metabolic complications. As a result, enteral nutrition therapy is easier to administer in low-intensity hospitals and patient care settings, including the home.

INDICATIONS FOR ENTERAL NUTRITION

Enteral nutrition should be considered for any patient with a functional gastrointestinal tract who requires nutritional support. Indications for enteral nutrition in pediatric patients are listed in Table 56-1. With developments in options for gastrointestinal access, delivery systems, and enteral formulas, the list of absolute contraindications for enteral nutrition therapy has been reduced significantly. Contraindications include gastrointestinal ischemia, including necrotizing enterocolitis and toxic megacolon; intractable vomiting or diarrhea; paralytic ileus; diffuse peritonitis; and intestinal obstruction (either mechanical or functional).[7,31] Extreme care should be taken when administering enteral nutrition in patients in whom the gastrointestinal blood flow could be compromised, such as during treatment with hypothermia or infusions of specific drugs.

The goal of enteral nutrition therapy varies considerably among patients or within an individual patient at different phases of the disease process. In many patients, enteral nutrition will be aimed at providing their full macro- and micronutrient requirements. However, in some patients this might not be possible, and parenteral nutrition might be needed to supplement insufficient enteral intake. Conversely, a patient might require enteral nutrition to supplement an inadequate oral intake caused by increased disease requirements (eg, cystic fibrosis), malabsorption (eg, chronic liver disease), or voluntarily reduced intake (eg, anorexia nervosa).[7,31] Although enteral nutrition has mainly a therapeutic intent, it can also be used to prevent the development of malnutrition, such as can occur during cancer chemotherapy.[32] Advances in the understanding of the role of nutrients in the modification of inflammation and specific disease processes have led to the development of disease-specific formulas (eg, for Crohn's disease).[33] A more recent concept is that of minimal enteral feeding, in which enteral nutrition is provided at a very slow rate and volume with the aim of presenting nutrients to the intestinal mucosa without attempting to contribute significantly to total-body nutrition.[34]

TABLE 56-1 Indications for Pediatric Enteral Nutrition

1. **Inability to ingest adequate nutrition orally**
   - i. Disorders of sucking and swallowing
     - • Prematurity
     - • Neurologic impairment (eg, cerebral palsy, dysphagia)
   - ii. Congenital abnormalities of the upper gastrointestinal tract or airways
     - • Tracheoesophageal fistula
   - iii. Tumors
     - • Oral cancer
     - • Head and neck cancer
   - iv. Trauma
   - v. Critical illness
     - • Mechanical ventilation
   - vi. Severe gastroesophageal reflux
   - vii. Drug related
     - • Chemotherapy
   - vii. Severe food aversion
   - viii. Severe depression
2. **Disorders of digestion or absorption**
   - i. Cystic fibrosis
   - ii. Short-bowel syndrome
   - iii. Inflammatory bowel disease
   - iv. Congenital abnormalities of the gastrointestinal tract
     - • Microvillus inclusion disease
     - • Tufting enteropathy
   - v. Enteritis
   - vi. Intractable diarrhea of infancy
   - vii. Immunodeficiency
     - • AIDS
     - • Severe combined immunodeficiency
   - viii. Chronic liver disease
   - ix. Graft-versus-host disease
   - x. Intestinal fistulae
3. **Disorders of gastrointestinal motility**
   - i. Chronic pseudo-obstruction
   - ii. Ileocolonic Hirschsprung's disease
4. **Increased nutritional requirements**
   - i. Cystic fibrosis
   - ii. Chronic renal disease
   - iii. Congenital heart disease
   - iv. Chronic pulmonary disease
     - • Bronchopulmonary dysplasia
5. **Growth failure or chronic malnutrition** (in addition to above)
   - i. Anorexia nervosa
   - ii. Psychosocial causes
   - iii. Chronic liver disease
   - iv. Solid organ transplantation
6. **Metabolic diseases**
   - i. Inborn errors of metabolism
   - ii. Diabetes mellitus
7. **Acute or acute/chronic pancreatitis**

ROUTES OF ADMINISTRATION

During enteral nutrition therapy, nutrients are directly delivered via a tube into the stomach, duodenum, or jejunum. The tube is inserted either through the nose or mouth for short-term enteral nutrition (less than 3 weeks) or through a surgically or endoscopically created stoma for long-term enteral nutrition (more than 3 weeks). The choice of the location and the route of administration will depend on the patient's underlying medical or surgical condition, including gastrointestinal anatomy and function, the indication and duration of enteral nutrition therapy, and psychosocial factors. Additional factors, such as local technical expertise, tube availability, and cost, will also influence the route and type of device selected.

Noninvasive Access for Enteral Nutrition

Nonsurgical or nonendoscopic placement of a feeding tube through the mouth or nose is the most common method of establishing gastrointestinal access in infants and children. The tube is generally of small diameter (5 to 10 F) and is well suited to nutritional support of short or

intermediate duration. The nasal access is usually preferred, except in preterm infants or patients with nasopharyngeal abnormalities or obstructions, such as trauma or congenital malformations.

There is a wide range of enteric feeding tubes available for use in children. The original nasogastric tubes were made of polyethylene or polyvinyl chloride. However, because of their inherent stiffness, they require routine changing to reduce the risk of skin necrosis, gastric ulceration, and perforation. The current generation of feeding tubes is made of flexible silicone, polyurethane, or elastomer and usually may stylets to assist placement.

Despite their increased flexibility, these tubes have a longer life span and can have a number of specialized features. These include (1) aids for tube placement and to prevent dislodgment, including water-activated hydrophilic lubricant at the distal end and in the lumen, plastic-coated stylets to minimize the risk of tube perforation, marked reference points on the tubing to allow proper tube selection and positioning, and a rounded, nonweighted bullet-shaped tip to favor insertion; (2) a combination of distal-end and side exit ports to prevent blockage; and (3) a double port at the proximal end to allow for feeding and side injections. Accurate tube positioning is enhanced by radiopaque material within the tube wall. Tube sizes differ in length and port diameter, with the longer tubes suited for jejunal feeding (Table 56-2). Weighted tips are designed to allow gravity to assist with small-bowel placement and to prevent retrograde displacement. However, with the possible exception of intubated patients, the weighted tubes have not been shown to have significant benefit over nonweighted tubes.[35–37]

Nasogastric Tube Nasogastric tubes can be safely inserted by allied health staff, caregivers, family members, and even the patients themselves, with training. Prior to insertion, the desired length of tube is estimated by measuring the distance from the tip of the nose to the ear and down to the xiphisternum. A small amount of lubricant is applied to the nostril and along the length of the tube. The tube is then advanced through the nose past the nasopharynx into the stomach. Voluntary swallowing by the patient can aid the passage of the tube. Once the tube is in place, the stylet is removed and the proximal end of the tube is secured close to or behind the ear. Before commencing any infusion, tube location should be verified. Fluoroscopy or endoscopy can be used to assist difficult gastric tube placement.

Nasoduodenal or Nasojejunal Tube Advances in tube technology and the techniques for placement of nasoenteric tubes in children have provided an opportunity for postpyloric feeding in children in whom gastric feeding is difficult or contraindicated.[38] Nasoenteric tubes can be placed blindly or under fluoroscopic or endoscopic guidance.[39] The blind tube placement technique relies on the spontaneous passage of an enteric feeding tube from the stomach into the small intestine. This can occur after a period of hours or days and be facilitated by positioning the patient on the right side; the "corkscrew" technique, whereby a wire stylet is twisted when the tube is in the stomach; or the administration of prokinetic drugs, such as metoclopramide.[40,41] The use of erythromycin for postpyloric intubation is controversial, with both positive and negative effects observed in children.[42,43]

Postpyloric tube placement can also be attempted under fluoroscopic control.[44] Using this method, the passage of the tube is monitored with the aid of the radiopaque markings on the tube. Endoscopic placement of a nasoenteric tube has a number of advantages over the other methods of placement. The tube is placed under direct vision with a guidewire within the tube lumen using a drag and pull technique.[39,45,46] This method avoids exposure to ionizing radiation and can be performed in high-dependency patient care areas such as the intensive care unit.[38,39] Complications such as dislodgment, ampullary obstruction, and jaundice are reported with nasoenteric tubes.[47]

TABLE 56-2 Pediatric Enteric Tubes

	Tube French Size	*Tube Length (cm)*
Premature to neonate	4–5	38–41
Infants to young children	6–8	51–91
Older children to adolescents	8–14	91–114

Invasive Access for Enteral Nutrition

Placement of a feeding tube using surgical, radiologic, or endoscopic techniques is recommended for long-term enteral nutrition therapy or gastric decompression. There are a number of important advantages of these tubes over nasogastric or nasoenteric tubes in children. The gastrostomy or jejunostomy tube can be maintained in position for a longer period because it is fixed against the anterior abdominal wall, hidden under clothing. The tube does not interfere with breathing and avoids potential complications of chronic nasal discharge, sinusitis, and developmental abnormalities of the nose. In addition, for some children, repeated insertion of a nasogastric tube is associated with psychological trauma and feeding aversion. As these tubes are aimed at providing long-term home enteral nutrition therapy, once the decision has been made to place a gastrostomy or jejunostomy, education of the patient, parents, and caregivers should be initiated.

Gastrostomy Tube Gastrostomy tubes are usually large-bore tubes to deliver high feeding volumes and medications with minimal risk of occlusion. The original gastrostomy tubes were made of latex with a balloon retention device, such as the Foley catheter. Today, most gastrostomy tubes are made of a biocompatible material such as silicone and are anchored in place with either parallel bumpers or a mushroom or balloon at the gastric site and a retention disk at the skin. This allows the tube to be secured to the stomach wall without sutures. A wide range of gastrostomy tubes is available for use in children. The gastrostomy tube can extend through the stoma with at least two access ports for simultaneous administration of feed and medica-

tions. The low-profile gastrostomy tube devices allow the tube to be easily disguised under clothing, with the feeding tube connected only at the time of infusion. These tubes are particularly popular with older children and adolescents. Most tubes have an antireflux valve to prevent the reflux of gastric contents when the tube is accessed.

The introduction of the percutaneous endoscopic gastrostomy (PEG) technique has revolutionized the placement of enteric feeding tubes in children.[48] This relatively simple and fast procedure can be performed during esophagogastroduodenoscopy in an endoscopy suite with the use of conscious sedation and local anesthesia or general anesthesia. Although several techniques (Ponsky pull, Sachs-Vine push, Russel introducer) have been developed, all have in common the basic principle that the endoscope locates the site of tube placement from within the stomach while transillumination of the light from the endoscope through the abdominal wall identifies the site of skin incision. The ideal site is on the greater curvature of the stomach with the stoma sited on the anterior abdominal wall, below the costal margin with consideration of the axis of bending and of clothing.

With the Ponsky pull technique, the anterior abdominal wall is indented at the point of maximal transillumination of the endoscope light. This should be seen as a sharp indentation on the gastric wall by the endoscopist. A poorly defined indentation could indicate an overlying viscus (eg, transverse colon) and either an alternative site should be sought or the procedure converted to a surgical gastrostomy. After sterile preparation of the abdominal wall, local anesthetic is instilled and a small incision is made. The endoscopist distends the stomach with air and prepares the snare. A cannula is inserted perpendicular to the abdominal wall through the incision and punctures the gastric wall. The stylet is then removed; a thick suture is introduced along the cannula and is snared by the endoscopist. The endoscope and the suture are retrieved. The gastrostomy tube is tied to the suture and is slowly pulled back, by tension at the abdominal wall, through the mouth, along the esophagus, and into position on the gastric wall under direct vision by the endoscopist. Once the position has been verified by endoscopy, the external bolster can be opposed to the abdominal wall and the tube cut to the desired length. Postinsertion edema at the stoma site is common, and care should be taken not to pull the bolster too tight. To minimize infection at the stoma site, perioperative antibiotic prophylaxis is advocated.[49] The tube can be used within 12–24 hours in most patients.

Immediate complications of PEG placement include abdominal wall skin infection, necrosis of the skin or mucosa caused by a tight bolster, perforation of a viscus, and pharyngeal or esophageal trauma associated with the passage of the internal fixation device. Pneumoperitoneum is common following PEG placement and does not necessarily indicate a complication of insertion. Long-term complications include gastroesophageal reflux, granulation tissue formation, recurrent stoma-site infection, and dislodgment of the tube distally into the small bowel or proximally along the fistula track (ie, buried bumper syndrome).[50] Contraindications to the PEG technique include gastric varices, severe esophageal stricture, or abnormalities that might restrict the ability to oppose the stomach against the anterior abdominal wall, such as ascites, previous gastrointestinal surgery, or abnormalities in gastrointestinal rotation or position. Extreme care must be taken in patients with musculoskeletal deformities, hyperinflation of the lungs, organomegaly, immunodeficiency disease, cyanotic heart disease, or prior gastrointestinal surgery, including ventriculoperitoneal shunts.

Radiologic placement of gastrostomy tubes has been shown to be safe and relatively cost-effective in pediatric patients.[51,52] During this procedure, the stomach is distended with air instilled via a nasogastric tube. The stomach is then directly punctured under fluoroscopic control. A guidewire is inserted, followed by an introducer, a dilator, and then finally the feeding tube.

Because of the development of the PEG technique, surgical placement of a gastrostomy tube is generally restricted to patients who have a contraindication for PEG placement, have had a failed previous PEG placement, or require another surgical procedure in conjunction with tube placement, such as a fundoplication. Placement of the feeding tube can be performed using an open surgical approach or by laparoscopy. In the classic open gastrostomy technique (Stamm and Witzel techniques), the tube is inserted into the stomach along a serosa-lined tract, whereas in the revised version (Janeway technique), a small portion of the stomach is used to make a mucosa-lined tube attached to the skin as a modified fistula. The procedure for laparoscopic gastrostomy tube placement requires the creation of pneumoperitoneum and insertion of an umbilical catheter. The anterior stomach wall is fastened to the abdominal wall with temporary sutures. An opening (by a needle and a J-wire) is made in the stomach and progressively enlarged using dilators to finally allow the insertion of the feeding tube.[53] In experienced hands, laparoscopic gastrostomy is faster than the open procedure and is associated with reduced length of hospital stay and patient discomfort.[54]

Jejunostomy Tube The percutaneous endoscopic technique can be used to place an enteric tube using either a direct approach (direct percutaneous endoscopic jejunostomy; DPEJ) or by the creation of a PEG and placement of a specialized double-lumen tube (percutaneous endoscopic gastrostomy jejunostomy; PEJ).[55] The method for the DPEJ is similar to the PEG technique but with the endoscope placed in the jejunum. Transillumination of the bowel through the anterior abdominal wall and a sharp indentation easily seen within the small bowel by the endoscopist is necessary prior to the direct puncture of the duodenum or jejunum.[55] The suture is advanced along the cannula and is grasped by forceps rather than a snare. The PEGJ can be inserted as part of an initial PEG procedure or through an existing gastrostomy stoma. The specialized tube has a gastric lumen and port and another longer lumen and port for the small bowel. This enables gastric decompression during postpyloric feeding. Once the tube is inserted into the stomach, the intestinal lumen of the tube can then be advanced

into the duodenum or jejunum under direct endoscopic vision using a guidewire and grasping forceps.

Among the range of surgical techniques described for jejunostomy tube placement, the needle-catheter jejunostomy is the most common. Using this technique, a large-bore needle is tunneled through the seromuscular layers of the jejunum distal to the ligament of Treitz. The jejunum is then anchored to the anterior abdominal wall and the tube is secured to the skin. The tunneling procedure limits reflux of formula and heals quickly upon tube removal. In the presence of intestinal adhesions, severe intestinal disease, or high risk of infection or bleeding, straight insertion of a tube into the jejunum (Stamm technique) or direct jejunal stoma (Maydl technique) might be preferred. Laparoscopic placement of a jejunostomy tube requires two additional cannulae to bring the proximal jejunum into proximity of the abdominal wall and secure it there.[56]

Monitoring Tube Position

Before infusing any fluid through a gastric or enteric feeding tube, the position of the tube should be confirmed. Complications owing to incorrect placement or tube dislodgment can potentially be fatal. Plain or contrast radiography is a universally accepted method for assessing tube position. However, repeat radiologic studies are impractical and potentially unsafe in patients requiring long-term enteral nutrition therapy. As a result, bedside methods have been developed to screen for correct tube position. These include clinical observation, auscultation, and analysis of tube aspirate. If a nasogastric tube is incorrectly placed in the airways, cough, choking, and pulmonary distress can occur. However, these features can be minimal or absent if the tube is small or if tracheal reflexes are absent (eg, in coma or intubated patients). Although commonly used, auscultation does not reliably distinguish between either gastric and pulmonary placement or gastric and small-bowel placement.[57–59] Aspirates from either the feeding tube or the lungs can be assessed for color, appearance, pH level, and enzyme measurement (Table 56-3).[60–66] Aspirate pH value can be measured with a qualitative colorimetric test strip or a quantitative pH meter. Bilirubin can also be measured with spectrophotometer readings, using urine bilirubin test strips, or on the colorimetric visual bilirubin scale. Factors such as fasting for 4 or more hours, intermittent or continuous feeding, and use of acid inhibitors can modify these measurements.[60–66]

New approaches are being developed to confirm correct tube position. The measurement of myoelectric slow-wave frequencies has been proposed because these differ in the stomach (3 cycles/minute) and the duodenum (11 to 12 cycles/minute) and are not influenced by other gastrointestinal contractions.[67] The "bubbling under water" method relies on the exit of bubbles from the external end of the tube when placed under water if it has been misplaced in the lungs. However, misplacement of the tube into the bronchioles or pleura does not produce bubbles.[60] Other options under development include electromagnetic navigation devices, self-propelling tubes, fiberoptic tube tips, and ultrasonography-guided tube placement.[68–71]

DELIVERY OF ENTERAL NUTRITION

The method of delivery of enteral nutrition will depend on the route of administration (gastric, duodenal, or jejunal), characteristics of the feeding tube (small- versus large-bore catheter), the desired feeding pattern (bolus, intermittent, or continuous), and the cost and availability of equipment. Bolus tube infusion usually mimics the normal meal pattern based on age. Intermittent feedings are delivered at a specified rate over 1 or more hours, with up to 8 hours per day of gut rest. Continuous feeding delivers a constant-rate infusion, usually by a pump, over a prolonged period with less than 8 hours per day of gut rest.

Gastric feeding is preferred because it is considered more physiologic, allows bolus feeds through large-bore tubes, and is generally cheaper and easier to administer.[7] Many patients intolerant of bolus feeds can be successfully fed intragastrically using an intermittent or continuous feeding regimen. Jejunal feeding is an option for patients with disorders of gastric or esophageal anatomy or function and in the nutritional management of the critically ill.[2,3,8,9,38,39] Jejunal feedings are usually delivered as an intermittent or continuous infusion because rapid-rate infusion of nutrients is often limited by abdominal discomfort, diarrhea, or dumping syndrome.

There are specific physiologic and metabolic considerations associated with continuous-rate feeding. During continuous intragastric feeding, gastric emptying increases parallel to the rate of infusion if the infusion rate is maintained at less than 3 kcal/minute.[71] Because increased caloric density and osmolarity of the formula can delay gastric emptying, formulas with caloric densities greater than 1 kcal/mL should be avoided. In animals, the absorptive capacity of the proximal small intestine is unchanged during continuous enteral nutrition. However, the protein and DNA content of the distal small intestine and the enzymatic and functional capacity of the distal small intestine and colon are reduced.[72] The relative lack of nutrients

TABLE 56-3 Bedside Evaluation Tests for Tube Placement in Children[61,63–67]

Aspirate	*Color and Appearance*	*pH Value*	*Pepsin (μg/mL)*	*Trypsin (μg/mL)*	*Bilirubin (mg/dL)*
Gastric secretions	Yellow-gray or white-tan; cloudy	< 6	> 100 (> 20)*	< 30 (< 50)*	< 5
Intestinal secretions	Green	> 6	< 100 (< 20)*	> 30 (> 50)*	> 5
Respiratory secretions	Yellow-gray; mucoid	6–8	< 100 (< 20)*	< 30 (< 50)*	< 5

*Trypsin and pepsin ranges specific for children.

reaching the distal gut during jejunal feeding with an elemental or hydrolyzed formula could explain this observation. This might provide an opportunity for the treatment of gastrointestinal inflammatory diseases, such as Crohn's disease, by providing nutrients to the proximal intestine but reducing antigenic stimulation to the distal gut.[73]

Energy intake goals are more successfully achieved in critically ill patients receiving postpyloric feeds compared with those receiving intragastric feeds.[74] In addition, energy expenditure owing to the thermic effect of feeding is lower in patients receiving continuous enteral nutrition than in patients receiving the same quantity of nutrients delivered by bolus.[75] The continuous delivery of nutrients into the small intestine affects glycemic control by modifying the typical fluctuating pattern of insulin and glucagon production.[76,77] The reduction in steatosis during continuous enteral nutrition compared with parenteral nutrition with the same carbohydrate intake is also consistent with this observation.

ENTERAL FORMULAS

In the early days of enteral nutrition, a mixture of blenderized diets and milk products was administered. This approach was associated with the potential for nutritional imbalance, micronutrient deficiencies, feeding intolerance, and tube blockage. Today, there is a wide range of enteral nutrition products suitable for use in infants and children (see Chapter 55, "Standard and Specialized Enteral Formulas" and Appendix 3). Most formulas are designed to provide complete macro- and micronutrient requirements as the sole nutritional intake. Specific needs of different ages and stages of development are reflected in the composition of preterm infant, full-term infant, and pediatric enteral nutrition formulations. Modular formulas are specialized combinations of nutrients that provide a nutritional supplement or fulfill a specific nutrient requirement. A recent area of development has been the introduction of disease-specific enteral formulas. These formulas aim to modify the metabolic or gastrointestinal response to feeds by limiting some nutrients, supplementing others, or both (eg, branched-chain amino acid formula for hepatic failure and immune-enhancing formula for critical illness).[78–81]

The majority of patients with normal gastrointestinal tracts will tolerate the gastric administration of a polymeric formula. In polymeric formulas, intact protein or polypeptides are usually derived from cow's milk or soybeans. The nitrogen to non-nitrogen calorie ratio approximates 1 to 150. Carbohydrates are sourced from different starches, including corn and tapioca. Maltodextrin and hydrolyzed cornstarch, glucose-derived saccharides, and corn syrup are commonly used. Formulas can have different lactose contents. Fats are usually present as polyunsaturated fatty acids from corn, safflower, sunflower, or soybean oil or from animal fat. Some enteral nutrition formulas contain soluble fiber. The soluble fiber is added primarily to normalize gastrointestinal transit, but after it is converted to short-chain fatty acids it provides an additional source of calories and can exert trophic effects on the colonic mucosa. Electrolytes, vitamins, and trace elements are added to approximate the Recommended Dietary Allowance at the target volume. At standard dilution, the caloric content of infant formula is usually 0.67 kcal/mL, and of standard enteral formula, 1 kcal/mL. Concentrated enteral nutrition formulas are also available (2 kcal/mL). The osmolality can range widely depending on the nutrient composition and caloric density (~ 200 to 750 mOsm/L).

In patients with underlying gastrointestinal disease or those requiring jejunal feeding, an oligomeric formula might be indicated. The protein in oligomeric formulas is hydrolyzed to peptides or a combination of peptides and amino acids. The carbohydrate complexity varies among formulas, although many oligomeric formulas are lactose free. A proportion of medium-chain triglycerides is often provided to improve fat absorption. Elemental formulas contain completely digested macronutrients, such as monosaccharides, medium-chain triglycerides, and crystalline amino acids, with an essential to nonessential amino acid ratio reflecting high biologic protein values. Lactose and gluten are absent and residues are low. The unpalatability and high osmotic load of simple sugars and amino acids limit the use of elemental formulas to tube feeding when feeding intolerance occurs with other types of formula (eg, severe malabsorption or short-bowel syndrome).

Advances in the understanding of the role of specific nutrients and their effects on metabolism have led to modification of enteral nutrition formulas for treatment of specific diseases. The aim of the disease-specific formulas is to provide therapeutic benefits in addition to the maintenance of general nutritional status. Glutamine-enriched formula has been advocated for the prevention and treatment of intestinal mucosa injury associated with chemotherapy and critical illness.[78,80] Omega-3 fatty acids have been supplemented in infant formula to enhance neurologic development.[82] So-called immune-enhancing formulas supplemented with arginine, glutamine, ribonucleic acid nucleotides, medium-chain triglycerides, or omega-3 fatty acids have been used in the treatment of critically ill patients.[78–81] Evidence for improved clinical and economic outcomes of many of the disease-specific formulas, compared with standard formulas, is still required to justify recommendations of their routine use.[78,80]

COMPLICATIONS OF ENTERAL NUTRITION THERAPY

Despite the potential benefits of enteral nutrition, complications can occur (Table 56-4).[83–88] Fortunately, life-threatening events are rare. However, problems related to the tube, the method of delivery, or the composition of the formula can seriously interfere with achieving nutritional goals. To minimize complications, prior consideration should be given to the patient's medical and physical condition, including any metabolic or electrolyte abnormalities, previous diet, dietary tolerance, and the time that has elapsed since the last significant oral or enteral nutrition.

Gastrointestinal Complications

Intestinal discomfort, bloating, cramping, diarrhea, nausea, and vomiting can occur during enteral feeding. Whenever symptoms occur, the position and integrity of the tube should be confirmed. In some cases, these symptoms relate to the high osmolality of the formula or the rate of infusion; alterations to the formula composition or infusion rate will be sufficient to improve feeding tolerance. The assessment of a sample of stool from a patient with diarrhea can assist in directing further investigations as required (bacterial culture, guaiac test, absorptive status by pH, microscopy, and reducing substances). The use of concomitant medications should be reviewed for possible drug–nutrient interactions or gastrointestinal side effects. Bacterial contamination of the feed or the tubing can result in diarrhea or vomiting. The method of formula preparation and storage and the technique of hanging and administering should be reviewed.[83] Samples of the feed, the tubing, and the feeding reservoirs are necessary to confirm this diagnosis.

Patients with a primary gastrointestinal disorder could be at risk of bacterial overgrowth owing to disturbances in gut motility. Bacterial culture of an intestinal biopsy or a lactulose breath hydrogen test will assist in establishing the presence of bacterial overgrowth of the small intestine. Constipation associated with enteral nutrition is uncommon and when it occurs is usually associated with insufficient fluid or fiber intake, intestinal dysmotility or obstruction, or medications. Gastroesophageal reflux can be exacerbated by tube feeding. The nasogastric tube can split open the lower esophageal sphincter, and irritation owing to tube trauma can contribute to lower sphincter incompetence. Placement of a gastrostomy tube plicates the stomach against the anterior abdominal wall, distorting the normal gastric anatomy, with a potential impact on gastric function. Owing to the frequency of this complication in high-risk patients, such as those with cerebral palsy or cystic fibrosis, assessment for gastroesophageal reflux with a 24-hour pH probe and nuclear gastric emptying study is routine prior to gastrostomy tube placement may be considered.

If the gastrostomy or jejunostomy tube is no longer required, the tube can be removed after consideration of the original method of insertion. For tubes inserted using a PEG, DPEJ, or PEGJ technique, the tube can usually be withdrawn and the stoma edges opposed using a dressing or suture. In most cases, this will be sufficient to allow closure of the stoma and tract within days to weeks. This process can be assisted with the use of gastric acid suppression aimed at minimizing gastric secretion. If the gastro- or jejunocutaneous fistula does not close spontaneously, formal surgical closure might be required. Patients in whom the gastrostomy or jejunostomy tube has been inserted using the traditional surgical approach usually require surgical closure of the fistula.

Pulmonary Complications

Aspiration of gastric contents—and pneumonia owing to aspiration—incorrect tube placement, or tube dislodgment into the airway can be fatal. Children at high risk include those with chronic neurologic disease, depressed conscious state, intestinal dysmotility, or severe gastroesophageal reflux and those patients requiring mechanical ventilation. In addition to checking tube position, tracheal aspirates can be measured for glucose content or fat-laden macrophages.[84] The addition of blue dye to the formula to assess tube position and aspiration in intensive care patients should be avoided because it has been associated with fatalities.[26]

Infectious Complications

Irritation owing to the mechanical trauma of tubes or exposure to gastric or intestinal secretions render the skin and mucosa susceptible to infection. A well-fitting, well-maintained device specifically designed for enteral nutrition use will limit this complication. Contamination of the formula and the delivery set can occur as a result of preparation or administration of the feed.[83] Nasogastric tubes are also associated with chronic nasal discharge, otitis media, and sinusitis.

Mechanical Complications

Mechanical complications related to enteral tube feeding are common. However, these can generally be treated and do not involve the same risks as a central venous catheter in critically ill children.[85–88] Tube occlusion can occur as a result of problems related to the tube (length, caliber, characteristics), the infusion (formula, drugs), pumps and clamps, the method and rate of delivery, and the level of tube care (method, frequency). Infusions that contain a highly viscous formula or crushed or powdered drugs are often associated with tube occlusion.

If flushing the tube with warm water is unsuccessful in clearing the blockage, a number of other options are available. The instillation of pancreatic enzyme supplements is sometimes successful in clearing a blockage. The use of meat tenderizer is not recommended because of its high sodium content and the risk of tube breakage during infusion. Cytology brushes, guidewires, neonatal tubes inserted into larger tubes, and specially designed catheters have been developed to treat tube occlusion. A biliary catheter for endoscopic retrograde cholangiopancreatography was recently described for the treatment of an occlusion in a nasojejunal tube.[89] The key to the prevention of tube occlusion is careful monitoring and repeated flushing of the tube. Mixing of drugs and formula should be avoided.

Irritation can occur anywhere along the interface between the tube and the skin or mucosa, resulting in inflammation, ulceration, or even perforation. Granulation tissue formation at the stoma site can occur as a result of chronic irritation. The migration of tubes with an internal balloon or retention device distally along the gastrointestinal tract can cause bowel obstruction. Migration of a gastrostomy tube along the fistula tract can cause pain and inflammation around the site or buried bumper syndrome.[50]

Metabolic Complications

Compared with what is seen with parenteral nutrition, metabolic complications associated with enteral nutrition are uncommon. Patients with chronic malnutrition or cardiac, hepatic, or renal impairment require careful monitoring of fluid and electrolyte status to prevent imbalance.[90] Patients

TABLE 56-4 Complications Associated with Enteral Tube Feeding

Complication	*Possible Cause*	*Prevention and Treatment*
Tube occlusion	Failure to flush tube regularly, inappropriate feed or medications placed down tube, inadequately dissolved feed, high-energy feed	Flush tube regularly with water; use prescribed feeds and medications only
Tube dislodgment	Inadequate securing of tube, inadequate monitoring of tube position	Check tube placement every 8 hours during continuous feeds and before every bolus or intermittent feed
Accidental tube removal	Inadequate securing mechanism, deterioration of tube (balloon rupture)	Review method of securing tube; consider specific dressings or clothing to prevent access to tube; regularly review tube function and integrity; ensure availability of replacement or "emergency" tube to prevent stoma closing prior to reinsertion
Diarrhea	Gastroenteritis, medications (antibiotics, sorbitol-containing drugs), rapid administration or bolus feeds, malabsorption, formula intolerance (lactose, hyperosmolar)	Review for possible causative factors including medications, formula, and gastrointestinal absorptive function; consider changing rate of delivery or formula as indicated (reduced osmolality, fiber enriched, lactose free)
Bloating, abdominal cramps	Gastrointestinal dysmotility, bowel obstruction, intolerance to formula (lactose intolerance), bacterial overgrowth	Reduce or cease feeds according to severity until cause is defined; consider investigations to address possible causes
Constipation	Inadequate fluid intake or large fluid losses, gastrointestinal dysmotility, medications, immobilization, underlying medical condition	Correct fluid losses and provide adequate ongoing fluid requirements; review medications; consider stool softeners or fiber supplementation
Dumping syndrome	Rapid infusion of high-volume or hypertonic feeds into duodenum or jejunum, postgastric surgery or vagotomy, gastrostomy sited in distal gastric antrum	Administer continuous feeds, reduced volume or osmolality of formula; use uncooked cornstarch
Nosocomial infection (bacteremia, pneumonia)	Enteral feed or equipment contamination, aspiration, increased risk with gastric acid suppression in paralyzed or ventilated patients	Change sets every 24 hours; limit feed hang time; use sterile system and sterile water to reconstitute feeds; culture feeds and equipment if contamination suspected; review for "silent" reflux or aspiration or tube dislodgment
Metabolic complications (increased or decreased glucose, phosphate, potassium or magnesium)	Complication of the primary disease (renal failure) or treatment (amphotericin), refeeding syndrome	Correct any significant electrolyte abnormalities prior to initiating enteral nutrition; undertake regular biochemical monitoring particularly in malnourished patients; gradually increase feed volume and concentration if at risk of refeeding syndrome
Malabsorption	Underlying gastrointestinal disease (cystic fibrosis), inappropriate formula selection or rate of administration	Assess absorptive status and alter formula and rate of delivery as appropriate
Perforation	Tube malposition, wrong type of tube, disorders of mucosal integrity	Ensure appropriate tube selection and placement technique; regularly check tube position; surgical treatment might be required
Gastric Tube Feeding (General)		
Vomiting, nausea	Gastroenteritis, intolerance to formula, rate of infusion too rapid, medications, bacterial contamination of feed, delayed gastric emptying	Review feeding regime and medications; culture feeds and equipment if contamination is suspected; consider intermittent or continuous infusion, postpyloric administration, or prokinetic agents
Gastroesophageal reflux	Underlying abnormality of esophagus or stomach associated with reflux or medical illness (eg, neurologic, pulmonary diseases), mechanical aspects related to tube	Assess for underlying reflux; consider antireflux therapies or postpyloric feeding
Large-volume gastric aspirates	Delayed gastric emptying related to underlying medical condition (eg, neurologic disease, critical illness, diabetes, intestinal pseudo-obstruction) or medications	Review medications; consider continuous or postpyloric feeds or prokinetic agents
Pulmonary aspiration	Incorrect tube placement, tube dislodgment, gastroesophageal reflux, gastric stasis, or vomiting (neurologic disorders, coma)	Cease feeds and check tube position; consider postpyloric feeding
Gastrointestinal bleeding	Tube-related irritation, ulceration, or perforation; vitamin K deficiency	Review tube position and gastrointestinal status; assess for alternative tube placement sites; try gastric acid suppression; supplement with vitamin K when indicated
Cellulitis	Postplacement contamination of wound, inadequate cleaning of stoma site, bolster too tight, chronic leakage through stoma	Perioperative antibiotics during tube placement, regular skin care, antibiotic therapy as appropriate; check tube and stoma site for areas of mechanical irritation and poor fit
Stoma leakage	Site infection; incorrect tube size, type, or position; perished tube; gastric stasis (eg, diabetes, pseudo-obstruction); medications	Examine site; assess tube integrity, suitability, and position; check balloon volume; replace with larger or different type of tube if appropriate; treat stoma site infection
Nasogastric Tube Feeding		
Nasal airway obstruction	Inappropriate tube size, nasopharynx disorders	Insert smaller-bore tube
Chronic nasal discharge or ulceration Epistaxis Sinusitis or otitis media	Inappropriate tube size or composition, immunodeficiency, disorder of mucosal or skin integrity	Re-evaluate tube size and type; regularly change tube; assess for alternative sites for tube placement
Feeding aversion	Repeated tube replacement in infants and young children, development implications of tube feeding	Consider alternatives to nasogastric route in infants requiring long-term enteral nutrition; involve speech therapist early
Esophageal perforation	Incorrect tube placement, ulceration related to tube position, underlying disorders of mucosal integrity (eg, epidermolysis bullosa)	Use appropriate tube placement technique; regularly check tube position
Pulmonary intubation	Incorrect tube placement or tube dislodgment	Use appropriate tube placement technique; take particular care in children with neurologic disorders or disturbances of conscious state

Continues

TABLE 56-4 Complications Associated with Enteral Tube Feeding (*Continued*)

Complication	*Possible Cause*	*Prevention and Treatment*
Gastrostomy Tube Feeding		
Granulation tissue formation	Chronic inflammation at stoma site, leakage, tube moving too freely along tract	Check tube size, type, and position; specialized dressings, corticosteroid cream, or cautery might be required
Site swelling or tenderness	Site infection, migration of tube along tract, tube shaft too short or bolster too tight	Examine site; tube removal and replacement might be required
Fasciitis	Incorrect tube or bolster position	Remove tube; obtain surgical opinion; administer intravenous antibiotics
Buried bumper syndrome	Retaining device and bolster secured too tight	Remove tube; administer antibiotics
Gastritis, gastric ulceration, or perforation	Trauma caused by tube, often of wall opposite insertion site, wrong tube type (composition or design)	Consider change in tube design to minimize trauma and gastric acid suppression
Duodenal or Jejunal Tube Feeding		
Reflux into stomach	Tube placed in proximal small intestine, dysmotility	Consider more distal placement
Bowel obstruction	Tube too large, tube malposition, disorder of gastrointestinal anatomy	Review tube size and position
Volvulus	Tube providing an abnormal fixation point	Remove tube; obtain surgical review

commencing enteral nutrition who have had a period of prolonged fasting or inadequate nutritional intake or significant weight loss (> 10% body weight) should be monitored for the metabolic features of refeeding syndrome. Daily monitoring of fluid status, serum sodium, potassium, phosphate, and magnesium levels is required until stability has been achieved with feeding advancement. Serum glucose levels, which are usually stable during continuous enteral nutrition therapy, can increase with overfeeding or as part of a stress response during critical illness. Hypoglycemia during intermittent feeding can be prevented with a progressive slowing of the rate of infusion in the period prior to disconnection. Dumping syndrome is reported in patients during enteral feeding in response to the presence of nutrients within the proximal intestine.[91] This is often associated with a rapid infusion of a formula with a high nutrient density and can be treated with modifications to the formula (such as adding uncooked cornsatch) or rate of delivery.[91]

HOME ENTERAL NUTRITION

Over the past two decades, advances in tube design, methods of delivery, and formulas have made enteral nutrition therapy safer, cheaper, and easier to administer for a wide range of disorders in childhood.[5,92–94] With attention to appropriate patient selection, education, and providing adequate technical support, enteral nutrition therapy can be safely and effectively provided in the home.[92–94] In 1992, data from Medicare and insurance companies estimated that there were about 152,000 patients of all ages receiving home enteral nutrition in the United States.[5] The rapid growth of home enteral nutrition therapy observed in the United States in 1987 had reached a plateau in 1992.[5]

In contrast, in Britain, home enteral nutrition therapy has been increasing rapidly—at a rate of up to 20% per year—and is about 10 times more common than home parenteral nutrition therapy.[94] Of patients receiving home enteral nutrition therapy in Britain, 40% are children, compared with 5 to 20% in three US cohorts.[95]

Best-practice guidelines for the administration of safe and effective home enteral nutrition therapy have been developed by national nutrition support organizations.[7,94] These guidelines take into consideration patient selection, assessment, monitoring, and the development of the enteral nutrition plan, including methods of implementation, documentation, and protocols for termination of therapy. Education about and management of home enteral nutrition therapy is ideally performed by a multidisciplinary team, including the gastroenterologist or surgeon, dietitian, stomal therapist, or nurse specialist.[9,94] An essential component of a successful home enteral nutrition service is availability of health professionals to provide support to the patient or caregivers at home to address concerns and direct appropriate intervention when necessary. A mechanism should be established to manage after-hours tube malfunction. To facilitate this process, all patients should carry a card with the type and size of tube and the date of last insertion clearly listed. Written documentation of routine tube care, as well as the recommended steps to take in the event of tube malfunction, is invaluable to the patient and caregiver at home.

Regular review by the multidisciplinary home enteral nutrition team should be a part of the routine management of patients using this therapy. At these appointments, all aspects of the administration of enteral nutrition are assessed. The tube is examined for size, function, and integrity and can be changed if necessary. The stoma site is examined. The method of delivery is reviewed, along with protocols for formula preparation. The intake of formula is assessed with reference to the nutritional goals. The patient is examined for growth, weight gain, and nutritional status; changes to the feeding regimen can be made where appropriate. Laboratory markers of nutritional status can be obtained as indicated. Complications of the tube or feeding protocol can be addressed.

INTERACTIONS BETWEEN DRUGS AND ENTERAL FEEDING

Administration of medications through an enteral feeding tube, either in combination with formula or alone, is problematic because only a few drugs have been tested and

approved for tube delivery. Characteristics of the tube's composition can influence the binding of drug to the tube wall (eg, carbamazepine reacts with polyvinyl chloride feeding tubes).[7,96] Interactions between a drug and a nutrient can result in an undesired side effect of the drug or feeding intolerance. Drug–nutrient interactions can result in changes in medication bioavailability, distribution, metabolism, or excretion.[97] Drug–nutrient interactions are described with substances containing calcium, zinc, and iron or when acidic and neutral liquid medications are combined with casein or soy protein. Impaired absorption of phenytoin is well documented in the literature and occurs as a result of pharmacokinetic incompatibility.[7] Long-chain fatty acids can enhance the absorption of lipid-soluble drugs but hasten the degradation of other medications (eg, carbamazepine).

Liquid preparations of medications are preferred by children and for enteral administration. However, liquid drug preparations tend to have a high osmolality, which can cause gastrointestinal intolerance if infused into the jejunum. The majority of oral liquid medications have an osmolality of between 1,000 and 11,000 mOsm/kg.[98] The osmotic properties of these liquids are usually attributable to the presence of sorbitol, propylene glycol, or polyethylene glycol. Although included among the inactive ingredients in labels, they are not quantified. Osmotic diarrhea and delayed gastric emptying can occur if the cumulative dose is more than 20 g (range, 7.5 to 30 g). The resolution of diarrhea after cessation of a liquid medication containing sorbitol in tube-fed patients is suggestive of a cause–effect relationship.[99]

CONCLUSION

Advances in tube placement techniques, tube design, delivery systems, and enteral formulas have enabled the safe and effective provision of enteral nutrition therapy for a broad range of disease indications in children. Successful enteral nutrition therapy has enabled the limitation of parenteral nutrition therapy, resulting in important benefits in terms of safety, manageability, and cost. The management of nutritional problems in patients with chronic diseases, such as neurologic disorders and cystic fibrosis, can be enhanced by home enteral nutrition therapy. The development of disease-specific formulas provides new therapeutic options. Further improvements in technology enabling light, simple, feeding pumps and modifications to tube design will continue to assist in the administration of enteral nutrition to children.

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CHAPTER 57

PARENTERAL NUTRITION

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Intravenous nutritional care was introduced more than 50 years ago when protein hydrolysates first became available. In the late 1930s, Shohl and colleagues demonstrated positive nitrogen balance with infusion of glucose plus protein hydrolysates in pediatric patients.[1] In 1944, Helfrick and Abelson infused 50% glucose, 10% casein hydrolysate, and a homogenized emulsion of olive oil and lecithin in an alternating manner into a 5-month-old marasmic infant for 5 days via a peripheral vein.[2] During the next 20 years, parenteral nutrition (PN) in infants and children was unsuccessful, largely because of the inability of peripheral veins to tolerate the hyperosmolar infusates. Significant side effects, including allergic reactions and marked elevations of body temperature, further complicated attempts at PN. Often, there was inadequate provision of calories to allow the nitrogen to be used efficiently. Intravenous fat preparations also were used, but they were removed from general use because of toxic side effects, such as thrombosis, embolism, fever, vomiting, rash, eosinophilia, and thrombocytopenia.[3,4]

In the late 1960s, a group of surgeons at the University of Pennsylvania demonstrated, first in beagle puppies and later in an infant, that the continuous intravenous infusion of hypertonic dextrose and amino acids through deep central venous catheters (CVCs) could provide adequate caloric intake safely and allow normal growth and development.[5–7] The development of a safe intravenous fat preparation, Intralipid (Kabivitrum, Alameda, CA), was another major advance in clinical PN. Fat emulsions offered the dual advantage of high caloric density and isotonicity, thereby meeting caloric requirements with less damage to peripheral veins. In the mid-1970s, protein hydrolysates were replaced by crystalline amino acid solutions. Their composition was more controlled than that of the hydrolysates, reducing the risk of allergic reactions. In the 1980s, crystalline amino acid solutions specifically designed for newborn infants became available. Finally, appreciation of the vitamin and trace element requirements of neonates and older children led to the development of the infusible vitamin and mineral solutions designed to meet these needs.

INDICATIONS

PN is indicated for most patients who are unable to tolerate enteral feedings for a significant period of time.[8] Four or 5 days without adequate oral nutrient intake is an indication for instituting some form of PN. Even 2 to 3 days without adequate nutritional intake for very low birth weight infants or infants with preexisting nutritional depletion is likely to result in significant depletion of their limited endogenous stores. PN is not indicated in patients with adequate intestinal function, in whom nutrition can be maintained by oral or tube feedings. Relative contraindications to PN include intended use for fewer than 5 days and the probability that a patient will die imminently because of underlying disease. Although PN is a potentially life-saving therapy and is now an accepted practice, experience has demonstrated metabolic, mechanical, and infectious complications. Therefore, candidates for PN should be selected carefully (Table 57-1).

PN is supportive therapy for some illnesses and primary therapy for others. It is supportive for burn patients, patients with protracted diarrhea and malnutrition, and patients with congenital gastrointestinal anomalies. Studies have documented its value as primary therapy for patients with gastrointestinal fistulas, short-bowel syndrome, renal failure, and Crohn's disease. In addition, PN is suggested for use in malnourished oncology patients, patients with hepatic failure, malnourished patients before major surgery, patients with cardiac cachexia, and those requiring prolonged respiratory support. Nutritional repletion in these patients seems to reduce the incidence of sepsis and encourage proper wound healing and a return of normal skin test reactivity. Although PN is used to replenish the malnourished child, it can be started prophylactically in clinical situations in which prolonged starvation is expected (eg, after extensive intestinal surgery in the newborn infant and after bone marrow transplantation in the older child). Other indications for PN include a recent loss of more than 10% of body weight with a concomitant inability to ingest sufficient nutrients to reverse this state, and marginal nutritional reserves in a patient who is unable to ingest sufficient calories to prevent further negative nitrogen balance.

Infants receiving central venous PN retain nitrogen and grow as well as normal infants fed human milk or standard formulas. PN has been directly credited with improving the survival of infants with certain conditions. The mortality rate of patients with gastroschisis and intractable diarrhea has decreased to approximately 10%

TABLE 57-1 Indications for Parenteral Nutrition in Pediatric Patients

Condition	*Examples*
Surgical gastrointestinal disorders	Gastroschisis, omphalocele, tracheoesophageal fistula, multiple intestinal atresias, meconium ileus and peritonitis, malrotation and volvulus, Hirschsprung's disease with enterocolitis, diaphragmatic hernia
Intractable diarrhea of infancy	
Inflammatory bowel disease	Crohn's disease, ulcerative colitis
Short-bowel syndrome	
Serious acute alimentary diseases	Pancreatitis, pseudomembranous colitis, necrotizing enterocolitis
Severe malabsorption	Idiopathic villous atrophy
Chronic idiopathic intestinal pseudo-obstruction syndrome	
Gastrointestinal fistulas	Fistulas in Crohn's disease
Hypermetabolic states	Severe burns and trauma
Renal failure	
Low birth weight infants	Asphyxiated infants, very low birth weight infants, respiratory distress syndrome
Malignancies	Especially those receiving abdominal irradiation (causing radiation enteritis) or chemotherapy, which leads to severe nausea and intestinal dysfunction
Marrow and organ transplantation	
Special circumstances	Anorexia nervosa, cystic fibrosis, cardiac cachexia, hepatic failure, sepsis
Rare disorders	Congenital microvillous inclusion disease, chylothorax and chylous ascites, *Cryptosporidium*-induced secretory diarrhea

from the 75 to 90% rate before the development of PN.[8] This drop in mortality seems to be attributable to the prevention of starvation.[8]

Low birth weight infants constitute the largest group of pediatric patients who receive parenteral nutrients.[9] Premature infants, especially those who have respiratory distress syndrome and are incapable of full oral feedings, often receive PN because of their extremely limited substrate reserve, very rapid growth rate, and possible susceptibility to irreversible brain damage secondary to malnutrition. A classic study that remains a model for nutritional support in the very low birth weight infant was performed by Cashore and colleagues.[10] They described 23 infants who weighed less than 1,500 g at birth in whom peripheral PN was begun on day 2 of life to supplement enteral feedings; these infants regained their birth weight by the age of 8 to 12 days and achieved growth rates that approximated intrauterine growth.

Most centers do not feed an asphyxiated infant enterally for the first 5 to 14 days after the insult. This practice is extrapolated from animal data on gut cellular proliferation and migration. The intestinal mucosa of newborn and suckling rats has a very slow rate of cellular proliferation and migration compared with that of adult animals.[11–13] This same slower rate of turnover of intestinal epithelia could exist in the newborn human.[14] Asphyxia, which in itself can cause significant injury to the gastrointestinal tract, can predispose the premature infant to necrotizing enterocolitis (NEC). Because enteral feedings impose additional risks in this fragile situation, they should be withheld and PN given instead. There is evidence that enteral feeding could be the critical element that triggers postnatal gut maturation through release of gut peptide hormones.[15] Intestinal development is arrested when animals receive PN with no enteral nutrients, but maturation resumes on reintroduction of intraluminal nutrients.

PARENTERAL NUTRIENT REQUIREMENTS

Calories (Energy)

There are many different recommendations and methods to calculate the caloric needs of children. The World Health Organization (WHO) recommendations are based on evaluations of several thousand children and have proven to be relatively accurate for children more than 1 year of age.[16] The WHO recommendations provide an estimated resting energy expenditure (REE), which can then be multiplied by a factor to adjust for catch-up growth, activity, and medical status, to provide an estimate of total daily caloric needs. In obese patients (weighing more than 120% ideal body weight), the Schofield height/weight equation more accurately predicts energy needs.[17] Tables A-23 to A-26 show energy expenditures for infants and children, along with activity and stress adjustment factors, and Tables 57-2 and 57-3 show protein and caloric needs. Predictive equations often do not accurately reflect patients' needs.[18] Indirect calorimetry (measurement of oxygen consumption and carbon dioxide production) provides a precise and practical measurement of REE.[19] This measurement should be used when possible, especially for patients with increased needs and for those not responding to nutritional therapy. Indirect calorimetry technology in the nonintubated patient not receiving supplemental oxygen is well standardized, but measurements in the newborn baby and the intubated patient receiving supplemental oxygen are fraught with technical difficulties.

Adequate protein intake must be provided with adequate caloric intake for optimal caloric use and growth (see Tables 57-2 and 57-3). In a controlled trial of 14 premature appropriate-for-gestational-age infants, two isocaloric (60 kcal/kg/day) intravenous feeding regimens were compared, one with glucose alone and the other with glucose plus 2.5 g/kg/day of crystalline amino acids.[20] Infants on the glucose-only regimen had a nega-

TABLE 57-2 Protein and Energy Requirements for Infants

	Full Term		
	Preterm	*0–6 mo*	*6–12 mo*
Energy (kcal/kg/d)	100–120	90–110	80–100
Protein (g/kg/d)	2.5–3.5	2.5–3.0	2.0–2.5

tive mean nitrogen balance, whereas those fed glucose plus amino acids had a positive balance. There was no significant weight gain in either group. Additionally, intravenous intakes of 70 to 90 kcal/kg/day have resulted in weight gain in premature infants, and energy intakes providing more than 70 kcal/kg/day (including intakes of 2.7 to 3.5 g/kg/day of protein) resulted in nitrogen accretion and growth rates similar to in utero values.[21] Earlier studies of adults suggested that additional stresses, such as sepsis, increase caloric requirements by as much as 40%. These conclusions have been questioned[22]: severe stress in children probably does not increase requirements by any more than 15%. The impact of stress on caloric requirements in preterm infants has not been critically studied, but decreased physical activity could reduce demands and balance the increased needs owing to the stress associated with the underlying disorders. Adult studies suggest that energy requirements of patients with disease are similar to or less than those of healthy subjects for the same reasons.

Early aggressive nutritional support is being recommended by many neonatologists to improve premature infants' nutritional status.[23] One key component is protein intake. In most nurseries around the world, preterm infants start at only 0.5 g/kg/day. When given parenteral glucose alone, an infant will lose 1% of body protein stores per day (approximately 1 g/kg/day). Parenteral protein is usually started on day 1 or 2 of life, or as soon as serum electrolytes are stable. A number of studies over the past 12 years indicate that most preterm infants will tolerate 1.5 to 2 g/kg/day of parenteral amino acids in the first day of life and that these infants are not catabolic. Several studies have shown that the parenteral intake required to avoid catabolism in extremely low birth weight infants could be as low as 1.1 to 1.5 g/kg/day when administered with 30 kcal/kg/day of energy. To achieve intrauterine rates of protein deposition, the upper limit of protein intake is 3 g/kg/day for full-term infants and up to 4 g/kg/day for most preterm infants.[24]

Fluid restrictions mandated by severe respiratory, cardiac, or renal disease can prevent the delivery of adequate calories—even when the calories are given as central PN. Peripheral PN seems best suited for minimally stressed patients undergoing a limited course of PN for whom full growth and development are not the therapeutic goals. Central PN is indicated either for nutritional repletion of a seriously malnourished patient or when full growth and development are essential. Concentrations of glucose of up to 30 to 35% might be necessary to provide sufficient carbohydrate calories. PN solutions should be balanced, especially when there is a risk of PN-induced liver disease. Regimens high in carbohydrate increase the respiratory quotient, resulting in excessive carbon dioxide retention, which leads to increased difficulty in weaning from the ventilator.

TABLE 57-3 Protein Requirements: Children and Adolescents

Age (yr)	*Protein (g/kg/d)*
1–6	1–2
7–10	1–2
11–14	1–2
15–18 (boys)	0.9–2
15–18 (girls)	0.8–2

Fluids

Fluid requirements depend on hydration status, size, age, environmental factors (eg, radiant warmers, phototherapy), and underlying disease. Daily maintenance fluid requirements for children are outlined in Table 57-4. Premature babies have unique requirements. Factors that increase fluid requirements include radiant warmers, conventional single-walled incubators, and phototherapy; those that decrease fluid requirements include heat shields, thermal blankets, and double-walled incubators. Furthermore, excess fluid intake (more than 150 mL/kg/day) in low birth weight infants can be associated with patent ductus arteriosus, bronchopulmonary dysplasia, NEC, and intraventricular hemorrhage.[25]

During PN, it might be necessary to give fluids in excess of maintenance amounts to provide adequate calories, especially if using a peripheral vein, but one must be careful to avoid fluid overload. Highly concentrated glucose solutions and 20% fat emulsion are used to decrease total fluid volume. It is important not to use PN for replacing ongoing losses because the fluid contains not just electrolytes but protein, vitamins, and minerals. We recommend the provision of PN to meet maintenance fluid needs and the use of specifically designed replacement solutions for ongoing losses.

Carbohydrate

The major source of nonprotein calories in PN is D-glucose, which is provided in the monohydrate form for intravenous use, reducing its caloric yield to 3.4 kcal/g rather than the 4 kcal/g of enteral glucose or other carbohydrates. Glucose provides most of the osmolality in the PN solution; peripheral PN concentrations with more than 10% glucose increase the risk of phlebitis and, thus, decrease the life span of peripheral venous lines. The carbohydrate load is initiated in a stepwise fashion to allow an appropriate response of endogenous insulin and thus prevent glucosuria (and subsequent osmotic diuresis). Solutions containing excessive glucose can contribute to hepatic steatosis. Using glucose as the sole calorie source leads to greater water retention than when it is combined with lipids.[26] As mentioned previously, a balanced PN solution, including carbohydrate and fat (as non-nitrogen calories) can avoid fatty infiltration of the liver, water retention, and worsening respiratory compromise in acutely ill ventilator-dependent patients. Carbon dioxide production is higher with glucose as the only source of nonprotein

TABLE 57-4 Fluid Recommendations for Parenteral Nutrition

Initial volume for patients free of cardiovascular or renal disease
< 10 kg = 100 mL/kg/d
10–30 kg = 2,000 mL/m^2/d
30–50 kg = 100 mL/hour (2.4 L/d)
> 50 kg = 124 mL/hour (3 L/d)
Volume can be increased by
10 mL/kg/d in infants until the desired caloric intake is achieved (maximum of 200 mL/kg/d, if tolerated)
> 10 kg: by 10% of initial volume per day until desired caloric intake is achieved (maximum of 4,000 mL/m^2/d, if tolerated)

calories than it is when fat emulsion provides some of the total caloric content.[27]

Small, premature infants have poor glucose tolerance in the first days of life, and hyperglycemia (more than 125 mg/dL of sugar) occurs frequently. The infusion, along with glucose, of alternative carbohydrate sources, such as galactose and fructose, has enabled investigators to increase the total number of carbohydrate calories infused into the very premature infant, while avoiding the development of hyperglycemia. The potential side effects of these regimens, however, argue against their routine use. Glucose infusions are well tolerated by the newborn infant if the initial rate of administration does not exceed the hepatic rate of glucose production (6 to 8 mg/kg/minute). The premature infant can develop hyperglycemia even at lower rates of infusion. Glucose infusion rates between 5 and 12 mg/kg/minute are recommended in neonates and 2 and 5 mg/kg/minute in older children and adolescents. Serum glucose measurements should be monitored when PN solutions are abruptly stopped.[28]

The response of premature infants to insulin is highly variable; some develop profound hypoglycemia with minuscule insulin doses, and others have no response. There have been numerous studies in very low and extremely low birth weight infants (weighing less than 1,000 g) documenting improved weight gain, increased tolerance of intravenous glucose, normalization of serum glucose levels, and increased caloric intake with the use of continuous insulin infusions.[29,30] There are still serious concerns about the use of insulin in the neonate because (1) suppression of muscle proteolysis might not be desirable (the glutamine released is an important substrate for intestinal epithelial cells and the immune system), (2) there is a lack of understanding of the composition of the weight gain (especially protein accretion) in these infants, and (3) it is not known whether increased glucose use deprives the brain of this important substrate or whether increased glucose can be efficiently oxidized. Otherwise, it might be converted to fat. In older children and adolescents, insulin might be required to improve caloric intake in the face of hyperglycemia. Adding insulin to the PN bag is not recommended; rather, deliver the insulin as a separate infusion that can be titrated according to serum glucose.

Protein

The problems of hyperammonemia and poor use of nitrogen often seen with protein hydrolysates have been alleviated by the use of purer, crystalline amino acid formulations. Hyperammonemia, seen with earlier solutions, rarely occurs with the increased amounts of arginine and decreased glycine in the newer formulations. Hyperchloremic metabolic acidosis, a problem noticed with earlier crystalline amino acid solutions, has been ameliorated by the substitution of acetate for chloride in the salts of lysine and the use of basic salts of histidine. In addition to decreased toxicity, crystalline amino acids promote greater rates of nitrogen retention than do protein hydrolysates. All amino acid formulations currently marketed consist of crystalline amino acids; most were designed according to the requirements of normal, orally fed adult subjects and not for growing infants and children. These solutions produced weight gain and positive nitrogen balance in the stable neonate or infant when adequate nonprotein calories were also provided. However, use of these solutions leads to high plasma concentrations of such amino acids as methionine, glycine, and phenylalanine (a cause for safety concerns) and to low plasma concentrations of such amino acids as the branched-chain amino acids (BCAAs), tyrosine and cysteine.

Heird and Malloy found that free amino acid patterns, total weight, and protein content of brains in beagle puppies that received PN were grossly abnormal compared with those of suckled puppies.[31] The abnormal free amino acid patterns of the brains of the PN-fed puppies reflected plasma amino acid levels. Extensive research led to the production of a parenteral formula, TrophAmine (B. Braun, Irvine, CA), that normalizes plasma amino acid levels to within the range recommended by Wu and colleagues (normal 2-hour postprandial levels in healthy 30-day-old breast-fed full-term infants[32]). TrophAmine is unique in that it provides the essential amino acids (including taurine, tyrosine, and histidine) in adequate amounts, as judged by the normalized plasma amino acid profile, plus aspartic acid, glutamic acid, and the dicarboxylic acids at appropriate levels. Studies of this product have been conducted in preterm and full-term infants and in older children.

Helms and colleagues compared TrophAmine with a standard amino acid formula (Freamine III; B. Braun) in neonates[33] and found that the TrophAmine group had significantly greater weight gain and nitrogen retention and had plasma amino acid concentrations within the postprandial neonatal target range.[32] Levels of methionine, glycine, and phenylalanine were above and levels of tyrosine were below the target range when Freamine III was used. L-Cysteine was supplemented in both groups.

An uncontrolled, nonblinded multicenter study of the clinical, nutritional, and biochemical effects of intravenous administration of TrophAmine with a cysteine additive was conducted in infants and children (2.0 to 12.6 kg in weight) receiving only PN for 5 to 21 days, 2.5 g/kg/day of TrophAmine, 1.0 mmol/kg/day of cysteine hydrochloride, and approximately 110 kcal/kg/day of nonprotein calories.[34] The subjects gained approximately 11 g/kg/day and all were in positive nitrogen balance and had normalization of the plasma amino acid profile without adverse effects. Serial γ-glutamyl transpeptidase values actually

declined during the course of the study. Only 1 of the 31 subjects who received PN for more than 10 days had an increase in direct bilirubin, despite a predicted incidence of cholestasis of 30 to 50%. TrophAmine has been shown to be equally efficacious in preterm infants.[35] This distinct decrease in cholestatic tendency with TrophAmine could be because of the solution's taurine content, which results in "normal" plasma levels of taurine. Taurine deficiency has been proposed as a possible cause of cholestasis in patients receiving PN for prolonged periods.[36] Overall imbalance of amino acids or toxicity of one or more amino acids elevated in plasma could also be responsible for hepatic dysfunction and cholestasis.

Of the standard amino acid solutions, Aminosyn (Abbott Laboratories, North Chicago, IL), with its low pH value, allows the addition of greater amounts of calcium and phosphate for growing preterm infants.[37] TrophAmine has a lower pH level than Aminosyn does and allows even larger amounts of calcium and phosphorus to be added to the PN solution without precipitation.[38]

TrophAmine contains 60% and Aminosyn-PF (Abbott Laboratories), a comparable product, contains 50% essential amino acids. A large multicenter study comparing TrophAmine and Aminosyn-PF in low birth weight infants described similar nitrogen balance and weight gain in both groups.[39] However, one center (from the multicenter study) reported improved nitrogen balance and better levels of methionine and tyrosine in the TrophAmine group. Both formulas contain supplemental taurine, based on data showing a potentially deleterious effect of taurine deficiency on the developing brain and retina[40] and the concern that taurine deficiency might be a cause of cholestasis. Adult formulations lack taurine, which is essential because it conjugates bile acids. Taurine has also been shown to promote bile flow and bile acid secretion. Both Aminosyn-PF and TrophAmine appear to better meet the metabolic needs of the preterm infant than do standard amino acid solutions.

Cysteine is considered an indispensable amino acid for infants because hepatic cystathionase activity is absent or low until some time after full-term birth (cystathionase converts methionine to cysteine). In addition, removal of cysteine from an otherwise adequate diet inhibits the rate of weight gain and nitrogen retention. Enterally fed infants do not have a major problem because both human milk and infant formulas contain cysteine. Because cysteine is unstable and is only sparingly soluble in aqueous solution, parenteral amino acid solutions previously did not contain cysteine. Infants receiving PN have low plasma cysteine levels; furthermore, nitrogen retention is usually lower than in infants receiving the same nitrogen enterally. Cysteine hydrochloride (HCl) can be added to PN solutions, but within 24 hours, approximately 50% of it forms a complex with glucose, making D-glucocysteine. Previous studies of this method of cysteine supplementation of PN failed to show improvement in growth or nitrogen retention. This might have been because the regimens used were also deficient in tyrosine. Kashyap and colleagues showed that supplementation of PN with cysteine HCl (where the amino acid solution contained tyrosine), by either admixture or piggyback, resulted in cysteine retention, higher plasma cysteine concentrations, possible improved nitrogen retention, and increased acidosis (which required increased acetate to offset it).[41]

Helms and colleagues reported positive nitrogen balance (greater than 200 mg/kg/day) and weight gain (more than 10 g/kg/day) with low doses of TrophAmine (2 g/kg/day) and calories (50 kcal/kg/day) in preterm infants receiving PN.[42] In the past, these results were achievable only with higher-calorie and standard protein intakes.

Glutamine

Clinical experience with glutamine added to PN solutions is expanding, despite glutamine's short shelf-life in solution. Glutamine, a primary fuel source for enterocytes, colonocytes, lymphocytes, and macrophages, is a precursor for nucleotide synthesis and for glutathione, an important antioxidant that could be protective in a variety of circumstances. A nonessential amino acid by definition, cellular uptake of glutamine can exceed synthesis and release from skeletal muscle during catabolic illness, making glutamine essential under these conditions.[43] Supplemental glutamine seems to

- Increase protein synthesis
- Decrease protein breakdown
- Improve nitrogen balance
- Enhance intestinal adaptation after massive small-bowel resection
- Attenuate intestinal and pancreatic atrophy associated with PN or elemental enteral feeding
- Reduce bacterial translocation after radiation therapy
- Reduce bacteremia and mortality after chemotherapy[43]

In critically ill humans, glutamine supplementation can enhance D-xylose absorption, reflecting increased small-bowel absorptive capacity, and in stable patients, it can attenuate the villous atrophy and increased intestinal permeability associated with PN.[43] Variable results have been found in studies of glutamine-supplemented PN in bone marrow transplant recipients.[44] In a child with short-bowel syndrome, clinical improvement (weight gain, improved intestinal absorption, improvement of histology of an intestinal biopsy) occurred at least coincidentally with the addition of 5 g/day of parenteral glutamine administered separately from the PN solution (the patient weighed 12.6 kg at the onset of treatment; dosage was 0.4 g/kg/day).[45] The patient tolerated the infusion well with no obvious side effects.

Preliminary studies in very low birth weight (VLBW) infants have shown benefit of glutamine-supplemented PN. Lacey and colleagues performed a randomized trial in VLBW infants of glutamine-supplemented PN (15 to 20% of administered amino acids as L-glutamine); the infusion was safe and was associated with improved plasma glutamine levels without elevation of ammonia or glutamate.[46] In addition, of the 44 randomized infants, in the group with birth weights of less than 800 g, the glutamine-

supplemented group required fewer days (13 versus 21) on total parenteral nutrition (TPN), had a shorter length of time to reach full feedings (8 versus 14 days), and needed less time on the ventilator (38 versus 47 days). Wilmore and colleagues successfully used supplemental glutamine (0.56 g/kg/day) by the intravenous or oral route, parenteral growth hormone (0.14 mg/kg/day), and a modified enteral diet (about 60% of calories from carbohydrate, 20% from fat, and 20% from protein) in long-term PN patients with short-bowel syndrome.[47] Treatment resulted in improved protein absorption, decreased stool output, and reduction in dependence on PN as a source of nutrition. The findings suggested a significant potential role for glutamine in promoting intestinal adaptation in short-bowel syndrome. Alternative methods of administration (eg, enteral administration or the addition of the stable dipeptide alanyl glutamine to PN,[48] or providing intravenous α-ketoglutarate to PN, which is converted to glutamine) might need to be explored to facilitate long-term therapy.

Other researchers have attemped to reproduce the positive results from intravenous or oral glutamine supplementation. Scolapio and colleagues studied eight patients with short-bowel syndrome (two with colon) with a mean residual small-bowel length of 71 cm who had required home TPN for 13 years.[49] Treatment included growth hormone (0.14 mg/kg/day), glutamine (oral, 0.63 mg/kg/day), and a complex carbohydrate diet. No benefit of this treatment could be demonstrated; small intestinal morphology did not change, with no improvement in D-xylose absorption, and the "treatment" group had obvious fluid retention and peripheral edema.

Powell-Tuck and colleagues performed a randomized, double-blind, controlled trial in 168 heterogeneous patients needing PN; the treatment group received 20 g of free glutamine.[50] Overall, there was no difference between the two groups in infectious complications or length of hospital stay. Glutamine was associated with a significant ($p < .03$) reduction in length of stay in the subset of surgical patients (45 versus 30 days).

The National Institute of Child Health and Development (NICHD) Neonatal Research Network performed a randomized trial of parenteral glutamine supplementation for extremely low birth weight infants.[51] Fifteen centers randomized infants with birth weights between 401 and 1,000 g to TrophAmine or an isonitrogenous amino acid solution with 20% glutamine. A total of 1,430 patients were studied. There were no differences between the two groups for late-onset sepsis, NEC, days to full enteral feedings, days to regain birth weight, length of hospital stay, or survival, even though glutamine concentrations in plasma significantly increased in the treatment group.

In contrast, in a study of severely burned patients, glutamine administration reduced gram-negative bacteremia in a prospective, randomized, double-blind trial versus isonitrogenous control.[52] A study of pediatric patients with burns supported the notion that exogenous glutamine supplementation in pediatric patients with severe injuries might be needed.[53]

Guidelines: Amino Acids

Guidelines for protein requirements in PN are shown in Tables 57-2 and 57-3. Preterm neonates given 2.5 to 3.5 g/kg/day of amino acids and approximately 80 kcal/kg/day achieve nitrogen retention at levels that approximate intrauterine nitrogen retention; intakes for older children and adolescents vary from 1.0 to 2.0 g/kg/day. In neonates, we start at 1.5 to 2.5 g/kg of amino acids per day and increase to the desired goal. In older infants and children, we start at the goal dose, except in cases in which there is hepatic or renal insufficiency or disorders of protein metabolism. Special amino acid solutions are available for use in patients with maple syrup urine disease. Daily quantitative serum amino acid estimation in these patients allows for advancement and adjustment of the protein dose. Solutions high in BCAAs have been used in patients with liver failure and encephalopathy. These solutions are expensive, and the data justifying their use are not well substantiated. We often use TrophAmine (with its higher percentage of BCAAs) in patients less than 6 months old and those with cholestasis. In an attempt to decrease cholestasis and hepatic dysfunction, we consider the use of TrophAmine for all of our long-term PN patients (eg, children with short-bowel syndrome or intestinal pseudo-obstruction).

We have described two siblings (16 and 11 years old) with microvillus inclusion disease who have received TrophAmine as their amino acid source since infancy.[54] Even though they have a disease that usually has a short life expectancy and significant morbidity from lifelong dependence on TPN, these two boys continue to thrive and lead normal lives. The older boy was free of significant morbidity until he was 14 years old, when he was found to have a large liver mass and eight additional hepatic nodules, leading to a right hepatic lobectomy. Final pathology confirmed the diagnosis of adenoma, with the remainder of the liver biopsy showing no evidence of TPN-related liver disease. The younger child has no evidence of TPN-induced liver disease; he has not developed cholestasis and is free of hepatic nodules on ultrasonography.

Calorie-to-Nitrogen Ratio

To promote efficient net protein use and not use the protein as an energy source, it is often recommended to provide approximately 150 to 200 nonprotein calories per gram of nitrogen, as follows: nitrogen content (g) equals protein (g)/6.25; 1 g protein contains 0.16 g nitrogen; therefore, 24 to 32 non-nitrogen calories must be supplied per gram of protein infused to yield a desirable ratio of 150 to 200:1:

- Non-nitrogen calories/N (g) = 24/0.16 = 150/1; 32/0.16 = 200/1
- If 2 g/kg/day of protein as amino acids is supplied, then 48 to 64 kcal/kg/day of non-nitrogen calories must be supplied to ensure adequate protein use.
- If 2.5 g/kg/day of protein is supplied, then 60 to 70 kcal/kg/day of non-nitrogen calories must be supplied.

Albumin

Albumin at a concentration of 0.5 to 1.0 g/kg/day can be administered to PN patients who are hypoalbuminemic from non-nutritional causes. Such infusions are for oncotic, not nutritive, benefits. Albumin has a long half-life when synthesized endogenously, in contrast to its short intravascular half-life when given exogenously. Albumin should be infused separately via a "Y" connector and not placed in the PN solution because (1) albumin is a blood product and should not be hung for more than 8 hours, (2) recent concerns exist about flocculation of albumin in PN solutions, and (3) albumin in PN solutions increases the risk of sepsis.[55]

Fat

Intravenous fat is an integral part of the PN regimen. It provides a concentrated isotonic source of calories (20% solution supplies 2.0 kcal/mL) and prevents or reverses essential fatty acid deficiency. Patients who cannot tolerate large glucose or fluid loads can receive sufficient calories if intravenous fat is added to the glucose-amino acid regimen.[10] In addition, continuous administration of intravenous fat with the PN regimen prolongs the viability of peripheral intravenous lines in infants who might have limited venous access.[56] The intravenous fat must be infused separately from the PN solution because these solutions can "crack" (disturb) the fat emulsion. It is given using a "Y" connector near the infusion site and beyond the micropore filter.

The rate of elimination and metabolic fate of intravenous fat particles are the same as those of naturally occurring chylomicrons, so plasma clearance is dependent on the activity of lipoprotein lipase in the capillary endothelial cells, primarily in muscle and adipose tissue. The intravenous fat should be infused over 24 hours whenever possible. Continuous intravenous fat infusions (24 hours/day) are better tolerated than are intermittent infusions (8 to 18 hours/day),[57,58] with less fluctuation and lower concentrations of plasma lipids, especially at higher rates of infusion. Early studies argued against exceeding a rate of 0.15 g/kg/hour (3.6 g/kg/day). Slower infusion rates are required for small-for-gestational-age infants. Infusion rates of 0.12 g/kg/hour or less resulted in less elevation of plasma lipid levels than did rates of 0.17 g/kg/hour or more.[58]

Biochemical evidence of essential fatty acid deficiency has been observed in the serum of fasted newborn infants as early as 2 days after initiating fat-free PN.[59] Biochemical evidence precedes clinical signs of deficiency: reduced growth rate, flaky dry skin, poor hair growth, thrombocytopenia, increased susceptibility to infections, and impaired wound healing.[59] An essential fatty acid deficiency can be assessed by determination of the ratio of 5,8-11-eicosatetraenoic to arachidonic acid (triene-to-tetraene ratio). An elevated ratio is an indicator of essential fatty acid deficiency. An initial report that topically applied sunflower seed oil reversed biochemical and clinical essential fatty acid deficiency in two newborn babies on fat-free PN could not be duplicated in subsequent studies.[60] Interestingly, 15 mL twice a day of corn oil, sunflower oil, or safflower oil enterally provides as much linoleic acid as 150 mL of 10% intravenous fat at less than 5% of the cost.

Many PN patients not on complete bowel rest tolerate such a regimen. An essential fatty acid deficiency can be prevented by providing 2 to 4% of total calories as intravenous fat (1 to 2% linoleic acid)—an intravenous fat dose of 0.5 to 1.0 g/kg/day. Linoleic and linolenic acids are essential fatty acids. There is the possibility that too much linolenic acid inhibits the conversion of linoleic acid to arachidonic acid. These concerns led to the development of Liposyn II (Abbott Laboratories), a blend of safflower oil (0.1% linolenic acid) and soybean oil (8.0% linolenic acid). Currently used intravenous fat products are shown in Table 57-5. One study demonstrated that hypertriglyceridemia is more common in preterm infants who receive

TABLE 57-5 Currently Available Intravenous Fat Emulsions*

	Oil (%)		*Fatty Acid Content (%)*				
Product (Distributor)	*Safflower*	*Soybean*	*Linoleic*	*Oleic*	*Palmitic*	*Linolenic*	*Stearic*
Intralipid† 10% (Fresenius Kabi Clayton)	—	10	50	26	10	9	3.5
Intralipid† 20% (Fresenius Kabi Clayton)	—	20	50	26	10	9	3.5
Intralipid† 30% (Fresenius Kabi Clayton)	—	30	50	26	10	9	3.5
Liposyn II‡ 10% (Abbott)	5	5	65.8	17.7	8.8	4.2	3.4
Liposyn II‡ 20% (Abbott)	10	10	65.8	17.7	8.8	4.2	3.4
Liposyn III‡ 10% (Abbott)	—	10	54.5	22.4	10.5	8.3	4.2
Liposyn III‡ 20% (Abbott)	—	20	54.5	22.4	10.5	8.3	4.2

Product (Distributor)	*Egg Yolk Phospholipids (%)*	*Glycerine %*	*kcal/mL*	*Osmolarity (mOsm/L)*	*Phospholipid/ Triglyceride Ratio*
Intralipid† 10% (Fresenius Kabi Clayton)	1.2	2.25	1.1	260	0.12
Intralipid† 20% (Fresenius Kabi Clayton)	1.2	2.25	2	260	0.06
Intralipid† 30% (Fresenius Kabi Clayton)	1.2	1.7	3	200	0.04
Liposyn II‡ 10% (Abbott)	1.2	2.5	1.1	276	0.12
Liposyn II‡ 20% (Abbott)	1.2	2.5	2	258	0.06
Liposyn III‡ 10% (Abbott)	1.2	2.5	1.1	284	0.12
Liposyn III‡ 20% (Abbottt)	1.2	2.5	2	292	0.06

*Available in the United States.
†Store at 25°C (77°F) or below; do not freeze.
‡Store at 30°C (86°F) or below; do not freeze.

safflower oil–based as opposed to soybean oil–based intravenous fat.[61] However, studies in newborn babies comparing Liposyn II and Intralipid found no difference in the incidence of hypertriglyceridemia between the two products, with comparable plasma fatty acid profiles.

Carnitine is necessary for optimal oxidation of fatty acids. Solutions currently used for intravenous alimentation contain no carnitine, but they do contain all of the precursors for its endogenous production. Infants and newborns maintained on PN solutions have decreased total plasma and tissue carnitine levels. Normalization of serum carnitine levels occurs in infants receiving long-term PN and supplemental oral L-carnitine (50 μmol/kg/day = 8.1 mg/kg/day)[62] or intravenous L-carnitine.[63] The latter study also led to lower peak triglyceride levels after delivery of a fat bolus (suggesting an enhanced ability to use fat for energy) and modest increases in growth and nitrogen accretion. The very low birth weight infants requiring PN developed low carnitine levels and impaired ketogenesis that appeared to improve with parenteral carnitine. In very low birth weight infants on PN supplemented with L-carnitine (50 μmol/kg/day), increased carnitine levels and improved tolerance to intravenous fat were noted (only in the infants in the 1,001 to 1,500 g and not the 750 to 1,000 g birth weight range).

Other studies of carnitine supplementation have failed to demonstrate significant improvement in clinical outcome.[64,65] Some experts recommend 10 mg/kg/day intravenous L-carnitine for very low birth weight infants. Higher doses of carnitine seem to have pharmacologic effects, leading to increased protein and fat oxidation with associated energy loss. Supplementation with 48 mg/kg/day of L-carnitine (about 300 μmol/kg/day) increased the metabolic rate, decreased fat and protein accretion, and prolonged the time to regain birth weight in preterm infants receiving PN with lipids.[66] We do not routinely supplement PN solutions with carnitine. Cholestatic infants and children without enteral intake on long-term PN are supplemented when serum carnitine levels are low.

Structured lipids are being considered as an alternative energy source.[67] They contain medium- and long-chain fatty acids esterified to the same glycerol molecule. They are different from physical mixtures of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs). Fat emulsions containing MCTs have been released in Europe; their advantage is that they are not stored in the liver or adipose tissue, and they undergo hydrolysis and rapid beta-oxidation independent of the carnitine enzyme system. Although early laboratory and clinical studies demonstrated intravenous MCTs to be a safe, carnitine-independent energy substrate, subsequent studies have shown increased mortality in previously starved animals and central nervous system toxicity in dogs.[68] The potential advantage in pediatric patients would be for cases in which endogenous lipoprotein lipase levels are low, as in infants of less than 28 weeks gestation or those with sepsis or trauma.

Some reports suggest a benefit of adding MCTs to intravenous preparations compared with using LCTs alone. Fifty-one newborn infants received Lipofundin MCT/LCT (50% MCT, 50% LCT; B. Braun Medical, Germany) or conventional intravenous fat over 20 hours. Triglyceride and fatty acid levels were not significantly different in the two groups. After 6 days of intravenous fat, mean plasma cholesterol was 100% higher in the group receiving conventional intravenous fat.[69] A second study of neonates showed elevation of triglycerides and free fatty acids in the MCT/LCT group.[70] Further studies are needed to evaluate the MCT/LCT regimen for pediatric patients. Finally, Canadian investigators were concerned that preterm infants lacked transplacental accretion for eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), so they designed a soy emulsion enriched with EPA and DHA and found no toxicity or biochemical abnormalities in piglets that received it. These fatty acids are essential for brain development but are not available in any current intravenous fat products.

Fat can frequently contribute 30 to 40% of total nonnitrogen calories, but, generally, it should not exceed 60%. Four grams per kilogram per day of 20% intravenous fat caused less increase of plasma lipids than did 2 g/kg/day of 10% intravenous fat. Hyperlipidemia occurs with PN with 10% intravenous fat but not 20% intravenous fat and is caused by an increase in lipoprotein X. The phospholipid-to-triglyceride ratio is 0.12 in 10% intravenous fat and 0.06 in 20% intravenous fat (see Table 57-5).[71,72] Phospholipid is believed to inhibit lipoprotein lipase, which is the main enzyme responsible for intravenous fat clearance, probably explaining why 20% intravenous fat is cleared more rapidly than 10% intravenous fat. Twenty percent intravenous fat is currently used exclusively in our institution. The dose should not exceed 0.15 g/kg/hour. Thirty percent intravenous fat has been shown to be safe and has metabolic effects similar to those of 20% intravenous fat. It is administered as a three-in-one solution and cannot be given alone via a peripheral intravenous line.[73] Suggested dosing for intravenous fat is shown in Table 57-6.

Electrolytes

The ranges of recommended daily intakes of electrolytes and minerals for PN solutions in pediatrics are shown in Table 57-7. Calcium and phosphorus requirements change with age and are much greater in preterm infants than in full-term infants, older children, and adults (Table 57-8).[74]

TABLE 57-6 Dosing for Intravenous Fat*

Age	*Starting Dose*	*Daily Dose Increase*	*Maximum Dose*
Preterm	0.5–1.0	1.0	3.5
Full-term (0 to 6 mo)	1.0–1.5	1.0–1.5	3.5
Older infants (6 to 12 mo)	1.0–1.5	1.0–1.5	3.0
Children (1 to 10 yr)	1.0	1.0–1.5	3.0
Adolescents (11–18 yr)	1.0	1.0	2.0–3.0

*In grams per kilogram per day.

TABLE 57-7 Parenteral Provision of Electrolytes and Minerals

Electrolytes and Minerals	*Daily Amount*
Phosphate	0.5–2.0 mM/kg
Sodium	2.0–4.0 mEq/kg
Potassium	2.0–3.0 mEq/kg
Chloride	2.0–3.0 mEq/kg
Acetate	1.0–4.0 mEq/kg
Magnesium	0.25–0.5 mEq/kg
Calcium gluconate*	50–500 mg/kg

*Gluconate is the recommended calcium salt for use in parenteral nutrition solutions. Calcium chloride dissociates more readily than calcium gluconate solutions and can lead to precipitation problems with phosphate.

During the last 6 to 8 weeks of gestation, calcium and phosphorus are incorporated into the bone matrix. Thus, premature infants are at risk for developing rickets and handling fractures. Any radiograph taken should be checked for the early bone changes of rickets. Serum calcium, phosphorus, and alkaline phosphatase levels should be monitored. The serum calcium level will be maintained at the expense of bone (demineralization), so normal serum calcium does not necessarily mean that adequate amounts of calcium are being delivered. The serum phosphorus level does not fluctuate as rapidly and is a better indicator of total body stores. Kovar and colleagues suggest screening for rickets in preterm infants with plasma alkaline phosphatase: levels six times the upper limit of the normal adult reference range should prompt a radiograph to exclude rickets.[75]

Calcium and phosphorus requirements for some patients might exceed the solubility of these two elements in PN solutions, particularly when patients are fluid restricted or have several other intravenous fluid lines in place. The maximum amounts of calcium and phosphorus that can be admixed in PN solutions are determined primarily by the pH of the solution,[37] which, in turn, is determined primarily by the amino acid product and concentration. Currently, TrophAmine and Aminosyn-PF have low enough pH values to allow adequate amounts of calcium and phosphorus for growth. Of the other amino acid solutions designed for use in adults, Aminosyn has the lowest pH level and is probably the next best choice for use in children with active bone growth. Continuous infusion of calcium in the PN solution is preferable to bolus administration. With bolus administration, large amounts of calcium are lost in the urine.[76] Also, the potential tissue damage from line infiltration is much greater with concentrated calcium given as a bolus than with dilute calcium as a continuous infusion.

Infusions of solutions containing both calcium and phosphorus result in stable calcium and phosphorus concentrations. Calcium concentrations of 50 mEq/L and phosphate concentrations of 20 mmol/L are compatible in solutions containing 2% TrophAmine, 10% glucose, and 0.08% L-cysteine.[38] Calcium-phosphorus solubility is less in Aminosyn-PF than in TrophAmine.[77] Previously, experts recommended a calcium-to-phosphorus ratio of 1.3:1 by weight or a 1:1 molar ratio. Recently, a higher, more physiologic ratio of 1.7:1 by weight (1.3:1 by molar ratio, similar to the fetal mineral accretion ratio) allowed for a higher absolute retention of both minerals and came closest to in utero accretion of calcium and phosphorus.[78,79] This successful ratio provided 76 mg/kg/day of calcium and 45 mg/kg/day of phosphorus, using Aminosyn-PF as the amino acid source. There could be an advantage to using calcium glycerophosphate versus conventional calcium gluconate because the former is more soluble.[80,81] Dunham and colleagues have generated calcium and phosphorus precipitation curves for neonatal PN, using TrophAmine, to guide pharmacists and clinicians to help avoid compounding PN solutions that will precipitate.[82]

Calcium phosphate is more soluble at cooler temperatures than at room or body temperature. Thus, serious concerns have been raised about the recent advocacy of three-in-one infusates[83] that contain glucose, amino acids, and lipid emulsion in the same bottle or bag with electrolytes, minerals, and vitamins. Because these infusates must be administered without an in-line filter, the presence of lipid in the infusate obscures any visual detection of precipitation that can occur either on removal from refrigeration and warming before administration or during the time of infusion. Their use in low birth weight infants seems unwise, especially when efforts are being made to maximize calcium and phosphate intakes. One retrospective review of the use of three-in-one solutions in infants found their use safe, efficacious, and cost-effective for infants younger than 1 year of age.[84] The amino acid solutions compatible in three-in-one solutions are not those with the lowest pH values. In the review of Rollins and colleagues, Travenol was the amino acid solution used[84]: it does not have the lowest pH level of the adult standard solutions. Thus, maximal calcium and phosphorus levels cannot be achieved with three-in-one solutions, and they should not be used routinely in the neonate.

In April 1994, the US Food and Drug Administration (FDA) issued a safety alert regarding three-in-one solutions after a report was received from one institution of two deaths and at least two cases of respiratory distress that developed during peripheral infusion of a three-in-one (amino acids, carbohydrate, and lipids) PN admixture. The admixture contained 10% Freamine III, dextrose, calcium gluconate, potassium phosphate, other minerals, and a lipid emulsion, which were combined using an automated compounder. The solution might have contained a precipitate of calcium phosphate. Autopsies revealed diffuse microvascular pulmonary emboli containing calcium phosphate. The presence of a lipid emulsion in the PN admixture would have obscured the presence of any precipitate. The American Society for Parenteral and Enteral

TABLE 57-8 Recommended Amounts of Calcium and Phosphorus

	Calcium Gluconate	*Phosphate*
Premature infants	300–500 mg/kg/d	1–1.5 mM/kg/d
Full-term infants	300–400 mg/kg/d	1–1.5 mM/kg/d
Older infants and children	100–200 mg/kg/d	1.0 mM/kg/d
Adolescents	50–100 mg/kg/d	0.5–1.0 mM/kg/d

Nutrition's safe practice guidelines state clearly that given the limited amount of published stability information available, the use of two-in-one formulation with a separate administration of intravenous fat is recommended for neonatal and infant patients.[85]

VITAMINS

In 1975, the Nutrition Advisory Group of the Department of Food and Nutrition, American Medical Association (AMA), proposed adult and pediatric guidelines for parenteral multivitamins.[86] In the United States, the FDA accepted the AMA adult formulation MVI-12 (Armour Pharmaceutical, Blue Bell, PA) in 1979. The pediatric formulation MVI-Pediatric (Armour Pharmaceutical), which was not approved until 1981, has been tested primarily in medically stable infants and children receiving PN. The specific recommendation from a 1988 review is to use one vial of MVI-Pediatric per day for term infants and children and 40% of a vial per kilogram per day for preterm infants.[87] Patients receiving oral multivitamin supplements might need adjustments in parenteral multivitamin dose. For several years, there was a shortage of MVI-Pediatric, resulting in clinical deficiency states, especially thiamin deficiency.[88] Alternative ways to provide multivitamins, if there is an MVI-Pediatric shortage in the future, are supplied by the American Society for Parenteral and Enteral Nutrition, both in their newsletters and on the Internet (<http://www.clinnutr.org>). Recommended intakes of parenteral vitamins are shown in Table 57-9.

Lipid-Soluble Vitamins Lipid-soluble vitamins must be dispersed in an aqueous solution if they are to be provided in a single vitamin mixture. To "solubilize" these lipid-soluble molecules for intravenous use, synthetic detergents, such as polysorbate, have been used. There are concerns about the safety of these detergents given intravenously to preterm infants.[89,90] In Europe, Vitalipid (KabiVitrum, Stockholm) is a preparation containing vitamins A, D, E, and K dissolved in fractionated soybean oil and emulsified with fractionated egg phospholipids in the same manner in which Intralipid is prepared. Infants requiring PN receive water-soluble vitamins in the glucose amino acid solution and the lipid-soluble vitamins with intravenous fat (devoid of synthetic emulsifiers). Such use has proven successful for years.

Intravenous vitamins, including vitamin A, can be lost through adsorption to plastic PN bags and tubing or biodegradation in the presence of light. Using radiolabeled vitamins, researchers found that only 31% of vitamin A, 68% of vitamin D, and 64% of vitamin E were actually delivered to the patient over a 24-hour period.[91] Retinol depletion during PN is much more severe in very low birth weight infants because of the higher light intensity in nurseries and lower infusion rates of PN, which result in longer exposure time.[87]

Armour Pharmaceutical originally recommended MVI-Pediatric doses of 5 mL/day for all patients weighing more than 3 kg and 3.25 mL/day for infants weighing less than 3 kg. Unfortunately, at the 3.25 mL dose, infants weighing less than 1,000 g displayed elevated vitamin E levels (greater than 3.5 mg/dL).[92] Such elevations have been associated with an increased incidence of NEC and sepsis. The manufacturers subsequently modified their recommendations, suggesting that infants weighing less than 1,000 g receive 1.5 mL/day of MVI-Pediatric. At this lower dosage, vitamin E levels were less than 1 mg/dL in 44% of infants weighing less than 1,000 g,[93] which is lower than the safe and effective levels (1 to 2 mg/dL) suggested by the American Academy of Pediatrics.[94] The recommended dose of 40% of a vial (2 mL = 2.8 mg α-tocopherol) per kilogram per day results in normal serum vitamin E levels within the range of 1.0 to 2.5 mg/dL, even in infants with birth weights between 450 and 1,360 g.[95] However, this dose might be inadequate for some infants weighing 1,000 g or less because 15% of neonates receiving 50% of a vial of MVI-Pediatric (a larger dose than recommended) had vitamin E levels of less than 1 mg/dL. Vitamin D requirements of infants receiving PN are met with the recommended doses of MVI-Pediatric.

Greene and colleagues have shown that very low birth weight infants who receive PN for 1 month show a progressive decline in serum retinol levels,[96] a significant finding in light of two reports correlating a higher incidence of bronchopulmonary dysplasia (BPD) with low plasma retinol levels.[97,98] Shenai and colleagues, in a blinded, randomized trial, found that vitamin A treatment increased plasma retinol levels and reduced the incidence of BPD.[99] Pearson and colleagues were unable to duplicate these results,[100] but Robbins and Fletcher found similar results with early vitamin A supplementation.[101] Vitamin A should be administered early to small premature infants who are at risk for BPD.

Given the previous data on vitamin E and the above data on vitamin A, serum levels of vitamins A and E should be monitored in high-risk neonates so that adjustments in their PN regimen can be made, if needed. The benefits of adding fat-soluble vitamins to intravenous fat solutions (to prevent loss of vitamin A into the plastic tubing) was further demonstrated by increased plasma retinol levels in premature infants.[95] The authors concluded, however, that 280 μg/kg/day was insufficient to raise the blood levels in all infants into the normal range. Meta-analyses suggest that vitamin A supplementation could reduce chronic lung disease and sepsis in extremely low birth weight (ELBW) infants. A 14-center randomized trial of vitamin A supplementation was recently performed in such infants, using a higher dose of vitamin A than that used in most neonatal trials (based on a pilot study)—5,000 IU vitamin A given intramuscularly three times per week for 3 weeks.[102] This vitamin A supplementation reduced biochemical evidence of vitamin A deficiency and reduced the incidence of BPD at 36 weeks postconceptional age from 62 to 55% ($p < .03$). The investigators concluded that vitamin A supplementation is safe and reduces the incidence of BPD.

MVI-Pediatric contains 200 μg per vial of phytonadione, a lipid-soluble vitamin K preparation. No deficiency state or toxicity has been reported with this dose. Patients more than 10 years of age who receive one vial of MVI-12 (designed for patients older than 11 years) will need sup-

TABLE 57-9 Suggested Intakes of Parenteral Vitamins in Infants and Children

Vitamin	*Full-Term Infants and Children (dose per day)**	*Preterm Infants (dose/kg body wt; maximum not to exceed full-term infant dose)*	
		Current Suggestions†	*Best Estimate for New Formulation‡*
Lipid soluble			
A (μg)§	700.0	280.00	500.00
E (mg)§	7.0	2/80	2.80
K (μg)	200.0	80.0	80.00
D (μg)§	10.0	4.00	4.00
(IU)	400.00	160.00	160.00
Water soluble			
Ascorbic acid (mg)	80.0	32.00	25.00
Thiamin (mg)	1.2	0.48	0.35
Riboflavin (mg)	1.4	0.56	0.15
Pyridoxine	1.0	0.40	0.18
Niacin (mg)	17.0	6.80	6.80
Pantothenate (mg)	5.0	2.00	2.00
Biotin (μg)	20.0	8.00	6.00
Folate (μg)	140.0	56.00	56.00
Vitamin B_{12} (μg)	1.0	0.40	0.30

Adapted from Greene HL et al.[87]

*These guidelines for full-term infants and children are identical to those of the American Medical Association (Nutrition Advisory Group) published in 1979.[86] MVI-Pediatric (Armour; currently produced by Astra) meets these guidelines. Recent data indicate that 40 IU/kg/day vitamin D (maximum 400 IU/day) is adequate for full-term and preterm infants. The higher dose of 160 IU/kg/day has not been associated with complications and maintains blood levels within the reference range for fed orally full-term infants. This dosage therefore appears acceptable until further studies using the lower-dose formulations indicate their superiority.

†These represent a practical guide (40% of the currently available single-dose vial MVI-Pediatric formulation per kilogram of body weight), which will provide adequate levels of vitamins E, D, and K but low levels of retinal and excess levels of most of the B vitamins. The maximum daily dose is one single-dose vial for any infant.

‡Because of elevated levels of water-soluble vitamins, the current proposal is to reduce intake of water-soluble vitamins and increase retinal as described in the committee's report.[87]

§700 μg retinal equivalents = 2,300 IU; 7 mg α-tocopherol = 7 IU; 10 μg vitamin D = 400 IU.

plemental vitamin K intravenously daily instead of a weekly intramuscular injection. The regular addition of vitamin K (1 mg/day intravenously in the PN solution or 10 mg intramuscularly weekly) to PN regimens decreased the incidence of elevated prothrombin time.

Water-Soluble Vitamins Deficiency of thiamin results in acute or chronic beriberi. A possible case of Shoshin (cardiac) beriberi, determined by erythrocyte transketolase assay during PN, was reported in a 12-year-old girl who received PN with inadequate amounts of thiamin.[103] As much as one-third of riboflavin in PN solutions is inactivated by light, especially phototherapy lights; riboflavin deficiency causes abnormalities of epithelia (hyperemia and edema of the pharyngeal and oral mucous membranes, cheilosis, stomatitis, glossitis, and seborrheic dermatitis) and normocytic anemia.[87] Such deficiency has not been described in children maintained on PN. Findings of riboflavin-induced photohemolysis with excess riboflavin indicate the importance of maintaining normal blood levels of this vitamin. The recommended parenteral dose of pyridoxine in full-term infants (1 mg/day) might be more than necessary, but it has not resulted in toxicity or deficiency. For preterm infants receiving 40% of a MVI-Pediatric dose (0.4 mg/kg/day), pyridoxine levels increased more than 10-fold over cord blood and maternal levels; a lower dose of 0.18 mg/kg/day resulted in only twofold increases.[104]

Another study by the same group also argued that the current dosage of pyridoxine for very low birth weight infants is excessive and recommended a newer formulation with a lower dose. Pyridoxine also is destroyed by exposure to direct sunlight. The clinical syndrome resulting from omission of biotin from PN is characterized by scaly dermatitis, alopecia, pallor, irritability, and lethargy.[105] Biotin is currently included in MVI-Pediatric in doses that are not toxic but are adequate to prevent deficiency. Two studies support the continued use of the 1975 AMA Nutrition Advisory Group guidelines for water-soluble vitamin doses for full-term infants and children.[106,107]

Trace Elements

Guidelines for intravenous administration of trace elements to pediatric patients are summarized in Table 57-10.[87,108] Moukarzel and colleagues evaluated the chromium status of children on long-term PN receiving the standard recommendations.[109] Elevated serum chromium levels and lower glomerular filtration rates (GFRs) were noted. The GFRs were significantly inversely correlated with serum chromium concentration. After 1 year of PN without supplemental chromium, the mean serum chromium levels had fallen but were still higher than in controls. No change occurred in the GFRs. Unplanned chromium contamination of the PN solutions still provided 0.05 μg/kg of chromium, which is one-fourth of the amount currently recommended. Since 1990, the University of California, Los Angeles (UCLA) group has discontinued chromium supplementation in all long-term PN patients.[109]

Persistent diarrhea or other excessive gastrointestinal fluid losses from ostomy sites can grossly increase zinc losses. In adult balance studies, the following additional zinc replacement is required: (1) 17.1 mg of zinc per kilo-

TABLE 57-10 Recommended Intravenous Intakes of Trace Elements*

Element	Infants		Children (μg/kg/d)	Maximum (μg/d)
	Preterm† (μg/kg/d)	Full Term (μg/kg/d)		
Zinc	400.00	250 < 3 mo	50.00	5,000
	—	100 > 3 mo	—	—
Copper‡	20.00	20.00	20.00	300
Selenium§	2.00	2.00	2.00	30
Chromium§	0.20	0.20	0.20	5.0
Manganese‡	1.00	1.00	1.00	50
Molybdenum§	0.25	0.25	0.25	5.0
Iodide	1.00	1.00	1.00	1.0

Adapted from Greene HL et al.[87]

*When TPN is only supplemental or limited to less than 4 weeks, only zinc (Zn) need be added. Thereafter, addition of the remaining elements is advisable.

†Available concentrations of molybdenum (Mo) and manganese (Mn) are such that dilution of the manufacturer's product might be necessary. Neotrace (Lyphomed, Rosemont, IL) contains a higher ratio of Mn to Zn than suggested here (ie, Zn = 1.5 mg and Mn = 25 μg/mL).

‡Omit in patients with obstructive jaundice. (Manganese and copper are excreted primarily in bile.)

§Omit in patients with renal dysfunction.

gram of stool or ileostomy output and (2) 12.2 mg of zinc per kilogram of small-bowel fluid lost via fistula or stoma. Monitoring of serum zinc levels in patients with persistent losses is recommended.

Selenium deficiency causes Keshan disease, an often fatal cardiomyopathy affecting children and young women in a large geographic area of China.[110] Deficiency states associated with long-term PN have been seen in adults and children[111] with intermittent leg muscle pain and tenderness; white fingernails; increases in serum alanine aminotransferase, aspartate aminotransferase, and creatine kinase; and cardiomyopathy. Low selenium levels were also found in children receiving long-term PN[112] with similar findings and, additionally, profound muscle weakness. Long-term intravenous supplementation with 2 μg/kg/day of selenium resulted in improved clinical and laboratory findings. Similarly, regression of walking skills and a tender myopathy were seen in a 27-month-old child on long-term PN with low plasma selenium levels.[113] Intravenous repletion with sodium selenite resulted in complete disappearance of muscle pain and tenderness within 1 week; crawling and walking skills were regained within 6 weeks. Suggested selenium requirements are 1.5 μg/kg/day for maintenance and 3.0 μg/kg/day for replacement,[113,114] on the basis of an extrapolation from selenium intake in breast-fed infants, assuming 80% absorption.[87] There is no good evidence that selenium is required for short-term PN.

Molybdenum deficiency symptoms (tachycardia, tachypnea, vomiting, and central scotomas, with rapid progression to coma) have been reported in an adult on long-term PN.[115] The patient had an excellent clinical and biochemical response to 2.5 μg/kg/day of molybdenum.

Iron

Intravenous iron in PN regimens remains controversial owing to concerns about the risks of adverse effects. Excess iron is thought to enhance the risk of gram-negative septicemia. Iron has powerful oxidant properties and can enhance the demand for antioxidants, especially vitamin E; particular caution is needed in giving iron to the preterm infant.[87] Iron dextran (Imferon, Fisons Corp., Bedford, MA) has been added to PN infusates at a daily dose of 0.5 mg (1 mL)[116] and 2 mg of iron[117] with no adverse physiochemical or clinical effects. Porter and colleagues agree that malnourished patients with low transferrin could be at risk of receiving a substantial infusion of iron in the free form,[117] which can lead to stimulation of bacterial or fungal growth. In an otherwise stable patient who cannot take oral iron, starting at low doses (0.5 mg) of iron (as dilute Imferon) daily appears to be safe.

Serum iron, total iron-binding capacity, percent saturation, and ferritin should be assayed to assess repletion of iron stores. There is danger of adverse reactions, including death, when iron dextran is given intramuscularly or as a large infusion. We use iron dextran in maintenance doses in PN in all infants and children age 2 months or more, who are receiving long term PN, except those receiving chronic blood transfusions (for bone marrow transplantation and oncology treatment and in certain selected hematology patients).

Aluminum

Current PN solutions are contaminated with aluminum, which can accumulate in bone after only 3 weeks of PN in infants. Aluminum impairment of bone matrix formation and mineralization can be mediated by its direct effect on bone cells or indirectly by its effect on parathyroid hormone and calcium metabolism. Toxic effects are proportional to tissue aluminum load.[118] Intravenous calcium, phosphorus, and albumin solutions have high aluminum levels (greater than 500 μg/L), whereas crystalline amino acids, sterile water, and dextrose have low levels (less than 50 μg/L).[118] Calcium gluconate can contribute up to 80% of the total aluminum load from PN.

The FDA has proposed labeling requirements concerning aluminum content on PN additives, establishing an upper limit permitted in additives, and has suggested that manufacturers develop validated assay methods.[119] Bishop and colleagues demonstrated developmental delay in premature infants on PN solutions who were receiving 45 μg/kg aluminum per day.[120] Aluminum intake should be determined in children at high risk for toxicity; these include preterm infants, infants or children with impaired renal function, and patients on prolonged PN.[87]

Heparin

Heparin (1 U/mL) is added prophylactically to PN solutions to prevent thrombosis. It reduces the formation of a fibrin sheath around the catheter and possibly reduces phlebitis with peripheral PN solutions. No controlled studies have conclusively demonstrated heparin's benefits in PN. One controlled trial has shown that it reduces catheter-related sepsis[121] and that it stimulates lipoprotein lipase release, thereby enhancing clearance of intravenous fat. Heparin decreased total lipid levels and turbidity when given as a single injection of 50 to 100 U/kg to small-for-gestational-age infants.[122,123] One unit of heparin per milliliter of PN solution seems safe for full-term infants on up to adults. In premature babies, no definitive guidelines are available. We routinely give 0.5 units heparin per milliliter of PN solution to neonates.

ROUTE OF ADMINISTRATION

Caloric need is the primary determining factor for selecting the intravenous route for nutritional support. Solutions given in a peripheral vein are less calorically dense than are solutions given in a central vein; therefore, centrally alimented patients can receive more calories and gain more weight on a daily basis. Furthermore, if infiltration of the intravenous catheter occurs, the number of calories actually infused can often be lower than was ordered. Because peripheral venous PN regimens maintain existing body composition, this route is a reasonable choice for a normally nourished infant or child who is expected to need PN for less than 2 weeks. Central venous PN is a more reasonable choice for infants and older children, regardless of initial nutritional status, who will be intolerant of enteral feedings for more than 2 weeks. It is difficult to maintain peripheral venous PN for longer than 2 weeks.

Ziegler and colleagues compared the complication rates of PN using central and peripheral veins.[124] Although infectious complications occurred in approximately 10% of the central vein group and in none of the peripheral vein group, morbidity related to the administration of solution (primarily in the form of soft tissue sloughs) was more prevalent in the peripheral vein group. Complications such as pleural effusions and thrombosis occurred in the central-vein group. The overall complication rate was higher in the central vein group (20% versus 9% in the peripheral vein group). However, the complication rates per day in the two groups were not different. Heird has pointed out that pediatric patients who receive peripheral venous PN are not as likely to develop the characteristic cushingoid appearance as those on central venous PN.[9] In addition, the rate of weight loss immediately after cessation of peripheral venous PN is not excessive; the composition of the weight gain might not be hyperhydrated like that observed with central venous PN regimens.

Intradialytic PN given with hemodialysis or peritoneal dialysis can be an additional route of nutrient delivery in patients with chronic renal failure and end-stage renal disease.[125] Patients receiving PN while on extracorporeal membrane oxygenation (ECMO) life support can have a glucose–amino acid solution administered through the ECMO circuit.[126] Some centers administer intravenous fat through a peripheral intravenous line because of concerns that the fat could occlude the ECMO filter; however, other centers have not had this experience and infuse fat into the ECMO circuit directly.

Central Venous Catheters

To achieve a high caloric intake, a hyperosmolar infusate should be delivered through a central, large-bore vein with high-volume blood flow to minimize the risk of venous thrombosis and phlebitis. The definition of a CVC at Lucile Packard Children's Hospital/Stanford University Medical Center is as follows: The optimal location for the tip of the CVC is at the junction of the superior vena cava and right atrium. Venous catheters will be defined as "central" if the catheter tip is positioned in the distal superior vena cava (SVC), SVC/right atrial junction, or in the inferior vena cava (IVC) at or above the level of the diaphragm. Catheter tips positioned in locations other than these will be defined as peripheral catheters. The distal SVC and IVC at or above the level of the diaphragm are the largest veins with the highest flow rate in the venous system. Infusion of cytotoxic, hypertonic, hypotonic, acid, or alkaline solutions or drug admixtures in CVC locations minimizes the risk of venous thrombosis, postinsertion malposition, and vessel perforation.

At Children's Hospital, Boston, the definition of "central" venous access includes lines whose tips reside in the SVC (including the brachiocephalic-SVC junction), right atrium, or IVC; all other tip locations are considered "noncentral." Otherwise, their definition of "central" venous catheter is similar to the one used at our center. Like the policy at Stanford, Boston Children's Hospital's recommendation is that PN solutions infused in a noncentral catheter be limited in osmolarity to 900 mOsm/L or less (eg, 10% dextrose, 2% amino acids with standard additives). Silastic catheters, which have been used effectively in pediatric central venous PN for many years, are preferred to polyvinyl or polyethylene catheters because of their high degree of flexibility. They do not become rigid when in place for only a short time, unlike polyvinyl catheters, which are associated with an increased likelihood of perforation of a vessel.

Two specially designed catheters for long-term PN are the Hickman and Broviac catheters (Davol Evermed, Kirkland, WA), which can be placed by either a cut-down incision or a percutaneous method into the SVC. Improved catheter stability and decreased risk of infection are achieved by subcutaneously tunneling the catheter to a distant exit site. The Hickman and Broviac catheters differ from the traditional Silastic catheter in the following ways:

- The portions of the catheter extending from the patient and the catheter neck are reinforced with Teflon to reduce the risk of cracking and breakage.

- The distal end of the catheter has a Luer-Lok connector to enable snug insertion of intravenous tubing and to allow secure screw-capping of the catheter when not in use.
- A Dacron cuff attached to the midportion of the catheter is placed subcutaneously at the catheter exit site; this stimulates the formation of dense fibrous adhesions that anchor the catheter securely and create a barrier for ascending bacteria. This process takes approximately 2 weeks, at which time the cutaneous sutures at the exit site can be removed.
- Placement of the central venous PN catheters is by either a percutaneous approach (internal jugular, subclavian, or femoral vein) or a cut-down technique (scalp, common facial, external jugular, brachial, cephalic, or inferior epigastric vein).

Chung and Ziegler have reviewed central venous access.[127a] After the insertion of any type of CVC, chest films are mandatory to confirm proper line placement and to rule out mechanical complications secondary to catheter placement. Infusion of hypertonic PN solutions or fat emulsions should not be initiated until the film has been interpreted and line placement documented.

Umbilical Artery Catheters

In some newborn nurseries, umbilical arterial catheters are used for infusing PN. Yu and colleagues found no difference in mortality in 34 infants with birth weights of less than 1,200 g who received PN via umbilical arterial catheters or enteral feedings.[127b] No data on catheter-related complications were noted. Higgs and colleagues had similar results in a trial of PN versus formula feeding by continuous nasogastric drip in 86 infants (birth weight 500 to l,500 g).[128] Four of the 43 PN babies had "catheter problems," described in the text only as blockage of the catheter. Hall and Rhodes compared the administration of PN by umbilical arterial lines (80 infants), umbilical venous catheters (9 infants), and tunneled jugular catheters (23 infants) in high-risk infants unable to tolerate enteral feedings.[129] They found that morbidity, mortality, and common complications, such as infection and thrombosis, were similar in both groups (umbilical lines versus jugular catheters). Careful analysis of the data reveals that six deaths might have been catheter related. Five of those deaths occurred in the umbilical arterial catheter group (thrombosis of the aorta in one patient; candidal, streptococcal, or enterococcal sepsis in four patients). One death occurred in the jugular catheter group, with right atrial thrombosis, SVC syndrome, and *Staphylococcus epidermidis* on blood culture.

A retrospective review compared PN via umbilical arterial catheters with PN via CVC in 48 neonates (birth weight 1,700 ± 600 g).[130] There was no difference in the infection rate between the two groups when adjustment was made for the number of days of catheter life. Transient hypertension occurred in two patients (4%) in the umbilical arterial catheter group and in one (4%) in the CVC group. There was one aortic thrombus noted on autopsy in the umbilical arterial catheter group and one incident of vegetation on the tricuspid valve in the CVC group. The use of umbilical arterial catheters for PN is not recommended[131] because this practice is associated with a high incidence of arterial thrombosis. There is also a concern about long-term complications, such as inappropriate growth of one limb. Although the first three studies described above claimed no short-term complications, they did not address the important issue of long-term complications.

INITIATING THERAPY WITH PARENTERAL NUTRITION

Before initiating PN, a complete nutritional assessment, including anthropometric measurements, should be carried out to determine the potential need for nutritional repletion and to estimate caloric requirements. The PN solutions can be ordered using two formats: customized or standardized. Customized solutions are formulated specifically to meet the daily nutritional requirements of the individual patient and nutrients are dosed on a per-kilogram basis. Standardized solutions are designed to provide a formulation that meets most of the nutritional needs of patients with stable biochemical and metabolic parameters. We feel that a customized PN regimen is best suited for pediatric patients.

Preprinted PN order sheets (Figure 57-1) save time for physicians and pharmacy personnel. In addition, the order sheet helps to avoid errors of omission, ensuring that all necessary nutrients are ordered. The order sheet provides the necessary input for specific PN computer programs. Required data for some of these programs include the patient's weight in kilograms, total fluid intake (mL/kg/day), the amount of fat emulsion (g/kg/day), fluid volumes contributed by other parenteral solutions or enteral feedings, desired protein intake via amino acids (g/kg/day), and the percentage concentration of dextrose. The doses of trace elements, vitamins, and electrolytes are ordered in amounts per day or amounts per kilogram per day. The computer performs all necessary calculations. Protocol recommendations are provided in the right-hand column of the order sheet for reference. For teenage patients, it may be acceptable to use a standard adult solution. Depending on the patient's electrolyte and nutritional status, calorie, fluid, and electrolyte requirements are determined and the solution ordered appropriately. As mentioned earlier, doses of carbohydrate, fat, and protein are gradually advanced to avoid overtaxing the metabolic capacities of the patient. Our recommended advancing guidelines are shown in Table 57-11. Clinical pathways have been developed for the administration of PN.[132]

CYCLIC PARENTERAL NUTRITION

The administration of PN over a period of less than 24 hours a day is termed cyclic PN. It allows more physical activity, less stress, and more flexible PN scheduling for these patients.[133] Conditions necessary for instituting cyclic PN include stable metabolic status and electrolyte and fluid requirements, and steady weight gain for at least 2 to 4 days on continuous PN. Patients should be able to

(addressograph stamp)

A. Please send TPN orders to the pharmacy before 11:00 am DAILY.

B. Order all additives on a 24-hour basis: eg, mEq/kg/day, mM/day, mL/day, mL/kg/day

PERIPHERAL _____ or CENTRAL _____ TPN LINE (check one) Today's DATE_____

DATE DUE _____/_____/_____ TIME DUE _____ (am pm)

month day year

Today's WEIGHT _____ kg

TOTAL FLUID INTAKE (mL/kg/day) _____ Next Bottle # _____

AMOUNT OF FAT EMULSION (g/kg/day) _____ Fat Concentration _____ 10% _____ 20% (check one)

How many IV or IA lines exist that will not be used for TPN? _____

	Line		Line
Enter flow rates (mL/hr):	(1) _____	and % NaCl:	(1) _____
	(2) _____	(e.g., 0.45%)	(2) _____
	(3) _____		(3) _____

If taking enteral feedings, complete the following section (check one):

_____ 1. Total fluids administered as parenteral and advancing enteral, ie, "TPN + PO." (Additives are distributed assuming that the total fluids will be given parenterally)

_____ 2. Total fluids administered as parenteral and fixed enteral. (Additives are distributed in parenteral fluids only; ignores electrolyte content of enteral fluids.)

Enter Amount: _____ (mis), Frequency: q _____hrs, Calories/mL: _____, Product name: _____

Enter AMINO ACIDS (g/kg/day)† _____ Enter DEXTROSE CONCENTRATION _____%

TODAY'S ADDITIVES		PROTOCOL RECOMMENDATION
TRACE ELEMENTS AND VITAMINS		
1. PEDIATRIC TRACE ELEMENTS	_____mL/kg/day	0.2 mL/kg/day (weight < 20 kg)
2. ADULT TRACE ELEMENTS	_____mL/day	5 mL/day (weight > 20 kg)
3. ZINC (additional)	_____μg/kg/day	100 μg/kg/day—Preemies only
4. PEDIATRIC M.V.I.	_____mL/day	2 mL/kg/day—infants < 2.5 kg
	_____mL/day	5 mL/day—infants ≥ 2.5 kg and children up to 11 years of age
5. ADULT MVI–12 (or generic)	_____mL/day	10 mL/day—children > 11 years of age
6. VITAMIN K	_____mg/day	0.5 mg/day—children > 11 years of age
ELECTROLYTES AND MINERALS		
1. PHOSPHATE*	_____nM/kg/day	0.5–2 mM/kg/day
2. SODIUM	_____mEq/kg/day	2.4 mEq/kg/day (sodium from other IVs is included)
3. POTASSIUM	_____mEq/kg/day	2–3 mEq/kg/day
4. ACETATE*†	_____mEq/kg/day	1–4 mEq/kg/day
5. MAGNESIUM	_____mEq/kg/day	0.25–0.5 mEq/kg/day
6. CALCIUM GLUCONATE	_____ mg/kg/day	50–500 mg/kg/day
7. HEPARIN	_____Units/mL	0.5–1 Unit/mL
8. INSULIN	_____Units/liter	
9. OTHER (specify)	_____	
10. OTHER (specify)	_____	

*NOTE: Balance of anions will be provided as chloride.

†Each 0.5 g/kg/day of amino acid provides either 0.47 mEq/kg/day of acetate (TrophAmine) or 0.74 mEq/kg/day of acetate (Aminosyn).

RN _____MD_____

FIGURE 57-1 Example of a physician's order sheet for total parenteral nutrition (TPN).

TABLE 57-11 Parenteral Nutrition Advancing Guidelines

	Dextrose	*Fat (g/kg/d)*	*Amino Acids (g/kg/d)*
Premature infants			
Initial	4–6 mg/kg/min	0.5	1.5
Advance*	1–2 mg/kg/min	0.5	0.5–1.0
Full-term neonates			
Initial	5%	0.5-1.0	1.5
Advance*	2.5%	0.5	0.5–1.0
Older infants/children			
Initial	10%	1.0	1.5
Advance*	5%	0.5–1.0	1.0
Adolescents and older			
Initial	10%	1.0	1.5
Advance*	5–10%	1.0	1.0

*Rate of advancement might be limited by metabolic tolerance, eg, hyperglycemia, hypertriglyceridemia, or azotemia.

handle maintenance fluids over a short period and have well-positioned CVCs. Safe administration of cyclic PN has been described in all ages, including infants with weights as low as 5 kg.[134] Cyclic PN in the hospital has become standard for patients on stable regimens. If the glucose concentration exceeds 10% or if the glucose infusion rate is high, then tapering the rate over the last hour by 50% is recommended. Almost all home PN patients receive cyclic PN for ease of care.

TRANSITION FROM PARENTERAL TO ENTERAL NUTRITION

There is an approximately 50% decline in enteric mucosal mass in normal animals maintained on intravenous nutrition in positive nitrogen balance without enteric stimulation.[135] Pancreatic atrophy and impairment of function also occur.[136] All segments of the small intestine demonstrate a decrease in the rate of proliferation and migration of the epithelial cells in parenterally fed versus enterally fed animals. Numerous animal studies have demonstrated the positive impact that luminal nutrients have on maintaining the structural and functional integrity of the gastrointestinal tract. These trophic effects on the intestinal mucosa can be direct or can be mediated by gastrointestinal hormones. Although human data are limited, it seems prudent to maintain a small oral nutritional intake during PN whenever possible.

In infants with intractable diarrhea, Greene and colleagues have demonstrated more rapid recovery of intestinal disaccharidases with the combination of PN and elemental enteral feedings than with PN alone.[137] Intestinal development is arrested when animals receive PN with no enteral nutrients; resumption of intestinal maturation occurs on reintroduction of intraluminal nutrients. Unlike that of the intestine and pancreas, the digestive function of the stomach is not impaired during PN in the very preterm infant. PN without gastric feedings decreases acid and pepsin in human infants, but when these infants are placed on constant-rate enteral infusion, these secretions return to normal.[138]

The transition from parenteral to enteral feeding should be gradual because the sudden cessation of PN can result in severe rebound hypoglycemia (secondary to high levels of insulin produced from high glucose intake). Small-volume oral feedings are begun and then increased to full feedings. The volume of the PN is proportionally decreased. After prolonged PN, many infants and children are reluctant to feed orally for reasons that are not clear.[139] Early involvement of oromotor therapists with these patients (before starting oral feedings) could prove extremely helpful.

COMPLICATIONS

Patients receiving PN are at risk of technical, infectious, and metabolic complications. These complications can be avoided or minimized only by regular monitoring, strict aseptic technique, and a multidisciplinary nutrition support team. Possible complications are listed in Table 57-12.

Technical Complications

Possible complications at the time of catheter insertion include pneumothorax, hemothorax, hydromediastinum, arterial injury, hematoma formation, arterial laceration, arteriovenous fistula and air embolism, catheter embolism, malposition, cardiac perforation, and tamponade. Complications related to ongoing use of the catheter include venous thrombosis, catheter dislodgment, and perforation of the pericardium, pleura, and mediastinum with leakage of the PN solution.

Forty-two newborns who had Broviac catheter placement were followed prospectively with echocardiograms.[140] Six infants (14%) had thrombus formation after the catheter had been in place for a median of 7 weeks. Those with thrombus formation had significantly lower birth weights and gestational ages than those without

TABLE 57-12 Complications of Parenteral Nutrution

Catheter related	
Infection: local (site), tunnel infection, sepsis	
Catheter occlusion	
Air embolus	
Crack, breakage, or aneurysm of catheter	
Non–catheter related	
1. Electrolyte	Hypo-/hypernatremia
	Hypo-/hyperkalemia
2. Mineral	Hypo-/hypercalcemia
	Hypo-/hyperphosphatemia
	Hypo-/hypermagnesemia
3. Metabolic acidosis	
4. Lipid related	Hypertriglyceridemia
	Hypercholesterolemia
	Essential fatty acid deficiency
	Fat overload syndrome
5. Protein related	Hyperammonemia
	Uremia
6. Carbohydrate related	Hypo-/hyperglycemia
7. Hydration related	Dehydrated/fluid overload
8. Refeeding syndrome	
9. Hepatobiliary disease	
10. Metabolic bone disease	

thrombus, but there was no correlation of thrombosis with duration of catheter placement. Many nurseries employ percutaneous central venous catheterization. In a study of 481 catheters placed percutaneously in a neonatal intensive care unit over a 3-year period, 50% were placed in infants weighing 1,000 g or less.[141] Mean catheter life was 13 days; almost half were removed nonelectively for leaking, clotting, or suspicion of sepsis (6%). Catheter sepsis was confirmed in 1.3%. For catheter-related sepsis, three factors were important: prolonged catheter placement (3 to 5 weeks), infection by *S. epidermidis*, and infant weight of 1,000 g or less.[141]

These percutaneous lines result in lower complication rates than those reported with surgically placed venous catheters. Complications with this method include leakage or perforation of the catheter. Placement of the catheter in the atrium can stimulate cardiac arrhythmias or cause the catheter to incorporate itself into the endocardium. Cardiac tamponade can result from atrial perforation by the CVC.[142–144] Regular and meticulous care of the CVC, particularly the catheter exit site, is essential for prolonged, safe, complication-free use. Use of the catheter for purposes other than delivery of PN, particularly for blood transfusions and blood sampling, should be avoided. PN teams using strict aseptic techniques have reduced sepsis rates to 2%.[145]

For long-term venous access, the Broviac catheter continues to demonstrate a lower complication rate than the traditional Silastic catheter.[146] Long-term venous access can be safely accomplished even in infants weighing less than 1,000 g.[147] Broviac catheter–associated infections occur more often in very low birth weight infants (69%) than in infants weighing more than 1,500 g (20%).[148] Of these infections, 78% (14 of 18) were successfully treated with antibiotics without catheter removal. The rate of thrombosis was also higher in very low birth weight infants. Triple-lumen catheters are becoming available for pediatric use.[149]

Catheter-Associated Infection

The major catheter-related complication is infection, usually the result of improper care of the catheter. Most of these infections can be treated with the catheter in situ.[150] *S. epidermidis* is the most frequent organism encountered, so vancomycin and gentamicin can be used successfully as initial therapy,[151] pending final culture report and sensitivities. Lack of defervescence and continued positive blood cultures for 2 to 4 days despite antibiotic use are indications for catheter removal.[152] Otherwise, antibiotics should be continued for 10 to 21 days.[152] The complete cure of catheter sepsis in patients treated with antibiotics through the infected lumen has occurred in 75 to 86% of patients.[151,152]

When continued use of a Broviac or Hickman catheter is desired, a trial of antibiotic therapy should be attempted before catheter removal.[151] The gastrointestinal tract could be a source of microbial seeding of the bloodstream via the catheter. There is considerable interest in therapies that maintain or improve the integrity of the gut.[153] For example, the role of glutamine in preventing gut atrophy in parenterally fed, enterally fasted patients needs to be further explored[154] because gut atrophy can foster increased intestinal permeability of bacterial pathogens.

Catheter Occlusion

Estimates suggest that 25% of CVCs become occluded, with thrombosis as the most common etiology. Nonthrombotic causes include deposition of intravenous lipids, calcium-phosphorus precipitates, heparin-induced occlusion, and intraluminal drug precipitates (eg, antibiotics).

Before 1999, the only approved pharmacologic agent for the medical treatment of thrombosed CVCs was urokinase (Abbokinase–Open Cath; Abbott Laboratories, Abbott Park, IL) derived from human neonatal kidney cells. In January 1999, the FDA suspended the distribution of urokinase because of the theoretic concern for the transmission of infectious agents.

Recombinant tissue plasminogen activator (alteplase) has subsequently been shown to be very effective in the restoration of function of CVCs occluded by a thrombus.[155] In September 2001, CathFlo Activase (alteplase; Genentech Inc., San Francisco, CA) was approved by the FDA for occlusions caused by thrombus. Published pediatric data on alteplase to date have demonstrated both safety and efficacy, and many pediatric centers are using alteplase to treat CVCs believed to be obstructed by a thrombus, but the FDA has requested additional safety data in pediatric patients. Therefore, a multicenter, phase IV, open-label, single-arm study of the safety and efficacy of CathFlo Activase in pediatric subjects is under way.

Should a thrombolytic agent fail to clear an occlusion, alternative causes should be considered. Mechanical catheter occlusion can be caused by external clamps, kinking of the catheter, occluded port needles, and constricting sutures. Six pediatric patients with occlusion of CVCs by calcium phosphate crystals were successfully treated by irrigating their catheters with a dilute hydrochloric acid solution.[156] Temporary febrile reactions occurred in three of these cases, but no serious complications were encountered. In the meantime, clinicians can minimize such precipitation by closely watching that concentrations of calcium and phosphorus fall well within standard solubility curves. Catheter occlusion caused by lipid material associated with PN treatment has been successfully cleared with ethanol after urokinase failed to clear these occlusions.[157,158] A recent review provides specific guidelines for clearance of catheter occlusions.[158]

Metabolic Complications

Use of Intravenous Fat The incidence of complications associated with the use of intravenous fat is low. If the intravenous fat infusion exceeds its maximal clearance rate, hyperlipidemia occurs, which can cause impairment of pulmonary function, displacement of albumin-bound bilirubin by plasma free fatty acids (which can lead to kernicterus), and fat overload syndrome (hypertriglyceridemia, fever, lethargy, liver damage, and coagulopathy). Thus, careful monitoring of the use of intravenous fat emulsions is essen-

tial; regularly check serum triglyceride levels. Cyclosporine use has been associated with elevated serum cholesterol and triglycerides in patients undergoing bone marrow or renal transplantation.[159] Allergic or hypersensitivity reactions to intravenous fat are extremely rare.[160,161]

After boluses of intravenous fat are infused into newborn infants, several investigators have demonstrated significant drops of arterial oxygen tension (PaO_2) without alteration of other pulmonary function test results.[162] Two hypotheses exist to explain the fall in arterial oxygen saturation: (1) lipid microemboli block pulmonary capillaries and alter perfusion ventilation ratios, and (2) fat metabolism leads to increased production of certain prostaglandins, which leads to pulmonary hypertension. The use of intravenous fat in patients with pulmonary compromise has yielded conflicting results. Although fat emboli were found on postmortem examination of pulmonary capillaries in neonates and infants who received Intralipid,[163–166] other reports have found no consistent association.[167] Fat deposition in the pulmonary microcirculation also has been documented in babies who never received intravenous fat.[164]

McKeen and colleagues found that administering intravenous fat doses of 0.25 g/kg/hour to sheep caused an increase in pulmonary artery pressure, a decrease in arterial PaO_2, and an increase in pulmonary lymphatic flow.[168] Identical findings have been described with doses of only 0.125 g/kg/hour. Heparin treatment did clear the serum of triglycerides but did not change the other parameters; therefore, the pulmonary hypertension and hypoxia were not caused by hyperlipemia. Treatment with indomethacin, a potent prostaglandin inhibitor, blocked the rise in pulmonary artery pressure, the increase in lymphatic flow, and the fall in arterial PaO_2. In rabbits there were no blood gas or prostaglandin changes in lipid-infused normal animals.[169] However, when the rabbits' lungs were damaged with oleic acid and then infused with intravenous fat, significant deterioration in gas exchange occurred. Furthermore, these changes were blocked by indomethacin (implying prostaglandin-mediated effects of intravenous fat). Brans and colleagues found that oxygen diffusion in the lungs of premature infants was not affected by the infusion of up to 4 g/Kg/d of Intralipid over 24 hours.[170]

Studies evaluating the effect of early infusion of intravenous fat in low birth weight infants on the development of chronic lung disease are conflicting. Forty-two neonates (birth weights less than 1,750 g) were given PN with and without intravenous fat for 5 days in the first week of life.[171] Chronic lung disease was increased in duration and tended to be more severe after lipid administration. A study of small doses (approximately 1 g/kg/day) of lipids on the first day of life, compared with administration starting later in the first week, also resulted in an increase in chronic lung disease.[172] In two subsequent studies (one starting intravenous fat on the first day of life[173] and one starting on day 4[174]), the above findings were not seen. Gilbertson and colleagues concluded that when it is given at rates not exceeding 0.15 g/hour, sick very low birth weight infants can tolerate intravenous fat with stepwise dose increases from the first day of life, without increased incidence of adverse effects.[173] In the study by Adamkin and colleagues, intravenous fat doses were similar to those in the study by Gilbertson and colleagues (0.5 to 3.0 g/day); the mean free fatty acid albumin molar ratio was less than 1.0 at all doses (maximum ratio, 3.0). Interestingly, in the Adamkin study, 5% of the patients had triglyceride levels higher than 200 mg/dL.[174]

Cooke studied 195 infants of less than 30 weeks gestation between 1983 and 1989 who were ventilated 4 or more days and survived to at least 28 days; 87 developed chronic lung disease.[175] There was a *sevenfold increase* in the annual incidence of chronic lung disease (most of that increase occurred in 1988 and 1989). The observed increase was associated with earlier use of parenteral fat (up to 4 g/kg/day of 20% intravenous fat). Intravenous fat was started between day 0 and 9 of life in 1 patient in 1983, none in 1984, 1 in 1985, 1 in 1986, 5 in 1987, 19 in 1988, and 26 in 1989.

To assess the impact of early initiation of intravenous fat on the incidence and severity of chronic lung disease, 133 infants weighing 600 to 1,000 g were randomized to either receive intravenous fat at less than 12 hours of age[176] (at 0.5 g/kg/day, increased to a maximum of 1.5 g/kg/day on day 7) or to not receive intravenous fat in the first week of life. There was no difference between the two groups in the incidence of chronic lung disease. There was no difference in mortality in the total population studied, but the mortality rate significantly increased in the 600 to 800 g group receiving intravenous fat. In that group there was also more pulmonary hemorrhage. Both intravenous fat groups (600 to 800 g; 801 to 1,000 g) had larger numbers requiring supplemental oxygen at day 7 compared with controls. A meta-analysis of six randomized controlled trials (N = 522 patients) of early (day 1 to 5) versus late (day 5 to 14) introduction of intravenous lipids in preterm, low birth weight infants found no significant trend or effect on the incidence of death or chronic lung disease, either at 28 days or at 36 weeks of age.[177]

Unsaturated fatty acids are highly susceptible to peroxidation, and the products (hydroperoxides) can interfere with arachidonic acid metabolism or react to form organic free radicals, which can initiate peroxidative injury in tissues.

Helbock and colleagues demonstrated significant levels of lipid hydroperoxides in Intralipid.[178] These toxic hydroperoxides could represent a significant risk to premature infants, particularly those with preexisting lung disease. Neuzil and colleagues demonstrated oxidation of intravenous fat by ambient and phototherapy lights in a neonatal intensive care unit.[179] Minimizing exposure of lipids to ambient and phototherapy light decreases the hydroperoxide levels. At Primary Children's Hospital in Utah, staff cover the fat emulsion bottle or syringe (they do not cover the tubing).

Inositol is a component of membrane phospholipids. A deficiency of this nutrient can be secondary to a deficiency in the diet, intracellular uptake, endogenous synthesis, or an increase in elimination rate. Its administration to immature animals increases levels of pulmonary surfactant. Breast milk, especially colostrum, has a high inositol con-

centration; intravenous feedings lack it altogether (colostrum contains 1.5 to 2.5 mmol/L; mature breast milk, 1 to 2 mmol/L; infant formula, 0.2 to 0.8 mmol/L; PN, 0.1 mmol/L). In a double-blind, controlled, randomized clinical trial, preterm neonates with respiratory distress syndrome who were given intravenous inositol had better survival rates and a lower incidence of BPD and retinopathy of prematurity.[180]

A study by Park and colleagues confirms previous observations that septic infants can develop significant elevations in triglyceride levels.[181] A sudden rise in triglycerides not associated with an increase in intravenous fat dose should make caregivers suspicious of sepsis. Dahlstrom and colleagues also argue that the dose of intravenous fat should be lowered during acute illness.[182] In a 1-year prospective study of 15 children on home PN, they noted that acutely sick children had higher serum triglyceride levels and prothrombin and partial thromboplastin values than when they were well. Their monocyte activation and complement factors remained normal even with acute illness.[182] A study in neonates receiving intravenous fat for 2 weeks or more (N = 162) demonstrated that liver dysfunction and fetal growth retardation were associated with lipid intolerance (elevated triglycerides), perhaps secondary to reduced hepatic lipase activity and, hence, impaired triglyceride clearance. Infection was not independently associated with hypertriglyceridemia.[183]

There is a reluctance to use intravenous fat in patients with low platelet counts, on the basis of reports of varying degrees of thrombocytopenia with earlier intravenous fat preparations and on the basis of one case report with Intralipid. Many anecdotal reports of thrombocytopenia could be secondary to an underlying condition (eg, sepsis) rather than to intravenous fat use. Cohen and colleagues could not implicate intravenous fat as a cause of thrombocytopenia in any of the 128 patients they studied.[184] In addition, 10 patients with thrombocytopenia secondary to sepsis or chemotherapy had rises in platelet counts, concomitant with the improvement of the septicemic state or with marrow recovery after cessation of chemotherapy. Actually, PN without intravenous fat can lead to essential fatty acid deficiency, which, in turn, can cause thrombocytopenia and platelet dysfunction. A study in ill neonates also failed to document any association between intravenous fat and thrombocytopenia. Goulet and colleagues have the only documented association of intravenous fat with thrombocytopenia.[185]

We recommend that intravenous fat be started at 0.5 to 1.0 g/kg/day (preterm) and 1.0 to 1.5 g/kg/day (full term) in the first week of life and that the dose be increased depending on the triglyceride level and clinical status of the baby. In infants of less than 30 weeks gestation, we hold the dose at 1.0 to 1.5 g/kg/day until the second week of life.

Use of Carbohydrate Hyperglycemia and hypoglycemia can occur with inappropriate dosing of carbohydrate. Hyperglycemia can result in glucosuria. If urine glucose by Keto-Diastix (Ames Co., Elkhart, IN) strip is 0.25% (250 mg/dL) or greater, it should be monitored with Dextrostix strips. If the Dextrostix result is elevated, it should be confirmed with a blood glucose evaluation. The glucose content of the PN solution might need to be decreased to prevent osmotic diuresis. A systematic review of all possible etiologies for glucosuria should consider medications, including corticosteroids; dietary indiscretions; error in the PN delivery rate; and sepsis. Excessive carbohydrate intake can result in an increased respiratory quotient and carbon dioxide retention and so affect weaning from the ventilator.

Use of Protein Excessive amino acid infusions can result in increased blood urea nitrogen (BUN), increased ammonia production, and metabolic acidosis in at-risk patients with liver or kidney disease and in low birth weight infants who have limited tolerance.[186] Thus, frequent monitoring of serum electrolytes, blood pH level, BUN, and even ammonia could be indicated in these patients. In patients with ongoing protein losses and hypoproteinemia despite good protein intake, a 24-hour urine collection to test for urine urea nitrogen (UUN) might be necessary to determine nitrogen balance. The UUN is measured in milligrams per 100 mL:

$$N_2 \text{ balance} = \text{grams of protein (intake)}/6.25 - (\text{UUN} + 3)$$

The protein intake should include protein provided by oral or enteral feedings plus that provided by intravenous amino acids. Dividing by 6.25 converts the grams of protein intake into grams of nitrogen. The UUN in this equation is expressed in grams. For example, if UUN equals 500 mg/100 mL or 5,000 mg/L and the patient's 24-hour urine is 2 liters, UUN equals 10,000 mg or 10 g/24 hours. The constant of 3 in the equation corrects for non–urea nitrogen losses (approximately 2 g/day); fecal losses (approximately 1 g/day); and skin, hair, and nail losses (approximately 0.2 g/day). This constant has been established in adult balance studies. It is not clear that the same constant can be used in premature infants or young children.

Osteopenia of Prematurity

Premature infants are susceptible to a unique condition, osteopenia of prematurity or rickets of prematurity, a common but poorly defined metabolic bone disease causing decreased mineralization. In most cases, decreased bone mineralization is subclinical; this condition is diagnosed only after the development of bone fractures or overt rickets.[187] Experts believe that a deficiency of calcium and phosphorus is more likely than a defect in vitamin D metabolism as the cause of osteopenia in preterm infants.[188]

Hepatobiliary Dysfunction

Hepatic dysfunction, one of the most common and most serious complications of PN, has been reviewed extensively.[189–191] Cholestasis is especially prevalent in very premature infants and in infants on PN for more than 2 weeks. Hepatomegaly with mild elevation of serum transaminases in the absence of cholestasis can result from hepatic accumulation of lipid or glycogen secondary to either excess carbohydrate calories or an inap-

TABLE 57-13 Monitoring of Parenteral Nutrition

Short-Term Monitoring
1. Anthropometrics: daily weight check
2. Laboratory studies (baseline): complete blood count, serum electrolytes, triglycerides, cholesterol, calcium, magnesium, phosphorus, alkaline phosphatase, total protein, albumin, BUN, creatinine, ALT, GGTP, bilirubin (total and conjugated), iron studies, prealbumin
3. Daily laboratory studies (initial): serum electrolytes, BUN, creatinine, triglycerides, calcium, phosphorus, magnesium
4. Weekly laboratory studies (the above daily laboratory studies plus): ALT, alkaline, phosphatase, GGTP, bilirubin (total and conjugated), cholesterol, total protein, albumin, prealbumin

Long-Term Monitoring
1. Anthropometrics: < 2 years of age: Weight, length, head circumference, arm anthropometrics (every 2–4 weeks)
   > 2 years of age: Weight, height, arm anthropometrics (monthly)
2. Every 3 months: Iron studies (serum iron, TIBC, % saturation, ferritin)
3. Every 6 months:
   a) Vitamin A, E, 25-OH vitamin D, PT/PTT
   b) Serum selenium, zinc, copper,* chromium, whole blood manganese
2. Yearly:
   a) Abdominal ultrasonography
   b) Bone mineral density study
   c) Renal clearance

ALT = alanine aminotransferase; BUN = blood urea nitrogen; GGTP = γ-glutamyl transpeptidase; PT = prothrombin time; PTT = partial thromboplastin time; TIBC = total iron-binding capacity.
*Obtain monthly if copper has been removed from total parental nutrition secondary to cholestasis.

propriate non-nitrogen calorie-to-nitrogen ratio. Fatty infiltration of the liver as a result of excessive caloric intake is readily reversible in nearly all instances by reduction of total calories administered. Abnormal liver function test results are not uncommon in patients on PN for long periods of time. Those with chronic intestinal conditions complicated by infection and bacterial overgrowth are particularly susceptible to hepatic complications. In most of these patients, elevated liver enzymes improve with the initiation of partial enteral alimentation.

The earliest abnormality noted (at 2 weeks) is an elevated serum γ-glutamyl transpeptidase or bile acid level. A small percentage of infants and children go on to develop chronic liver disease associated with poor growth[192] and even cirrhosis and hepatic failure.[193] A follow-up study of patients on long-term PN documented a wide variety of complications, but all of them (except liver dysfunction) proved to be temporary.[194] In this study, 58% of the children showed liver dysfunction during PN; some showed long-term abnormalities after its cessation. If PN-associated liver disease is suspected, then excessive caloric or protein intake should be avoided, trophic feedings should be started if possible, PN solution should be cycled, and the percentage of calories from carbohydrates should be kept between 50 and 55%.

Long-term administration of PN increases the risk of gallstones in patients of all ages,[195–198] and children with ileal disease or resection are at particularly high risk.[197] The gallbladder disease appears to be secondary to bile stasis. Clinically, gallbladder disease can be detected by the demonstration of "sludge" or a stone (or stones) in a patient with liver function test results consistent with cholestasis. Messing and colleague demonstrated sludge in 6% of cases in the first 3 weeks of PN; the incidence increased to 50% between the fourth and sixth weeks and reached 100% after 6 weeks.[196] Roslyn and colleagues recommend periodic ultrasonography in children on prolonged PN, especially if they have an ileal resection or underlying ileal disease.[197] They advise clinicians to suspect cholecystitis in any child on PN who complains of abdominal pain. A review of 246 infants and children receiving PN for more than 4 weeks revealed significant biliary disease.[199]

Refeeding Syndrome

Refeeding syndrome is the term used to describe the metabolic disturbances that occur when malnourished patients are refed rapidly. Drops in serum phosphorus, potassium, and magnesium; changes in glucose metabolism; vitamin deficiency; and need for fluid resuscitation can occur.[200,201] The most important preventive measure is to identify the at-risk patient and then start caloric intake at 75% of the REE, followed by a cautious increase of caloric intake by 10 to 15% per day, provided that the electrolyte, calcium, phosphorus, and magnesium levels are within normal limits. See Chapter 53, "Protein-Energy Malnutrition," for additional discussion of refeeding syndrome.

MONITORING PARENTERAL NUTRITION

The suggested schedule for chemical and anthropometric monitoring of patients receiving PN is shown in Table 57-13. Such monitoring should allow detection of metabolic complications in sufficient time to permit alteration of the PN infusate, with resultant correction of any abnormality. Detailed guides for monitoring are readily available.[202a]

HOME PARENTERAL NUTRITION

For patients who require long-term chronic PN administration and who would need hospitalization solely for the provision of PN, techniques have been developed to provide PN at home. Since the first patients being managed on home parenteral nutrition (HPN) were described by

Scribner and others in 1970,[202b] the technique has been successfully adapted to children. Over the past two decades, the use of HPN has been greatly expanded, and it has come to be accepted as a useful supportive and therapeutic technique for various gastrointestinal diseases and other conditions as well.[203–207]

Indications

The clinical conditions requiring HPN are the same as those for PN in the hospital, except that the patient no longer requires acute hospital care. Discharge on HPN, although expensive, can save health care dollars. The most common indications for HPN[206] are as follows:

- Short-bowel syndrome, with and without the potential for bowel adaptation (eg, from NEC or Crohn's disease)
- Motility disorders (eg, pseudo-obstruction syndrome)
- Intractable diarrhea (eg, intestinal lymphangiectasia, Crohn's disease, microvillus inclusion disease)
- Acquired immune deficiency syndrome (AIDS)
- Cancer-related conditions (eg, after bone marrow transplantation, graft-versus-host disease)

Contraindications for HPN include a functional gastrointestinal tract and lack of vascular access. Patients with anorexia nervosa are generally not candidates for HPN. HPN also should not be used when no family member is dedicated to and capable of learning and performing the daily techniques required for a successful program.[203] Moukarzel and colleages believe that a child should require HPN for a minimum of 30 days to justify the time and expense involved in training family members and establishing the program.[203] However, discharging a patient on HPN might afford overall cost savings to all parties, even if the patient might be able to take adequate oral nutrition in fewer than 30 days after discharge (eg, a patient who has undergone bone marrow transplantation).

All HPN patients are encouraged to take some oral nutrients as soon as possible to ensure maximal stimulation of the gastrointestinal tract for its adaptation and to diminish bacterial translocation. Such oral intake applies even to infants who have minimal chance of surviving without PN. Failure to initiate oral feedings in infants can result later in sucking or swallowing problems.[203] Oral intake also stimulates bile flow and decreases the likelihood of the development of sludge or gallstone formation.

Implementation

Preparing a patient for HPN requires a multidisciplinary team approach, including medical specialists, nursing staff, pharmacists, dietitians, social workers, and psychologists or psychiatrists. Social workers need to assess the family's ability to perform HPN and then provide emotional support at home. Before discharge, parents must master the necessary technical skills for providing HPN on a continuous or cyclic basis. Such skills include using aseptic technique, adding medications to the HPN solution, administering HPN through a central venous line, operating the infusion pump, heparin-locking the line, and performing dressing changes. Once the child is home, the family is faced with integrating these procedures into their life, while coping with the child's illness and the demands of normal child development.[208]

General information outlining benefits and risks are the first aspects of HPN discussed with the family. Potential complications, including catheter infection, sepsis, thrombosis, bleeding from inadvertent tubing disconnection, hyperglycemia, hypoglycemia, and myriad other potential metabolic derangements, need to be discussed. These discussions with caregivers should also include the expected outcome of PN therapy and the predicted degree of bowel adaptation.[203] Ninety percent of children with short-bowel syndrome who have at least 25 cm of small intestine and an ileocecal valve eventually are able to discontinue PN support.[209] Children who have an intact ileocecal valve and 15 to 20 cm of small bowel ultimately might adapt completely or only partially.[203,209] The anticipated impact of HPN on the lifestyle of the patient and family also must be discussed openly.

For long-term PN, cuffed silicone elastomer (Silastic) tunneled CVCs, such as the Hickman and Broviac catheters, have been commonly used. Totally implantable venous access systems, for example, Infuse-A-Port (Intermedics Infusaid Corp., Norwood, MA) and Port-A-Cath (Pharmacia Laboratories, Piscataway, NJ), have been used in children for administering blood products, drugs, and PN. Instead of exiting from the skin, the end of the catheter is attached to a small chamber that is placed in a subcutaneous pocket, usually on the anterior chest wall. Venous access is achieved by passing a Huber needle through the skin into the chamber via a Silastic gel window. The port can remain accessed for as long as a week or can be accessed as needed just before an infusion. The catheter system has the advantage of requiring minimal care and allowing complete freedom of activity because there is no external portion. However, it is more expensive and must be accessed with a needle each time it is to be used, which some patients find unacceptable. In adults, the subcutaneous port has lower clotting and occlusion rates compared with a traditional CVC, but no comparable studies exist in pediatric patients. The choice of vascular access device should be based on patient needs, capability, lifestyle, preference, and the HPN team's experience and knowledge of the available products. Patients can be freed from multiple intravenous poles, bottles, and tubing with the advent of lightweight portable pumps carried in ambulatory vests or backpacks.

Home nutritional requirements and fluid needs are assessed as stated previously. Generally, patients are stabilized before discharge from hospital. Virtually all patients can receive a cyclic PN schedule. The duration of infusion time can vary from 8 to 17 hours, depending on the age, nutritional requirements, medications, and enteral intake of the patient.

Complications

Complications of HPN are fewer when an experienced team is involved. The three types of complications that can

occur are infectious, technical, and metabolic. In the series of De Potter and colleagues, the mean duration of HPN was 615 days (range, 30 to 3,532 days).[206] Twenty-nine patients died, but only three deaths were HPN related, one because of cirrhosis and two because of catheter-related sepsis. Catheter-related complications included sepsis (n = 105), occlusion (n = 10), and dislodgment (n = 9).

The most common HPN-related complication requiring hospital readmission is catheter sepsis,[203] but these infections are less common in HPN than in hospitalized PN patients.[203] The lower incidence of catheter infection at home reflects the positive impact of one dedicated caregiver, well trained in meticulous catheter care. The incidence of HPN catheter infections is higher in children than in adults.[210] Catheter infections usually are caused by some known or unsuspected break in standard technique for HPN. Fever can occur in children because of catheter infection but also from usual childhood illnesses. With each fever, HPN patients should be seen for a careful physical examination and history. If there is no recognizable source of infection, the most likely possibility is a catheter infection or an intercurrent viral infection. The patient should have central and peripheral venous blood cultures done for aerobes, anaerobes, and fungi; a complete blood cell count; urinalysis; and chest radiograpy; other tests depend on clinical findings. If infection is found, the patient should be treated with intravenous antibiotics because most HPN patients cannot absorb oral antibiotics. If no source of infection is found, antibiotic coverage might be started anyway.

The UCLA group treats catheter infections in HPN patients for 4 weeks "through the line."[211] In general, not removing a line is important because of the long-term need for vascular access. Catheter removal is required for the following reasons: fungal infection (almost always), septic shock, endocarditis, embolism, persistent fever with positive blood culture growth, or disseminated intravascular coagulation. Tunnel tract infections usually require catheter removal.[210] After a catheter is removed, antimicrobial therapy is continued for 5 to 7 days and a new catheter is inserted after the patient is afebrile for 72 hours and blood cultures no longer contain the infectious organism.[211] In a large series, 87% of gram-positive and 53% of gram-negative infections were treated successfully without catheter removal. Of exit-site infections, 50% were successfully treated without catheter removal. There was also a longer life span with the second catheter, as well as a higher incidence of catheter-related complications of HPN in the first 2 years versus later years.[211]

The major technical problem with HPN is catheter occlusion. Warfarin has been used to prevent catheter-related thrombosis.[212] Of a group of 12 children on HPN,[213] bilateral upper limb venography showed extensive deep vein thrombosis (DVT) in 8. Warfarin treatment lengthened the average life span of their catheters, and no catheter-related DVT had occurred on follow-up. The authors advocated venography as the reference test for the diagnosis of central venous line–related DVT. Magnetic resonance imaging (MRI) has been used to diagnose DVT in adults, but there are no comparable studies in children. Lineograms, consisting of injection of contrast media into the central venous line, were found to be insensitive. Sola and colleagues described their 6-year experience with 22 Infuse-A-Ports in 15 cystic fibrosis patients. The overall complication rate was low—1 in 1,483 catheter days—but the incidence of major thrombotic events in 3 of 22 catheters (14%) led to a policy of administering low-dose acetylsalicylic acid therapy (80 mg/day) in all patients who did not have liver disease or other risks of bleeding.[214]

Metabolic complications of HPN are similar to those previously described. In a 1-year prospective study of 15 children receiving HPN, Dahlstrom and colleagues observed that acutely sick children had significantly increased triglyceride levels and prolonged prothrombin and partial thromboplastin time compared with when they were well.[182] There is a report in the literature of thrombocytopenia in seven children on long-term HPN, all of whom were receiving only 1 to 2 g/day of fat emulsion.[185] Recurrent thrombocytopenia (platelets less than 100,000) occurred in all seven. Platelet life span measured with indium 111 was reduced. These data contrast with an 18-year HPN experience at UCLA, where no patient receiving long-term daily parenteral fat emulsion has developed significant thrombocytopenia.

Since the guidelines for intakes of trace elements and vitamins have been developed,[87] deficiency states previously described (copper, zinc, manganese, chromium, selenium, biotin) rarely occur on long-term HPN. As stated previously, extra serum zinc supplementation is required in patients who have massive diarrhea and malabsorption. Ament's group feels that standard recommendations for chromium in PN (0.2 μg/kg/d)[87] could lead to elevated chromium levels, so they no longer supplement PN with chromium.[109] Similarly, this group does not supplement PN with iodide because iodide is in the water used in PN and is also a natural contaminant of a number of the PN salts. If iodide antiseptic solutions are used in central venous line care, this iodide is absorbed through the skin and contributes to normal iodide levels.[203] Intravenous iron must be provided in patients who are unable to absorb it enterally. When patients receiving PN develop cholestasis (conjugated bilirubin of 2 mg/dL or more), it is routine to remove copper and manganese from the TPN solution because both are hepatotoxic and are cleared by the liver. Because many centers use a standard solution of four trace elements (zinc, copper, manganese, and chromium), the trace element solution is held and zinc is added back separately. Recently, severe copper deficiency has been reported in cholestatic patients, associated with symptoms such as pancytopenia, depigmentation of the hair, and pseudoscurvy. In these patients, it is wise to monitor serum copper at least monthly and replace it if values are low.

Recently, there have been reports of manganese toxicity in long-term TPN patients. Symptoms have included disturbances in thought processes and gait, hallucinations, and parkinsonian symptoms. MRI can detect accumulation of manganese in the brain, and T_1-weighted MRIs have shown high intensity in the basal ganglia, especially in the globus pallidus, in patients receiving TPN. Whole-blood

manganese is the best screen for excessive levels. In adults, the dose of 1 μmol/day in TPN keeps those blood levels normal.[215] Cholestatic patients should definitely have manganese held in their TPN.

Carnitine deficiency can be associated with abnormal oxidation of long-chain fatty acids and progressive hepatic dysfunction. In a longitudinal study of nine children on carnitine-free PN, plasma total and free carnitine were 50% lower than in healthy control subjects, but they did not decrease further during the 3-year prospective follow-up.[216] Mean alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were slightly increased at the onset of the study but remained unchanged 3 years later. Low plasma carnitine concentrations appeared to be without clinical consequences after 10 years of carnitine-free HPN.[216]

In the past, patients receiving long-term HPN were seen with bone pain, hypercalciuria with normocalcemia, normal phosphatemia, and normal 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, and parathyroid hormone levels. The pathogenesis of this syndrome was secondary to aluminum toxicity because casein hydrolysates (used as the protein source in PN at some centers) were heavily contaminated with aluminum. This symptomatic bone disease has not been seen since all children have been receiving crystalline amino acid solutions. Osteopenia is a characteristic of patients who receive long-term PN. Such patients have been demonstrated to have a mean loss of 25% of the calcium in their trabecular bone.[217] This osteopenia could be multifactorial. Deficiencies of manganese, fluoride, boron, and silicon have all been suggested as causative factors. Additionally, adequate amounts and proportions of calcium and phosphorus are sometimes difficult to achieve in PN solutions. In a recent study, Moukarzel and colleagues found that serum silicon levels in children receiving HPN were 50% lower than those in non-HPN controls.[218] Furthermore, a significant correlation between silicon intake and mineralization suggests an involvement of silicon in the pathogenesis of the bone disease.[218]

Buchman and colleagues reported that long-term PN is associated with a marked decrease in both GFR and tubular function.[219] The observed decline could not be entirely explained on the basis of nutritional status, age, duration of PN, protein load, exposure to nephrotoxic drugs, or frequency of infectious episodes. A previous study of renal function in children on long-term PN showed that GFR might be reduced in these patients.[220] No nephrocalcinosis or tubular dysfunction was identified in this group of patients.

Long-term effects of PN on the liver and biliary tree were discussed earlier. A comprehensive review concluded that excessive caloric provision,[221] especially in the form of carbohydrate, plays an important role in the pathogenesis of steatosis; loss of enteric stimulation rather than PN per se could be the critical determinant in the development of cholestasis, biliary sludge, and gallstones. In the extensive experience of Ament's group at UCLA, life-threatening liver disease occurred in five children over a 20-year period.[203] In recent years, there has been a dramatic reduction in PN-induced liver disease associated with two key differences in management practices: initiation of enteral feedings (even as little as 1 to 5 mL per feeding in the preterm neonate) and availability of balanced amino acid solutions (such as TrophAmine and Aminosyn-PF) specifically designed for infants, reducing the toxicity occurring with adult formulations.

In addition, choline deficiency plays a role in hepatocyte damage. In animal models, choline-deficient diets are associated with fatty infiltration of the liver, a process that is reversible by adding choline to the diet. Buchman and colleagues reported low free-plasma choline in HPN patients.[222] They found that there was a significant correlation ($p < .02$) between low free-plasma choline and elevations in serum aminotransferases. The same group reported the reversal of PN-associated hepatic steatosis in four long-term HPN patients using an intravenous choline supplement added to the PN, 1 to 4 g/day for 6 weeks.[223] Fifteen of their HPN patients who had low free-plasma choline levels were randomly assigned to receive oral lecithin at 40 g/day or placebo for 6 weeks.[224] Lecithin supplementation resulted in increased free-plasma choline and a significant and progressive reduction in hepatic fat as assessed by computed tomography.

A recent placebo-controlled trial demonstrated proof of a human choline requirement for long-term home TPN patients.[225] All 15 study patients had hepatic steatosis confirmed by computed tomography. Those randomized to choline received 2 g choline chloride per night, rather than placebo, and experienced resolution of hepatic steatosis, along with decreases in serum aspartate transaminase and alanine transaminase.

Long-Term Growth and Nutritional Problems

Children receiving only HPN can achieve normal height, weight, midarm circumference, midarm muscle circumference, and triceps skinfold thickness. HPN patients receiving 30 to 70% of their total nutrients orally or enterally do gain weight and grow, but not as well as those on exclusive TPN.[226] In this latter group, there could be a propensity to underestimate the amount of PN needed by patients who ingest some nutrients.[203] Enteral calories can be malabsorbed to various degrees, depending on the underlying disease. Periodically, one should assess the amount of nutrients these patients can absorb enterally. Frequently, long-term HPN patients have growth retardation in the face of an apparently adequate caloric support. Causes for such failure of growth might include essential fatty acid deficiency, trace element deficiency, various endocrine disorders, or α-ketoglutarate deficiency.[227] Six prepubertal children on HPN who were well below their expected 50th percentile for height were studied over two successive 5-month periods. A dose of 15 g of ornithine α-ketoglutarate was added to the HPN solution in the first 5 months but not in the second 5 months. During supplementation, height velocity significantly increased, two patients entered puberty, and insulin-like growth factor I levels increased.[227]

In general, the patients on HPN who have been assessed with standard developmental tests have had normal or near-normal intelligence and motor function.[228] Parents tend to be overprotective of children on HPN, with particular fear of harm to the CVC. Some children have poor muscle development of unknown cause.[203] Most children receiving long-term HPN have deficits in perceptual-motor performance, especially the older children,[228] but their overall ability to sustain normal age-related activity is judged to be partial or complete in more than 95% of cases.[207] In the large series of De Potter and colleagues (156 children on HPN), 86% of subjects achieved normal growth, 89% were regularly attending school, 91% took part in physical activities, and 50% were able to go on family vacations.[206]

Visual function might be altered in children receiving long-term HPN.[203] It has been noted that despite normal visual acuity, half of the children had at least one and usually two abnormalities on their electroretinograms.[229]

Monitoring

Standards of practice for home nutrition support have been developed[230] and recently updated.[204] As discussed previously, a multidisciplinary team responsible for ongoing nutritional assessments is the optimal way to manage HPN patients. Theoretically, HPN should be feasible and effective for an entire life span.

SUMMARY

PN remains an evolving therapy. New technology to help better assess caloric needs has been designed, and standards for nutritional support in hospitalized pediatric patients[231] and HPN patients have been recently updated.[204]

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CHAPTER 58

DIETARY SUPPLEMENTS (NUTRACEUTICALS)

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We constantly search for new substances that can improve biologic function or make us fitter and healthier. Recently, Western society has turned to foods as sources of these enhancing molecules. These products are called, variously, vitamins, dietary supplements, functional foods, "nutraceuticals," phytochemicals, biochemopreventatives, and designer foods. These terms vary in meaning from country to country, as does regulation of these agents. Dietary supplements are ingredients extracted from foods, herbs, and plants that are taken without further modification outside of foods for their presumed health-enhancing benefits. The term dietary supplements was formally defined for US government offices in 1994 as a product (other than tobacco) intended to supplement the diet to enhance health that bears or contains one or more of a vitamin, mineral, amino acid, herb, or other botanical or is a dietary substance for use to supplement the diet by increasing the total dietary intake and is intended for ingestion in the form of a capsule, powder, softgel, or gelcap and not represented as a conventional food or as a sole item of a meal or the diet (Dietary Supplement Health and Education Act [DHEA]).[1] The dose to be administered is not included as part of the definition. Although not legally defined, we suggest that the term nutraceuticals should apply to those dietary supplements that deliver a concentrated form of a presumed bioactive agent from a food, presented in a nonfood matrix, and used to enhance health in doses that exceed those that could be obtained from normal foods. (A good example is genistein purified from soybeans and delivered in a pill in doses greater than could be consumed in soy.) "Functional foods" are similar in appearance to conventional foods and are consumed as part of a normal diet. They deliver one or more active ingredients (that have physiologic effects and perhaps enhance health) within the matrix of a food (eg, a bread or breakfast cereal with added high-dose folic acid). Diet supplements, nutraceuticals, and functional foods are designed to supplement the human diet by increasing the intake of bioactive agents that are thought to enhance health and fitness. For the purposes of this chapter, diet supplements, nutraceuticals, and functional foods will be combined under the term dietary supplements.

Use of dietary supplements has increased rapidly since the 1960s. Although consumption dates back to early Greek and Chinese cultures, their popularity in the United States and Europe has only recently experienced rapid growth. A 1997 follow-up to a 1990 US survey on the prevalence and frequency of use of alternative therapies among adults showed that 12.1% of respondents used herbal medicines and 5.5% used megavitamins, representing considerable increases between 1990 and 1997 (130% and 380%, respectively). Of the 44% of respondents who reported regular prescription medicine use, 18.4% had concurrent use of herbal products, high-dose vitamins, or both.[2] The 1999 HealthFocus Trends Report estimated that 54% of Americans used vitamin and mineral supplements at least once a week and 35% used herbal supplements.[3] Use of dietary supplements by children is not well documented; however, children whose parents use dietary supplements are more likely to use them.[4] It is estimated that approximately 50% of US children receive some form of vitamin and mineral supplements.[5,6] Supplement use in children also has been studied in disease states such as inflammatory bowel diseases,[7] cancer,[8,9] attention-deficit/hyperactivity disorder (ADHD),[10] and autism.[11,12] The growth of the industry and the lack of product regulation raise serious concerns for the health and safety of children.

Medicine and the pharmaceutical industry have already developed an approach to introducing new drugs that depends on safety evaluations and controlled clinical trials. This is not always true for dietary supplements. To distinguish between useful, worthless, and potentially harmful dietary supplements, it is important that health professionals carefully define the effect that they are trying to obtain using the supplement, review efficacy data that are available, review safety data, and then establish the balance between benefit and risk before recommending the treatment (see Chapter 13, "Food Safety," for further details).

GROWTH OF THE DIETARY SUPPLEMENT INDUSTRY

A growing industry exists to commercialize dietary supplements. From 1996 to 2000, US consumers tripled to $16.8 billion.[13,14] The American Pharmaceutical Associa-

tion estimates that 80% of pharmacies in the United States sell these products.[15] Until a few years ago, most companies in this field were relatively small, but now multibillion-dollar companies (such as Roche, Central Soya, Archer Daniels Midland, Bristol-Myers Squibb, Lipton, Johnson & Johnson, DuPont, Procter & Gamble, and Novartis) commit major resources to discover health-enhancing activities within the foods we eat and to change traditional foods so that they contain more of these active ingredients. The National Institutes of Health (NIH), acting on directives from the US Congress, set up the Office of Dietary Supplements (ODS) within the Office of the Director of the NIH in 1995 to accelerate basic research to identify effective dietary supplements.

DRUGS IN OUR FOODS?

It is often difficult to distinguish among nutrients, food additives, and drugs. Independent of the matrix (food or pill) in which it is delivered, a dietary supplement can sometimes be food-like and other times drug-like. Nutrients are defined as having nutritive value (they participate in metabolism or are used to build the structures of our cells) and are presumed to be safe. Food additives enhance the aroma, color, structure, or taste of foods but are not nutritive. Under present conceptualizations, the boundary at which a food ingredient becomes a drug is not well defined; often the health claims made for the substance are used to make the determination.[16] Should a nutrient used as part of a treatment for a defined disease be considered a drug, whereas the same nutrient used to enhance health (reduce the risk of disease) is considered a functional food or dietary supplement? This approach could result in classifying a naturally occurring cholesterol-lowering agent as a drug when it is used to reverse atherosclerosis and as a dietary supplement when it is used to prevent atherosclerosis.

One way to differentiate between foods and drugs is to examine how people are exposed to them. Drugs can sometimes be found naturally in foods, and they can participate in metabolism. However, they are substances that humans are not normally exposed to at the doses at which they exert their beneficial effects. In contrast, a nutrient exerts its effects at doses that correspond to reasonably expected exposures for a given population. Some supplements are drug-like when ingested in amounts that could never be achieved in the diet, even though they are essential nutrients when ingested in smaller amounts. At low doses, tryptophan is a necessary amino acid required for metabolism and incorporation into proteins. At high doses, it (or the currently used 5-hydroxy-L-tryptophan) increases brain serotonin synthesis and thus acts as a drug that treats insomnia.[17,18] In this case, a substance normally part of most foods was administered in doses that exceeded dietary requirements to obtain a pharmacologic response and so was drug-like in this circumstance. Another case is a substance that is not usually consumed by humans. Some plant constituents (eg, ephedra and digitalis glycosides) are biologically active at even small concentrations and have toxicity relative to this activity at higher concentrations.[19,20] Even small doses of these constituents are beyond common human experience. Foods are presumed to be safe because we can extrapolate from a known history of exposure to them, whereas a drug that has no such widespread exposure history cannot be presumed to be safe. Thus, we must weigh the risk-to-benefit ratio before large populations of humans are encouraged to ingest drugs.

REGULATION

In 1994, the US Congress passed the DSHEA,[1] which established a new framework for regulation of dietary supplements by the US Food and Drug Administration (FDA). Legislators recognized that people believed that dietary supplements offer significant health benefits. The US Congress wanted to facilitate access to these so-called "natural" medicines so that the public could be empowered to take some measure of control of their own health care. The DSHEA gave manufacturers of dietary supplements freedom to sell these supplements and to provide information about product benefits on labels, with significantly reduced requirements (compared with those for drugs and food additives) for premarket review by the FDA. Dietary supplements on the market before October 1994, when the DSHEA was passed, were exempted (ie, presumed to be safe). For these supplements, the FDA must show they are unsafe before it can restrict marketing of the products. For new ingredients in dietary supplements, the manufacturers (not the FDA) are responsible for determining that the products they market are safe. The FDA must be notified of a new ingredient in a supplement, and this notice must provide information that supports the manufacturer's conclusion that the ingredient is safe. This is a less rigorous process than is required for review of food additives (used to enhance the aroma, color, structure, or taste of a food) or drugs, for which there is a formal process for evaluation of safety. A manufacturer wishing to use a new food additive or a drug must conduct safety studies in a manner defined by the FDA and must submit the results to the FDA for review and approval before the ingredient or drug can be used in marketed products. This is not the case for dietary supplements in the United States because they are legally in a class by themselves; they can be marketed without the manufacturer's satisfying the FDA that they are safe. For more information, see <http://www.fda.gov/>.

The DSHEA ensures rapid access to products that are taken by half of all Americans. This legislation makes it easy for a relatively small enterprise to create and market a product without investing the time and money typically needed to prove safety and efficacy. However, the DSHEA modifies the regulatory environment so that it becomes possible, even likely, that products will be marketed that inadvertently harm people. To date, the FDA has asked for the voluntary recall of a product containing the herbal ingredient plantain contaminated with *Digitalis lanata* after an individual consuming the product suffered a complete heart block. The FDA proposed a regulation to limit the amount of ephedrine alkaloids in dietary supplements (ephedra, ma huang) after serious side effects, including

death, were observed.[21,22] The FDA asked for the voluntary recall of supplements containing γ-butyrolactone because this agent was associated with serious side effects, including coma and death.[23] Because of concerns over severe liver toxicity, the FDA issued a consumer advisory regarding the use of kava (*Piper methysticum)*, a product used for relaxation, sleeplessness, and menopausal symptoms.[24]

Many believe that dietary supplements are natural and therefore must be safe; however, this concept is fallacious. A presumption of safety derives from a history of exposure to the agent as part of a normal diet (or as part of long-term practice); when the dose is in excess of historical exposure, there can be no presumption of safety. Normal metabolism of nutrients includes many physiologic regulatory protective mechanisms (eg, activation of hepatic enzymes that metabolize or store excess nutrient) that make adjustments for modest changes in intake of the nutrient. When a nutrient or chemical is eaten in amounts that greatly exceed normal exposures, these safeguards can be overwhelmed. Similar considerations apply to substances derived from plants. As long as supplements do not appreciably increase exposure to plant-derived substances, it is reasonable to think of these as food ingredients. When dosage of food components, botanicals, or their extracts exceeds levels achievable in normal diets, their bioactivity can be drug-like. Although the determination of normal dietary exposure for an individual is complex, it may be possible to implement policy based on the highest common dietary intake for a human population (eg, use the Japanese population's intake of soy products to set the upper bounds for soy components such as genistein).

It would be advisable to create the category of nutraceuticals for dietary supplements administered in large doses to obtain pharmacologic effects. The benefits and risks of nutraceuticals should be considered much more carefully than those for foods. For the smaller health effects usually seen after administration of nutraceuticals (compared with drug effects such as those of penicillin, which completely eliminate a disease pathogen), the cost of demonstrating efficacy (required of all drugs) may be prohibitive. Thus, it may be inappropriate to classify all nutraceuticals as drugs, but, clearly, we should require more rigorous safety evaluation than we do for foods. The FDA should be empowered to ask for this evidence before—and not after—humans are exposed to potential risk. Perhaps the FDA could regulate nutraceuticals by requiring safety data similar to those required for over-the-counter medications (such as cold remedies).

At any dose, there is further reason to regulate the preparation of dietary supplements, nutraceuticals, and functional foods. Some plants contain a wide variety of toxic chemicals that help them to survive in their environmental niche and defend against bacteria, insects, and herbivores. Manufacturers may inadvertently add toxic constituents during the manufacturing process; the recent experience with eosinophilia myalgia syndrome and impurities in tryptophan preparations is an example.[25] Natural ingredients stored improperly can be substrates for molds that make highly dangerous mycotoxins; mold on peanuts forms the potent carcinogen aflatoxin.[26] There is as much reason for oversight of natural supplements as there is for oversight of synthetic drugs and foods. The dietary supplement industry has adopted a voluntary code of good manufacturing practices (GMPs).[14] The FDA proposed reasonable rules for current GMPs for dietary supplement ingredients in 1997[27] and a public meeting was held in July 1999,[28] but, at this time, there is no mandatory code established by the FDA. These rules are an essential first step toward a rational oversight of dietary supplements.

In response to growing concerns about the quality of dietary supplements on the market, the US Pharmacopoeia (USP) established the Dietary Supplement Verification Program (DVSP) in 2000.[29] Through compliance testing and document review, adherence to GMPs, and postmarketing surveillance, the DSVP is designed to help ensure that dietary supplement products contain the declared ingredients in the declared quantities. Participation in the program is voluntary. A supplement that carries the USP DVSP symbol is certified to contain the ingredients stated on the label in the declared amount and strength, meet specified standards for product purity by meeting requirements for known contaminants, and has been manufactured properly by complying with USP and proposed FDA standards for GMPs.[29]

The increased review and regulation of dietary supplements could decrease the access of the public to some beneficial products. For supplements administered at doses that can be found in foods, the adoption of GMPs should not significantly alter availability. For nutraceuticals that expose humans to ingredients at doses to which they would normally not be exposed, demonstration of safety should be mandated. This may mean that it will take years rather than weeks to introduce a new product, and some products may never be introduced. This seems a reasonable cost to protect the public health. The proposed schema for regulation also is in the interest of supplement manufacturers. In a manner similar to the experience of the pharmaceutical industry after the thalidomide debacle,[30,31] a dietary supplement harming a large number of individuals, with ensuing publicity, could result in public reaction that would damage the marketplace for all dietary supplements. In addition, with no requirement to show efficacy or safety, corporate investments in research and development of better nutraceuticals are unlikely because competitors can jump in without having to amortize the costs of such research. Although the DSHEA has fostered a situation that encourages continued market growth, it has not fully protected the public or fostered an atmosphere conducive to continuous quality improvement through an investment in research.

Table 58-1 summarizes recommendations for monitoring the supplement industry.

MARKETING TO CHILDREN

Children have become a critical niche for dietary supplement manufacturers. The *Nutrition Business Journal*, which tracks the industry, reported 1999 sales of $120 million in herbal and nutritional supplements for

TABLE 58-1 Recommendations for Monitoring the Supplement Industry

Create the category of "nutraceuticals" for dietary supplements administered in large doses to obtain pharmacologic effects
Require safety data similar to those required for over-the-counter medications
Regulate the preparation of dietary supplements, nutraceuticals, and functional foods
Adopt a mandatory code of good manufacturing practices for dietary supplements
Require participation in the US Pharmacopoeia Dietary Supplement Verification Program

children.[32] In 1999, a study conducted by National Public Radio, the Kaiser Foundation, and the Kennedy School of Government found that 18% of parents were giving their children dietary supplements that were not vitamins or minerals.[32] In Germany, where dietary supplement use in children is lower than in US children, over 100 supplements are marketed directly or indirectly for use by children with products containing anywhere from 1 to 26 constituents per product.[33] There are myriad reasons for supplement use by children. Parents give dietary supplements to their children to enhance health, as a substitute for good nutrition, to be a good parent, because of personal positive experiences, or at the recommendation of alternative medicine specialists.[34] Teens often use supplements that are touted as appearance, energy, and athletic performance enhancers.

SPECIAL CONSIDERATIONS IN PEDIATRICS

The use of dietary supplements in children most likely falls into the following categories: optimization of growth, development, and performance; addressing dietary inadequacies; and prevention and treatment of childhood and adult diseases. When assessing the safety and efficacy of a dietary supplement for a child, several considerations must be made. Nutrients can compete for absorption and use in the body, making high-dose supplementation with single nutrients potentially dangerous. For example, supplemental zinc competes with iron absorption and can lead to iron deficiency.[35,36] Also, dietary supplements can interact with pharmaceuticals and either attenuate or dampen treatment effects of drugs and/or cause adverse side effects. For example, St. John's wort activates cytochrome P-450 and affects the metabolism of antiretroviral protease inhibitors.[37]

Although dosages may be recommended on dietary supplement labels, actual dosages necessary to achieve the desired effects can vary. Bioavailability of the active compound is affected by maturation of the gastrointestinal tract, growth, character of the child's diet, and nutritional status.[37] In addition, the chemical form of the nutrient, food, or supplement matrix in which the nutrient is consumed and other foods in the diet affect bioavailability.[38] Although vitamin and mineral supplements may deliver the dosage listed on the label, numerous reports on herbal supplements have shown that the amount of active substance is not necessarily consistent with what is reported on the label.[39,40] Consequently, a child may take a prescribed dosage and actually get much less or much more of the actual ingredients. Data on the bioavailability and toxicity of micronutrients were used in establishing the Dietary Reference Intake (DRI) values and should be used as guidance for recommendations of acceptable limits for nutrient consumption in children.[41] Supplementation of individual and multiple megadose preparations of vitamins and minerals often provides amounts far in excess of the recommendations. Supplement users assessed in the National Health Interview Survey consumed two times the Recommended Dietary Allowance (RDA) for vitamin A, 7 times the RDA for riboflavin, and 17 times the RDA for vitamin C.[42] The message that excess administration of vitamin/mineral supplements at levels far exceeding the recommendations can result in adverse health effects must be communicated to children and their caregivers.

FOLATE: A SUPPLEMENTATION SUCCESS STORY

One of the true success stories in supplementation is folate. Folate affects embryogenesis of the brain. Individuals with diminished folate status are much more likely to have babies with neural tube defects (anencephaly and meningomyelocele),[43] and pregnant mice with folate deficiency had increased rates of exencephaly.[44] Currently, it is recommended that all women be folate supplemented during the periconception period because this reduces the risk for these serious defects in brain development.[45–47] Folic acid administered to women who had previously had a child with a neural tube defect lowered the risk of recurrence by 72%.[48] Folate effects on brain function may have greater significance because genetic polymorphisms of folate metabolism are relatively common and increase dietary requirements for folate. A thermolabile variant of 5,10-methylenetetrahydrofolate reductase (MTHFR 677 C->T) occurs in as many as 8 to 15% of the European and Japanese populations and in 28% of individuals with premature vascular disease.[49,50] Heterozygotes and homozygotes have high homocysteine levels in tissues, which are lowered by dietary supplementation with folate.[49]

COMMONLY USED DIETARY SUPPLEMENTS

Vitamin and Mineral Supplements

A daily multivitamin and mineral supplement is often used to make up for inadequacies in a child's diet. American children generally fall short of achieving recommendations for dietary adequacy. Although the American Dietetic Association maintains that eating a balanced diet that adheres to the Food Guide Pyramid is the best way to meet nutrient needs, they recommend a daily supplement of 100% of the RDA for selected vitamins and minerals for certain individuals unable to meet needs.[51] The American Academy of Pediatrics sees no evidence for supplementing the diets of healthy children.[52] However, if the dietary intake of nutrients is chronically inadequate, the use of a multivitamin and mineral supplement may be advisable.

Herbal Supplements

The following descriptions are from the German Commission E monographs[52]:

Echinacea (*Echinacea purpurea*): Fresh or dried root of *E. purpurea* and its preparations. Contains caffeic acid derivatives, alkamides, polyacetylene derivatives, polysaccharides, glycoproteins, and essential oil. Approved by the Commission E for the treatment of symptoms of upper respiratory infections associated with colds.

Ephedra/ma huang (*Ephedra sinica)*: Dried, young branchlets, harvested in the fall, of *E. sinica* or equivalent *Ephedra* species; the herb contains alkaloids (eg, ephedrine, pseudoephedrine). In the United States, ephedra is regulated under the DSHEA in aqueous infusion, alcoholic tincture, and dry extract in capsules or tablets. The alkaloids of ephedra (ephedrine and pseudoephedrine) are approved as over-the-counter ingredients in remedies for the common cold, flu, and allergies by the FDA. Ephedra's use in products for weight loss, athletic performance enhancement, and nervous system stimulation has raised concern with questions about the safety of these products. The Commission E approved ephedra for internal use in the treatment of diseases of the respiratory tract with mild bronchospasms in adults and children over 6 years. The FDA has received reports of 80 deaths and 1,400 adverse effects associated with ephedra in dietary supplements, and ephedra has been linked to heart attack, stroke, seizures, and psychosis.[54]

St. John's wort (*Hypericum perforatum)*: Dried parts above ground, gathered during the flowering season, of the *H. perforatum* and their preparation in effective dosage. The Commission E approved the use of St. John's wort internally in the treatment of psychovegetative disturbances, depressive moods, anxiety, and nervous unrest. It is thought that the active ingredient for the treatment of depression is hyperforin; however, studies are still being conducted. Oily preparations are approved for external use in the treatment of acute and contused injuries, myalgia, and first-degree burns.

Ginkgo biloba *(Ginkgo biloba)*: Dry extract pharmaceutically prepared to a 35 to 67:1 ratio of dried leaves to final extract containing flavonone glycosides (quercetin and kaempferol), terpene lactones (eg, ginkgolides A, B, and C), and ginkgolic acids. Ginkgo biloba has been approved by the Commission E for symptomatic treatment of disturbed performance in organic brain syndrome within a therapeutic regimen, improvement in pain-free walking in peripheral arterial occlusive disease, vertigo, and tinnitus.

Garlic (*Allium sativum*): Fresh or dried compound bulbs of *A. sativum* with no less than 0.5% allicin. Active compounds include thiosulfinates (allicin). In clinical trials, garlic has been effective in lowering cholesterol in hyperlipidemia and in treating hypertension. Garlic has antibacterial, antimycotic, lipid-lowering, inhibiting of platelet aggregation, prolonging of bleeding and clotting time, tumor-inhibiting, and fibrinolytic activity–enhancing properties. Commission E approved the use of garlic as a support to dietary measures for lowering elevated levels of blood lipids and in age-dependent vascular change prevention. However, limited results in the use of garlic for pediatric patients with hyperlipidemia have been shown.

Saw palmetto berry (*Serenoa repens*): The berry is the ripe fruit of the *S. repens* tree and contains fatty oil with fatty acids, esters, phytosterols, and polysaccharides. Saw palmetto is native to North America and was used as a staple food and medicine of Native Americans. Considerable clinical studies support its safe and effective use in treating symptoms associated with benign prostatic hyperplasia. Commission E approved the internal use of saw palmetto berry for urination problems in benign prostatic hyperplasia stages I and II. It has also traditionally been used for chronic or subacute cystitis, catarrh of the genitourinary tract, testicular atrophy, and sex hormone disorders.

Chamomile (*Chamomilla recutita*): Fresh or dried flowerheads of *Matricaria recutita* and its preparations in effective dosage. It is a popular ingredient in herbal tea in the United States and is prepared for topical use in rinses, creams, ointments, and vapor baths. In German pediatrics, chamomile is widely used in caring for infants' and children's sensitive skin, particularly for inflammatory skin conditions. Commission E has approved chamomile for gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract. It is also approved for external use for skin and mucus membrane inflammation and bacterial skin diseases.

Ginger (*Zingiber officinale*): Peeled, fresh, or dried rhizome of *Z. officinale* and its preparations in effective dosages. Ginger contains oleoresin, volatile oil, carbohydrates, lipids, vitamins niacin and A, minerals, and amino acids. Ginger is used alone and as a component in digestive, antinausea, and cold and flu dietary supplements in the United States. Commission E approved ginger for dyspepsia and prevention of motion sickness.

Valerian root (*Valeriana officinalis*): Fresh underground plant parts or carefully dried parts of *V. officinalis* and its preparations in effective dosages. Valerian roots contain essential oil with monoterpenes and sesquiterpenes. Commission E approved the product for restlessness and sleeping disorders based on nervous conditions. Clinical data support its action as a mild sedative and sleep-promoting agent. The USP does not support the use of valerian owing to inadequate clinical studies.

Performance Supplements

There is evidence that the use of performance-enhancing supplements is prevalent among young people (see Chapter 51.2, "The Adolescent Athlete: Performance-Enhancing Drugs and Dietary Supplements," for further details).[55,56] In particular, androstenedione, creatine, and ephedra are touted to boost athletic performance, although none of these supplements has been shown to significantly enhance performance, and their safety in children is questionable.

Androstenedione is a steroid hormone and a precursor to testosterone that is taken to promote muscle growth and athletic performance. Clinical trials of androstenedione show that it raises estradiol and testosterone levels in healthy men.[57] Long-term use has not been studied, but it is thought that effects similar to those seen in chronic steroid use could be seen. Although the use of androstene-

dione is banned in most sports, both in the United States and abroad, many young athletes report using it.

Creatine is a nonessential dietary element that is present in meat and fish and is endogenously synthesized in the liver. Skeletal muscle phosphorylates creatine to create phosphocreatine, a high-energy compound. During exercise, if aerobic energy production cannot meet adenosine triphosphate (ATP) demand, phosphocreatine conversion assists in the production of ATP. There is also no evidence that dietary phosphocreatine is necessary for muscle contraction or that creatine stimulates protein synthesis. The American College of Sports Medicine (ACSM) released a consensus statement in 2000 concluding that creatine has a potential impact on intense short exercise, such as short-distance sprints that last 6 seconds. They also noted that owing to the lack of research in the pediatric population, they do not recommend supplementation for children under 18 years.[58] One study of sixth to twelfth graders in the northeastern United States found that 8.8% of surveyed boys and 1.8% of girls used creatine. Among grade 12 athletes, use was at 44%.[59]

Probiotics

Although widely used in other parts of the world, probiotics are recently achieving popularity in the United States. Often in the form of a functional food such as yogurt, a probiotic is a preparation containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects on the host.[60] They are marketed in single-bacteria and multiple-bacteria preparations, with some of the more common ones being *Lactobacillus casei, Lactobacillus acidophilus,* and *Bifidobacterium bifidum*. Although actual colonization by the live bacteria cannot be proven directly, it is inferred by bacterial shedding in the feces after the cessation of supplementation. In children, reports suggest that supplementation with *L. casei* shortens the duration of diarrhea[61] and helps eliminate recurrent *Clostridium difficile* colitis in children in whom antibiotics had failed.[62] Supplementation with a combination of *Bifidobacterium bifidum* and *Streptococcus thermophilus* shortened the duration of rotavirus shedding in hospitalized children.[63] Also, there is evidence that probiotics improve lactose tolerance when live cultures are present in fermented dairy products. They result in decreased cramping and gas as well as a decrease in the concentrations of exhaled hydrogen.[64] Probiotics have also been reviewed for their roles in immunomodulation, cholesterol levels, cancer prevention, *Helicobacter pylori* infection, allergy, inflammatory bowel disease, and mineral absorption.[65]

SUPPLEMENT INTERACTIONS AND POTENTIAL RISKS

In 2002, the National Toxicology Program, in partnership with the NIH ODS and FDA, reviewed the safety of a select number of dietary supplements including aloe vera gel, black walnut extract, comfrey, *E. purpurea* extract, gingko biloba extract, ginseng, goldenseal, grapeseed extract, pine bark extract, kava kava, milk thistle extract, pulegone, and thujone, focusing on characterization of potential adverse health effects.[66] The following are side effects and contraindications for popular herbs excerpted from the *Physician's Desk Reference for Herbal Medicines*[67] and medical literature:

- *Echinacea:* Because of a conceivable activiation of autoimmune and other overreactive immune responses, the drug should not be administered in the presence of multiple sclerosis, leukoses, ollagenoses, acquired immune deficiency syndrome (AIDS), or tuberculosis.[67]
- *Gingko biloba:* The ginkgolide B component has a potent inhibitory effect on platelet-activiting factor (PAF) by displacing PAF from receptor binding sites and thus may inhibit platelet activation.[67]
- *Kava:* May potentiate the effectiveness of substances that act on the central nervous system, such as alcohol, barbiturates, and psychopharmacologic agents.[67]
- *St. John's wort:* The most prominent adverse effect associated with this herb is photosensitivity attributed to its hypericin component.[67] It has also been shown to increase clearance of antiretroviral protease inhibitors.[37]
- *Ephedra:* Contraindications include death, states of anxiety and restlessness, high blood pressure, angle closure glaucoma, cerebral perfusions, prostate adenoma with residual urine volume, pheochromocytoma, and thyrotoxicosis.[67]
- *Eucalyptus:* Infants and young children should not have preparations containing the oil applied to their faces as this can lead to glottal spasm or bronchial spasms through asthma-like attacks or even death by asphyxiation.[67]

Table 58-2 outlines some potential pitfalls in the use of common dietary supplements.

PHYSICIANS' ROLE IN DIETARY SUPPLEMENT USE

The FDA maintains the MedWatch Program for reporting adverse events. Physicians should report adverse events experienced by their patients. The program can be accessed on-line at <http://www.accessdata.fda.gov/scripts/medwatch/>. Patients do not always discuss their use of dietary supplements with their physicians. In one survey of patients completing a survey during a routine physical, only 30% of dietary supplement users reported use.[68] Patients may think that the supplement use is not related to conditions for which care is being sought or may not feel supported by their physician.[34] It is extremely important to obtain a thorough history of supplement use in pediatric patients. Figure 58-1 provides a reasonable assessment tool for use by physicians. Often it is helpful to photocopy labels from supplement bottles brought in by patients.

ACCESSING INFORMATION ABOUT DIETARY SUPPLEMENTS

- The Institute of Medicine DRI publications provide extensive information on vitamin and mineral needs.[69–72]

Dietary Supplement Intake Form

DATE _____

PATIENT NAME _____ AGE _____

1) What kind of supplements does your child take? (check all that apply)
- ❑ none
- ❑ multivitamin/mineral supplement
- ❑ herbal or botanical supplement
- ❑ amino acid or protein supplement
- ❑ fiber supplement
- ❑ other (see question 19 checklist)

2) How long has your child taken this supplement(s)?
- ❑ 1 month or less
- ❑ 3 months
- ❑ 6 months
- ❑ 1 year
- ❑ more than 1 year (specify) _____

_____

3) How long do you plan to give your child this supplement(s)?
- ❑ indefinitely
- ❑ 1 year
- ❑ 6 months
- ❑ 3 months
- ❑ 1 month or less

4) What are your primary reason(s) for giving your child this supplement(s)?
- ❑ for its preventive effect against disease/medical condition
- ❑ to help treat a disease/medical condition
- ❑ general wellness
- ❑ energy
- ❑ weight loss
- ❑ other (specify) _____

_____

If used to *treat* specific medical condition:
What are the child's specific medical symptoms:_____
_____
_____
_____

5) How long has your child had these symptoms/medical conditions?
- ❑ 1 week or less
- ❑ 1 month
- ❑ 3 months
- ❑ 6 months
- ❑ 1 year
- ❑ more than 1 year (specify) _____

_____

6) Have symptoms improved since your child started taking this supplement?
- ❑ yes (explanation) _____

_____
_____
_____

7) Is your child currently taking or has your child recently taken any over-the-counter or prescription medications to treat these symptoms/medical condition?
- ❑ yes (explanation) _____

_____
_____
_____

8) Has your child experienced any adverse reactions after taking the supplement(s)?
- ❑ yes (explanation) _____

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

*Attach to this form copies of labels from dietary supplements taken by patient.

FIGURE 58-1 Assessment tool of supplement use. Adapted from American Dietetic Association. A healthcare professional's guide to evaluating dietary supplements. Chicago (IL): American Dietetic Assocation; 2002.

Dietary Supplement Intake Form (Continued)

B) What specific supplement(s)* does your child take, amount he takes, and how often is it taken?

	Brand Name	Amount/Dose	No. of Doses (/day or/week)
❑ Aloe			
❑ Amino acid(s)			
❑ Black cohoan			
❑ Bee pollen			
❑ Calcium			
❑ C			
❑ Chondrol			
❑ Chrom			
❑ Coenzyme			
❑ Cr			
❑ "Andro" OHEA			
❑ D q			
❑ Ech			
❑ Energy b			
❑ E p			
❑ F			
❑ Fiber			
❑ Flin			
❑ Folic acid			
❑ Garlic			
❑ Ginger			
❑ G			
❑ Gin			
❑ Go			
❑ Gr extract			
❑ Iron			
❑ Keve			
❑ Min hunag/e			
❑ Milk thinks			
❑ Multivitamin/minerals			
❑ Peppermint			
❑ Pyruvate			
❑ St. John's ward			
❑ Sew palmeto			
❑ Santo			
❑ Vitamin			
❑ Vitamin B complex			
❑ Vitamin C			
❑ Vitamin D			
❑ Vitamin E			
❑ Other			

FIGURE 58-1 (continued)

Based on exhaustive research, expert analysis, and diverse input, the DRIs are reference values for intake and include three categories: Estimated Average Requirement (EAR), RDA, and Tolerable Upper Intake Level (UL). The EAR is the intake value that is estimated to meet the requirement defined by a specified indicator of adequacy in 50% of an age- and gender-specific group. At this level of intake, the remaining 50% of the specified group would not have its needs met. The RDA is the dietary intake level that is sufficient to meet the nutrient requirements of nearly all individuals in the group. The UL is the maximum level of daily nutrient intake that is unlikely to pose risks of adverse health effects to almost all of the individuals in the group for whom it is designed.[73] DRI documents are produced by the Food and Nutrition Board of the Institute of Medicine, National Academies. Full text is available on the Web site at <http://www4.nationalacademies.org/IOM/IOMHome.nsf/Pages/Food+and+Nutrition+Board>.

There are also several reputable sources for information on other dietary supplements:

- *The Physician's Desk Reference for Herbal Medicines*[67]
- The Cochrane Database of Systematic Reviews is an evidence-based analysis prepared by the Cochrane Collaboration, an international nonprofit organization and part of Britain's National Health Service. It "prepares, maintains, and promotes the accessibility of systematic, up-to-date reviews of health care interventions" (<http://www.update-software. com/cochrane/order.htm>).
- The National Center for Complementary and Alternative Medicine (NCCAM) is 1 of the 27 institutes and centers that make up the NIH. Its mission is to support rigorous research on complementary and alternative medicine (CAM), to train researchers in CAM, and to disseminate information to the public and professionals on which CAM modalities work, which do not, and why. The Web site offers health, research, training, and clinical trials information (<http://nccam.nih.gov/>).
- The NIHODS plans, organizes, and supports conferences, workshops, and symposia on scientific topics related to dietary supplements. The Web site features dietary supplement fact sheets and the Computer Access to Research on Dietary Supplements (CARDS) Database (<http://ods.od.nih.gov/index.asp>). The ODS produces the International Bibliographic Information on Dietary Supplements (IBIDS), a database of published, international, scientific literature on dietary supplements, including vitamins, minerals, and botanicals. IBIDS assists the public, health care providers, educators, and researchers in locating credible, scientific information on dietary supplements (<http://ods.od.nih.gov/databases/ibids.html>).

TABLE 58-2 Potential Pitfalls in Common Dietary Supplements

Category	*Description and Examples*
Toxicity	Androstenedione may increase testosterone and estrogen levels. Not recommended for anyone under 25. Creatine may lead to kidney dysfunction. Side effects include cramping, diarrhea, and dehydration. Not recommended for children or adolescents owing to lack of safety data. St. John's wort has been associated with photosensitivity (at high doses), allergic reaction, and stomach and intestinal problems. Comfrey is a source of pyrrolizidine alkaloids, which have been shown to be hepatotoxic. There is also evidence that pyrrolizidine alkaloids may be carcinogenic. Ephedra has been associated with seizure, stroke, heart attack, psychosis, and death.* High-dose vitamin B supplements were thought to be the cause of rosacea fulminans in a 17-year-old girl.†
Interference with the absorption of other nutrients	Zinc supplementation may interfere with the absorption of iron and copper. Chitosan may interfere with the absorption of fat-soluble vitamins A, D, E, and K as well as the mineral calcium.
Interference with other pharmaceuticals	Oral aloe vera can act as a laxative and may interfere with absorption of other oral medications taken concurrently. St. John's wort may increase the effect of antidepressants and barbiturates and alter the metabolism of reserpine, digoxin, theophylline, immunosuppressive drugs, and protease inhibitors.
Inconsistency in dosage listed on label and dosage found in product, or product contamination	Examples of contamination and excessive dosages in dietary supplements reported by Consumer Lab include lead in a nettle product; excessive vitamin A in diet bars; and quintazene and hexachlorobenzene at 20 times the allowed amount in ginseng supplements.‡ In the case of a man with vitamin D toxicity, the bottles of the product taken contained 26 to 430 times the amount of vitamin D as that listed by the manufacturer.§
Lack of research or established safe levels of intake for children	Few dietary supplements have been studied in children. Although limited adverse effects have been reported for the majority of dietary supplements, it is best to consult the *PDR for Herbs* as well as monographs from the US Pharmacopoiea for information on individual dietary supplements.

*Samenak D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporarily associated with ma huang, an herbal source of epinephrine. Mayo Clin Proc 2002;77:12–6; and Jansen T, Romiti R, Kreuter A, Altmeyer P. Rosacea fulmicans triggered by high-dose vitamins B6 and B12. J Eur Acad Dermatol Venereol 2001;15:484–5.
†J Eur Acad Dermatol Venereol 2001;15:484–5.
‡Consumer Lab product reviews. Available at: www.ConsumerLab.com (accessed September 2002).
§Koutkia P et al.[40]
Remaining information adapted from the Dietary Supplement Information Bureau. Available at: www.supplementinfo.org (accessed September 2002).

- *The German Commission E Monographs: Therapeutic Monographs on Medicinal Plants For Human Use*[53]

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CHAPTER 59

SPECIAL DIETS

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The role of nutrient requirements in disease and the importance of providing essential nutrients to prevent disease were recognized by some of the earliest physicians. The recognition of fruits and vegetables as antiscorbutics in 1671 and the discovery of scurvy as a deficiency disease in 1734 are two examples of the early appreciation of the importance of diet. Some of the first scientific research related to diet was published in 1843 by Pereira, who experimentally fed underprivileged individuals and the sick in metropolitan institutions. Florence Nightingale, the founder of dietetics and modern nursing, was devoted to feeding and nursing the sick and wounded during the Crimean War. The concept of diet as an adjunct mechanism to support health and to prevent and treat various disease states has a strong historical foundation.

The term "special diets" refers to diets that are modifications of the normal adequate diet pattern based on the Dietary Reference Intakes suggested by the Food and Nutrition Board of the Institute of Medicine. Modern medical nutrition therapy promotes the use of diet in the prevention and treatment of a variety of diseases.

The majority of healthy children never require special diets. Typically, children thrive on a varied diet with erratic bursts in growth, usually coupled with concomitant changes in appetite. However, many children with chronic diseases require special diets for optimal health, growth, and development. Depending on the condition, the required nutrient adjustments might be acute or chronic. For example, a surgical procedure might necessitate the use of a special diet for a short duration. Other diseases, however, such as insulin-dependent diabetes mellitus, phenylketonuria, or celiac disease, require lifelong modifications in nutrient consumption. It is important to recognize that disease is not the only indication for implementation of a special diet. Various situations, including the prevention of unwanted disease, personal religious beliefs, and individual lifestyle preferences, can influence an individual to choose a special diet. In these instances, it is important to evaluate the safety of the special diet for a child.

To implement a special diet, adequate education and supervision are keys to successful compliance. For children who require permanent alterations of their diet, regular follow-up, ongoing education, re-evaluation of the diet, and continual attempts to motivate the family and maintain the child's commitment to the diet are important elements of success. Most special diets can be planned to meet 100% of the Dietary Reference Intakes for nutrients. However, some diets could be deficient in particular nutrients and might require vitamin or mineral supplementation. In particular, chronic use of special diets in the pediatric population necessitates periodic monitoring of macro- and micronutrient status. With the proper use of special diets, optimal growth and development can be achieved.

This chapter describes commonly used special *diets* for selected pediatric disorders. Chapter 55, "Standard and Specialized Enteral Formulas," reviews the rationale and development of types of special *formulas*, and Appendix III provides a comprehensive list of commercially available enteral formulas. The conditions and diets described here do not comprise a comprehensive list but rather represent the most common ailments seen in pediatrics. Special diets for clinical conditions such as food allergy, gastrointestinal disease, growth failure, hyperlipidemia, inborn errors of metabolism, mineral deficiency, and weight control are found in this chapter. Included are descriptions, rationales for implementation, and lists of specific foods allowed and to be avoided. Checking food labels diligently is strongly advised because manufacturers often change product recipes.

FOOD ALLERGY

Food allergies can require major dietary changes, depending on the food antigen in question. Some of the most common allergens in infancy include cow's milk protein, soy protein, fish, eggs, and grains. In older pediatric patients, the list expands to include berries, nuts, peanuts, and chocolate. Cow's milk protein allergy, one of the most common allergies in infancy and early childhood, occurs with a frequency of between 0.5 and 7.0% in the general population. Up to 60% of pediatric patients with immediate hypersensitivity to cow's milk protein are allergic to soy protein as well.[1]

The gold standard for the diagnosis of a potential food allergy is the double-blind placebo-controlled study. Liquid preparations can be used for infants and toddlers, and tablets or capsules can be used for older children. Such studies should be conducted in a hospital or clinic setting to ensure patient safety, especially in cases of suspected immunoglobulin E (IgE) mediation. Although elimination diets remain popular, they are fraught with problems, including the correct identifica-

tion of the allergen in question, patient compliance, and other potential agents (dietary or otherwise) that could elicit a similar response.[2]

Nutritional management includes complete exclusion of the dietary antigen. Families are instructed to read product labels for terms indicative of the antigen, such as whey and sodium caseinate in the case of cow's milk protein allergy (see "Milk-Free Diet" below for a complete list). A hypoallergenic infant formula is recommended to replace the cow's milk–based formula.[3] Fortified soy or rice milk can be substituted for cow's milk in diets for toddlers. When food allergies are severe or multiple, amino acid–based formulas can be used. Children not receiving complete enteral supplement should be assessed for mineral and vitamin deficiencies. In families with a high risk for the development of one or more food allergies, it would be prudent to initially breast-feed infants, use a hypoallergenic formula, or both, in conjunction with the avoidance of the common food allergens mentioned.

Periodic patient education updates are necessary. This is especially important with a diagnosis made in infancy because of the introduction of solid foods and the increased possibility of multiple caregivers. Education for family and even extended family should stress the necessity of continued dietary compliance. Support groups, cookbooks, and the like can be beneficial to patients requiring long-term dietary restrictions.

Corn-Free Diet

The corn-free diet is for individuals with an allergy to corn and its derivatives. Elimination of the following ingredients is necessary for individuals adhering to a corn-free diet: corn, cornstarch, corn syrup, corn oil, corn meal, corn sweeteners, maize, and popcorn.

The following ingredients might contain corn: hydrolyzed plant protein, hydrolyzed vegetable protein, and starch (99% likelihood of cornstarch content).

Egg-Free Diet

The egg-free diet is for use in patients with a suspected or documented allergic reaction to egg-related products.

Elimination of the following ingredients is necessary: egg albumin (also called ovalbumin), eggs, egg white, egg yolk, dried egg, egg powder, egg solids, egg substitutes (which contain eggs), eggnog, globulin, livetin, lysozyme (used in Europe), mayonnaise, meringue, ovoglobulin, ovomucin, ovomucoid, vitellin, and Simplesse.

Noteworthy Points

- The egg white, or albumin, is the most allergenic part of the egg.
- Many baked products that have a yellow color or shiny glaze are made with eggs or egg whites.
- Egg whites are often used as a clarifying agent in broths or soups. Always check with the chef when eating out.
- The measles, mumps, and rubella (MMR) vaccine is a source of egg exposure for children.
- Influenza vaccines are grown on egg embryos and could contain trace amounts of egg protein.
- Simplesse is used as a fat substitute in ice cream and frozen desserts and is made from either egg or milk protein.

Tips for Egg-Free Cooking

- Egg substitutes can be used if they are free of egg whites.
- Mashed bananas and apricot puree add flavor and act as both a binder and a thickener in place of egg in quick breads, cakes, cookies, and other sweets.
- Use 2 tbsp pureed fruit for each egg in recipe.
- Two tablespoons of pureed vegetables can replace an egg in soups, sauces, and other dishes.
- To bind or thicken fruit desserts, use 1 tsp dry, unflavored gelatin mixed with 2 tbsp of liquid to replace one egg.
- Because baked goods without eggs crumble easily, use smaller pans. For example, make cupcakes instead of a cake or muffins instead of bread.
- Xantham gum is excellent for holding baked goods together. Use 1 tsp for each egg.
- To help leaven baked goods, add an extra half-teaspoon egg-free baking powder for each egg called for in a recipe, along with another egg substitute to bind or thicken.
- For thickening cream dishes and sauces, add extra flour, cornstarch, or xantham gum.
- To enhance the flavor of egg-free cookies or cakes, add extra ingredients such as raisins, nuts, coconut, seeds, or spices.
- Use any of the following as a binder to replace each egg in your egg-free baked goods:
  - 2 tbsp tahini (ground sesame seeds)
  - 2 tbsp any nut butter
  - 2 tbsp oat flour plus 1 tbsp water
  - 1 tsp baking powder, 1 tbsp liquid, and 1 tbsp vinegar
  - 1 tsp yeast dissolved in $^1/_4$ cup warm water
  - $1^1/_2$ tbsp water, $1^1/_2$ tbsp vegetable oil, and 1 tsp baking powder

Milk Protein–Free Diet

The milk-free diet is for use in patients with a documented, or in some cases suspected, allergy to cow's milk protein. It should not be confused with a lactose-free diet. If the patient is taking a fortified milk substitute, then additional supplements might not be necessary. If a fortified milk substitute is not consumed, the diet could be deficient in calcium, phosphorus, and vitamin D; therefore, supplementation might be needed.

Elimination of the following ingredients is necessary: artificial butter flavor, butter, butter fat, buttermilk, casein, caseinate (ammonium, calcium, magnesium, potassium, sodium), cheese, cottage cheese, curds, cream, custard, pudding, ghee, half and half cream, hydrolysates (casein, milk protein, protein, whey, whey protein), lactoglobulin, lactose, milk (derivative, protein, solids, malted, condensed, evaporated, dry, whole, low fat, nonfat, skim), nondairy creamer (check for casein), nougat, rennet, sour cream, sour cream solids, whey (delactosed, demineralized, protein concentrate), and yogurt. Ingredients that might indicate the presence of milk proteins are brown

sugar flavoring, caramel flavoring, chocolate, high-protein flour (protein source could be skim milk powder), margarine (might contain whey), natural flavoring, and Simplesse (could be made from eggs or milk protein).

Noteworthy Points

- Product that have KD or (U)D on their labels indicate the presence of milk in the product. The ingredient list does not always list the milk source. It could be present as the result of cross-contamination from a milk-containing product that is produced in the same facility. Some labels now state "K_{DE}," which indicates that the product is kosher but made on dairy equipment.
- Parve or Pareve on the label indicates that the product may be milk free; check all labels to confirm.
- Certain vitamin and mineral supplements, as well as some prescription and over-the-counter drugs, contain lactose as a filler. Consult a doctor or pharmacist for specific information.
- The brines that surround prepackaged deli meats often contain whey or casein. There could also be cross-contamination from other meat or cheese products when meats are sliced in a store's deli area.

Suggested Milk-Free Foods

Fats: Kosher margarine, unsalted Mazola margarine, unsalted Fleishmann's stick margarine, lard, vegetable oil, mayonnaise, cocoa butter, Better than Cream Cheese (Tofutti brand), Sour Supreme (Tofutti brand).

Fruits: All types.

Meat, fish, poultry, and eggs: Plain beef, poultry, fish, pork, lamb, bacon, kosher frankfurters, kosher cold cuts (eg, Morrison & Schiff or Hebrew National), tofu, peanut butter, eggs.

Cheese: Soy cheese (without sodium caseinate).

Potatoes, pasta, and rice: All except prepackaged (canned or frozen) products, in which casein is added to pasta to maintain shape.

Soups: Clear canned soups and commercial and homemade soups made with allowed ingredients. Be sure to check labels as even some clear soups might contain margarine, which will probably contain milk products.

Beverages: Milk-free infant formulas such as Isomil, ProSobee, and Alsoy; fruit juices; carbonated beverages; Kool-Aid; cocoa without added milk solids; Nut Quick (Ener-G Foods); Westbrae Rice Drink, Amazake Original, Rice Dream; soy milks such as EdenSoy Original, Vitasoy Original, Vitasoy Light Original, and WestSoy Lite Plain.

Bread and crackers: French, Italian, Vienna, or Syrian bread; bagels are traditionally milk free but check labels.

Cereals: Most do not contain milk products in the ingredient list but often have the (U)D symbol, which suggests that the product could contain some milk and should be avoided.

Sweets: Sugar, jams, jellies, syrups, honey, candies such as gum drops, baking chocolate, Marshmallow Fluff.

Desserts: Jello, fruit sorbet, Italian ice (gelato), milk-free Popsicles; baked products made with Crisco, Spry, or allowed margarine; Royal brand instant pudding mix made with appropriate milk substitute.

Vegetables: All types.

Miscellaneous: Mustard, relish, ketchup, salt, pepper, spices, soy sauce, cocoa powder, carob powder, potato chips, pretzels (check labels for (U)D), olives, peanut butter without added milk, plain popcorn, corn chips.

Peanut-Free Diet

The peanut-free diet is for individuals with a known peanut allergy. The peanut is a legume and not a member of the nut family. Legumes are edible seeds enclosed in pods; others include soybeans, lima beans, carob, and sweet clover. Peanut allergy can be fatal.

Elimination of the following ingredients is necessary: cold-pressed peanut oil, ground nuts, mixed nuts, peanuts, peanut butter, peanut flour, and nut meats. Foods that could contain peanuts or peanut products include African, Chinese, and Thai dishes; baked goods (eg, pastries, cookies); candy; chili and spaghetti sauce (which might be thickened with peanut butter); chocolate candies; hydrolyzed plant protein; hydrolyzed vegetable protein; and marzipan (which can be a mixture of nuts).

Noteworthy Points

- Peanut allergies are usually not outgrown.
- Skin tests for peanut allergy are positive throughout life.
- Peanut oil is usually not a problem as long as it is free of peanut protein. Only oil prepared by the hot-solvent extraction processes that are commonly used in the United States is known to be free of protein.[4]
- Check all candy labels; often they will list peanuts on the label if the product was made in the same facility as another peanut-containing candy. For example, plain M&Ms and Raisinettes both note on the label that they may contain peanuts, but peanuts are not necessarily in the ingredients list.
- Avoid mixed nuts, which often contain peanuts.
- Some cuisines use peanuts in a variety of foods, which makes cross-contamination in restaurants highly possible.
- Egg rolls are occasionally sealed with peanut butter.

Shellfish-Free Diet

The shellfish-free diet is for individuals with a documented allergy to shellfish. Individuals allergic to one type of shellfish could be allergic to others in the same family. Edible shellfish are usually divided into two categories: mollusks and crustaceans. Mollusks, such as clams and mussels, have two shells, but also include the abalone, which has a shell covering and a soft underpart. The crustaceans, such as the lobster, have segmented bodies that are covered with an armor-like section of thick and thin shells.

Elimination of the following ingredients is necessary: mollusks, such as abalone, clams, mussels, oysters, scallops, mollusk, cockle, periwinkle, and sea urchin, and crustaceans, such as crab, crawfish, crayfish, ecrevisse, lobster, shrimp, prawn, and crevette.

Soy-Free Diet

The soy-free diet is for patients with a documented, or in some cases suspected, soy protein allergy. Patients with a soy protein allergy rarely have difficulty meeting their macro- and micronutrient requirements. However, patients with both cow's milk and soy protein allergies should be monitored for caloric and protein (quality and quantity) intakes, as well as for calcium, phosphorus, and vitamin D intakes. If possible, supplementation with a fortified milk-free, soy-free formula will assist in meeting nutrient requirements for growth.

Elimination of the following ingredients is necessary: hydrolyzed soy protein, miso, shoyu sauce, soy flour, soy grits, soy nuts, soy milk, soy sprouts, soy protein concentrate, soy protein isolate, soy sauce, tempeh, textured vegetable protein, and tofu. The following ingredients might indicate the presence of soy protein: flavoring, hydrolyzed vegetable protein, hydrolyzed plant protein, natural flavoring, vegetable broth, vegetable gum, and vegetable starch.

Noteworthy Point Most people with soy allergies can safely eat soy lecithin and soy oil. Soy lecithin is a mixture of fatty substances, a by-product of soybean processing. Lecithin is often used as a stabilizer, emulsifier, or an antioxidant.

Suggested Soy-Free Foods

Beverages: Milk, fruit juices, carbonated beverages, Kool-Aid, cocoa, hot chocolate; infant formulas such as Enfamil, Similac, Nutramigen, Alimentum, and Pregestimil; rice beverages such as Rice Dream and Westbrae Rice Drink.

Bread and crackers: Syrian and French bread.

Cereals: Oatmeal, cream of rice, cream of wheat; any cold cereals with allowed ingredients; infant cereals without soy (check labels).

Fats: Butter, cream, bacon, soy-free mayonnaise, lard, pure vegetable oil (eg, coconut, corn, cottonseed, olive, peanut, safflower, sunflower).

Meat, fish, poultry, cheese, and eggs: All types when plain or prepared with allowed ingredients, such as water-packed tuna; kosher 100% beef hot dogs; eggs; all cheese except soy cheese and imitation cheeses containing soy.

Meat alternatives: Legumes (eg, baked beans), nuts, and seeds, except soybeans.

Potatoes, rice, and pasta: All, including spaghetti, macaroni, and plain noodles.

Vegetables: All except soybeans.

Fruits: All fruit and fruit juices.

Soups: Homemade and canned soups made with allowed ingredients.

Desserts: Fruit, gelatin, homemade puddings (cornstarch, tapioca, rice); ice cream, sherbet, and fruit ices; Popsicles, Fudgsicles; homemade cakes, cookies, and pies made with allowed ingredients; baking chocolate; yogurt.

Sweets: Sugar, jams, jellies, honey, molasses, syrups, marshmallows.

Miscellaneous: Salt, pepper, spices, mustard, relish, ketchup, pickles, olives, coconut; snack foods only if prepared without soy (potato chips, popcorn, dry roasted peanuts).

Wheat-Free Diet

The wheat-free diet is for patients with a documented, or in some cases suspected, wheat allergy. The following ingredients should be eliminated from the diet: bread crumbs, bran, cereal extract, cracker meal, enriched flour, farina, flour, gluten, graham flour, high-gluten flour, high-protein flour, malt vital gluten, wheat bran, wheat grain, wheat gluten, wheat starch, and whole-wheat flour. The following ingredients could have wheat present: gelatinized starch, hydrolyzed vegetable protein, modified food starch, natural flavoring, soy sauce, starch, vegetable gum, and vegetable starch.

Noteworthy Points

- $^1/_2$ cup oat flour and $^1/_2$ cup rice flour can be substituted for 1 cup wheat flour.
- Hispanic and Asian cooking uses rice as a staple. Check multicultural cookbooks at the library for wheat-free recipes.
- Spaghetti squash, corn, and rice pasta make great substitutions for regular pasta.
- Fresh, frozen, and canned vegetables are your best choice. Prepackaged vegetables in sauces often contain wheat as fillers.
- Gluten free also means wheat free.

Suggested Wheat-Free Foods

Beverages: Milk, fruit juices, carbonated beverages, Kool-Aid, cocoa, hot chocolate.

Breads and crackers: Only those made with 100% rye, oat, corn, or rice flour with no wheat added; corn tortillas.

Cereals: Any corn, oat, rice, or rye cereal that has no wheat flour added (eg, puffed rice, corn flakes, crispy rice).

Potatoes, rice, and pasta: All plain rice and wheat-free pastas.

Fats: Butter, margarine, vegetable oils, lard, bacon, cream, mayonnaise, homemade gravy thickened with cornstarch.

Meat, fish, poultry, eggs, cheese: All types when plain or prepared with allowed ingredients; all eggs; all cheeses. Be sure to read the labels of processed cheeses.

Meat alternatives: Legumes, nuts, seeds (eg, peanut butter, baked beans, tofu).

Vegetables: All types; avoid those prepared with sauces.

Soups: Homemade soups with allowed ingredients.

Desserts: Fruit, gelatin, junket, cornstarch and tapioca puddings.

Miscellaneous: Salt, pepper, spices, mustard, ketchup, pickles, relish, olives, coconut, baking chocolate, potato chips, corn chips, popcorn.

Allergy Organizations, Support Groups, and Resources

- Food Allergy and Anaphylaxis Network
  10,400 Eaton Pl., Ste. 107
  Fairfax, VA 22030-2208
  Telephone: 800-929-4040
  Fax: 703-691-2713
  E-mail: faan@foodallergy.org

The Food Allergy and Anaphylaxis Network (FAAN) is a national nonprofit organization established to help families living with food allergies and to increase public awareness about food allergies and anaphylaxis. All resources are checked for medical accuracy by FAAN's Medical Advisory Board. There is a subscription fee.

- American Academy of Allergy and Immunology, 800-822-ASMA (2762), www.aaai.org
- American Academy of Pediatrics, 800-433-9016, www.aap.org
- American College of Allergy and Immunology, 800-842-7777, www.allergy.mcg.edu
- Asthma and Allergy Foundation of America, 800-7-ASTHMA (727-8462), www.aafa.org
- National Center for Nutrition and Dietetics Hotline, 800-366-1655, www.eatright.org
- www.peanutallergy.com

GASTROINTESTINAL DISEASES

A number of gastrointestinal diseases require dietary modification, both short and long term. Patients can have malabsorption, maldigestion, or both coupled with an inadequate intake, as seen in both celiac disease and Crohn's disease, for example. Patients often require individually tailored diets based on their degree of bowel integrity or function. Enteral formulas, both standard and special, are commonly used with several gastrointestinal disorders (see Appendix III). In addition, Chapter 55, "Standard and Specialized Enteral Formulas," reviews the rationale and development of many of these formulas. Below, we review the more common diets used in pediatric gastroenterology. Please refer to other chapters for a more detailed discussion of each disorder.

Fat Modification for Pancreatic Disease

A low-fat diet might be indicated in the treatment of chronic pancreatitis, as well as the later stages of acute pancreatitis. Acute pancreatitis usually warrants the discontinuation of oral feedings. As clinical parameters indicate improvement of the disease state, careful reintroduction of food might be allowed, with the eventual return to a normal diet.

Chronic pancreatitis with pancreatic enzyme insufficiency will necessitate enzyme replacement therapy; however, dietary modification is usually not necessary. Children with chronic pancreatitis and pancreatic enzyme sufficiency can consume a diet containing 20 to 30% of calories from fat, unless laboratory and clinical data suggest fat intolerance.

Low-fat diets are based on individual requirements and must be designed by using food tables, reading labels, and following the Food Guide Pyramid; they also must be evaluated for tolerance and acceptance. Caloric consumption should be carefully monitored whenever fat restriction is warranted. Fat restriction to less than 5% of total daily calories places the child at risk for the development of essential fatty acid deficiency.

For specific foods pertaining to the low-fat diet, see "Low Cholesterol and Low Saturated Fat Diet" below.

High-Fiber Diet

Dietary fiber is a food component that is neither digested nor absorbed by the body. This undigested material can itself absorb water, resulting in the formation of larger, softer stools, which are more easily moved through the intestines and then passed. A high-fiber diet can benefit the whole family. Diets high in fiber have been shown to control constipation, lower the risk of colon cancer, and reduce blood cholesterol levels. Children are more accepting of dietary changes when they are adopted by the entire family.

A general rule of thumb for recommended daily fiber intake is 5 plus the age (in years) of the child more than 2 years of age, to a maximum of 35 grams per day. For example, a 7 year old should receive 12 g per day (5 + 7 years).

Noteworthy Points To increase the fiber content in a child's diet, include fruits, vegetables, and whole grains (Table 59-1). During commercial processing the fiber content of these sources can be reduced. Therefore:

- Instead of white bread, use 100% whole-grain breads.
- Instead of processed cereals, use whole-grain cereals.
- Instead of canned fruits and juices, use fresh fruits.
- Maintain a well-balanced diet: choose a variety of foods from the Food Guide Pyramid (see Appendix).
- Increase fiber in the diet gradually. A sudden increase in dietary fiber intake can cause gas and bloating.
- If a child refuses high-fiber foods, remember that children often need to be introduced to foods several times before the foods become familiar and acceptable. Slow changes in a child's diet are often better accepted than rapid ones.
- Increase fluid intake with an increase in dietary fiber (Table 59-2). Inadequate fluid intake can also cause constipation.
- Give children choices as to what they would like to eat but provide appropriate choices.
- Add 2 to 4 tbsp of a high-fiber cereal to a favorite hot or cold cereal.
- Add unprocessed wheat bran to yogurt, applesauce, hot or cold cereal, soup, peanut butter, tuna salad, pancake batter, or spaghetti.

Gluten-Restricted Diet

The gluten-restricted diet is necessary for patients diagnosed with celiac disease. The diet is designed to provide adequate nourishment while eliminating foods containing the gliadin fraction of gluten, a protein found in many grains, which causes intestinal injury in susceptible people. Although many cereal grains contain gluten, only wheat, rye, barley, and oats contain the gliadin fraction. Gliadin from these grains is present in many everyday foods, including breads, rolls, crackers, cookies, and breakfast cereals, and might also be present as an incidental ingredient in food additives and derivatives (see the list below). For this reason, food labels must be read carefully. When all sources of gliadin are removed from the diet, the intestine will heal and function normally.

TABLE 59-1 Dietary Fiber Content of Foods

Food	*Little (< 0.5 g)*	*Low (1 g)*	*Moderate (2 g)*	*High (3 g)*	*Very High (> 4 g)*
Dairy	Milk, yogurt, pudding, ice cream, cheese	—	—	—	—
Protein	Eggs, beef, chicken, pork, turkey, fish	—	2 tbsp peanut butter	1/2 cup garbanzo beans, lima beans	1/2 cup lentils (5 g), northern beans (4 g), navy beans (5 g), pork and beans (6 g), kidney beans (6 g)
Fruit	Fruit juice, watermelon, cherries	1/2 cup canned pears, pineapple, fruit cocktail, peaches, fresh grapes	Fresh: 1 peach, 3 apricots, half a grapefruit; 1/2 cup applesauce, blueberries, strawberries	Fresh: 1 apple, orange, banana, 3 dates; 1/2 cup raspberries; dried: 1/4 cup raisins, peaches, apricots, apples	Fresh: 1 pear (5 g), half an avocado (4 g), 3 plums (4 g), 3 prunes (4 g)
Vegetables	—	1/2 cup tomato juice, lettuce, spinach, celery, cauliflower, cucumber, green beans	1/2 cup tomato, cabbage	1/2 cup sweet potato, broccoli, carrots, peas, potato salad, corn	1 baked potato with skin (4 g)
Breads	1 slice French, Italian, raisin, or white bread; 1 pancake or donut; half a bagel	1 slice cracked wheat, pumpernickel, or rye bread; 1 tortilla or whole-wheat pancake	1 slice 100% whole-wheat bread	1 slice Branola; 1 bran muffin	1 slice flourless bread (5 g)
Cereals	1/2 cup corn flakes, Frosted Flakes, Lucky Charms, Cheerios	1/2 cup oatmeal, Life, Nutrigrain, Wheaties, Total, Honey Nut Shredded Wheat	1/2 cup shredded wheat, granola, Crispy Wheats n' Raisins, Wheat Chex	1/2 cup Bran Flakes, Raisin Bran, Grape Nuts, wheat germ	1/2 cup 100% bran (9 g), All Bran, (9 g), Fiber 1 (12 g); 1/4 cup unprocessed wheat bran (7 g; 2 g/tbsp)
Pasta and rice	1/2 cup white pasta	1/2 cup egg noodles, white rice	1/2 cup brown rice	—	1/2 cup whole-wheat pasta
Crackers	Goldfish, saltines, Ritz	2 graham; 16 Wheat Thins, 1 granola bar	3 Harvest Wheats, 3 Triscuits	1 rye crisp	Metamucil wafers
Desserts	Chocolate chip cookies	Oatmeal cookies	Fig Newtons, Peak Freans, Bran Crunch (3 g)	—	—
Miscellaneous	Beverages, fats, sweets	1 cup popcorn	1/4 cup cashews, pecans	1/4 cup almonds, peanuts, walnuts	1/4 cup coconut

Modified from Hendricks KM et al. Manual of pediatric nutrition. 3rd ed. Hamilton (ON): B.C. Decker; 2000.

Noteworthy Points

- Despite the restrictions, the gluten-restricted diet should be well balanced based on the Food Guide Pyramid. Table 59-3 lists foods allowed and restricted while following a gluten-restricted diet. Table 59-4 provides sample menus for a gluten-restricted diet.
- Read food labels carefully to avoid gluten-containing grains and gluten derivatives such as
  - Flour and cereal products: avoid textured vegetable protein
  - Colorings: avoid hydrolyzed vegetable protein
  - Emulsifiers: avoid hydrolyzed plant protein
  - Flavorings: avoid starch
  - Malt or malt flavoring: avoid modified food starch
  - Preservatives: avoid vegetable gum
  - Vinegar: avoid distilled white or grain vinegar
  - Product ingredients can change from one batch to another. To check an ingredient, contact the Celiac Sprue Association/USA, the Gluten Intolerance Group of North America, or the manufacturer of the product. Foods of unknown composition should be omitted. Brand names of gluten-free products are available from the celiac sprue support groups. Table 59-5 provides a list of additives and ingredients to avoid while following a gluten-free diet; Table 59-6 lists those that are permitted.
- Many gluten-free foods can be purchased at grocery stores, Asian food markets, and health food stores.
- Eating in restaurants requires planning and a basic knowledge of foods and food preparation. Choose foods prepared simply, such as broiled or roasted meats, plain vegetables, plain salads, and foods without breading, gravies, or sauces.
- A lactose-restricted diet might be necessary in the early treatment of newly diagnosed celiac disease if symptoms of malabsorption are severe. Milk and

TABLE 59-2 Recommended Fluid Intake

Child's Weight (pounds)	*Total Fluid per 24 Hours (cups)*
7	2
12	3⅓
21	5
26	6
35	7
44	8
63	9½
99	10½

TABLE 59-3 Gluten-Restricted Diet

Type of Food	*Allowed*	*Avoid*
Grains and flours	Arrowroot starch, corn flour, cornstarch, cornmeal; maize and waxy maize; potato flour, potato starch flour; rice bran; rice flours: plain, sweet, brown, and rice polish; soy flour; tapioca starch	Low-gluten flours; all flours containing wheat, rye, barley, and oats; durham wheat, all purpose flour, white enriched flour, wheat germ, whole-wheat flour, wheat starch; wheat bran; oat bran; amaranth; buckwheat, buckwheat groats; bulgar; graham; kasha; matzo; millet; rusks, semolina, sorghum; triticale
Breads	*Specially prepared breads using only allowed flours* (100% potato, corn, rice, arrowroot, soybean); special commercial gluten-free baking mixes (Ener-G Foods, Dietary Specialties)	All breads, rolls, etc, made with wheat, rye, barley, or oats
Cereals	Hot or cold cereals made from corn meal, rice, hominy*	All containing wheat, rye, barley, oats, farina, bran (except rice bran), graham, wheat germ, kasha, bulgar, buckwheat, millet, triticale *Do not eat cereals that contain malt unless the source is known.*
Noodles and pasta	Gluten-free corn pasta; special gluten-free pasta (Aproten and other brands); oriental rice noodles or bean noodles	Regular noodles, spaghetti, macaroni, etc
Crackers and snacks	Pure cornmeal tortillas; rice wafers; rice cakes without added rye or millet*; popcorn; crackers made with allowed flours (100% potato, corn, rice, arrowroot, soybean); some potato chips*	All containing wheat, wheat snack foods, starch, rye, barley, oats, bran (except rice bran), graham, wheat germ, malt, kaska, bulgar, buckwheat, matzo, millet, durham wheat, sorghum, rusks, amaranth, triticale
Milk products	Fresh, dry, evaporated, or condensed milk; cream; sour cream†; whipping cream,† yogurt†	Malted milk; commercially prepared milkshakes; some nondairy cream*; some commercial chocolate drinks*
Meat and alternatives	Fresh meat, fish, poultry, and eggs; fish canned in oil, brine, or water; luncheon meats, frankfurters, and prepared meat products packaged without food starch or gluten derivatives; peanut	Any meat or meat products containing wheat, rye, barley, oats, or gluten derivatives; some canned tuna in vegetable broth,* some sausages,* frankfurters, luncheon meats, and sandwich spreads; canned chili and stews; bread-containing products such as Swiss steak, pot pies, croquettes; self-basting turkey with hydrolyzed vegetable protein (HPV) injected as part of the basting solution
Cheese	Aged cheese (100% cheddar, Swiss, parmesan, etc); cottage cheese,† cream cheese; processed cheese*	Cheese foods; cheese spreads or dips; imitation cheese products
Fruit and juices	Most fresh, frozen, dried, or canned fruit	Thickened or prepared fruits as in pie fillings*
Vegetables	Most plain, fresh, frozen, or canned vegetables; dried beans, peas, and lentils; tomato puree and paste; white and sweet potatoes; yams; hominy; rice	Vegetables in sauces*; commercially prepared vegetables; canned baked beans; most packaged rice mixes
Fats	Most margarines,* butter, vegetable oil, lard, shortening; nuts; pure mayonnaise made without distilled white vinegar*	Commercial salad dressings and dips,* unless product contents are known
Sweets and desserts	Special commercial gluten-free cakes, cookies, and baking mixes; homemade puddings with cornstarch, rice, or tapioca; some pudding mixes,* gelatin desserts, custards, and ices; sherbet and ice cream if they do not contain gluten stabilizers,* hard candy flavored with sugar, honey, molasses, marshmallow, coconut, or chocolate; most jams and jellies*; most nonbuttered syrups*; some candy*	Most commercially prepared cakes, cookies, and other baked goods; "instant" puddings and bread pudding; ice cream cones; frozen desserts containing gluten stabilizers; check contents of commercial candies
Beverages	Fruit juice; plain tea; brewed coffee; hot chocolate made with pure cocoa powder; carbonated drinks except most root beers; wine and brandy without dyes or preservatives; most rums; vodka distilled from potatoes	"Instant" drinks, such as tea, coffee, cocoa, and fruit punch, which are processed with additives, stabilizers, or emulsifiers*; ground coffee with added grain; some flavored coffees*; some herbal teas*; most root beers*; all beer and ale; all whisky (including corn whisky); bourbon; any liquor made from grain alcohol; vodka distilled from grain
Soups	Homemade broths and soups made with allowed ingredients; special gluten-free commercial soups (Ener-G Foods)	Most canned soups and soup mixes,* bouillon, bouillon cubes or powder
Miscellaneous	Cider, rice, or wine vinegar; salt; black or red pepper; herbs; spices; monosodium glutamate (MSG); bicarbonate of soda; pure cocoa; most yeast; baking powder; cream of tartar; flavoring if not made with alcohol (choose imitation)	Distilled white vinegar; most white pepper; some curry powder*; some dry seasoning mixes (such as chili seasoning mix)*; some gravy extracts and meat sauces*; yeast flakes*; extracts,* natural flavorings containing alcohol; ketchup,* prepared mustard, and horseradish

Commercially prepared condiments (pickles, ketchup, mustard, mayonnaise, steak sauce) are usually made with distilled white vinegar, which is made with grain. A very small amount of protein may be carried over into white vinegar during distillation. Moderate use of commercially prepared condiments is allowed by some physicians. However, individuals with newly diagnosed or extreme gluten sensitivity should avoid these condiments.

*Some products may be used if checked with the manufacturer and found to be gluten free.

†Check label for oat gum.

milk products are generally restricted for 6 weeks and gradually reintroduced into the diet.

Tips for Gluten-Restricted Cooking Gluten's elasticity is an important element in baked products. Special recipes to compensate for this are required when gluten-free flours are used for baking. Cookbooks specifically for the gluten-restricted diet are available. When gluten-free flour or starch is used as a substitute in baked goods, it is necessary to increase the amount of leavening (baking powder, baking soda, yeast, or eggs) and protein (eggs, milk or powdered milk, soy flour, tofu, or cottage cheese). A mixture of flours gives a better result in gluten-free baking.

The following grains can also be used in the quantities listed as a substitute for 1 cup of wheat flour:

- 5/8 cup potato starch flour (1/2 cup plus 2 tbsp)
- 7/8 cup white rice flour (3/4 cup plus 2 tbsp)
- 1/2 cup soy flour plus 1/2 cup potato starch flour
- 1 cup corn flour
- 1 cup fine cornmeal
- 3/4 cup coarse cornmeal

To substitute for 1 tbsp of wheat flour as a thickener in sauces, gravies, and puddings, use one of the following:

- 1 1/2 tsp cornstarch
- 1 1/2 tsp potato starch
- 1 1/2 tsp white rice flour
- 1 1/2 tsp arrowroot starch
- 2 tsp quick-cooking tapioca

TABLE 59-4 Sample Menus for a Gluten-Restricted Diet

Breakfast	*Lunch*	*Dinner*	*Snack*
Orange juice Scrambled egg Gluten-free muffin with margarine Milk	Corn pasta with tomato and meat sauce Fresh fruit Milk	Tossed salad with gluten-free dressing Grilled chicken Rice Ice cream (check label) Milk	Potato chips Fruit juice
Grape juice Gluten-free waffles with strawberries or gluten-free syrup Milk	Tacos (pure corn tortilla, beef, cheese, beans, lettuce, tomato) Mixed fruit cup Milk	Oven-fried whitefish (gluten-free cornflake crumbs) French fries Carrot coins Pudding (check label)	Milk Gluten-free pound cake
Apple juice Hot rice cereal Gluten-free toast Margarine, jelly Milk	Grilled cheese on gluten-free bread Fresh fruit Gelatin Milk	Baked pork chop Whipped potatoes Corn Applesauce Gluten-free cookies	Peanuts and raisins Milk

TABLE 59-5 Additives and Ingredients to Avoid on Gluten-Free Diet

Additives*	Modified starch*
Alcohol*	Mono- and diglycerides*
Amaranth	Oat
Barley	Oat groats
Bran*	Oatmeal
Buckwheat	Oat gum
Buckwheat groats	Preservatives*
Bulgur	Rye
Cereal products*	Rusks
Coloring*	Semolina
Distilled white vinegar	Sorghum
Durum wheat	Stabilizers*
Emulsifiers*	Starch*
Farina	Textured vegetable protein (TVP)*
Flavorings*	Triticale
Flour*	Vegetable gum*
Groats	Vegetable protein*
Hydrolyzed plant protein (HPP)*	Wheat
Hydrolyzed vegetable protein (HVP)*	Wheat flour
Kasha	Wheat germ
Malt flavoring*	Wheat germ oil
Matzo cake meal	Wheat starch
Matzo farfel	White enriched flour
Matzo meal	Whole-wheat flour
Millet	Wheat stabilizers
Modified food starch*	

*Some products can be used if the manufacturer verifies that they are gluten free.

Celiac Disease Organizations, Support Groups, and Resources Support groups provide a network for people with celiac disease. Group services include information and referrals; publications, such as newsletters and gluten-free diet instructions; and annual conferences; and workshops provide up-to-date information about celiac disease and the gluten-free diet.

National groups include

- Celiac Sprue Association/United States of America, Inc. (CSA/USA), PO Box 31700, Omaha, NE 68131-0700; telephone: 402-558-0600; fax: 402-558-1347; www.csaceliacs.org
- Canadian Celiac Association National Office, 5170 Dixie Rd., Ste. 204, Mississauga, ON L4W IE3; telephone: 800-363-7296; fax: 905-507-4673; www.celiac.ca
- Gluten Intolerance Group of North America (GIG), 15110 10th Ave. SW, Ste. A, Seattle, WA 98116; telephone: 206-246-6652; www.gluten.net
- Celiac Disease Foundation, 13251 Ventura Blvd., Ste. 3, Studio City, CA 91604; telephone: 818-990-2354; fax: 818-990-2379; www.celiac.org
- Celiac Support Group; www.childrenshospital.org
- www.celiac.com

Organizations that can be of assistance in following the gluten-free diet include

- American Dietetic Association, National Center for Nutrition and Dietetics; telephone: 800-366-1655 (consumer hotline); www.eatright.org
- United States Department of Agriculture, Dr. Donald D. Kasarda, 800 Buchanan St., Albany, CA 94710; telephone: 415-559-5687 or 559-5650 (messages); fax: 415-559-5777; www.usda.gov

TABLE 59-6 Additives and Ingredients Allowed on Gluten-Free Diet

Adipic acid	Mannitol
Ascorbic acid	Microcrystalline cellulose
BHA	Monosodium glutamate (MSG)
BHT	Niacin
Betacarotene	Polyglycerol
Biotin	Polysorbate 60 and 80
Calcium phosphate	Potassium citrate
Calcium chloride	Potassium iodide
Calcium pantothenate	Propylene glycol monostearate
Carboxymethylcellulose	Propylgallate
Carrageenan	Pyridoxine hydrochloride
Citric acid	Riboflavin
Corn sweetener	Sodium acid pyrophosphate
Corn syrup solids	Sodium ascorbate (ascorbic acid)
Demineralized whey	Sodium benzoate
Dextrimaltose	Sodium caseinate
Dextrose (dextrins)	Sodium citrate
Dioctyl sodium sulfosuccinate	Sodium hexametaphosphate
Folic acid (folacin)	Sodium nitrate
Fructose	Sodium silaco aluminate
Fumaric acid	Sorbitol
Gums: acacia, arabic, carob bean, cellulose, guar, locust bean, tragacanth, xanthan	Sucrose
	Sulfosuccinate
	Tartaric acid
Invert sugar	Thiamine hydrochloride
Lactic acid	Tricalcium phosphate
Lactose	Vanillin
Lecithin	Vitamins and minerals
Magnesium hydroxide	Vitamin A (palmitate)
Malic acid	

Adapted from Hartsook EI. Gluten-restricted, gliadin-free diet instruction. Seattle (WA): Clinical Research Center, Univ. of Washington Hospital; 1987.

- US Food and Drug Administration, www.fda.gov

Lactose-Free Diet

The lactose-free diet is intended for the individual who must eliminate sources of lactose from the diet, such as patients with galactosemia (an inborn error of metabolism) or those who have difficulty digesting lactose.

Lactose is the primary carbohydrate of dairy products; therefore, foods containing milk or milk products are to be excluded from the diet. People with lactose intolerance might not produce enough intestinal lactase to break down the lactose in their diet. The undigested lactose can cause symptoms such as gas, abdominal pain, diarrhea, and poor weight gain. Table 59-7 outlines the foods that are permitted and those that are to be avoided while following the lactose-free diet.

Noteworthy Points This diet is not intended for those who are sensitive to cow's milk protein. Read labels carefully. Avoid any food containing milk, nonfat milk solids, skim milk, butter, cream, lactose, casein, caseinate, sodium caseinate, or whey.

Calcium Supplements If a nutritionally complete lactose-free infant formula, enteral product, or nutritional supplement is taken, this diet can be sufficient in all nutrients. If a lactose-free fortified milk substitute is not consumed, the diet could be deficient in calcium, phosphorus, and vitamin D. If a milk-free diet is followed for more than 4 to 6 weeks, calcium and other vitamin or mineral supplementation might be needed. Choose a supplement that is complete, well absorbed, and cost efficient. Calcium supplements are available in several acceptable forms: carbonate, gluconate, lactate, and citrate. Avoid dolomite or bonemeal supplements because they have been linked with lead poisoning.

Low-Lactose Diet Guidelines These guidelines are intended for individuals who can tolerate small amounts of lactose or those who are reintroducing lactose after following the lactose-free diet. Note that a lactose-containing diet is not appropriate for persons with galactosemia.

Some foods that contain lactose might be better tolerated than others owing to natural processing. Examples are naturally aged cheeses and yogurt with live cultures. After a period of lactose-free intake, the reintroduction of lactose into the diet should be gradual, based on individual tolerance. Better tolerance might be achieved by consuming lactose-containing foods in small amounts. There are products available that are designed to aid in the digestion of lactose. Lactase enzymes are commercially available as chewable tablets and drops. Refer to Table 59-7 for further information about lactose-containing foods.

GROWTH FAILURE

Growth failure and failure to thrive are terms that describe the condition of infants, children, and young adults whose physical growth deviates significantly from standards or falters from their individual growth pattern. Growth failure can be a result of a variety of factors, including medical, social, and psychological conditions. In most cases, these factors create an environment in which caloric intake is inadequate to meet requirements for normal growth and development. See Chapter 52, "Failure to Thrive: Malnutrition in the Pediatric Outpatient Setting," for more details.

Nutritional management is the cornerstone of therapy for individuals afflicted with growth failure. Therapy should aim to reverse nutrient deficits, achieve ideal body weight for height, and restore optimal body composition. Diets rich in calories and adequate in protein facilitate reversal of growth failure and failure to thrive. The following section provides guidelines for increasing the caloric content of the diet and outlines sample foods and meal plans designed to promote a high-calorie intake with adequate protein.

High-Calorie Diet

The high-calorie diet is indicated for promoting weight gain or preventing excessive weight loss during periods of increased nutritional needs (eg, infectious or postoperative states). A well-balanced diet based on the Food Guide Pyramid with an emphasis on foods that are high in protein and calories should be followed.

TABLE 59-7 Lactose-Free Diet

Foods Allowed	*Foods to Avoid*
Milk: none Soy protein infant formulas	All milk, milk drinks—including whole, skim, low-fat, dried, evaporated, and condensed milk, breast milk; yogurt (any type, cream or sour); infant formulas other than those permitted, frappes, ice cream sodas
Fortified soy or rice milk	An enzymatic preparation such as LactAid may be added to milk to convert lactose into digestible sugars; instructions are for conversion of 70 to 95% of the lactose to glucose and galactose; check with your nutritionist or physician before beginning use of LactAid
Eggs: As desired	Eggs prepared with milk—use specific formula; do not prepare with butter
Meats: Any except those to be avoided	Creamed or breaded meat, fish, or poultry; prepared meats that contain dried milk solids including bologna and cold cuts, frankfurt, salami, commercially prepared fish sticks, and some sausage; kosher products are milk free
Beverages: Powdered, fruit-flavored drinks, ginger ale, tonics	Any made with milk, such as frappes, eggnog, hot chocolate
Cheese: Soy or lactose-free cheeses	All types of cheeses and cheese dishes that are not listed as allowed
Breads: Breads made without milk, such as French bread, Italian bread, water bagels, or parve breads	Any baked products made with milk; muffins, biscuits, waffles, pancakes, donuts, sweet rolls, commercial mixes
Cereal: Any made without milk, cooked or ready to eat. Macaroni, spaghetti, pasta, rice—all prepared without milk	Any prepared cereal that contains dry milk solids
Vegetables and potatoes: All cooked, canned, frozen, or fresh	Any vegetable prepared with milk, butter, milk solids, bread, or bread crumbs; no cheese or cream sauces
Fruit: All	
Desserts: Any made without milk or milk products, such as gelatin desserts, fruit crisp, snow puddings, fruit and water sherbets, pie with fruit filling, angel food cake	All commercial cake and cookie mixes, ice cream, custard puddings, junket, ice milk or sherbets that contain milk; frosting made with milk or butter, dessert sauces, cheese cakes
Soup: Any prepared without milk or milk products; homemade or canned (eg, chicken rice)	All creamed soups, chowders; no cheese
Fats: Milk-free margarine or parve margarine; oils, nuts, peanut butter	Butter, margarine, some commercial salad dressings
Sugar and seasonings: Sugar, honey, molasses, maple syrup, corn syrup, jelly and jam, hard candy, gum drops, marshmallow, hard peppermints, fondant; salt, pepper, spices, herbs, condiments, vinegar, ketchup, relish, pickles, olives, tomato sauce, coconut, wheat germ; artificial flavoring or extracts	Any product made from milk, butter, cream, chocolate, toffee, cream mints, caramel candy, candy with cream centers
Miscellaneous	Medications that use lactose as filler or bulk agents; party dips, nonprescription vitamins; spice blends; Easter egg dyes; dietetic foods and foods advertised as high protein sometimes contain lactose or dry milk solids

Adatped from Hendricks KM, Walker WA, editors. Manual of pediatric nutrition. 2nd ed. Toronto: BC Decker Inc; 1990.

Suggestions for Increasing Calories and Nutrient Density

Milk and Milk Products

- Use high-calorie milk (recipe follows) or half and half cream as a beverage and as a substitute for milk or water in cooking whenever possible (pudding, cocoa, milkshakes, cream soup, custard, eggnog).
- Add powdered milk to yogurt, casseroles, bread, muffins, sauces, and gravies.
- Melt cheese on sandwiches, meats, potatoes, vegetables, rice, pasta, and cream sauces; add cheese to salads.
- Have cream cheese or cottage cheese on crackers or added to vegetables or pasta.
- Make Instant Breakfast with whole or high-calorie milk.
- Add whole-milk yogurt to fruit or desserts and use as a topping for cereal, pancakes, and waffles.

Protein Group

- Add small pieces of cooked meat, fish, poultry, or eggs to salads, casseroles, soups, vegetables, omelets, and noodles.
- Use peanut butter with all grain products, spread on fruit or vegetables, or blended in milk drinks, ice cream, or yogurt.
- Add nuts to desserts, salads, ice cream, vegetables, or fruits (nuts are not recommended for children under 3 years of age).
- Add textured vegetable protein or legumes to casseroles or soups.
- Offer simple fried foods such as chicken or fish.
- Serve meat with extra gravy or sauce when appropriate.

Fruits and Vegetables

- Add mashed fruit to milk, yogurt, shakes, ice cream, and pudding.
- Add dried fruits to muffins, cookies, cereal, and grains or combine with vegetables and nuts (children under

3 years of age can be at increased risk for choking with dried fruits and nuts).
- Serve vegetables raw with a dip, cooked cream style, or topped with melted cheese.
- Add butter, sour cream, or mayonnaise to vegetables.

Grains
- Make hot cereals with milk instead of water.
- Use high-protein noodles and grains in casseroles and soups.
- Coat meat with breading or flour before cooking.
- Top muffins, toast, crackers, and pancakes with margarine, cream cheese, syrup, jam, peanut butter, cheese, or honey (honey is not recommended for children under 1 year of age).
- Serve granola over ice cream, frozen yogurt, or fruit or mixed with nuts or dried fruit.

Tips for Increasing Caloric Intake
- Eat small, frequent meals throughout the day.
- Keep snacks handy for nibbling.
- Try eating a snack or drinking a high-calorie beverage before going to bed in addition to other meals.
- Instead of drinking water, select beverages that contain calories, such as high-calorie milk or frappes (see recipes).
- Notice the times of day that appetite is best and eat more at those times.

Sample Meal Plan The following daily food plan is one example of a high-calorie diet:

Breakfast
1/2 cup citrus juice
1 protein serving (eg, 1 egg, 1/4 cup cottage cheese, 2 tbsp peanut butter, 1 oz cheese, or 1 oz meat)
2 servings of whole-grain bread products or enriched cereal
margarine, butter, jam, jelly, sugar
1 cup high-calorie milk (recipe follows)

Morning Snack
Frappe

Lunch
3 to 4 oz of protein
1/2 cup vegetable
2 servings whole grain, potato, rice, or other starch
1 serving fruit or dessert
butter, margarine, jelly, sugar
1 cup high-calorie milk

Afternoon Snack
Frappe or high-calorie milk
Peanut butter or cheese with crackers or as a sandwich

Dinner
3 to 4 oz of protein
2 servings vegetable (one deep-green or yellow vegetable)
2 servings whole grain, potato, rice, or other starch
1 serving fruit or dessert
margarine, butter, jelly, sugar
1 cup high-calorie milk

Evening Snack
Frappe or high-calorie milk
Pizza, grilled cheese sandwich, or pudding

Recipes
The following recipes are revised from those developed by clinical nutrition staff at Children's Hospital, Boston.

Fortified Milk (180–210 calories)
Add 2–4 tbsp of powdered nonfat dry milk to 8 oz of whole milk

Vanilla Shake/Frappe (400 calories)
1 1/2 cups ice cream (3–4 scoops)
1/2 cup whole milk
3 tbsp nonfat milk powder
(Can also add 2 tbsp of strawberry, chocolate, or coffee syrup)
Mix in blender.

Strawberry Shake/Frappe (530 calories/8 oz)
2 cups whole milk
2/3 cup nonfat dry mild powder or 1 pkg of Carnation Instant Breakfast
2 1/2 cups strawberry ice cream
2 tbsp heavy cream
Mix in blender.

Creamsicle Shake/Frappe (560 calories)
1/2 cup whole milk
2 tbsp instant nonfat dry milk powder
1/2 cup orange juice
1 cup orange sherbet
1 pkg of vanilla Instant Breakfast
Mix in blender.

Peanut Butter Shake/Frappe (400 calories)
1 cup whole milk
3 tbsp smooth peanut butter
3 tbsp chocolate syrup
Mix in blender.

Banana Orange Shake/Frappe (690–790 calories)
1/2 cup milk
1/2 cup orange juice
1 cup vanilla ice cream
2 whole bananas
Mix in blender.

Super Pudding (326 calories)
1 cup fortified milk
1 cup heavy cream
1 pkg (4 1/2 oz) instant pudding
Make into 1/2 cup servings.

Super Grilled Cheese
Dip cheese sandwich into egg fortified milk mixture before grilling with lots of butter or margarine. This will be like French toast with cheese in the middle.

CONGENITAL HEART DISEASE AND HYPERLIPIDEMIA

Pediatric patients with congenital heart disease or hyperlipidemia require careful nutritional monitoring to ensure optimal growth and development. Growth failure in congenital heart disease is common and can be attributable to anorexia, hypermetabolism, frequent respiratory infections, decreased peripheral blood flow, malabsorption, or pulmonary hypertension, among other factors.[5,6] Patients requiring dietary fat restriction because of hyperlipidemia are placed at greater risk for caloric deficits, as well as deficits in calcium and iron. Nutrition education with frequent monitoring is necessary to prevent these deficiencies.

Fluid-restricted and sodium-restricted diets are often used in the management of congenital heart disease.

Fluid-Restricted Diet

The fluid-restricted diet is a modification of the normal diet in which all fluids are limited to a prescribed level. Individuals with renal, liver, or cardiac insufficiency might require it.

Noteworthy Points

- All foods contain water in varying amounts. All foods that are liquid at room temperature are considered to be fluids. These include water, tonic, coffee, tea, fruit and vegetable juices, milk, ice, ice cream, sherbet, Popsicles, fruit ices, gelatins, soups, gravies, sauces, cream, and alcohol.
- Fluid from solid foods is not routinely restricted in a fluid-restricted diet. Solid foods with the highest water content are fruits and vegetables. Excessive consumption of these foods should be avoided.
- Liquid medications and fluids consumed while ingesting medications must be accounted for in the fluid-restricted diet.
- The following measurements are useful in calculating daily fluid allowance:
  - 1 oz = 30 cc = 2 tbsp
  - 4 oz = 120 cc = $^1/_2$ cup
  - 8 oz = 240 cc = 1 cup
  - 32 oz = 960 cc = 4 cups = 1 quart
  - 1 liter = 1,000 cc = 1 kg

Sodium-Restricted Diet

The sodium-restricted diet is a modification of the normal diet in which the sodium content is limited to a prescribed level. Many people consume much more than the Recommended Dietary Intake of sodium. Conditions that might require sodium restriction include hypertension, congestive heart failure, liver disease, renal disease, and corticosteroid therapy. If a strict sodium restriction is necessary, see Table 59-8 for lists of foods allowed and to avoid. For children, a no added salt diet might be a sufficient restriction.

Suggestions for Limiting Sodium Intake

- Do not use salt in cooking and do not add salt to food at the table. Do not put the salt shaker on the table.
- Read labels carefully on all canned, frozen, and packaged foods. Avoid products with added sodium or salt. Ingredients are listed on the package by weight, from the largest amount to the smallest.
- Use low-sodium or sodium-free canned soups, broth, potato chips, crackers, and nuts.
- Try spices and flavorings such as herbs, onion powder, thyme, or lemon juice to add flavor to foods.
- Limit fast foods and restaurant foods that are high in sodium. Most restaurant meals can be made without added salt or salt-containing ingredients such as monosodium glutamate or soy sauce.
- Evaluate medications for sodium content because some medicines contain sodium. Examples are laxatives (Ex-Lax), antacids (Maalox), and some pain relievers, such as acetaminophen (Tylenol).

Low-Cholesterol and Low–Saturated Fat Diet

Cardiovascular disease is associated with a variety of risk factors, including hypercholesterolemia. Blood cholesterol levels can be reduced by as much as 10 to 15% by lowering cholesterol and saturated fat consumption. Exercise, in conjunction with dietary modifications, should be encouraged as this can aid in lowering cholesterol, as well as in weight management.

Low-cholesterol and low–saturated fat diets are used for the management of hypercholesterolemia. The American Academy of Pediatrics' Committee on Nutrition has recommended the implementation of more restrictive Step One and Step Two diets in children who consistently demonstrate cholesterol values greater than the 75th percentile; these diets are described in Tables 59-9 and 59-10 (see Chapter 8, "The Prudent Diet: Preventive Nutrition").[7] Step Two diets are indicated for children who fail to improve on the Step One diet. The American Heart Association has recommended that Step One and Step Two diets be used only in children 2 years of age and older because of the rate of central nervous system development at an earlier age.[8] Because of the potential risk of insufficient caloric intakes, careful monitoring is necessary to ensure normal growth and development in all children on these diets.

Definition of Dietary Fats There are three types of fat in the food we eat: saturated fat, polyunsaturated fat, and monounsaturated fat. Saturated fats are believed to increase blood cholesterol, so the amount of saturated fat in the diet should be limited. Saturated fat is usually solid at room temperature. Examples are butter, shortening, meat fats (suet, lard, salt pork, bacon fat), chicken fat, coconut oil, palm oil, and hydrogenated oils. As well, the fat in whole milk, cheese, yogurt, and cream is saturated.

Polyunsaturated fats lower total blood cholesterol, that is, both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. Polyunsaturated fat is liquid at room temperature. Examples are corn, safflower, sunflower, soybean, cottonseed, walnut, and sesame oil. Monounsaturated fat lowers serum LDL while maintaining HDL levels. Examples are olive, canola, and peanut oils and some nut oils.

TABLE 59-8 Sodium-Restricted Diet

Type of Food	*Allowed*	*Avoid*
Meat, fish, fowl, and cheese	Fresh or frozen beef, lamb, pork, rabbit, veal, chicken, turkey, liver; fresh fish except shellfish, canned salt-free tuna; salt-free cottage cheese; eggs (one a day); salt-free peanut butter	Smoked, processed, or canned meat or fish; frankfurters, ham, sausage, pepperoni, Spam, bacon, luncheon meat, chipped or corned beef, salted kosher meats, salt pork, smoked tongue, canned tuna or salmon, anchovies, caviar, salted and dried cod, herring, frozen fish fillets; frozen meat pies, frozen entrees; shellfish: clams, crabs, lobsters, oysters, scallops, shrimp; egg substitutes; cheese (unless low sodium); peanut butter (unless low sodium)
Breads and cereals	Low-sodium breads, cereals, and cereal products; breads and rolls made without salt; quick breads made with sodium-free baking powder or potassium bicarbonate and without salt or made from low dietetic mix; the following cooked cereals without added salt: pearl barley, cracked wheat, plain farina, Ralston, maltex rolled oats, pettijohns, wheatena, rice; dry cereals: puffed rice, puffed wheat, shredded wheat; macaroni, spaghetti, noodles (cooked without added salt); salt-free melba toast, salt-free venus wafers, low-sodium crackers, plain, unsalted matzo, yeast waffles	Breads and rolls made with salt or commercial mixes; quick breads (pancakes, waffles, cakes, pastries, muffins) made from baking powder, baking soda, salt, monosodium glutamate or commercial mixes; quick cooking and enriched cereals that contain a sodium compound (read label); dry cereals (except those allowed); crackers (except low sodium); "self-rising" flour or cornmeal
Fruits and juices	All fresh; frozen, canned, or dried to which salt, sodium benzoate, or sodium sulfite has not been added; read labels	Regular tomato and vegetable juices, maraschino cherries, any fruit or fruit product that contains salt or sodium benzoates, sodium-preserved dried fruits
Vegetables	Fresh, frozen, or dietetic canned without salt: asparagus, green beans, dried lima beans, dried navy beans, brussels sprouts, cabbage, cauliflower, corn, cowpeas, cucumbers, eggplant, endive, lettuce, mushrooms, okra, onions, parsley, parsnips, peas (fresh), peppers, potatoes, sweet potatoes, pumpkin, radishes, rutabaga, soybeans, squash (winter, summer), tomatoes, turnip greens	All regular canned vegetables; beets, beet greens, carrots, celery, dandelion greens, hominy, kale, mustard greens, pickles, sauerkraut, spinach, white turnips, frozen peas or lima beans if processed with salt; commercially seasoned frozen vegetables, frozen mixed vegetables
Desserts	Fruit and fruit juices as allowed above; gelatin (made with plain, unflavored gelatin, sugar, fruit and fruit juices); homemade cornstarch, rice, or tapioca pudding made from part of milk allowance or low-sodium milk; ice cream as allowed; candy, cake, cookies, pastry: homemade, salt free, or special low sodium	Commercial candies, cakes, cookies, or homemade unless prepared with allowed ingredients; packaged puddings, Jello or other commercial sweetened gelatin desserts
Fat	Lard, vegetable oil, shortening, salt-free butter or margarine, unsalted nuts	Salted butter or margarine, bacon fat, salt pork, commercial mayonnaise or other salad dressing (except low sodium), salted nuts, olives
Sugar and sweets	Sugar, honey, syrups, jams, marmalades, and jellies that contain no preservatives	Molasses, commercial jams containing sodium benzoate or other sodium preservatives (read labels)
Beverages	Fruit juices, lemonade, milk (regular or low sodium as allowed), coffee, tea, Postum, Hershey's cocoa (made with allowed milk or water)	Fountain beverages, "Dutch process" cocoa, instant cocoa mixes, powdered milk, prepared beverages, mixes including fruit-flavored powders, mineral waters, buttermilk
Seasonings and condiments	All spices, extracts, herbs, except those with sodium as an ingredient; lemon juice, vinegar, salt substitute (with doctor's approval), low-sodium bouillon cube	Salt; celery salt, seeds, and flakes; onion salt, garlic salt, prepared mustard, ketchup, horseradish prepared with salt, barbecue sauce, chili sauce; meat extracts, sauces, gravies, and tenderizers; monosodium glutamate (Accent), soy sauce, Worcestershire sauce, saccharin and other sugar substitutes containing salt, regular bouillon cubes, olives, relishes, pickles. Avoid all foods with above seasonings added.
Miscellaneous		Canned, dehydrated, or frozen potato; spaghetti, macaroni, or noodle products; pre-prepared gravies; canned or dehydrated soups, except low sodium; salted popcorn, potato chips, pretzels, and other snack items such as corn chips or Doritos; party spreads and dips; regular baking powder, baking soda (sodium bicarbonate), rennet tablets, laxatives, Chinese/Asian food, Italian food, fast foods, bread stuffing

Suggestions for Lowering Cholesterol and Saturated Fat Intake

- Limit red meat to a maximum of two or three servings (2 to 3 oz per serving) per week. Cut away any visible fat from meat before cooking.
- Bake, broil, boil, or stir-fry meats, fish, or poultry. Remove skin from poultry.
- Use nonstick fry pans or nonstick spray coatings.
- Eat no more than three or four egg yolks per week. Substitute two egg whites for a whole egg in recipes. Use egg whites to batter meats and vegetables, coat with crumbs moistened with acceptable oil, and then bake. Use low-cholesterol commercial egg substitutes in place of whole eggs.
- Read labels of commercially prepared products and avoid those containing ingredients not allowed.
- Limit all fats and oils to reduce total fat intake.
- Avoid fast foods that could be high in fat (eg, fried chicken, french fries).
- Increase fish meals to three or four servings per week.
- Try some meatless dishes, such as pasta with tomato sauce or vegetarian stir-fry dishes.
- Use high-protein vegetables such as legumes (kidney, red, or pinto beans) and fat-free dairy products to supply protein.

To reduce high triglyceride levels, take the following steps to decrease simple carbohydrate intake (if LDL is also high, it will be necessary to also reduce saturated fat intake):

- Avoid sweetened drinks such as soda, fruit juices, and coffee beverages; replace with water, skim or 1% milk, or smoothies made with fat- and sugar-free yogurt and fresh fruit.
- Avoid large or frequent servings of sugary foods such as cookies, candy, ice cream, fruit rollups, and regular chewing gum.

To determine how many calories come from fat in a particular product, using the information on the food label, divide the calories coming from fat by the total calories and then multiply by 100. This equals the percentage of calories from fat. If the percentage from fat is less than 30%, the product is appropriate; if it is more than 30%, the product is too high in fat. The goal is to balance any high-fat food with low-fat foods so that at the end of the day, total fat intake is less than 30% of calories.

Determining Percentage of Calories from Fat: An Example

Product: Cheez-it
Serving size: 12 crackers (nutrition information is per serving)
Calories: 70; calories from fat: 36
Protein: 2 g
Carbohydrates: 7 g
Fat: 4 g (total fat per serving)
Polyunsaturated fat: less than 1 g
Saturated fat: 1 mg
Cholesterol: less than 2 mg
Sodium: 135 mg
Ingredients: enriched flour, riboflavin, vegetable shortening (contains one or more of the following: partially hydrogenated oils: soybean, cottonseed, canola), skim milk, cheese, salt, paprika, yeast, paprika extractives (vegetable color). (Ingredients are listed in descending order, with the largest amount first.)
Thirty-six calories from fat divided by 70 calories per serving = $0.51 \times 100 = 51$; therefore, 51% of calories are from fat. This product is high in fat.

TABLE 59-9 Characteristics of Step One and Step Two Diets for Lowering Blood Cholesterol

	Recommended Intake	
Nutrient	*Step One Diet*	*Step Two Diet*
Total fat	Average of no more than 30% of total calories	Same
Saturated fatty acids	Less than 10% of total calories	Less than 7% of total calories
Polyunsaturated acids	Up to 10% of total calories	Same
Monounsaturated fatty acids	Remaining total fat calories	Same
Cholesterol	Less than 300 mg/d	Less than 200 mg/d
Carbohydrates	About 55% of total calories	Same
Protein	About 15–20% of total calories	Same
Calories	To promote normal growth and development and to reach or maintain desirable body weight	Same

INBORN ERRORS OF METABOLISM

Medical nutritional therapy plays a key role in the management of several metabolic disorders, including those related to carbohydrate, fatty acid, and amino acid metabolism.[9] Dietary alterations are often necessary in re-establishing a balance in metabolic function through provision of deficient products and restriction of toxic substrates. In addition, nutritional management is important to stabilizing altered protein enzymes, replacing cofactors that might be deficient, and supplying products that are deficient owing to an inhibited secondary pathway.

Several formulas currently available for the management of metabolic disorders are age and diagnosis specific (see Appendix). Frequent monitoring is imperative to ensure optimal growth and neurologic development in these medically complex patients. The Appendix provides an extensive list of known metabolic disorders and their suggested dietary modifications, including appropriate enteral formulas.

MINERAL-RICH DIETS

A number of acute and chronic pediatric medical conditions might require mineral supplementation, either in the diet or

TABLE 59-10 Diet for Hyperlipidemia (Step One* and Step Two)

Food Group	*Choose*	*Decrease*
Fats and oils	Unsaturated oils—safflower, sunflower, corn, soybean, cottonseed, canola, olive, peanut	Coconut oil, palm kernel oil, palm oil
	Margarine made from unsaturated oils listed above; light or diet margarine	Butter, lard, shortening, bacon fat
	Salad dressings made with unsaturated oils listed above; low fat or oil free	Dressings made with egg yolk, cheese, sour cream, whole milk
	Seeds and nuts—peanut butter, other nut butters	Coconut
	Cocoa powder	Chocolate
Breads and cereals	Breads—whole-grain bread, hamburger and hot dog bun, corn tortilla	Bread in which eggs are a major ingredient, croissants
	Cereals—oat, wheat, corn, multigrain	Granola made with coconut
	Pasta	Egg noodles and pasta containing egg yolk
	Rice	
	Dry beans and peas	
	Crackers—low-fat animal type, graham, saltine type	High-fat crackers
	Homemade baked goods using unsaturated oil, skim or 1% milk, and egg substitute—quick breads, biscuits, cornbread muffins, bran muffins, pancakes, waffles	Commercial baked pastries, muffins, biscuits
Soup	Chicken or beef noodle, minestrone, tomato, vegetarian, potato	Soup containing whole milk, cream, meat fat, poultry fat, or poultry skin
Vegetables	Fresh, frozen, or canned	Vegetables prepared with butter, cheese, or cream sauce
Fruits	Fruit—fresh, frozen, canned, or dried	Fried fruit or fruit served with butter or cream sauce
	Fruit juice—fresh, frozen, or canned	
Sweets and modified fat desserts	Beverages—fruit-flavored drinks, lemonade, fruit punch	
	Sweets—sugar, syrup, honey, jam, preserves, candy made without fat (candy corn, gumdrops, hard candy), fruit-flavored gelatin	Candy made with chocolate, coconut oil, palm kernel oil, palm oil
	Frozen desserts—sherbet, sorbet, fruit ice, popsicles	Ice cream and frozen treats made with ice cream
	Cookies, cake, pie, pudding—prepared with egg whites, egg substitute, skim or 1% milk, and unsaturated oil or margarine; gingersnaps; fig bar cookies, angel food cake	Commercial baked pies, cakes, donuts, high-fat cookies, cream pies
Meat, poultry, and fish	Beef, pork, lamb—lean cuts well trimmed before cooking	Beef, pork, lamb—regular ground beef, fatty cuts, spare ribs, organ meats, sausage, regular luncheon meats, wieners, bacon
	Poultry without skin	Poultry with skin, fried chicken
	Fish, shellfish	Fried fish, fried shellfish
	Processed meat—prepared from lean meat (eg, turkey ham, tuna wieners)	Regular luncheon meat (eg, bologna, salami, sausage, wieners)
Eggs	Egg whites (two whites equal one whole egg in recipes), cholesterol-free egg substitute	Egg yolks (if more than four per week on Step One or if more than two per week on Step Two diet); includes egg used in cooking
Dairy products	Milk—skim or 1% fat (fluid, powdered, evaporated), buttermilk	Whole milk (fluid, evaporated, condensed), 2% low-fat milk, imitation milk
	Yogurt—nonfat or low-fat yogurt or yogurt beverages	Whole-milk yogurt, whole-milk yogurt beverages
	Cheese—low-fat natural or processed cheese (part-skim mozzarella, ricotta) with no more than 6 g fat per oz on Step One or 2 g fat per oz on Step-Two	Regular cheeses (American, blue, Brie, cheddar, Colby, Edam, Monterey Jack, whole-milk mozzarella, Parmesan, Swiss), cream cheese, Neufchatel cheese
	Cottage cheese—low fat, nonfat, or dry curd (0 to 2% fat)	Cottage cheese (4% fat)
	Frozen dairy dessert—ice milk, frozen yogurt (low fat or nonfat)	Ice cream, cream, half and half, whipping cream, nondairy creamer, whipped topping, sour cream

Adapted from National Cholesterol Education Program Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. US Department of Health and Human Services. Public Health Service. National Institutes of Health. National Heart, Lung, and Blood Institute; September 1991. NIH Publication No.: 91-2732.
Data from American Academy of Pediatric Statement on Cholesterol. Committee on Nutrition. Pediatrics 1992;90:469–72.
*The Step One diet has the same nutrient recommendations as the eating pattern recommended for the general population. These diets are best implemented in consultation with a registered dietitian.

by therapeutic measures during their course. Included in this list is cow's milk protein allergy, lactose intolerance, hypercholesterolemia, renal disease, and celiac disease. Some diets chosen for personal reasons, such as the vegan or lacto-ovovegetarian diets, can be inadequate in certain micronutrients.

Included in this section are lists of food sources high in calcium and iron, the minerals most commonly found to be deficient in the pediatric population. It is recommended that any child on a special diet be assessed for micro- and macronutrient intake periodically to ensure an optimal intake for growth and development.

Calcium-Rich Diet

A calcium-rich diet is recommended for all individuals as part of a healthful, well-balanced diet. In particular, growing children have high dietary requirements for calcium. Consuming calcium-rich foods daily will help minimize resorption of calcium from the bones and thus promote dense, strong bones.

Milk and dairy products are the primary source of calcium in the North American diet; the other food groups—breads, meats, fruits, and vegetables—provide the remainder. See the Appendix for Dietary Reference Intakes and Table 59-11 for calcium food sources.

Calcium Information

- Dietary Reference Intakes, National Academy Press: www.nap.edu
- Pennington JAT. Bowes and Church's Food Values of Portions Commonly Used. 17th ed. Philadelphia: Lippincott-Raven Publishers; 1997.
- National Dairy Council: www.nationaldairycouncil.org

Iron-Rich Diet

The iron-rich diet might be indicated for individuals with anemia. Anemia can occur as a result of dietary deficiencies, blood loss, or inadequate absorption of iron.

The body more readily absorbs iron from animal sources (heme iron) than from vegetable sources (nonheme iron). Consuming foods high in vitamin C at the same meal can enhance the absorption of nonheme iron. Vitamin C–rich foods include citrus fruits and juices, cantaloupe, strawberries, tomatoes, and dark-green vegetables. See the Appendix for Dietary Reference Intakes; Table 59-12 lists iron food sources.

WEIGHT CONTROL

The National Center for Health Statistics reports that the prevalence of overweight in children and adolescents is on the rise and has nearly tripled since the 1960s.[10] Being overweight is considered to be the result of an imbalance of energy intake and energy expenditure. Many factors can influence the upward trend in the prevalence of overweight in children, such as alterations in nutrient intake, changes in physical activity patterns, television viewing habits, level of nutritional knowledge, genetics, and parental influence. See Chapter 23, "Energy and Substrate Regulation in Obesity," for more information.

Successful weight reduction and control incorporates a combination of caloric reduction, behavior modification, and exercise. Below are guidelines for healthful eating and weight reduction and control in children.

Goal 1: Plan All Meals and Snacks

- Preplan menus to avoid impulse food choices.
- Do not skip meals; try to eat at the same times each day. Three meals and two or three snacks are sometimes better than only three large meals. There might be a greater risk of eating fattening snack foods when you are very hungry.
- Keep a box of low-calorie foods ready for between-meal snacks (eg, a variety of raw vegetable strips, rice cakes, popcorn, pretzels, fresh fruit).
- When away from home, take food along or know where appropriate foods can be purchased.
- Help make the shopping list and plan for low-calorie selections.
- Read food labels to limit products that list fats or sugars as main ingredients.
- Avoid fried foods (such as french fries and fried chicken), creamed products, and gravies.
- Avoid empty calories (foods such as chips, cakes, cookies, pies, pastry, regular soda, candy, jellies, and syrups) because these foods have very few nutrients and are high in fat or sugar calories or both.
- Preportion food for meals and snacks. Never eat food directly from the serving container or bag; this makes it too easy to overeat.

Goal 2: Eat a Well-Balanced Diet

Eat a variety of foods from the Food Guide Pyramid to meet nutritional needs. The recommended number of servings and serving sizes for the various food groups are listed below:

- **Milk group**: Skim or 99% fat-free milk; nonfat yogurt (some yogurts contain large amounts of added sugar; compare labels); low-fat cheeses (less than 3 g fat per serving). Recommended number of servings: ages 1 to 10: three servings/day; ages 11 to 24: four servings/day. One serving = 1 cup skim milk; 1 cup nonfat yogurt; 1 oz low-fat cheese; $^1/_2$ cup low-fat cottage cheese.
- **Meat group**: Lean cuts with little fat marbling; trim all fat from meat; remove skin of poultry; choose fish canned in water instead of oil; avoid processed deli meats, bacon, and sausage. Recommended number of servings: two servings/day. One serving = 2 to 3 oz lean meat or chicken, cooked; 1 egg; $^1/_4$ cup canned fish; $^1/_2$ cup cooked dried beans.
- **Breads and cereals group**: Choose whole-grain or enriched products and plain cereals (not presweetened). Recommended number of servings: four servings/day. One serving = 1 slice bread, half an English muffin, $^1/_2$ cup starch (potatoes, corn, peas, pasta, rice, or cooked cereal), 1 oz (approximately $^1/_2$ to 1 cup) of ready-to-eat unsweetened cereal.

TABLE 59-11 Calcium Food Sources

Food Group	*Milligrams of Calcium/Serving*
Milk and dairy	
Milks, 1 cup	300
Buttermilk	285
Chocolate	280
Malted	347
Whole*	291
1% low fat	300
2% low fat	297
Skim	302
Soy Plus-West Soy (soy milk)	300
Cheeses	77–337
American, pasteurized process, 1 oz	174
Blue, 1 oz	150
Brick, 1 oz	191
Caraway, 1 oz	191
Cheddar, 1 oz	204
Cheese food	
American, pasteurized process, 1 oz	163
Swiss, pasteurized process, 1 oz	205
Colby, 1 oz	194
Cottage, 2% low fat, ½ cup	77
Edam, 1 oz	207
Monterey, 1 oz	212
Mozzarella, part skim, 1 oz	207
whole, 1 oz	147
Muenster, 1 oz	203
Ricotta, part skim, ½ cup	337
whole, ½ cup	257
Swiss, 1 oz	272
Frozen desserts, ½ cup	88–137
Ice cream, ½ cup	88
Ice milk, hardened, ½ cup	88
Ice milk, soft serve, ½ cup	137
Sherbet, 1 cup	51
Frozen yogurt, ½ cup nonfat	104
Yogurt low fat, 1 cup	345–415
Flavored	389
Fruit	345
Plain	415
Pudding, ½ cup	150
Protein	
Beans, dried, cooked, 1 cup	90
Clams, 4 oz	100
Crab, 3 oz	132
Cod, 3 oz	136
Halibut, 3 oz	191
Oysters, raw, ½ cup	113
Perch, 3 oz	117
Salmon, with bones, 3 oz	167
Sardines, with bones, 3 oz	371
Shrimp, canned, 3 oz	98
Tofu, piece, ½ cup	434
Trout, 1 serving	210
Nuts/legumes (½ cup)	
Almonds	188
Beans, dried, cooked	45
Brazil nuts	123
Garbanzo beans	150
Hummus	66
Lima beans	35
Peanuts	77
Pistachio	86
Pork and beans	67
Refried beans	58
Soybeans	130
Walnuts	55

Food Group	*Milligrams of Calcium/Serving*
Grain foods	
Pancakes, 1 (2–3")	150
English muffin	105
Waffles (7")	179
Wonder Calcium Rich bread (white/whole wheat), 1 slice	290
Wonder Light Calcium Enriched bread, 2 slices	290
Vegetables/legumes (½ cup cooked)	
Beet greens	82
Bokchoy	79
Broccoli	89
Butternut squash	42
Cabbage	79
Carrots	35
Collards	74
Kale	90
Lima beans	35
Mustard greens	38
Okra	50
Pumpkin	31
Stewed tomatoes	42
Spinach	61
Sweet potatoes	38
Tomato soup	80
Tomato soup, with milk (1 cup)	159
Turnip greens	99
Fruits/juices	
Rhubarb, ½ cup	174
Dried figs, ½ cup	144
Orange	92
Orange juice (calcium fortified) 8 oz	300
Dates, dried cut, ½ cup	53
Prunes, dried, (4)	49
Hawaiian Punch (calcium fortified), 8 oz	150
Cereal (1 cup)	
Total	282
Total Raisin Bran	200
Total Corn Flakes	200
Basic Four	200
100% Natural	181
Oatmeal	170
Life	154
Other	
Molasses Blackstrap, 1 tbsp	137
Carnation Breakfast Bar, 1 each	500
Combination and fast foods	
Pizza Hut supreme personal pan pizza	520
Lasagna (2½" × 2½")	460
Macaroni and cheese, homemade (1 cup)	362
Enchilada, cheese (1 enchilada)	324
McDonald's Big Mac (1 sandwich)	256
McDonald's Egg McMuffin (1 sandwich)	256
Wendy's broccoli and cheese potato (1)	250
Chef's salad, without dressing (1 ½ cups)	235
Quiche (⅛ pie)	224
McDonald's Filet-o-Fish (1 sandwich)	165
Cheeseburger, regular (1 sandwich)	182
Pizza, meat and veg., thin crust (¼ of 12")	166
Burger King's Croissan'wich (1 sandwich)	136
Spaghetti with meat balls (1 cup)	124
Submarine sandwich (3"–4" sub)	95
Taco Bell's taco (1 taco)	84
Dairy Queen's hot dog (1 sandwich)	80

TABLE 59-12 Iron Food Sources

Food	*Approximate Measure*	*Iron (mg)*
High-iron sources		
Cream of Wheat (quick or instant)*	½ cup	7.8
Heart, beef†	2 oz	3.7
Kidney, beef†	2 oz	5.3
Kidney, lamb†	2 oz	6.1
Kidney, pork†	2 oz	5.3
Liver, beef†	2 oz	5.8
Liver, calf†	2 oz	9.0
Liver, chicken†	2 oz	6.0
Liver, lamb†	2 oz	10.9
Liver, pork†	2 oz	15.6
Liverwurst†	2 oz	3.6
Prune juice	½ cup	5.1
Moderate-iron sources		
All-Bran Cereal	½ cup	2.9
Almonds, dried unblanched	½ cup	3.0
Dried beans and peas		
Baked beans, no pork	¼ cup	1.5
Blackeye peas, cooked	¼ cup	0.8
Broad beans, dry	¼ cup	3.6
Chick peas, dry	¼ cup	3.5
Cow peas, cooked	¼ cup	0.8
Great northern beans, cooked	¼ cup	1.3
Green peas, cooked	¼ cup	1.4
Lentils, dry	¼ cup	3.4
Lima beans, cooked	¼ cup	1.3
Mung beans, dry	¼ cup	3.6
Navy beans, cooked	¼ cup	1.3
Red beans, dry	¼ cup	3.5
Soybeans, cooked	¼ cup	1.4
White beans, dry	¼ cup	3.9
Beef, cooked	2 oz	2-3‡
Clams	3 medium	2.1
Ham, cooked	2 oz	1.3
Heart, pork, cooked	2 oz	1.8
Lamb, cooked	2 oz	1.9
Mackerel, canned	½ cup	1.0
Malt-O-Meal, cooked	½ cup	1.4
Oysters	3-4 medium	2.8
Peaches, dried	¼ cup	2.4
Peanuts, roasted w/o skins	3 ½ oz	3.2
Pork, cooked	2 oz	2-3§
Prunes, dried	2 large	1.1
Sardines	8 medium	3.5
Scallops	2 oz	1.6
Turkey, cooked	2 oz	1.7
Veal, cooked	2 oz	2.0
Venison, cooked	2 oz	2.0
Wheat germ	1 oz (3 tbsp)	2.6
Contributing iron sources		
Apricots, dried	4 large halves	1.4
Breads, white enriched	1 slice	.6
Bread, whole wheat	1 slice	.5
Chard	½ cup	1.5
Chicken	2 oz	1.0
Dandelion greens	¼ cup	0.9
Dates, dried	¼ cup	1.3
Egg, large	1	1.2
Heart, chicken	9–10 medium	1.7
Kale	¼ cup	.6
Mustard greens	¼ cup	.9
Macaroni, enriched	½ cup	.6
Noodles, enriched	½ cup	.7
Peanut butter	2 tbsp	.6
Raisins, dried seedless	¼ cup	1.25
Rice, long grain or instant	½ cup	.6
Salmon, canned	2 oz	.7
Shrimp, raw	2 oz	.9
Spaghetti	½ cup	.8
Spinach	¼ cup	1.3
Strawberries, raw cleaned	1 cup	1.5
Tomato juice, canned	½ cup	1.05
Tuna, canned	2 oz	1.1
Turnip greens	¼ cup	0.8
Waffle, enriched	5½" diameter	1.3
Approximate iron content of children's favorite foods		
Hamburger, small	1	3.0
Hamburger, large	1	5.2
Big Mac	1	4.3
Quarter Pounder	1	5.1
Spaghetti with meatballs	1 cup	3.3
Frankfurters and beans	1 cup	4.8
Pork and beans	1 cup	5.9
Raisins‖	⅝ cup	3.5
Cereals, fortified	1 serving	4.5–17.8
Nuts‖	1 cup	5.0–7.0
Seeds, sunflower‖	3½ oz	7.1
Chile con carne	1 cup	3.6
Beef burrito	1 medium	4.6
Beef tostado	1 medium	3.4
Cheese pizza	2 slices	3.0
Cheese pizza with beef	2 slices	4.8

*Or other fortified cereals that contain 10 mg of iron per ounce or 100% Recommended Dietary Allowance per serving.
†As organ meats are generally high in cholesterol, these iron-rich foods should be eaten in moderation.
‡Depending on cut. The greatest amounts of iron are generally found in the chuck, flank, and bottom round cuts of beef.
§Depending on cut. The greatest amounts of iron are generally found in the loin, sirloin, tenderloin, and picnic shoulder cuts of pork.
‖Raisins, nuts, and seeds are not generally recommended for children under age 3 because of the risk of choking.

- **Fruit and vegetables group**: Choose whole fruits that are fresh or canned in water and frozen fruits without added sugar. Choose unsweetened juice and limit to 4 oz per day. Choose vegetables that are fresh, canned, or frozen and serve without butter, cheese, or sauces. Recommended number of servings: four total servings/day. One serving = 1/2 cup canned fruit, juice, or cooked vegetable; 1 cup raw vegetables; 1 small piece fresh fruit; 1/4 cup dried fruit.

Goal 3: Prepare Foods the Low-Calorie Way

- Bake, broil, steam, roast, grill, or stir-fry foods.
- Spray pans with fat-free coating instead of using oil when frying.
- Do not add extra fat (eg, butter, margarine, oil, bacon, gravy) when cooking or for serving. Use herbs and spices to season foods instead of fats. Low-calorie but-

ter substitutes (eg, Butter Buds) can provide the flavor of butter without the fat.
- Trim meats of all skin and visible fat.
- Choose fat-free mayonnaise and fat-free salad dressings.
- Skim fat from homemade soups, stews, and gravies (refrigerate or freeze the product until the fat hardens and then spoon it off).
- Use skim milk in place of whole milk or cream when preparing soups, puddings, and home-baked products.

Goal 4: Avoid Excess Sugar

- Sugar and sugary foods provide many calories and very little nutrition and can cause tooth decay.
- Large amounts of sugar are contained in desserts such as cakes and cookies, as well as in soft drinks and candies.
- Sugar can be "hidden" in foods under such names as corn syrup, honey, fructose, and glucose. Read the label. If a sugar is listed as one of the first three ingredients on a food label, the product is probably very high in sugar.
- Beverages can be a major contributor of sugar and extra calories. Choose sugar-free sodas and sugar-free packaged drink mixes or water. Limit juice intake because even naturally sweetened products contain calories.
- It is not necessary to buy dietetic foods. Products marked "dietetic," "lite," or "light" are not necessarily low in calories. When a treat is desired, choose a lower-calorie item such as Popsicles, Italian ice, Fudgsicles, angel food cake, fat-free frozen yogurt, or sugar-free pudding.

Goal 5: Exercise

Activity is an important part of most successful weight-control programs. Regular exercise will help burn extra calories all of the time, not just while exercising. Exercise also helps to strengthen the heart and tone muscles. Exercise at least three times a week for a minimum of 20 to 30 minutes. A 150-pound person will burn calories as listed in 30 minutes of continuous activity:

- Brisk walking, 93
- Dancing, 126
- Playing baseball, 141
- Cycling, 150 to 360
- Swimming, 180
- Playing basketball, 180 to 270
- Playing soccer, 270
- Running, 300 to 450
- Skipping rope, 300 to 450
- Walking up stairs, 300 to 540

Goal 6: Eat Out Intelligently

- Limit restaurant and fast-food eating because such foods are generally high in fat and calories.
- Plan food selections to avoid meats and vegetables that have been fried (eg, select baked or broiled chicken in place of fried chicken).
- Choose a baked potato instead of fries.
- Order pizza without sausage, pepperoni, or extra cheese.
- When eating at fast-food restaurants, take advantage of salads, lean hamburgers, and fresh fruit cups.
- When selecting prepared-to-order foods, ask that the food be prepared with as little fat as possible.
- Avoid vegetables, meats, and starches that are topped with cheese, cream sauces, gravy, butter, or margarine.
- Because restaurant portions are often large, plan to take home some of your food.
- Ask for the salad dressing to be served on the side or request a low-calorie topping. If possible, eat salad without any dressing at all.
- Always ask for water with meals. Request low-fat or skim milk or sugar-free beverages.
- Plan ahead for school lunches. Review the menu and take lunch from home when the school lunch is high in fat or sugar.
- Order sandwiches without mayonnaise, special sauce, or extra cheese. Use mustard or fat-free spreads.

Goal 7: Make Positive Changes

- Maintain a positive attitude.
- When family members or friends are eating tempting foods, choose a low-calorie food (such as a sugar-free ice cream bar) or noncaloric beverage.
- Slow down the pace of eating to a minimum of 20 minutes per meal. This will allow the feeling of fullness to set in and help you enjoy the flavor of the food. If hunger persists after a meal, wait 20 minutes; if you are still hungry, choose low-calorie items such as plain vegetables or fresh fruit. Try to avoid second helpings of meats, desserts, and other high-calorie foods.
- Eat foods high in fiber, such as fresh fruits, vegetables, and whole grains, because they increase the feeling of fullness.
- Keep a food diary. Record everything eaten in order to become more aware of what and how much is actually eaten.
- Realize that change takes time. Select a few areas to work on and focus just on those until they have been mastered. Then add a few more areas needing change.
- If you eat too much of something, do not give up. Think about the positive changes that have been made and just get back on track.
- Measure weight only every 1 to 2 weeks to monitor progress. Do not get frustrated if sometimes results are not seen. A successful weight control program takes time, and a change in behavior is more important than any one weight measurement.
- Note that if a child has not attained adult height, significant weight loss could interfere with growth. Therefore, a dietitian might advise that weight maintenance rather than weight loss should be the goal while continuing to grow taller. The dietitian and physician will help to determine weight goals. If a child is on a weight loss program, a 1- to 2-pound weight decrease per week is usually appropriate.

VEGETARIANISM

A vegetarian is typically defined as a person who avoids the consumption of animal flesh, such as meat, poultry, and fish.[11] Dairy products and eggs might be included or avoided. When all dairy and egg sources are avoided, the diet is referred to as a vegan diet. A vegetarian diet can offer health advantages as a result of its high fiber and low saturated fat content. The American Dietetic Association's position statement on vegetarian diets indicates that appropriately planned vegan and lacto-ovovegetarian diets can meet the nutrient needs of infants, children, and adolescents and can promote normal growth.

Dietary deficiencies, however, are possible with overly restrictive diets. All children following a vegan diet should have a reliable source of vitamin B_{12} and vitamin D (ie, they should receive a vitamin supplement). In addition, emphasis should be placed on the intake of foods rich in calcium, iron, and zinc. Children following a vegetarian diet might need to eat foods higher in fat to meet energy needs for appropriate growth and development.

Vegetarian Groups and Resources

Vegetarian Resource Group, PO Box 1463, Baltimore, MD 21203; telephone: 410-366-8343; www.vrg.org

American Dietetic Association: Position statement on vegetarian diets. J Am Diet Assoc 1997;97:1317–21.

Katzen M. The new enchanted broccoli forest. Berkeley (CA): Ten Speed Press; 2000.

Katzen M. New Moosewood cookbook. Berkeley (CA): Ten Speed Press, 2000.

Lappe FM. Diet for a small planet. 20th anniversary ed. New York: Ballantine Books; 1991.

Robertson L, Flinders C, Ruppenthal B. The new Laurel's kitchen: a handbook for vegetarian cookery and nutrition. Berkley (CA): Ten Speed Press, 1986.

Vegetarian Times, PO Box 420235, Palm Coast, FL 32142-0235; telephone: 877-717-8923; www.vegetariantimes.com

WEB SITES FOR GENERAL INFORMATION

American Acadamy of Pediatrics: www.aap.org

American Dietetic Association: www.eatright.org

American Heart Association: www.americanheart.org

National Acadamy Press Dietary Reference Intakes: www.nap.edu

United States Department of Agriculture Food and Nutrition Information Center: www.usda.gov

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11. American Dietetic Association. Vegetarian diets. Position of the American Dietetic Association. J Am Diet Assoc 1997;97:1317–21.

APPENDIX 1

Nutritional Assessment

Gina Hardiman, RD, LD

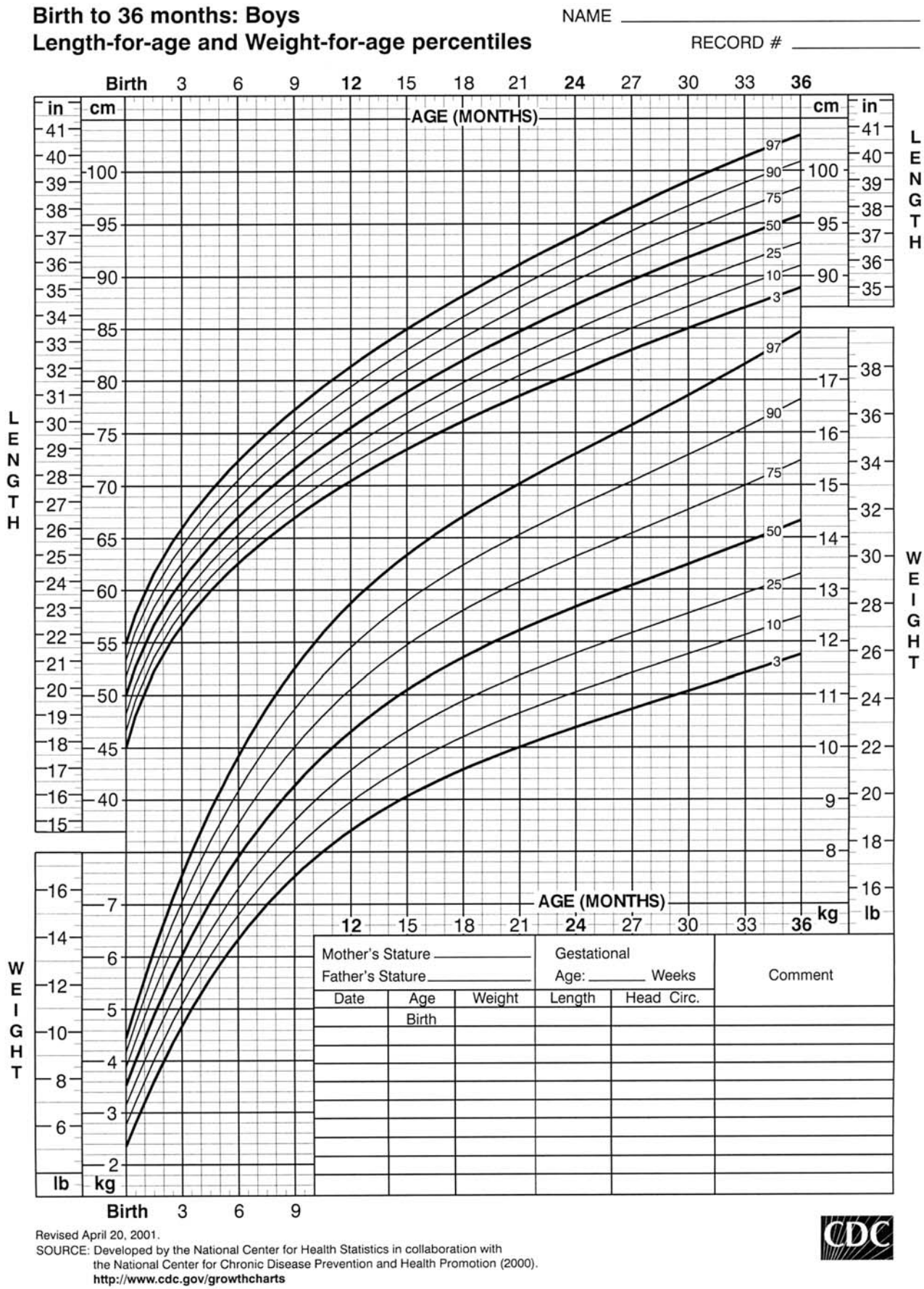


FIGURE A-1 Birth to 36 months: boys, length-for-age and weight-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). <http://www.cdc.gov/growthcharts>.

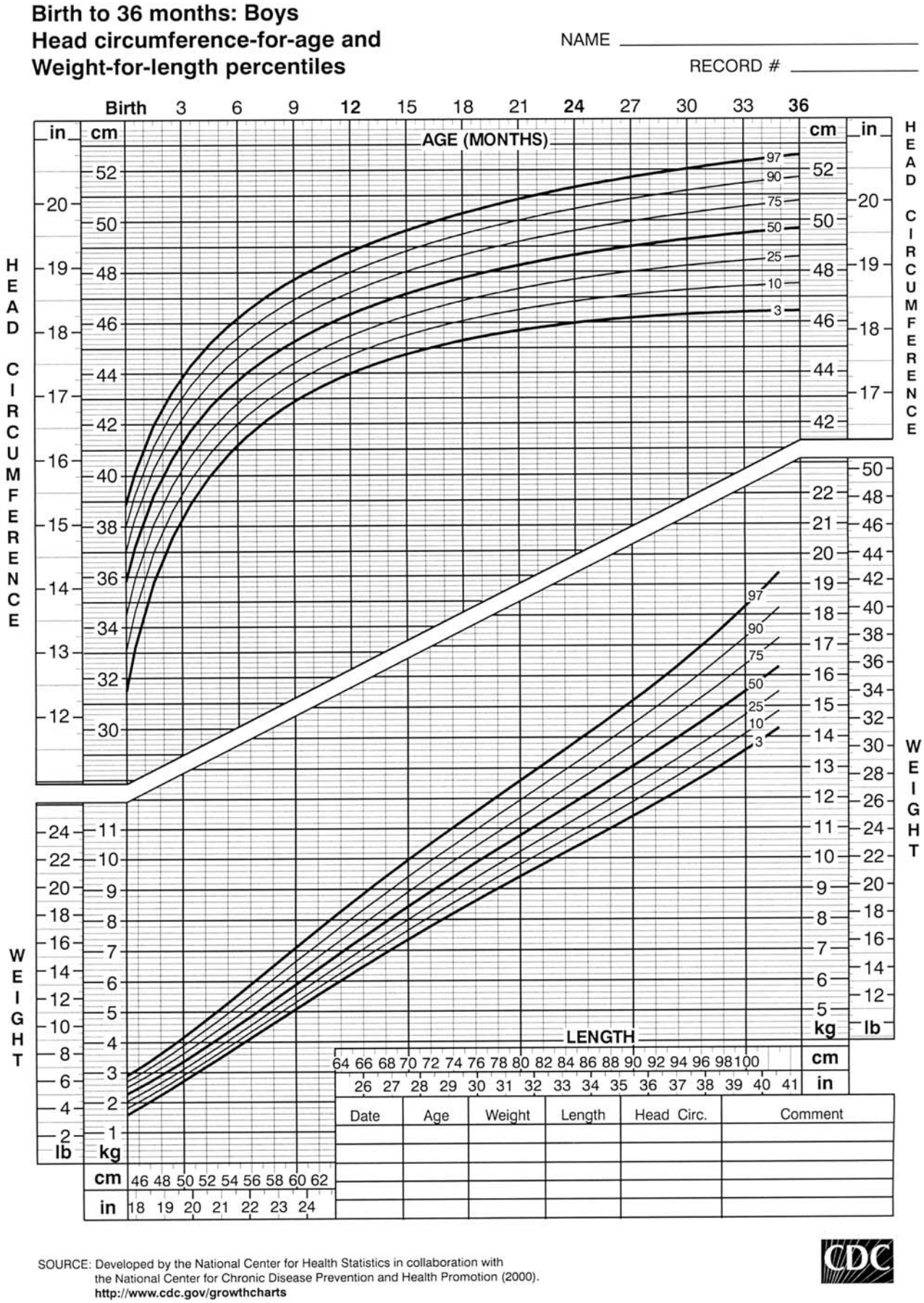


FIGURE A-2 Birth to 36 months: boys, head circumference-for-age and weight-for-length percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). <http://www.cdc.gov/growthcharts>.

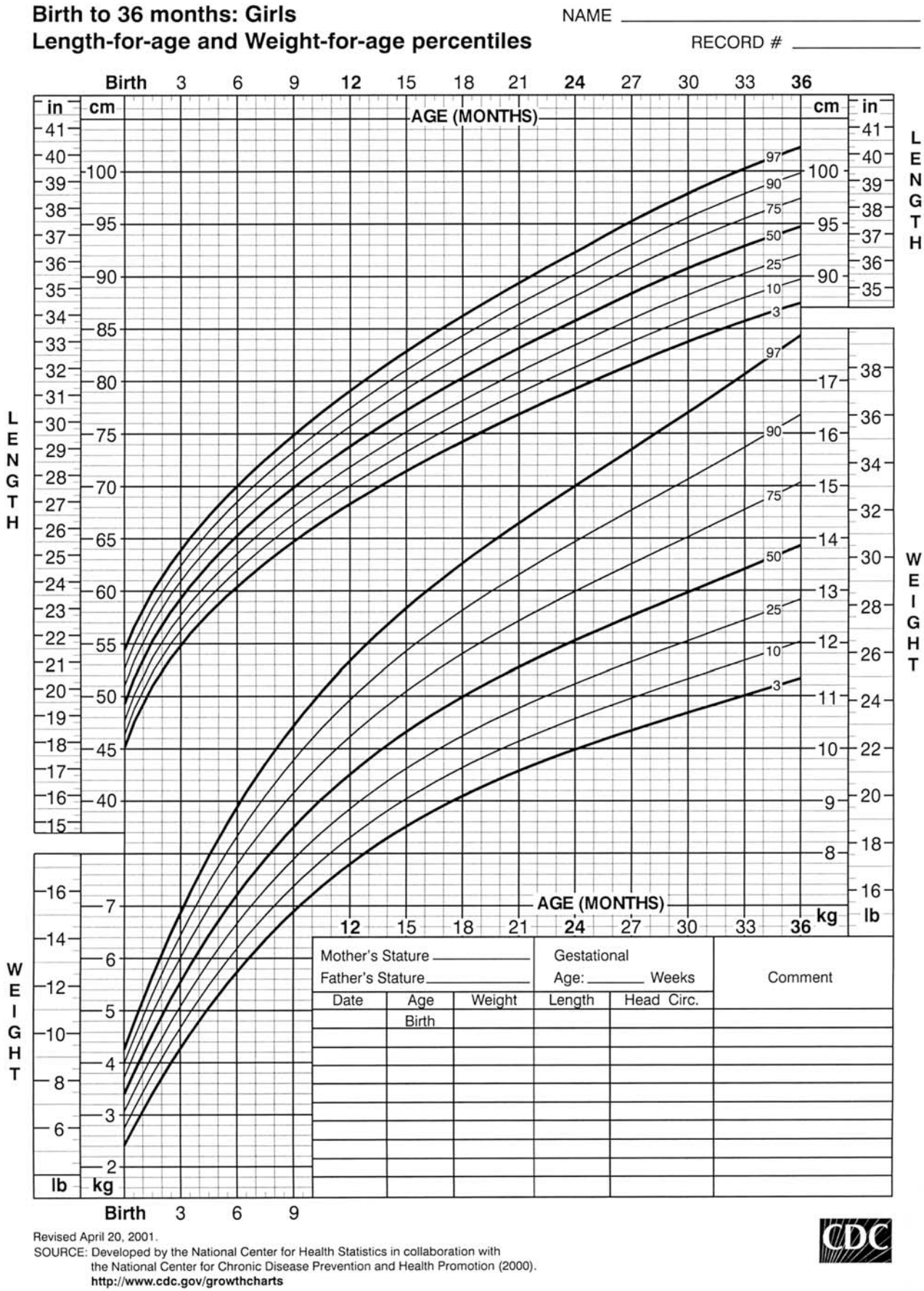


FIGURE A-3 Birth to 36 months: girls, length-for-age and weight-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). <http://www.cdc.gov/growthcharts>.

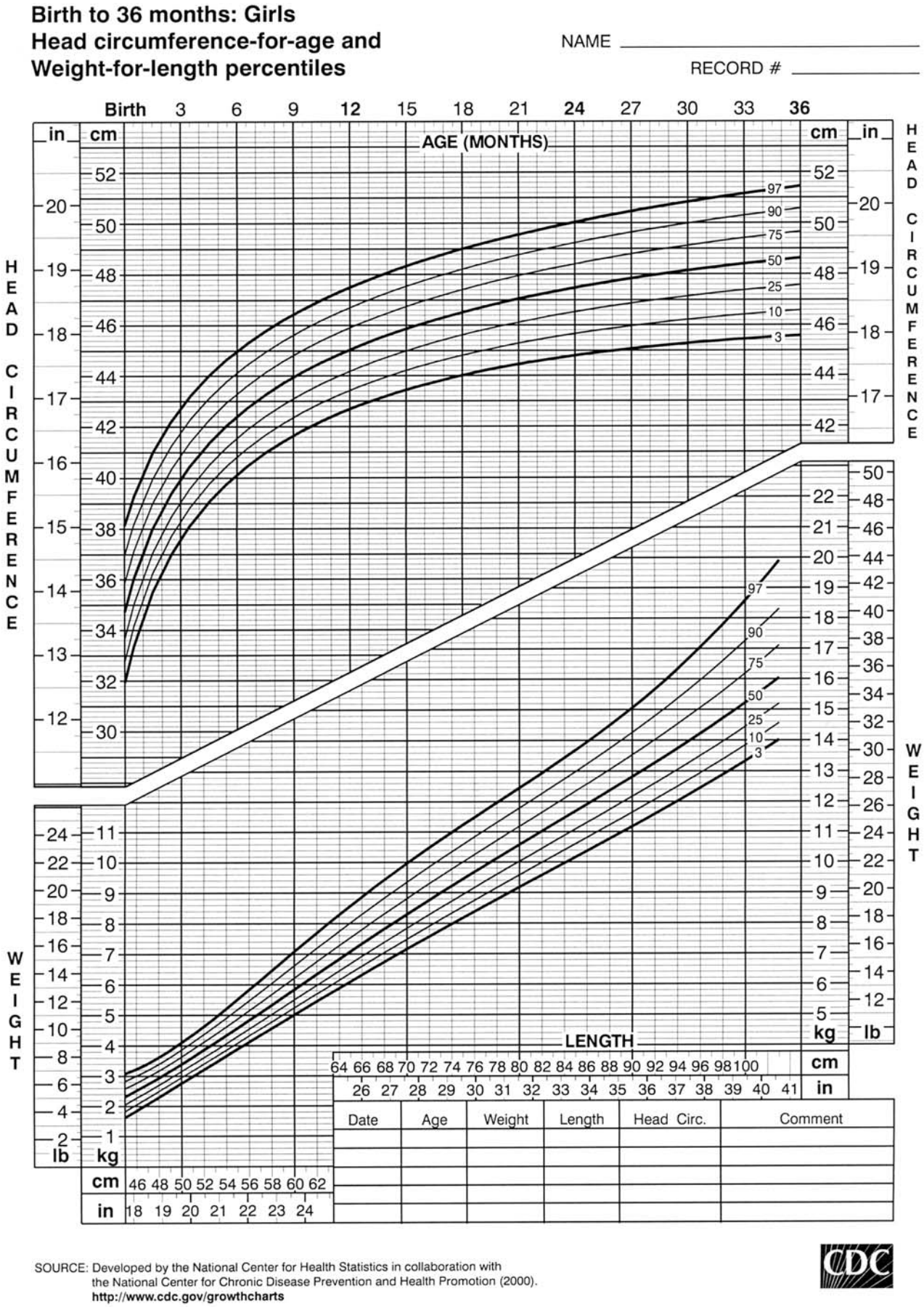


FIGURE A-4 Birth to 36 months: girls, head circumference-for-age and weight-for-length percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). <http://www.cdc.gov/growthcharts>.

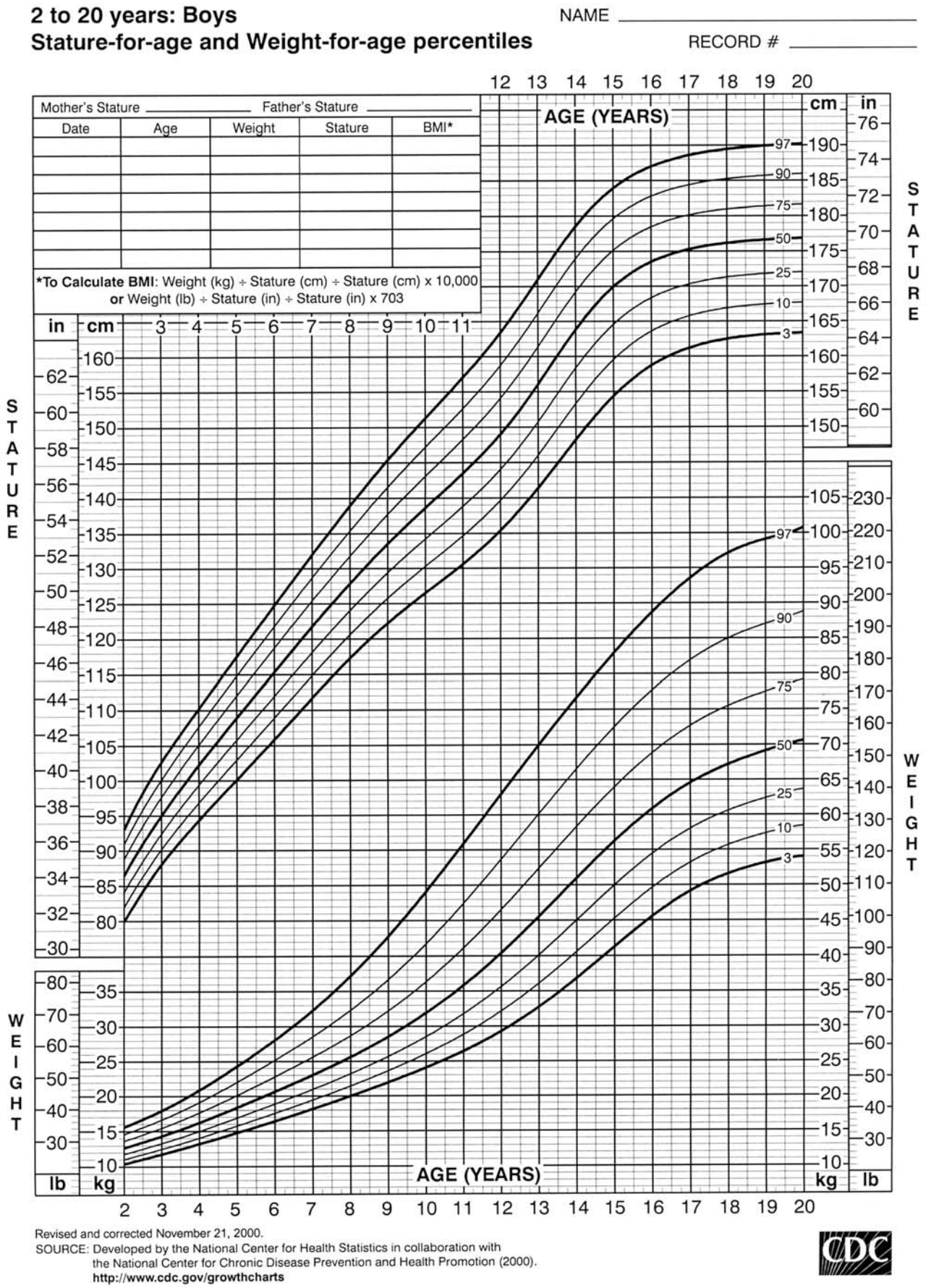


FIGURE A-5 Two to 20 years: boys, stature-for-age and weight-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

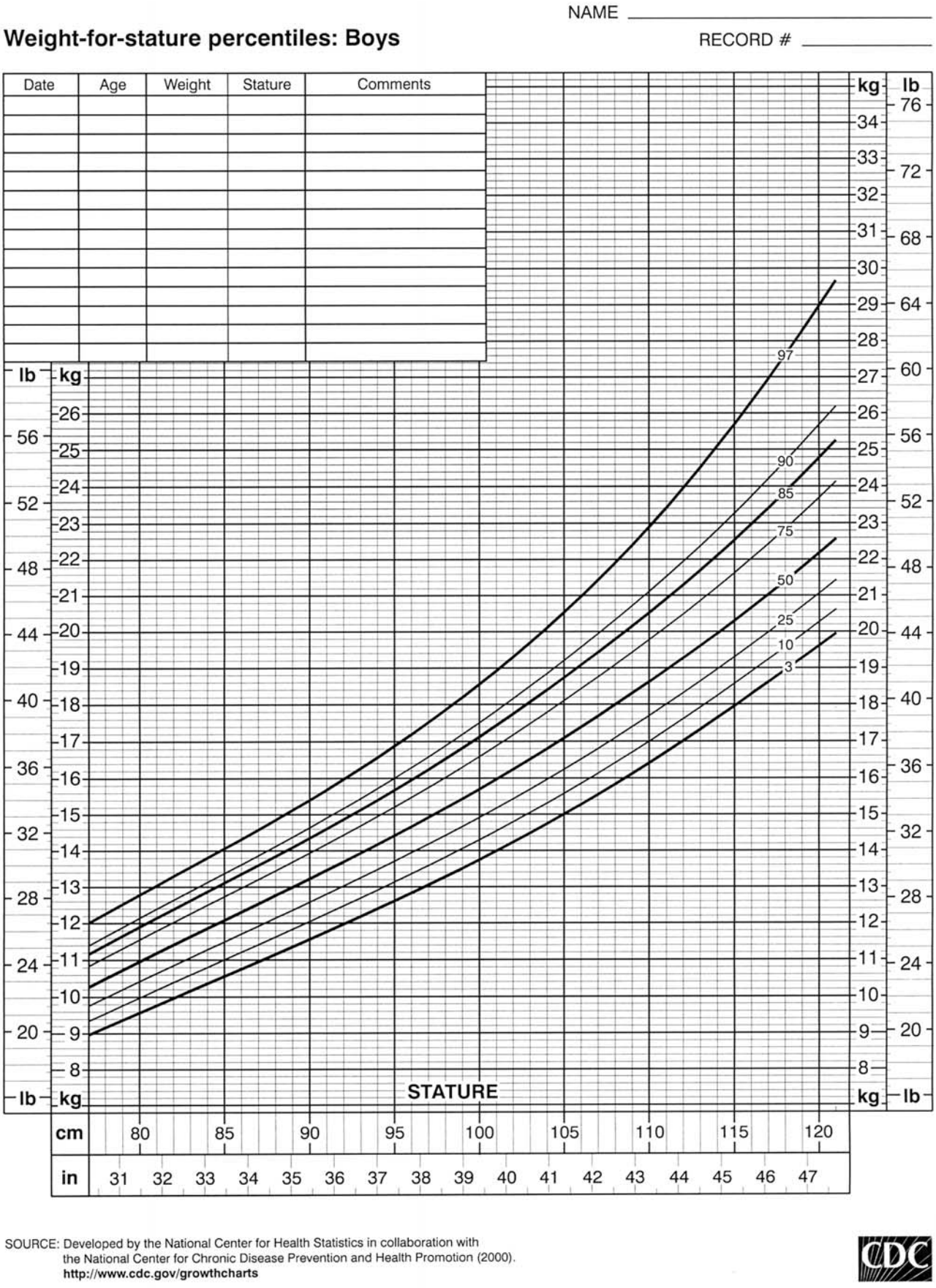


FIGURE A-6 Boys, weight-for-stature percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

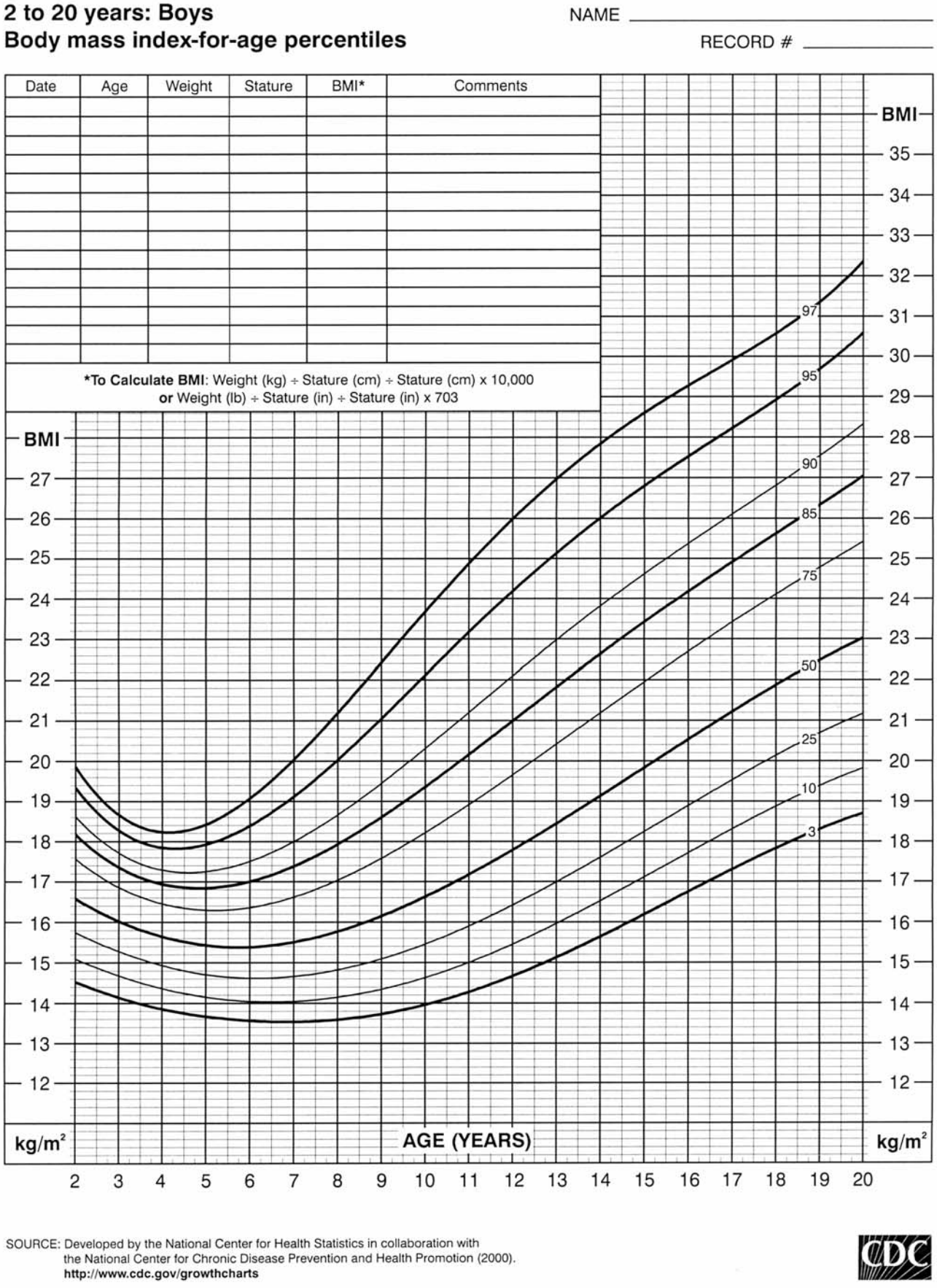


FIGURE A-7 Two to 20 years: boys, body mass index-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

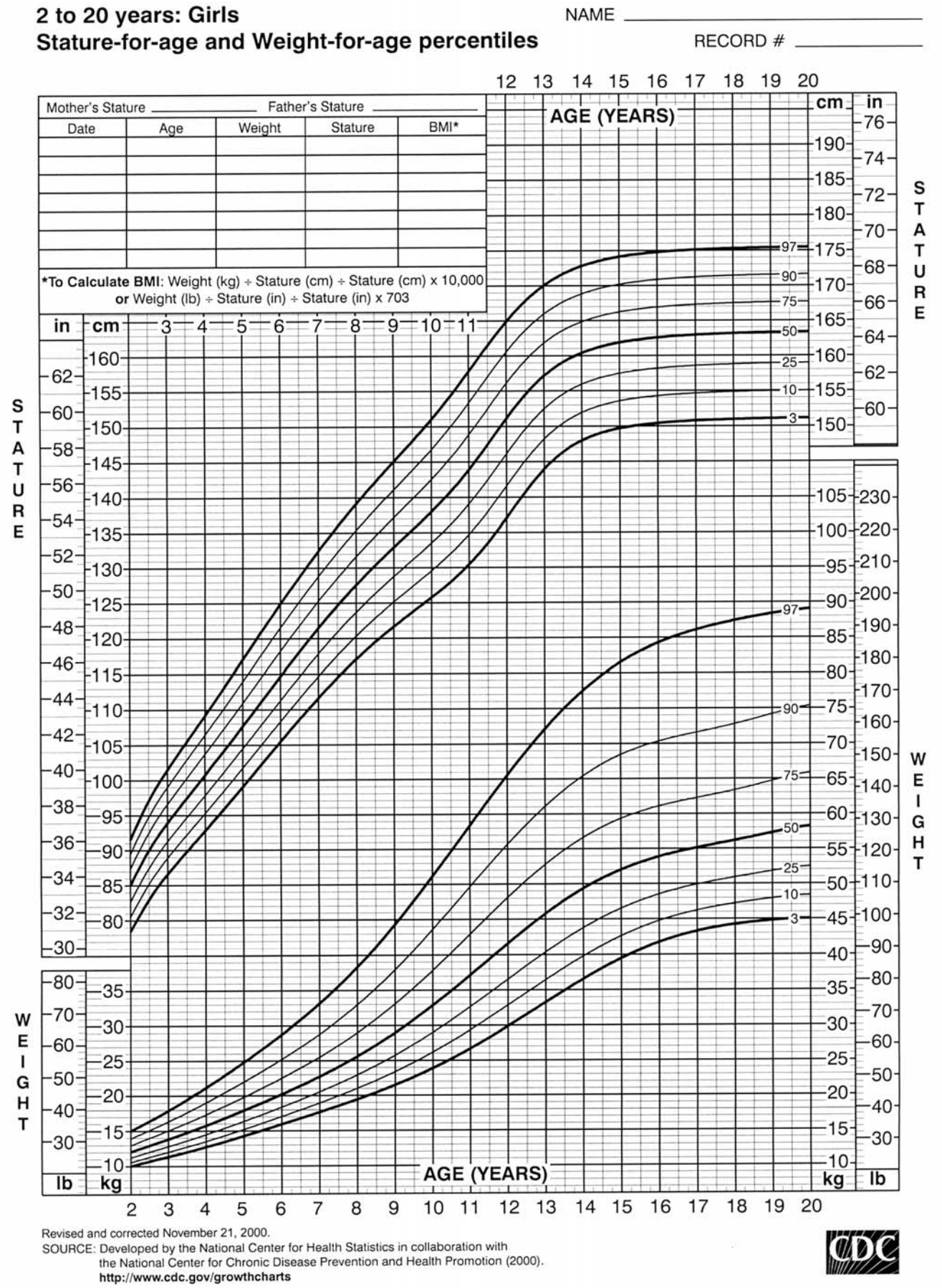


FIGURE A-8 Two to 20 years: girls, stature-for-age and weight-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

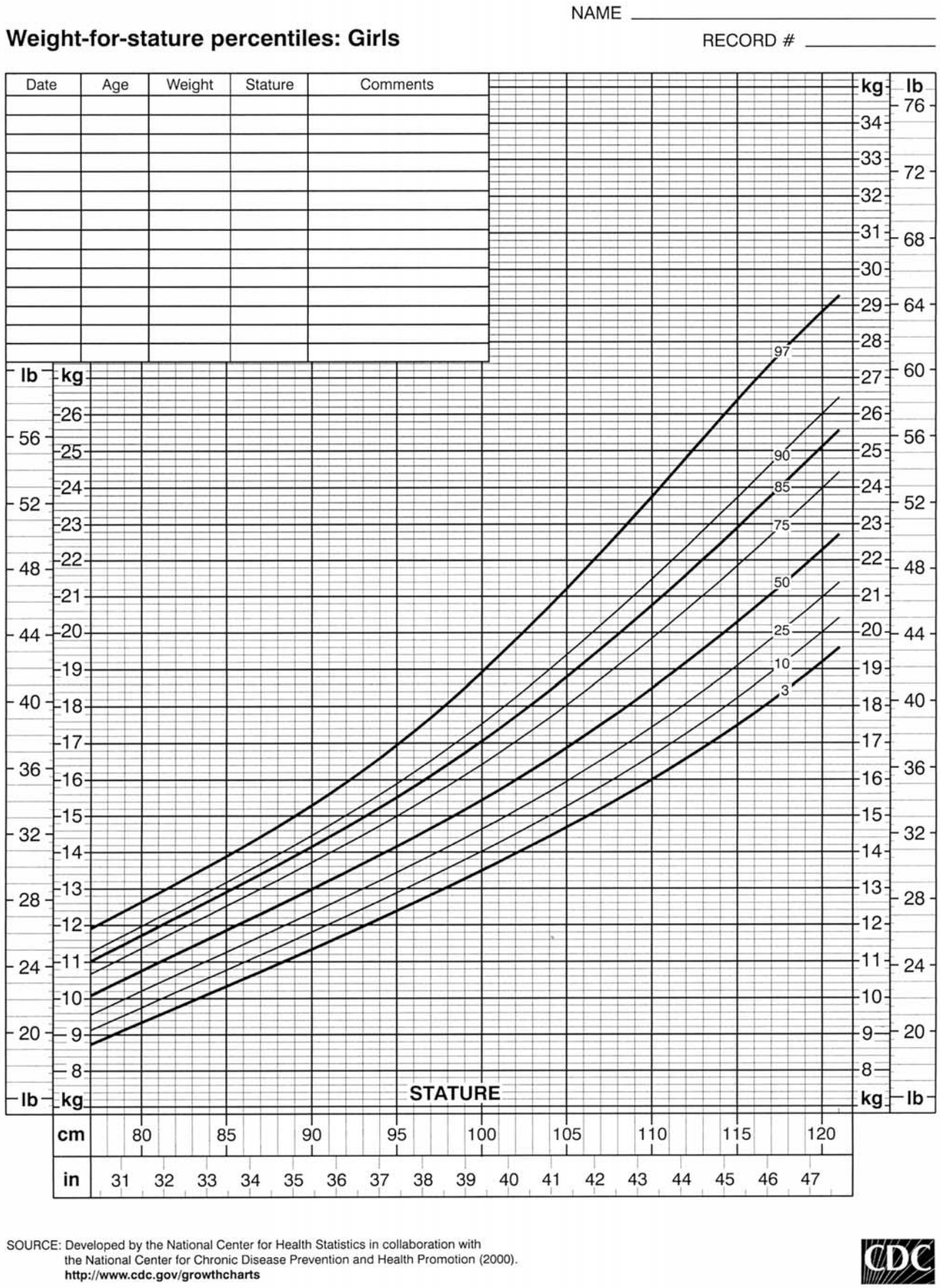


FIGURE A-9 Girls, weight-for-stature percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

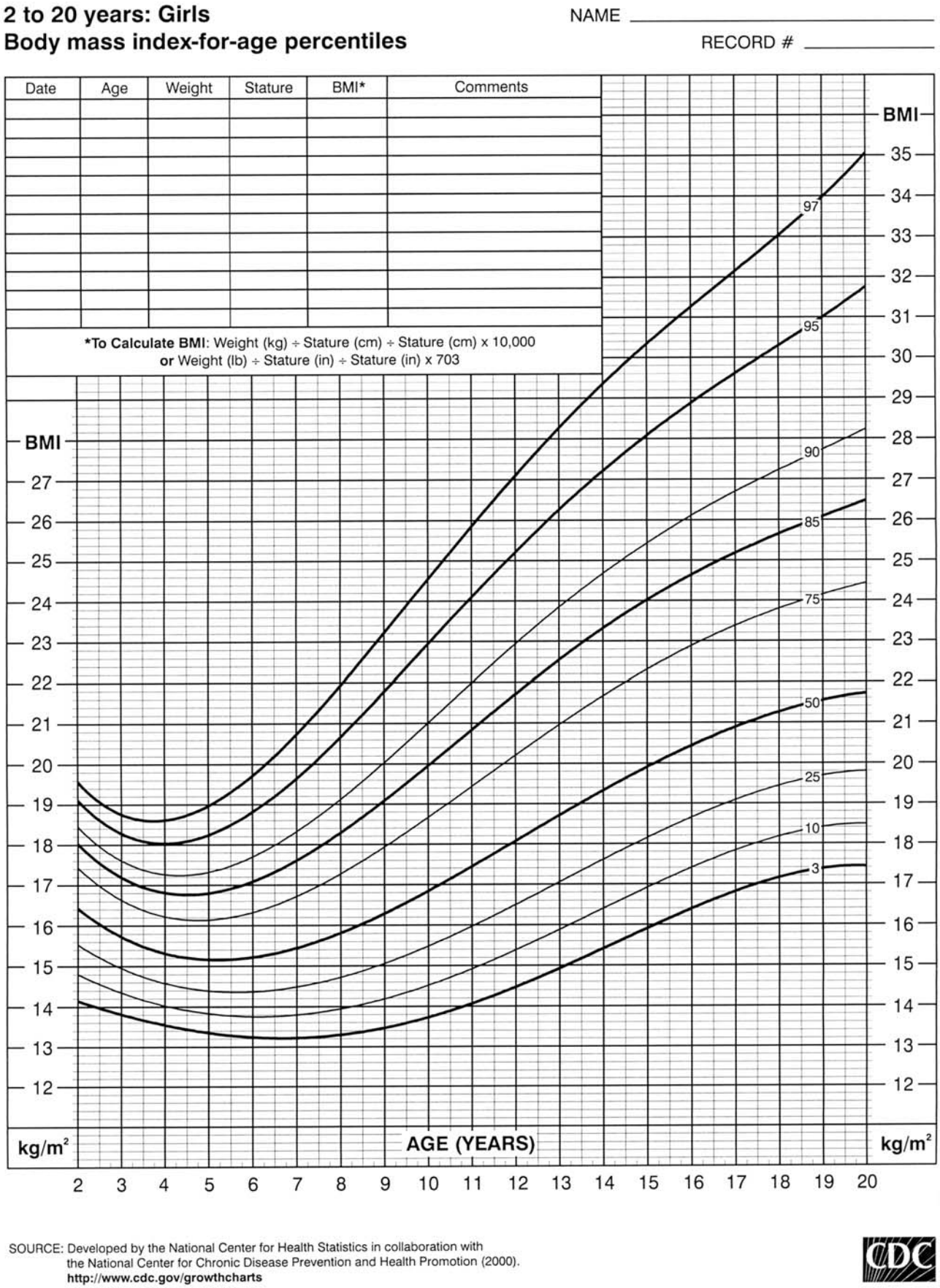


FIGURE A-10 Two to 20 years: girls, body mass index-for-age percentiles. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

TABLE A-1 Typical Progression of Female Pubertal Development

Pubertal development in size of female breasts
- Stage 1: The breasts are preadolescent. There is elevation of the papilla only.
- Stage 2: Breast bud stage. A small mound is formed by the elevation of the breast and papilla. The areolar diameter enlarges.
- Stage 3: There is further enlargement of breasts and areola with no separation of their contours.
- Stage 4: There is a projection of the areola and papilla to form a secondary mound above the level of the breast.
- Stage 5: The breasts resemble those of a mature female as the areola has recessed to the general contour of the breast.

Pubertal development of female pubic hair
- Stage 1: There is no pubic hair.
- Stage 2: There is sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, primarily along the labia.
- Stage 3: The hair is considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.
- Stage 4: The hair, now adult in type, covers a smaller area than in the adult and does not extend onto the thighs.
- Stage 5: The hair is adult in quantity and type, with extension onto the thighs.

Adapted from Tanner JM. Growth at adolescence. 2nd ed. Oxford: Blackwell Scientific Publisher; 1962.

TABLE A–2 Typical Progression of Male Pubertal Development

Pubertal development in size of male genitalia
- Stage 1: The penis, testes, and scrotum are of childhood size.
- Stage 2: There is enlargement of the scrotum and testes, but the penis usually does not enlarge. The scrotal skin reddens.
- Stage 3: There is further growth of the testes and scrotum and enlargement of the penis, mainly in length.
- Stage 4: There is still further growth of the testes and scrotum and increased size of the penis, especially in breadth.
- Stage 5: The genitalia are adult in size and shape.

Pubertal development of male pubic hair
- Stage 1: There is no pubic hair.
- Stage 2: There is sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, primarily at the base of the penis.
- Stage 3: The hair is considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.
- Stage 4: The hair, now adult in type, covers a smaller area than in the adult and does not extend onto the thighs.
- Stage 5: The hair is adult in quantity and type, with extension onto the thighs.

Adapted from Tanner JM. Growth at adolescence. 2nd ed. Oxford: Blackwell Scientific Publishers; 1962.

TABLE A-3 Thickness of Triceps and Subscapular Skinfolds

Age			*Triceps (mm)*		*Subscapular (mm)*	
(mo)	*Percentiles*	*SD*	*Males*	*Females*	*Males*	*Females*
1		–2	2.9	3.5	3.1	3.8
	10		4.0	4.5	4.2	4.9
	25		4.7	5.2	4.8	5.4
	50		5.3	5.8	5.6	6.2
	75		6.2	6.7	6.5	7.0
	90		7.0	7.6	7.5	7.9
		+2	8.1	8.3	8.3	9.0
3		–2	4.5	5.0	3.5	4.7
	10		6.0	6.2	4.9	5.9
	25		6.8	7.2	5.8	6.9
	50		8.1	8.2	6.9	8.0
	75		9.2	9.2	8.1	8.6
	90		10.3	10.5	9.0	9.4
		+2	11.7	11.8	10.7	11.1
6		–2	6.3	6.7	3.8	4.0
	10		7.8	8.2	5.5	5.9
	25		8.6	9.0	6.2	6.9
	50		9.7	10.4	7.1	8.1
	75		11.1	11.3	8.4	8.9
	90		11.8	12.7	10.1	10.3
		+2	13.5	13.9	11.0	12.4
9		–2	6.0	6.7	3.4	4.7
	10		7.5	7.9	5.3	6.0
	25		8.7	8.8	6.0	6.7
	50		9.9	10.1	7.1	7.6
	75		11.2	11.3	8.5	8.8
	90		12.5	12.5	9.7	10.1
		+2	14.0	13.5	11.4	11.1
12		–2	6.2	6.4	3.8	4.5
	10		7.8	7.6	5.3	6.0
	25		8.6	8.7	6.0	6.5
	50		9.8	9.8	7.2	7.5
	75		11.1	11.2	8.6	8.7
	90		12.2	12.2	9.6	9.8
		+2	13.8	13.6	11.0	10.9
18		–2	6.4	6.8	3.9	4.2
	10		7.7	7.9	5.3	5.7
	25		8.6	8.9	6.0	6.2
	50		9.9	10.3	6.8	7.1
	75		11.4	11.3	7.9	8.0
	90		12.2	12.3	9.3	9.0
		+2	13.6	13.6	10.3	10.2
24		–2	5.8	6.5	3.0	3.9
	10		7.4	8.3	4.6	5.3
	25		8.5	8.9	5.4	5.6
	50		9.8	10.1	6.5	6.5
	75		11.6	11.6	7.4	7.3
	90		13.1	12.8	8.3	8.4
		+2	14.2	14.1	10.2	9.5
36		–2	6.6	6.4	2.9	2.6
	10		7.8	8.2	4.5	4.7
	25		9.0	9.4	5.0	5.2
	50		9.8	10.3	5.5	6.1
	75		11.0	11.5	6.4	7.2
	90		12.2	12.5	7.1	8.6
		+2	13.4	14.4	8.9	10.6

Adapted from Karlberg P, Engstrom I, Lichtenstein H, Svennberg I. The development of children in a Swedish urban community: a prospective longitudinal study. III. Physical growth during the first three years of life. Acta Paediatr Scand Suppl 1968;187:48.

TABLE A-4 Percentiles of Upper Arm Circumference and Estimated Upper Arm Muscle Circumference*

	Arm Circumference (mm)							*Arm Muscle Circumference (mm)*						
Age Group	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males														
1–1.9	142	146	150	159	170	176	183	110	113	119	127	135	144	147
2–2.9	141	145	153	162	170	178	185	111	114	122	130	140	146	150
3–3.9	150	153	160	167	175	184	190	117	123	131	137	143	148	153
4–4.9	149	154	162	171	180	186	192	123	126	133	141	148	156	159
5–5.9	153	160	167	175	185	195	204	128	133	140	147	154	162	169
6–6.9	155	159	167	179	188	209	228	131	135	142	151	161	170	177
7–7.9	162	167	177	187	201	223	230	137	139	151	160	168	177	190
8–8.9	162	170	177	190	202	220	245	140	145	154	162	170	182	187
9–9.9	175	178	187	200	217	249	257	151	154	161	170	183	196	202
10–10.9	181	184	196	210	231	262	274	156	160	166	180	191	209	221
11–11.9	186	190	202	223	244	261	280	159	165	173	183	195	205	230
12–12.9	193	200	214	232	254	282	303	167	171	182	195	210	223	241
13–13.9	194	211	228	247	263	286	301	172	179	196	211	226	238	245
14–14.9	220	226	237	253	283	303	322	189	199	212	223	240	260	264
15–15.9	222	229	244	264	284	311	320	199	204	218	237	254	266	272
16–16.9	244	248	262	278	303	324	343	213	225	234	249	269	287	296
17–17.9	246	253	267	285	308	336	347	224	231	245	258	273	294	312
18–18.9	245	260	276	297	321	353	379	226	237	252	264	283	298	324
19–24.9	262	272	288	308	331	355	372	238	245	257	273	289	309	321
25–34.9	271	282	300	319	342	362	375	243	250	264	279	298	314	326
35–44.9	278	287	305	326	345	363	374	247	255	269	286	302	318	327
45–54.9	267	281	301	322	342	362	376	239	249	265	281	300	315	326
55–64.9	258	273	296	317	336	355	369	236	245	260	278	295	310	320
65–74.9	248	263	285	307	325	344	355	223	235	251	268	284	298	306
Females														
1–1.9	138	142	148	156	164	172	177	105	111	117	124	132	139	143
2–2.9	142	145	152	160	167	176	184	111	114	119	126	133	142	147
3–3.9	143	150	158	167	175	183	189	113	119	124	132	140	146	152
4–4.9	149	154	160	169	177	184	191	115	121	128	136	144	152	157
5–5.9	153	157	165	175	185	203	211	125	128	134	142	151	159	165
6–6.9	156	162	170	176	187	204	211	130	133	138	145	154	166	171
7–7.9	164	167	174	183	199	216	231	129	135	142	151	160	171	176
8–8.9	168	172	183	195	214	247	261	138	140	151	160	171	183	194
9–9.9	178	182	194	211	224	251	260	147	150	158	167	180	194	198
10–10.9	174	182	193	210	228	251	265	148	150	159	170	180	190	197
11–11.9	185	194	208	224	248	276	303	150	158	171	181	196	217	223
12–12.9	194	203	216	237	256	282	294	162	166	180	191	201	214	220
13–13.9	202	211	223	243	271	301	338	169	175	183	198	211	226	240
14–14.9	214	223	237	252	272	304	322	174	179	190	201	216	232	247
15–15.9	208	221	239	254	279	300	322	175	178	189	202	215	228	244
16–16.9	218	224	241	258	283	318	334	170	180	190	202	216	234	249
17–17.9	220	227	241	264	295	324	350	175	183	194	205	221	239	257
18–18.9	222	227	241	258	281	312	325	174	179	191	202	215	237	245
19–24.9	221	230	247	265	290	319	345	179	185	195	207	221	236	249
25–34.9	233	240	256	277	304	342	368	183	188	199	212	228	246	264
35–44.9	241	251	267	290	317	356	378	186	192	205	218	236	257	272
45–54.9	242	256	274	299	328	362	384	187	193	206	220	238	260	274
55–64.9	243	257	280	303	335	367	385	187	196	209	225	244	266	280
65–74.9	240	252	274	299	326	356	373	185	195	208	225	244	264	279

*Data collected from whites in the United States Health and Nutrition Examination Survey 1 (1971–1974).

Adapted from Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 1981;34:2540.

Table A-5 Percentiles for Estimates of Upper Arm Muscle Area*

	Arm Muscle Area Percentiles (mm^2)						
Age Group	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males							
1–1.9	956	1014	1133	1278	1447	1644	1720
2–2.9	973	1040	1190	1345	1557	1690	1787
3–3.9	1095	1201	1357	1484	1618	1750	1853
4–4.9	1207	1264	1408	1579	1747	1926	2008
5–5.9	1298	1411	1550	1720	1884	2089	2285
6–6.9	1360	1447	1605	1815	2056	2297	2493
7–7.9	1497	1548	1808	2027	2246	2494	2886
8–8.9	1550	1664	1895	2089	2296	2628	2788
9–9.9	1181	1884	2067	2288	2657	3053	3257
10–10.9	1930	2027	2182	2575	2903	3486	3882
11–11.9	2016	2156	2382	2670	3022	3359	4226
12–12.9	2216	2339	2649	3022	3496	3968	4640
13–13.9	2363	2546	3044	3553	4081	4502	4794
14–14.9	2830	3147	3586	3963	4575	5368	5530
15–15.9	3138	3317	3788	4481	5134	5631	5900
16–16.9	3625	4044	4352	4951	5753	6576	6980
17–17.9	3998	4252	4777	5286	5950	6886	7726
18–18.9	4070	4481	5066	5552	6374	7067	8355
19–24.9	4508	4777	5274	5913	6660	7606	8200
25–34.9	4694	4963	5541	6214	7067	7847	8436
35–44.9	4844	5181	5740	6490	7265	8034	8488
45–54.9	4546	4946	5589	6297	7142	7918	8458
55–64.9	4422	4783	5381	6144	6919	7670	8149
65–74.9	3973	4411	5031	5716	6432	7074	7453
Females							
1–1.9	885	973	1084	1221	1378	1535	1621
2–2.9	973	1029	1119	1269	1405	1595	1727
3–3.9	1014	1133	1227	1396	1563	1690	1846
4–4.9	1058	1171	1313	1475	1644	1832	1958
5–5.9	1238	1301	1423	1598	1825	2012	2159
6–6.9	1354	1414	1513	1683	1877	2182	2323
7–7.9	1330	1441	1602	1815	2045	2332	2469
8–8.9	1513	1566	1808	2034	2327	2657	2996
9–9.9	1723	1788	1976	2227	2571	2987	3112
10–10.9	1740	1784	2019	2296	2583	2873	3093
11–11.9	1784	1987	2316	2612	3071	3739	3953
12–12.9	2092	2182	2579	2904	3225	3655	3847
13–13.9	2269	2426	2657	3130	3529	4081	4568
14–14.9	2418	2562	2874	3220	3704	4294	4850
15–15.9	2426	2518	2847	3248	3689	4123	4756
16–16.9	2308	2567	2865	3248	3718	4353	4946
17–17.9	2442	2674	2996	3336	3883	4552	5251
18–18.9	2398	2538	2917	3243	3694	4461	4767
19–24.9	2538	2728	3026	3406	3877	4439	4940
25–34.9	2661	2826	3148	3573	4138	4806	5541
35–44.9	2750	2948	3359	3783	4428	5240	5877
45–54.9	2784	2956	3378	3858	4520	5375	5974
55–64.9	2784	3063	3477	4045	4750	5632	6247
65–74.9	2737	3018	3444	4019	4739	5566	6214

*Data collected from whites in the United States Health and Nutrition Examination Survey 1 (1971–1974).

Adapted from Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 1981;34:2540.

TABLE A-6 Selected Percentiles for 1-Month Increments in Weight from Birth to 6 Months

				Percentile (g/d)						
Age (mo)	*Infants* (n)	*Mean (g/d)*	*SD (g/d)*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males										
Birth to 1	580	30	9.4	15	18	24	30	36	42	45
1–2	580	35	8.5	22	25	29	35	40	46	50
2–3	580	27	7.9	15	18	22	26	31	36	41
3–4	298	20	3.6	15	16	18	20	22	24	26
4–5	298	17	3.4	12	14	15	17	19	21	23
5–6	298	16	3.5	11	12	14	15	17	19	21
Females										
Birth to 1	562	26	8.4	11	16	20	26	32	36	39
1–2	562	29	7.7	18	20	24	29	34	39	42
2–3	562	23	7.2	12	14	19	23	28	32	35
3–4	298	19	5.3	13	15	17	19	21	23	26
4–5	298	16	5.0	11	13	14	16	18	20	22
5–6	298	15	4.7	10	11	13	14	16	18	18

Adapted from Guo S, Roche AF, Fomon SJ, et al. Reference data for gains in weight and length during the first two years of life. J Pediatr 1991;119:355–62.

TABLE A-7 Selected Percentiles for 2-Month Increments in Weight from Birth to 12 Months

				Percentiles (g/d)						
Age (mo)	*Infants* (n)	*Mean (g/d)*	*SD (g/d)*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males										
Birth to 2	580	33	7.0	21	24	28	32	38	42	44
1–3	580	31	6.9	20	22	27	31	35	39	43
2–4	65	23	4.7	—	17	19	23	26	29	—
3–5	298	19	3.2	14	15	17	18	20	22	24
4–6	298	16	2.9	12	13	14	16	18	20	21
5–7	233	15	2.4	11	12	13	15	16	18	18
6–8	233	13	2.4	10	11	12	13	15	16	17
7–9	233	12	2.4	9	10	11	12	14	15	16
8–10	233	12	2.4	9	9	10	11	13	15	15
9–11	233	11	2.3	8	8	9	11	12	14	14
10–12	233	10	2.3	7	8	9	10	12	13	14
Females										
Birth to 2	562	28	6.5	17	20	23	28	32	36	38
1–3	562	26	6.3	16	19	22	26	30	34	37
2–4	72	22	5.4	—	16	19	21	24	27	—
3–5	298	18	4.7	13	14	16	17	19	21	22
4–6	298	15	4.6	11	12	14	15	17	18	19
5–7	224	14	4.7	11	11	13	14	15	17	17
6–8	224	13	4.6	10	10	12	13	14	16	16
7–9	224	12	4.5	9	10	11	12	13	15	15
8–10	224	12	4.5	8	9	10	11	13	14	14
9–11	224	11	4.4	8	8	9	10	12	13	14
10–12	224	10	4.3	7	8	9	10	11	13	13

Adapted from Guo S, Roche AF, Fomon SJ, et al. Reference data for weight, length, and gains in weight and length during the first two years of life. J Pediatr 1991;119:355–62.

TABLE A-8 Selected Percentiles for 3-Month Increments in Weight from Birth to 14 Months

				Percentile (g/d)						
Age (mo)	*Infants* (n)	*Mean (g/d)*	*SD (g/d)*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males										
Birth to 3	580	31	5.9	21	23	27	31	34	38	41
1–4	65	27	5.1	—	21	23	27	30	34	—
2–5	65	21	4.3	—	15	17	21	23	27	—
3–6	298	18	2.9	13	14	16	18	19	21	23
4–7	233	16	2.4	12	13	14	15	17	18	19
5–8	233	14	2.4	11	11	13	14	15	17	18
6–9	233	13	2.4	10	10	11	13	14	16	17
7–10	233	12	2.4	9	9	10	12	13	15	16
8–11	233	11	2.4	8	9	10	11	12	14	15
9–12	233	11	2.3	8	8	9	10	12	14	14
10–13	233	10	2.3	7	8	9	10	11	13	14
11–14	233	10	2.3	7	7	8	9	11	12	13
Females										
Birth to 3	562	26	5.5	17	20	23	26	30	33	36
1–4	74	24	5.1	—	19	21	24	27	30	—
2–5	74	20	3.9	—	16	17	19	21	25	—
3–6	298	17	4.6	12	13	15	17	18	20	21
4–7	224	15	4.8	11	12	13	15	16	17	18
5–8	224	14	4.7	10	11	12	13	15	16	17
6–9	224	13	4.6	10	10	11	12	14	15	16
7–10	224	12	4.5	9	9	10	12	13	14	15
8–11	224	11	4.4	8	9	10	11	12	14	14
9–12	224	11	4.3	8	8	9	10	12	13	14
10–13	224	10	4.2	7	8	9	10	11	12	13
11–14	224	10	4.2	7	7	8	9	11	12	13

Adapted from Guo S, Roche AF, Fomon SJ, et al. Reference data for weight, length, and gains in weight and length during the first two years of life. J Pediatr 1991;119:355–62.

TABLE A-9 Selected Percentiles for 2-Month Increments in Length from Birth to 6 Months

				Percentiles (mm/d)						
Age (mo)	*Infants* (n)	*Mean (mm/d)*	*SD (mm/d)*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males										
Birth to 2	580	1.10	0.15	0.87	0.90	1.00	1.10	1.18	1.28	1.34
1–3	580	1.08	0.14	0.85	0.90	0.98	1.08	1.17	1.26	1.31
2–4	65	0.93	0.75	—	0.75	0.82	0.95	1.02	1.07	—
3 to 5	255	0.73	0.09	0.60	0.63	0.68	0.73	0.79	0.86	0.90
4 to 6	255	0.64	0.08	0.49	0.54	0.59	0.63	0.69	0.74	0.78
Females										
Birth to 2	562	1.03	0.13	0.80	0.87	0.93	1.03	1.11	1.20	1.25
1–3	562	0.99	0.13	0.79	0.84	0.92	0.98	1.07	1.15	1.18
2–4	74	0.89	0.13	—	0.72	0.80	0.90	0.97	1.05	—
3–5	241	0.71	0.10	0.57	0.60	0.66	0.71	0.77	0.82	0.87
4–6	241	0.62	0.08	0.48	0.52	0.57	0.63	0.67	0.70	0.73

Adapted from Guo S, Roche AF, Fomon SJ, et al. Reference data for weight, length, and gains in weight and length during the first two years of life. J Pediatr 1991;119:355–62.

TABLE A-10 Selected Percentiles for 3-Month Increments in Length from Birth to 14 Months

				Percentile						
Age (mo)	*Infants* (n)	*Mean (mm/d)*	*SD (mm/d)*	*5th*	*10th*	*25th*	*50th*	*75th*	*90th*	*95th*
Males										
Birth to 3	580	1.07	0.11	0.89	0.92	0.99	1.06	1.14	1.21	1.26
1–4	65	1.00	0.08	—	0.94	1.01	1.06	1.09	—	
2–5	65	0.84	0.09	—	0.74	0.79	0.84	0.91	0.95	—
3–6	255	0.69	0.08	0.56	0.60	0.64	0.68	0.73	0.79	0.82
4–7	190	0.62	0.06	0.54	0.55	0.58	0.61	0.65	0.73	0.72
5–8	190	0.56	0.05	0.49	0.50	0.53	0.56	0.59	0.69	0.65
6–9	190	0.52	0.05	0.46	0.46	0.49	0.52	0.54	0.58	0.60
7–10	190	0.48	0.05	0.42	0.43	0.45	0.48	0.51	0.54	0.57
8–11	190	0.45	0.04	0.39	0.40	0.43	0.45	0.48	0.51	0.53
9–12	190	0.43	0.04	0.36	0.38	0.40	0.43	0.45	0.48	0.51
10–13	190	0.41	0.04	0.34	0.36	0.38	0.41	0.43	0.46	0.49
11–14	190	0.39	0.04	0.33	0.34	0.36	0.39	0.41	0.44	0.47
Females										
Birth to 3	562	0.99	0.10	0.82	0.86	0.93	0.99	1.06	1.11	1.15
1–4	74	0.95	0.10	—	0.84	0.87	0.95	1.02	1.07	—
2–5	74	0.80	0.10	—	0.67	0.73	0.81	0.87	0.92	—
3–6	241	0.67	0.08	0.55	0.58	0.63	0.67	0.72	0.77	0.79
4–7	167	0.60	0.06	0.53	0.54	0.57	0.61	0.64	0.67	0.69
5–8	167	0.56	0.05	0.49	0.50	0.52	0.56	0.59	0.62	0.63
6–9	167	0.52	0.05	0.45	0.46	0.48	0.52	0.55	0.57	0.58
7–10	167	0.48	0.04	0.42	0.43	0.45	0.49	0.52	0.54	0.55
8–11	167	0.46	0.04	0.39	0.41	0.43	0.46	0.49	0.51	0.52
9–12	167	0.44	0.04	0.37	0.38	0.41	0.44	0.46	0.48	0.49
10–13	167	0.42	0.04	0.35	0.37	0.39	0.42	0.45	0.46	0.48
11–14	167	0.40	0.04	0.34	0.35	0.37	0.40	0.43	0.44	0.46

Adapted from Guo S, Roche AF, Fomon SJ, et al. Reference data for weight, length, and gains in weight and length during the first two years of life. J Pediatr 1991;119:355–62.

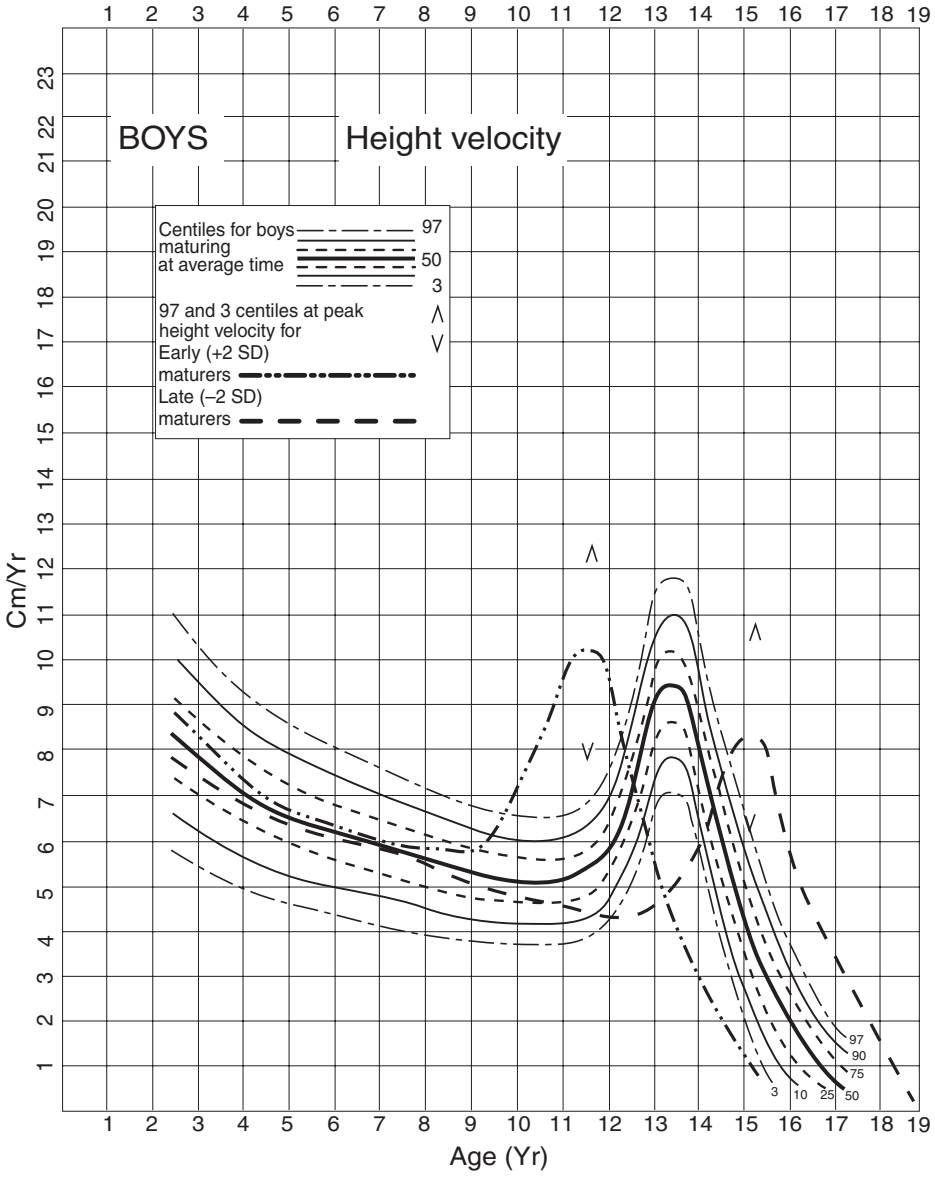


FIGURE A-11 Height velocity for American boys. Reproduced with permission from Tanner JM, Davis PSW. Clinical longitudinal standards for height and weight velocity for North American children. J Pediatr 1985;107:317–29.

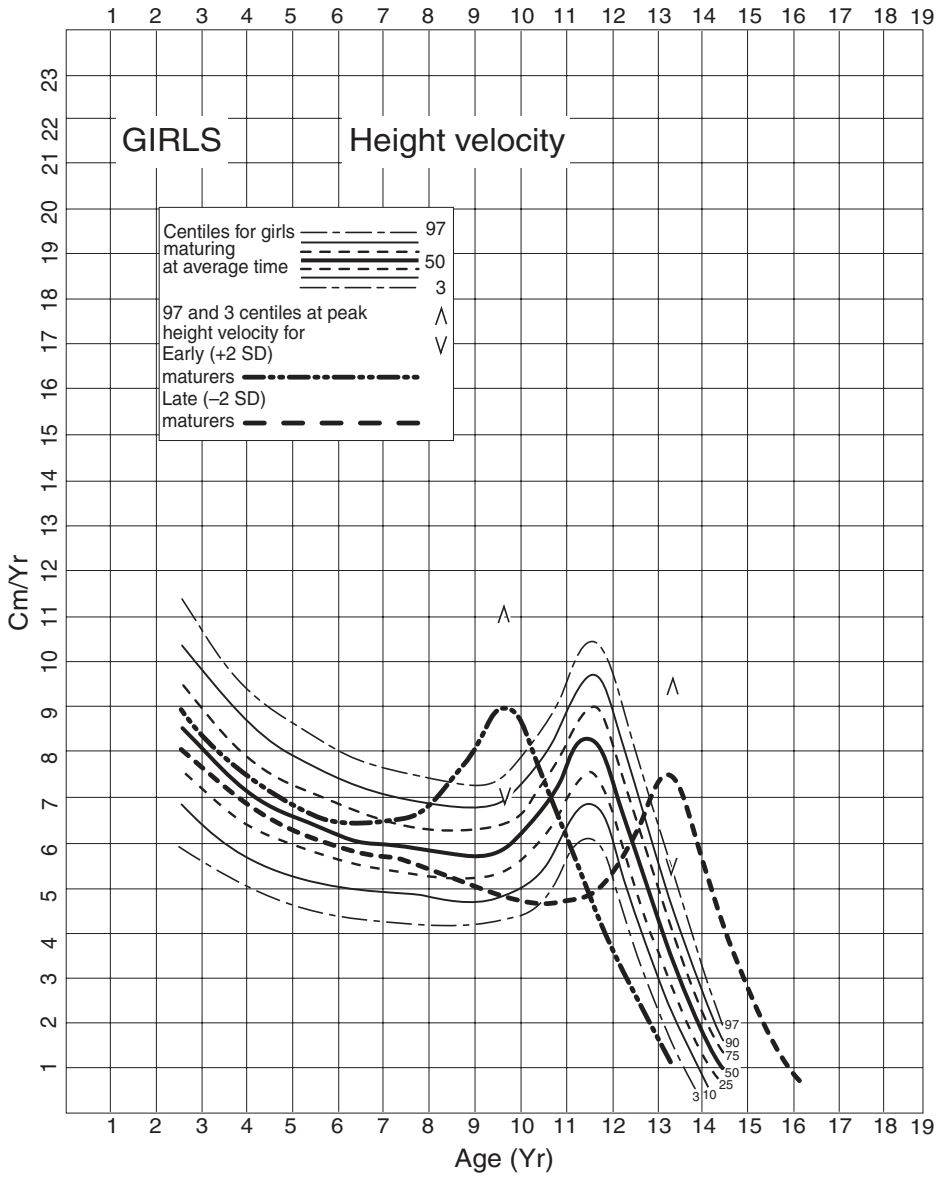


FIGURE A-12 Height velocity for American girls. Reproduced with permission from Tanner JM, Davis PSW. Clinical longitudinal standards for height and weight velocity for North American children. J Pediatr 1985;107:317–29.

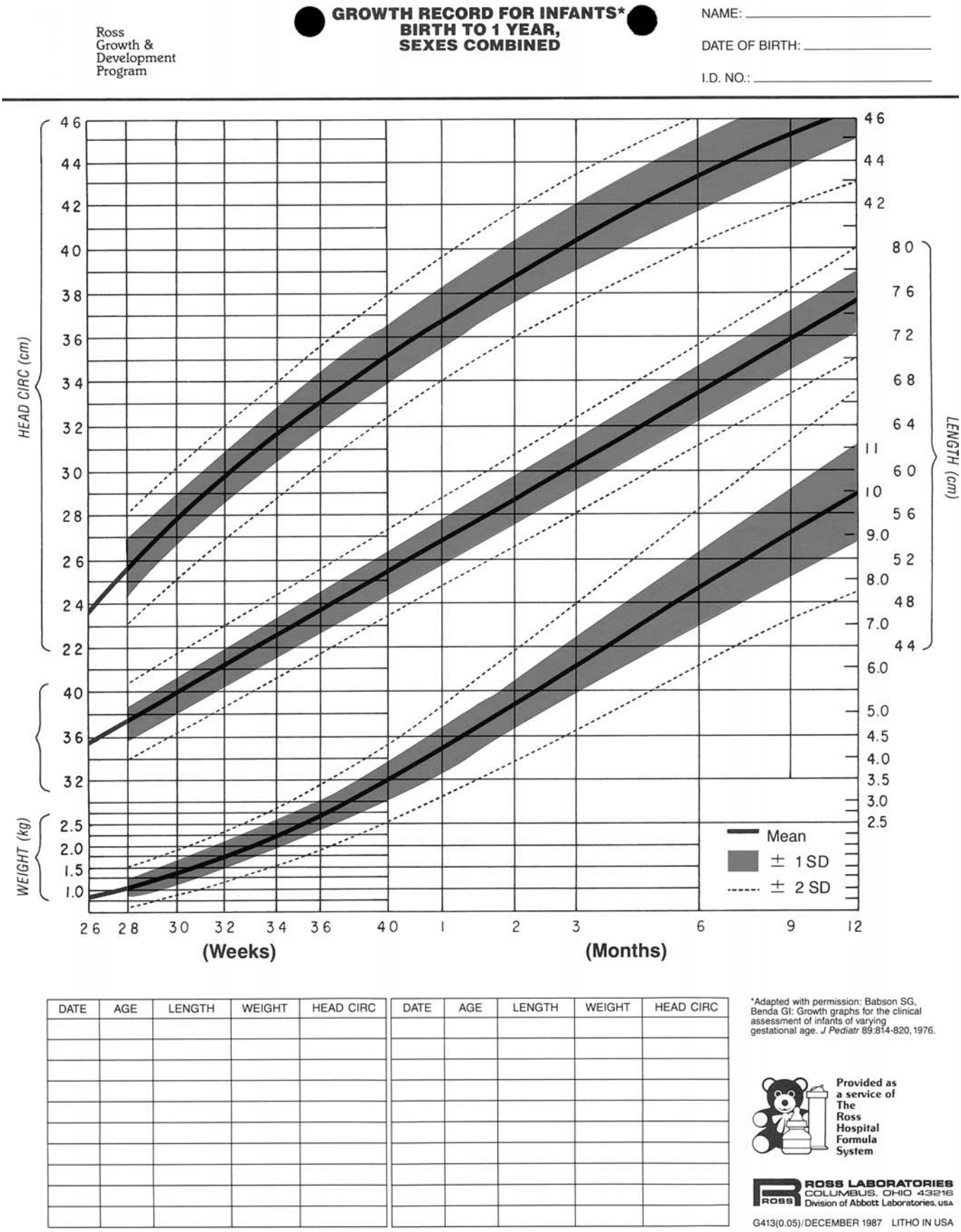
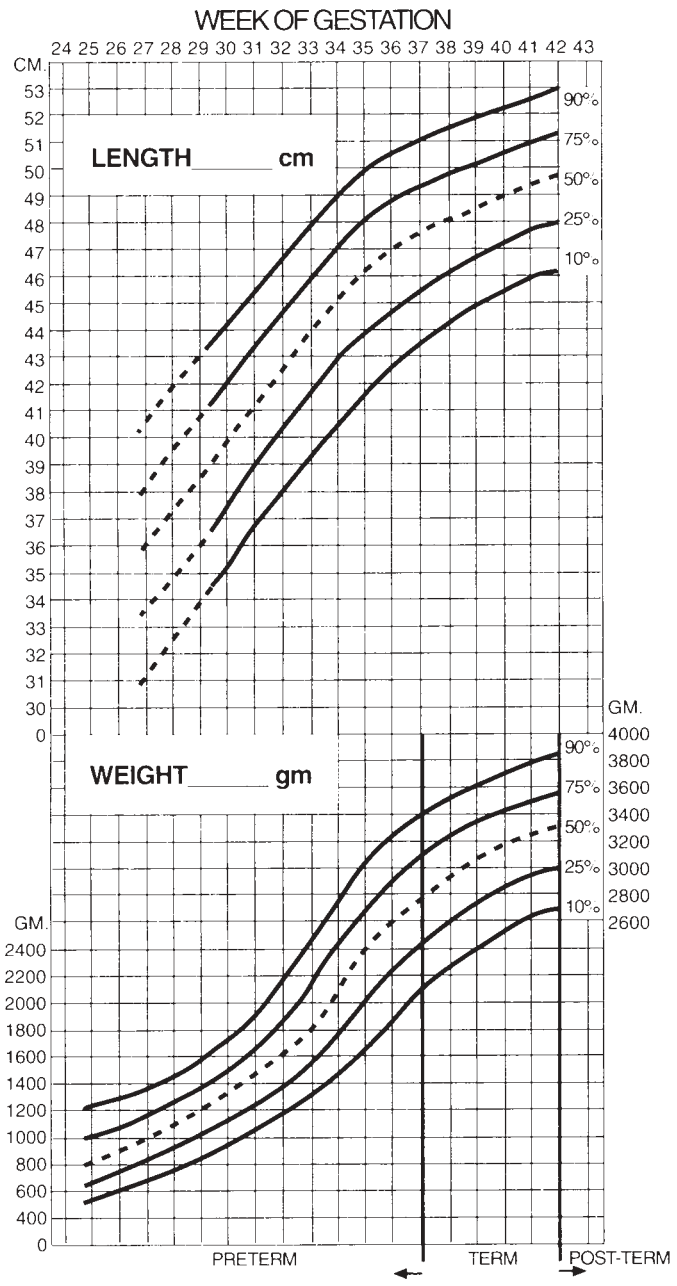


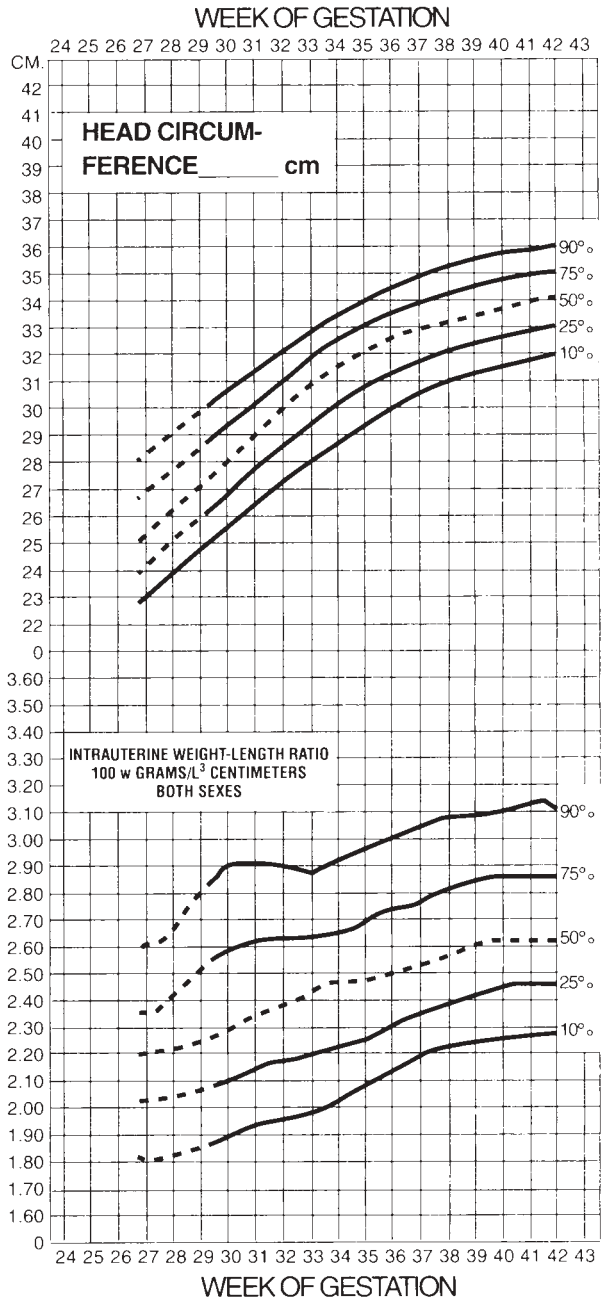
FIGURE A-13 Growth rate for infants, birth to 1 year, sexes combined. Adapted from Babson SG, Benda GI. Growth graphs for the clinical assessment of infants of varying gestational age. J Pediatr 1976;89:813–20.

CLASSIFICATION OF NEWBORNS - BASED ON MATURITY AND INTRAUTERINE GROWTH

Side 2

Symbols: X - 1st Exam O - 2nd Exam





	1st Exam (X)	2nd Exam (O)
LARGE FOR GESTATIONAL AGE **(LGA)**		
APPROPRIATE FOR GESTATIONAL AGE **(AGA)**		
SMALL FOR GESTATIONAL AGE **(SGA)**		
Age at Exam	hrs	hrs
Signature of Examiner	M.D./R.N.	M.D./R.N.

Adapted from Lubchenco LO, Hansman C, and Boyd E: *Pediatr.* 1966;37:403; Battaglia FC, and Lubchenco LO: *J Pediatr.* 1967;71:159.

FIGURE A-14 Classification of newborns, based on maturity and intrauterine growth. Adapted from Lubchenco LO, Hansman C, Boyd E. Pediatrics 1966;37:403; and Battaglia FC, Lubchenco LC. J Pediatr 1967;71:159.

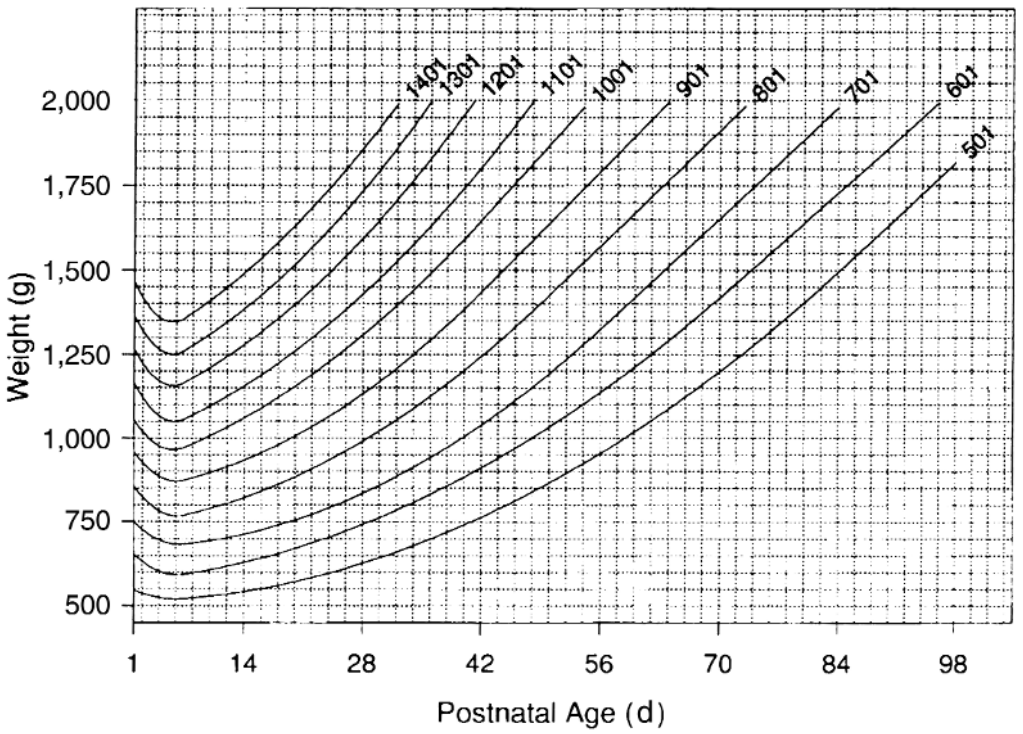


FIGURE A-15 Average daily body weight versus postnatal age in days for infants stratified by 100 g birth weight intervals. Reproduced with permission from Ehrenkranz R, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104:280–9.

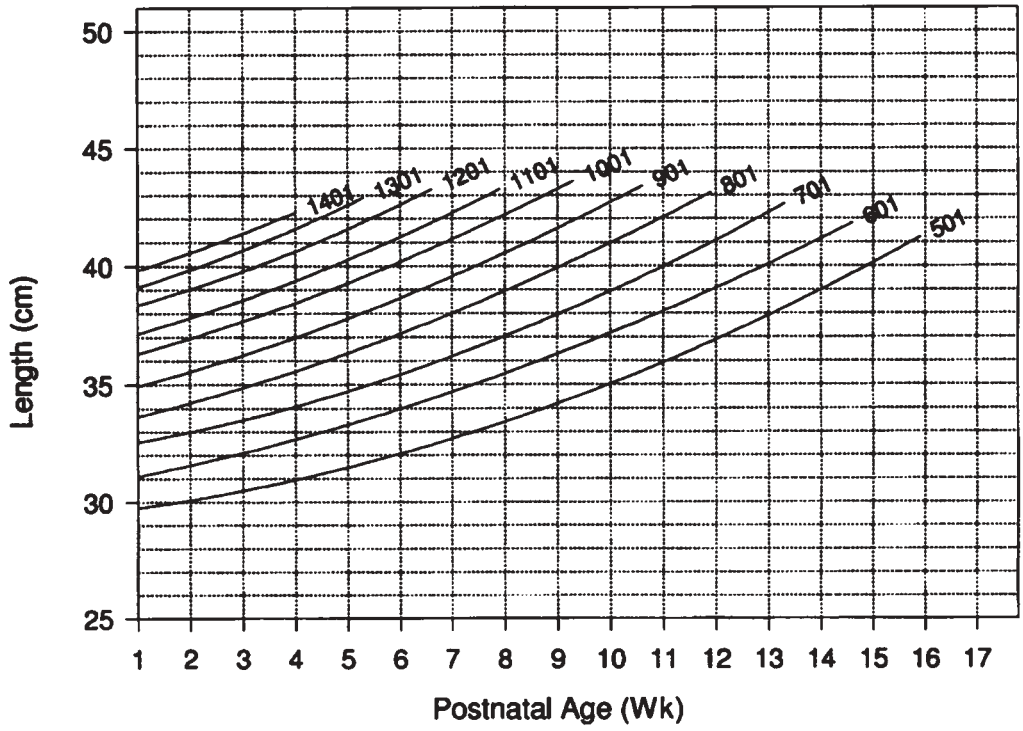


FIGURE A-16 Average weekly length versus postnatal age in weeks for infants stratified by 100 g birth weight intervals. Reproduced with permission from Ehrenkranz R, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104:280–9.

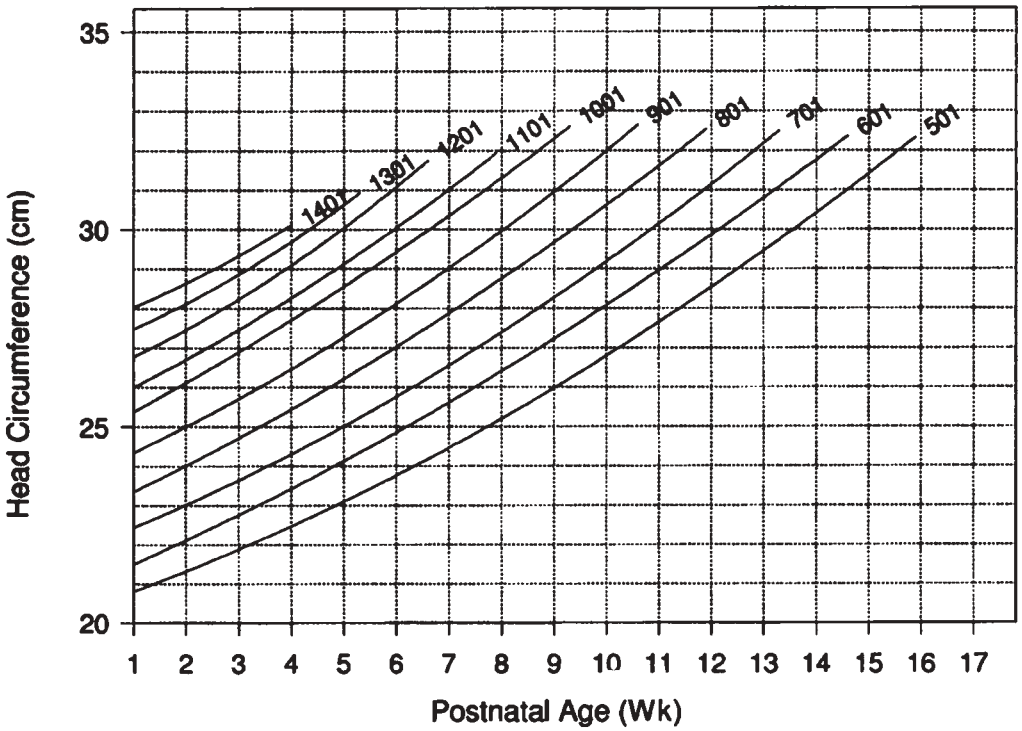


FIGURE A-17 Average weekly head circumference versus postnatal age in weeks for infants stratified by 100 g birth weight intervals. Reproduced with permission from Ehrenkranz R, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104:280–9.

TABLE A-11 Most Common Classification of Protein-Energy Malnutrition

	Normal	*Mild*	*Moderate*	*Severe*
Weight for height*	110–90	90–85	85–75	< 75
Weight for age†	110–90	90–81	80–61	< 60
Weight for age‡	> 90	90–75	75–61	< 60
Height for age§	> 95	98–87	87–80	< 80
Weight for height§	> 90	90–80	80–70	< 70

Presence of edema indicates kwashiorkor; no edema indicates marasmus.
*Adapted from McLean DS, Read WWC. Weight/length classification of nutrition status. Lancet 1975;2:219.
†Adapted from Jelliffe D. The assessment of the nutritional status of the community. World Health Organization Monograph 53. Geneva: WHO; 1966.
‡Adapted from Gomez F, et al. Malnutrition in infancy and childhood with special reference to kwashiorkor. Adv Pediatr 1955;7:131.
§Adapted from Waterlow JC. Classification and definition of protein calorie malnutrition. BMJ 1972;3:565.

TABLE A-12 Clinical Examination in Nutritional Deficiencies and Excesses

Nutrient	*Major Physiologic Functions*	*Deficiency Signs*	*Excess Signs*	*Important Food Sources*	*Potential Causes of Deficiency or Excess*
Carbohydrate	Supplies energy at an average of 4 cal/g of glucose (sparing protein) and is the major energy source for CNS function; unrefined, complex carbohydrates supply fiber that aids in normal bowel function	Ketosis	May cause diarrhea, obesity	Bread, cereals, crackers, potatoes, corn, simple sugar (sugar, honey), fruits and vegetables, milk, breast milk, infant formula	Malabsorption
Fat	Concentrated calorie source at an average of 9 cal/g; constitutes part of the membrane structure of every cell; supplies essential fatty acids and provides and carries fat-soluble vitamins (A, D, E, K)	Essential fatty acid deficiency; dry, scaly skin, poor weight gain, hair loss. Requirements are increased by cell turnover	Atherosclerosis may be affected by excessive intakes of certain dietary fats; altered blood lipid levels	Shortening, oil, butter, margarine, protein-rich foods (meat, dairy, nuts), breast milk, infant formula	Cystic fibrosis, biliary disease, short bowel
Protein	Constitutes part of the structure of every cell; regulates body processes as part of enzymes, some hormones, body fluids, and antibodies that increase resistance to infection; provides nitrogen and has a caloric density of 4 cal/g	Dry, depigmented, easily pluckable hair; bilateral, dependent edema, cirrhosis, fatty liver, decreased visceral proteins; skin is dry with pellagroid dermatoses in severe cases	Azotemia, acidosis, hyperammonemia	Meat, poultry, fish, legumes, eggs, cheese, milk, and other dairy products, nuts, breast milk, infant formula	Protein-losing enteropathy, liver disease, gastrointestinal disease, renal disease
Fat-soluble vitamins					
Vitamin A	Formation and maintenance of skin and mucous membranes; necessary for the formation of rhodopsin (the photosensitive pigment of the rods governing vision in dim light) and regulation of membrane structure and function. Necessary for growth and normal immune function	Night blindness, degeneration of the retina, xerophthalmia, follicular hyperkeratosis, poor growth, keratomalacia, Bitot's spots	Fatigue, malaise, lethargy, abdominal pain, hepatomegaly, alopecia, headache with increased intracranial pressure, vomiting	Carrots, liver, green vegetables, sweet potatoes, butter, margarine, apricots, melons, peaches, broccoli, cod liver oil, breast milk, infant formula	Liver disease, cystic fibrosis, short bowel, protein deficiency (alters transport)
Vitamin D	Promotes intestinal absorption of calcium and phosphate, renal conservation of calcium and phosphorus	Rickets, osteomalacia, costochondral beading, epiphyseal enlargement, cranial bossing, bowed legs, persistently open anterior fontanelle	Hypercalcemia, vomiting, anorexia, diarrhea, convulsions	Cod liver oil, fish, eggs, liver, butter, fortified milk, sunlight (activation of 7-dehydrocholesterol in the skin) infant formula	Liver disease, cystic fibrosis, short-bowel disease, renal disease
Vitamin E	Acts as an antioxidant and free radical scavenger to prevent peroxidation of polyunsaturated fatty acids in the body; neuromuscular function	Hemolytic anemia in the premature and newborn, enhanced fragility of red blood cells, increased peroxidative hemolysis	In anemia suppresses the normal hematologic response to iron	Oils high in polyunsaturated fatty acids, milk, eggs, breast milk, infant formula	Cystic fibrosis, short bowel, liver disease
Vitamin K	Necessary for prothrombin and the three blood-clotting factors VII, IX, and X; half of the vitamin K in humans is of intestinal origin, synthesized by gut flora; necessary for bone mineralization	Hemorrhagic manifestations (especially in newborns), cirrhosis, prolonged clotting	Hemolytic anemia, nerve palsy	Green leafy vegetables, fruits, cereals, dairy products, soybeans, breast milk, infant formula	Liver disease, antibiotic therapy
Water-soluble vitamins					
Ascorbic acid (vitamin C)	Forms collagen cross-linkage of proline hydroxylase, thus strengthening tissue and improving wound healing and resistance to infection; aids absorption of iron; is a water-soluble antioxidant and thus protects other lipid-soluble vitamins	Joint tenderness, scurvy (capillary hemorrhaging), impaired wound healing, acute periodontal gingivitis, petechiae, purpura, anemia	Increased incidence of renal stones, gastrointestinal distress. Documentation of a chronic high intake may result in "rebound" deficiency symptoms	Heat labile; broccoli, papaya, orange, mango, grapefruit, strawberries, tomatoes, potatoes, leafy vegetables, breast milk, infant formula	Stress
Biotin	Component of several carboxylating enzymes; plays an important role in the metabolism of fat and carbohydrate	Anorexia, nausea; vomiting; glossitis; depression; dry, scaly dermatitis; thin hair; loss of eyebrows	None known	Liver, kidney, egg yolk, breast milk, infant formula	Certain inborn errors of metabolism
Cobalamin (B_{12} intrinsic factor required)	Cobalamin-containing coenzymes function in the degradation of certain odd-chain fatty acids and in the recycling of tetrahydrofolate	Megaloblastic anemia, neurologic deterioration	None known	Animal products, breast milk, infant formula	Ileal disease, strict vegetarian

Continues

TABLE A-12 Clinical Examination in Nutritional Deficiencies and Excesses (Continued)

	Major Physiologic Functions	*Deficiency Signs*	*Excess Signs*	*Important Food Sources*	*Potential Causes of Deficiency or Excess*
Folacin	Used in methyl transfer and nucleotide synthesis	Megaloblastic anemia, stomatitis, glossitis	None known	Liver, leafy vegetables, fruit, yeast, breast milk, infant formula	Liver disease, alcoholism, celiac disease, inflammatory bowel disease
Niacin	Aids in energy use as part of a coenzyme (NAD+ and NADP+) in fat synthesis tissue respiration and carbohydrate use; aids digestion and fosters normal appetite; synthesized from the amino acid tryptophan	Pellagra (dermatitis, diarrhea, dementia, death), cheilosis, angular stomatic inflammation of mucous membranes, weakness	Dilation of the capillaries, vasomotor instability, "flushing" (use of muscle glycogen serum lipids, mobilization of fatty acids during exercise)	Liver, meat, fish, poultry, peanuts, fortified cereal products, yeast, breast milk, infant formula	B_6 deficiency (impairs conversion of tryptophan to niacin)
Pantothenic acid	Component of coenzyme A; plays a role in release of energy from carbohydrates and in synthesis and degradation of fatty acids	Infertility, abortion, slow growth, depression, vomiting, malaise, abdominal stress	Diarrhea, water retention	Meat, fish, poultry, whole grains, legumes, breast milk, infant formula	Severe malnutrition
Pyridoxine (B_6)	Coenzyme component for many of the enzymes of amino acid metabolism. All compounds implicated as neurotransmitters are synthesized and/or metabolized in the B_6-dependent reactions	Convulsions, loss of weight, abdominal distress, vomiting, hyperirritability, depression, confusion, hypochromic and macrocytic anemia	Neuropathy	Fish, poultry, meat, wheat, breast milk, infant formula	Elderly, high-protein intake
Riboflavin (B_{12})	Functions primarily as the reactive portion of flavoproteins concerned with biologic oxidations (cellular metabolism)	Cheilosis, glossitis, photophobia, angular stomatitis, corneal vasculation, scrotal skin changes, seborrhea, magenta tongue	None known	Dairy products, liver, almonds, lamb, pork, breast milk, infant formula	Alcoholism, starvation, chronic diarrhea, malabsorption
Thiamin (B_1)	Aids in energy use as part of coenzyme component to promote the use of carbohydrate; promotes normal functioning of the nervous system; coenzyme for oxidative carboxylation of 2-keto acids	Beriberi, neuritis, edema, cardiac failure, anorexia, restlessness, confusion, loss of vibration sense and deep tendon reflexes, calf tenderness	None known	Pork (lean), nuts, whole grain and fortified cereal products, breast milk, infant formula	Alcoholism, refeeding after starvation, prolonged dialysis
Minerals					
Calcium	Essential for calcification of bone (matrix formation); assists in blood clotting; functions in normal muscle contraction and relaxation and in normal nerve transmission	Osteomalacia, osteoporosis	Hypercalcemia vomiting, anorexia, lethargy	Dairy products (milk, cheese), sardines, oysters, salmon, herring, greens, breast milk, infant formula	Renal disease, liver disease
Magnesium	Essential part of many enzyme systems; important for maintaining electrical potential in nerves and muscle membranes and for energy turnover	Tremor, convulsions, hyperexcitability (hypocalcemia tetany)	Diarrhea sedation, transient hypocalcemia	Widely distributed, especially in food of vegetable origin; breast milk, infant formula	PEM, refeeding
Phosphorus	Important intracellular anion; involved in many chemical reactions within the body; necessary for energy turnover (ATP)	Weakness, anorexia, malaise, bone pain, growth arrest	Hypocalcemia (when parathyroid gland not fully functioning)	Dairy products, fish, legumes, pork, breast milk, infant formula	Renal disease, liver disease, refeeding syndrome
Trace elements					
Chromium	Maintenance of normal glucose metabolism, cofactor for insulin	Disturbed glucose metabolism (lower glucose tolerance caused by insulin resistance)	None known	Brewer's yeast, meat products, cheeses	PEM, elderly
Copper	Constituent of proteins and enzymes, some of which are essential for the proper utilization of iron, immunity, skeletal development	Anemia (hemolytic), neutropenia, bone disease	Excess accumulation of the liver, brain, kidney, cornea, anemia, diarrhea	Oysters, nuts, liver, kidney, corn oil margarine, dried legumes	Menke's kinky hair syndrome, excess: Wilson's disease
Fluoride	The main target organs of fluoride in humans are the enamel of teeth and bones, where fluoride is incorporated into the crystalline structure of hydroxyapatite and produces increased caries resistance	Poor dentition, caries, osteoporosis	Mottling, brown staining of teeth (in excess of 4 ppm); fluorosis occurs after prolonged (10–20 yr) ingestion of 20–80 mg/d	Fluoridated water, depends on the geochemical environment and therefore amount in food varies widely	Unfluoridated water, bottled water

Continues

TABLE A-12 Clinical Examination in Nutritional Deficiencies and Excesses (Continued)

	Major Physiologic Functions	*Deficiency Signs*	*Excess Signs*	*Important Food Sources*	*Potential Causes of Deficiency or Excess*
Iodine	Component of thyroid hormones triiodothyronine and thyroxine, important in regulation of cellular oxidation and growth	Goiter, depression thyroid function, cretinism	Thyroid suppression (thyrotoxicosis)	Iodized table salt, salt water, fish, shellfish (content of most other foods geographically dependent), breast milk, infant formula	Endemic goiter in low-iodine areas
Iron	Part of hemoglobin molecule; prevents nutritional anemia and fatigue; increases resistance to infection; functions as part of enzymes involved in tissue respiration	Anemia, malabsorption, irritability, anorexia, pallor, lethargy	Hemosiderosis, hemochromatosis	Red meats, liver, dried beans and peas, enriched farina, breast milk, infant formula, infant cereal	Protein-losing enteropathy, malabsorption, excess: hemochromatosis
Manganese	Essential part of several enzyme systems involved in protein and energy metabolism and in the formation of mucopolysaccharide	Impaired growth, skeletal abnormalities, lowered reproductive function, neonatal ataxia	In extremely high exposure of contamination: severe psychiatric and neurologic disorders	Nuts, whole grains, dried fruits, fruits, vegetables (leafy)	
Molybdenum	Essential for the function of flavin-dependent enzymes involved in the production of uric acid and in the oxidation of aldehydes and sulfites	Not described in man	Acts as an antagonist to the essential element copper; gout like syndrome associated with elevated blood levels of molybdenum, uric acid, and xanthin oxidase	Varies considerably, depending on growing environment; main contributions come from meat, grains, and legumes	
Selenium	Functions as a part of the enzyme glutathione peroxidase, which protects cellular component from oxidative damage	Cardiomyopathy, probably secondary to oxidative damage	In animals, blindness, abdominal pain	Seafoods, kidney, liver, meat, grains (depending on growing area)	Cystic fibrosis
Zinc	Constituent of enzymes involved in most major metabolic pathways (specifically nucleic acid synthesis for cellular growth and repair)	Growth failure, skin changes, delayed wound healing, hypogeusia, sexual immaturity, hair loss, diarrhea	Acute gastrointestinal upset, vomiting, sweating, dizziness, copper deficiency	Whole grains, legumes, beef, lamb, pork, poultry, nuts, seeds, shellfish, eggs, some cheeses, breast milk, infant formula	Malabsorption, chronic diarrhea, liver disease, sickle cell disease

Adapted from Hendricks KM, Walker WA. Manual of Pediatric Nutrition. St Louis: Mosby-Year Book, 1990.
ATP = adenosien triphosphate; CNS = central nervous system; NAD = nicotinamide adenine dinucleotide; NADP = nicotinamide adenine dinucleotide phosphate PEM = protein-energy malnutrition.

See Chapter 34 for growth charts for assessing children with developmental disabilities.

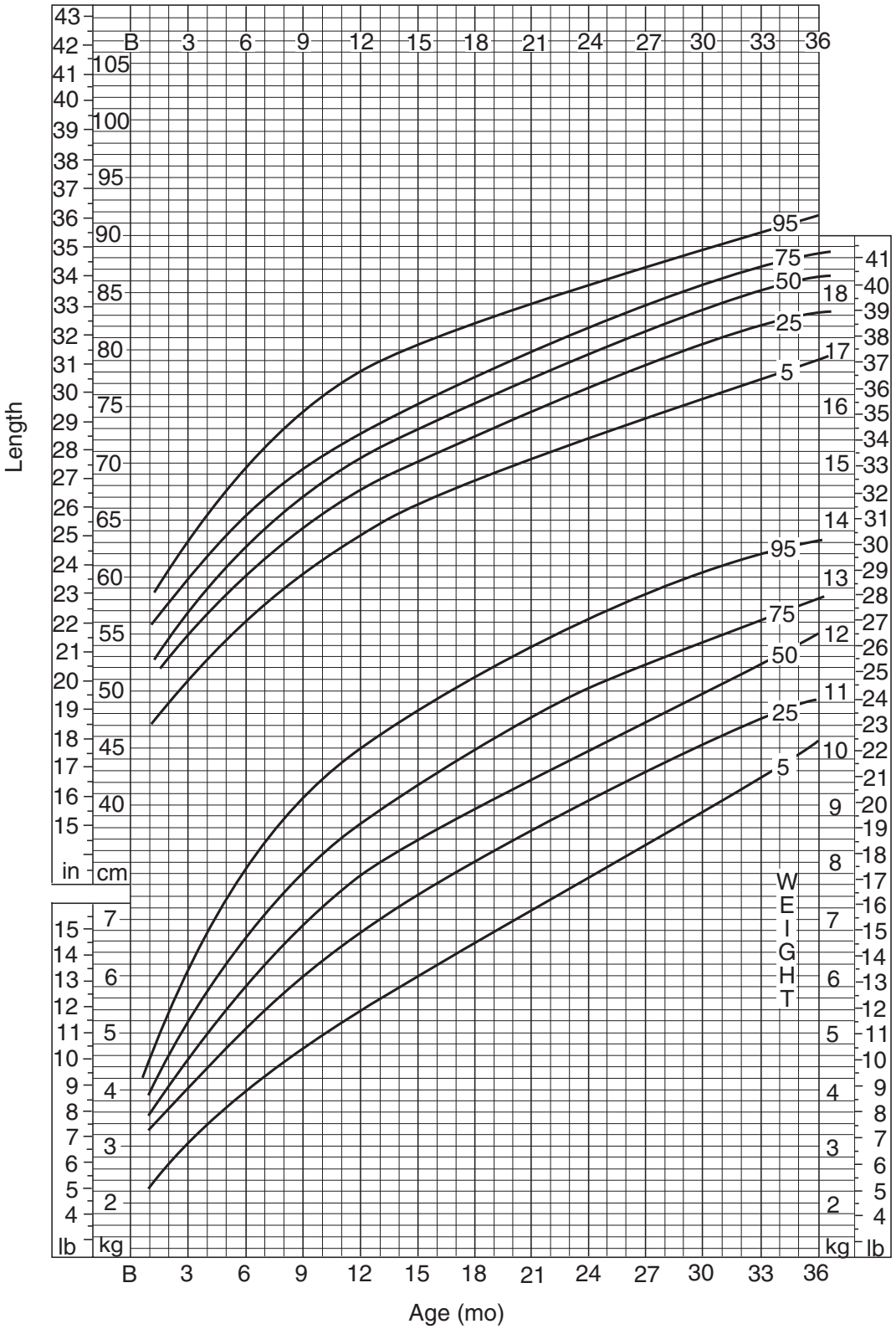


FIGURE A-18 Physical growth of females with Down syndrome (1 to 36 months). Reproduced with permission from Cronk et al.

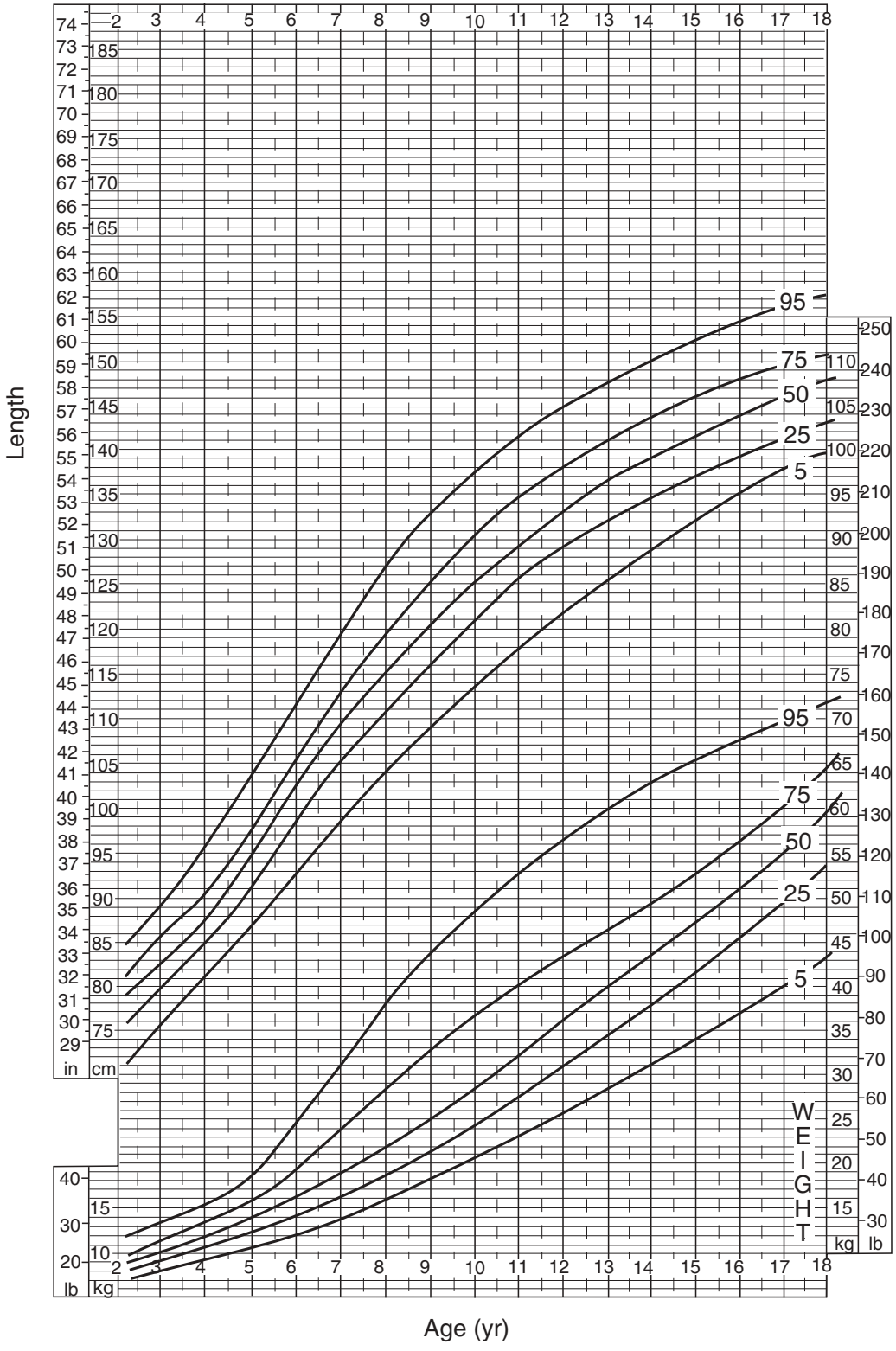


FIGURE A-19 Physical growth of females with Down syndrome (2 to 18 years). Reproduced with permission from Cronk et al.

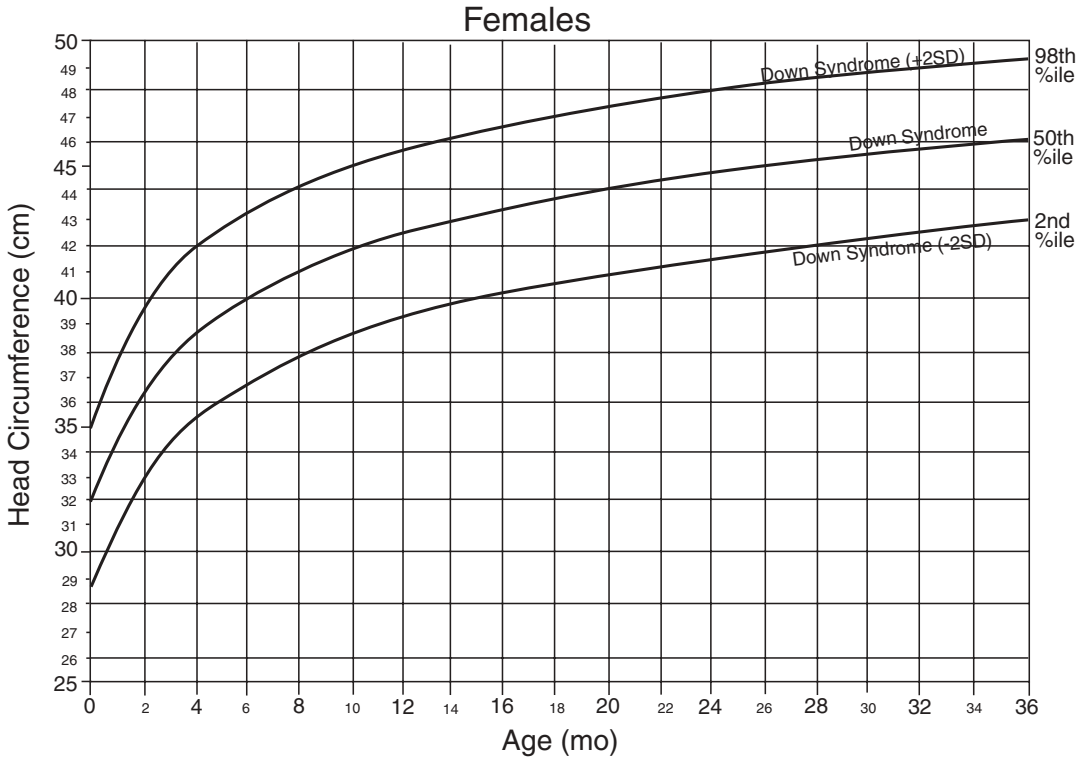


FIGURE A-20 Head circumference of females with Down syndrome (0 to 36 months). Reproduced with permission from Cronk et al.

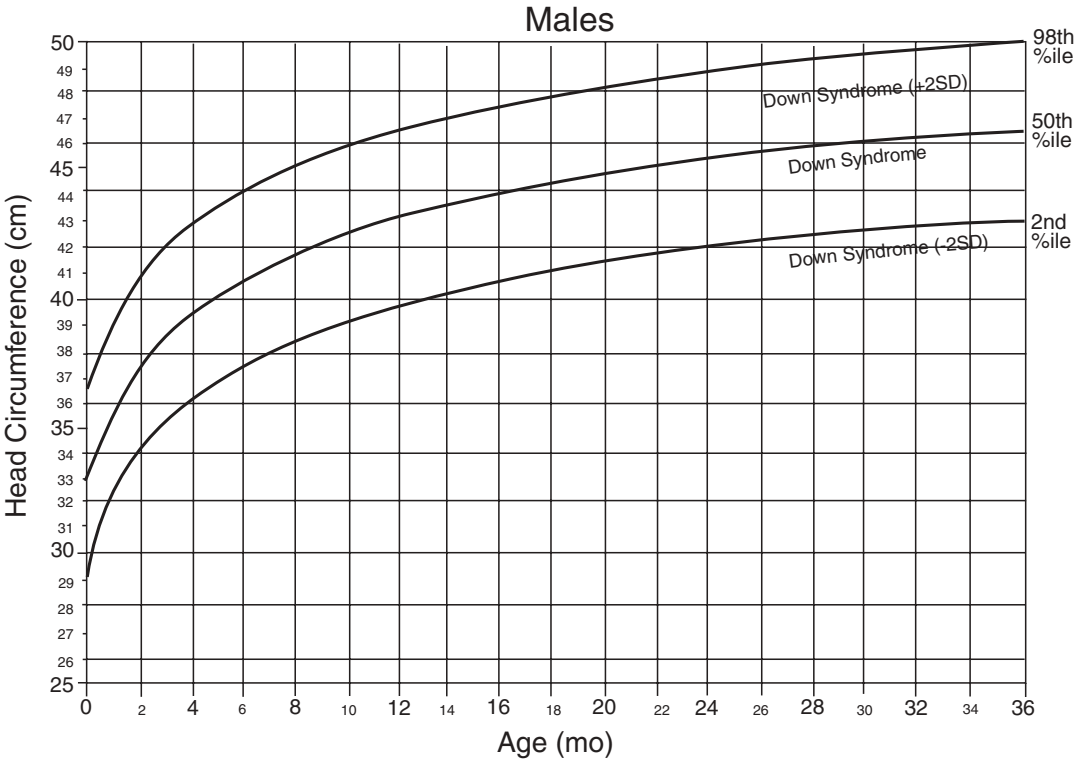


FIGURE A-21 Head circumference of males with Down syndrome (0 to 36 months). Reproduced with permission from Cronk et al.

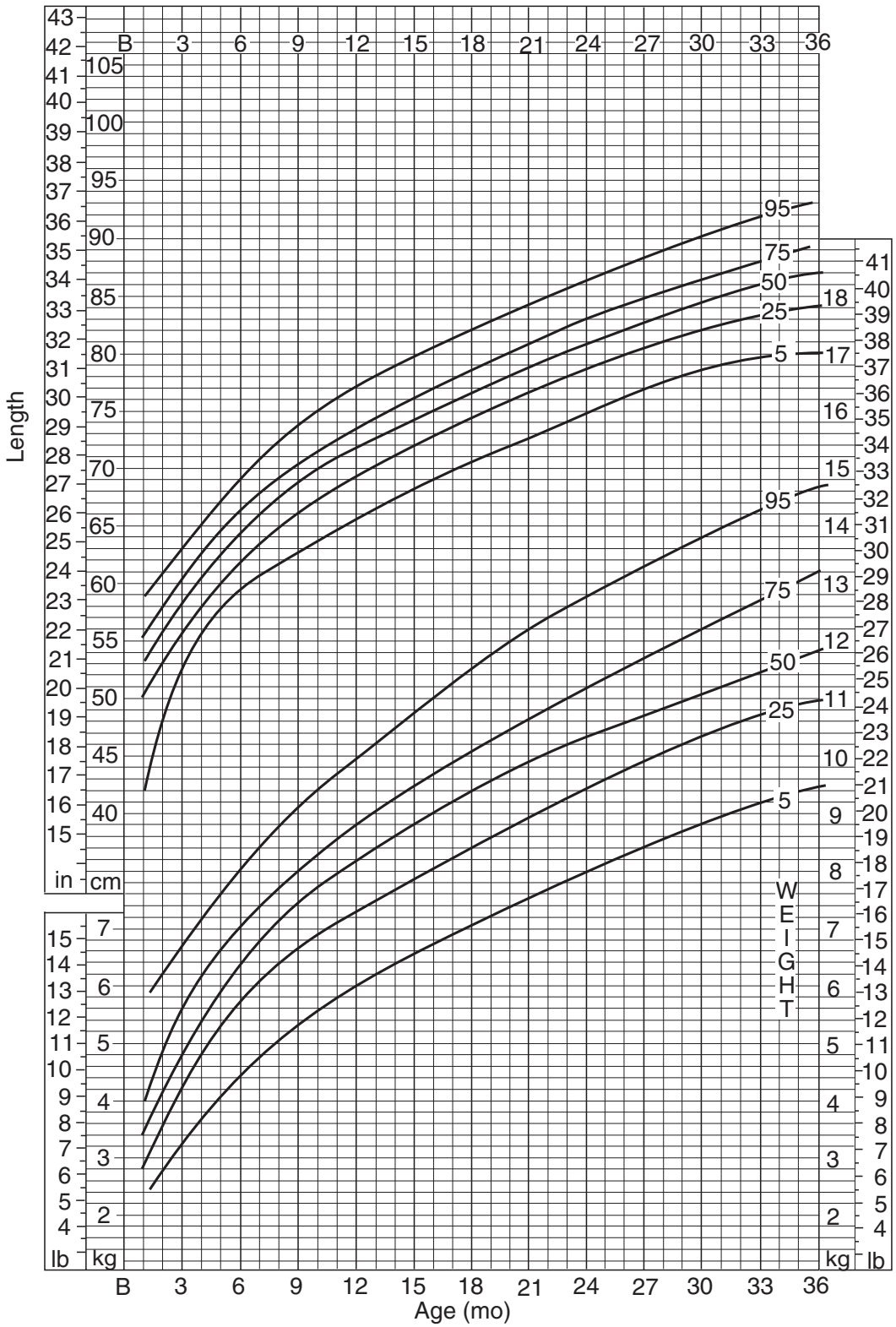


FIGURE A-22 Physical growth of males with Down syndrome (1 to 36 months). Reproduced with permission from Cronk et al.

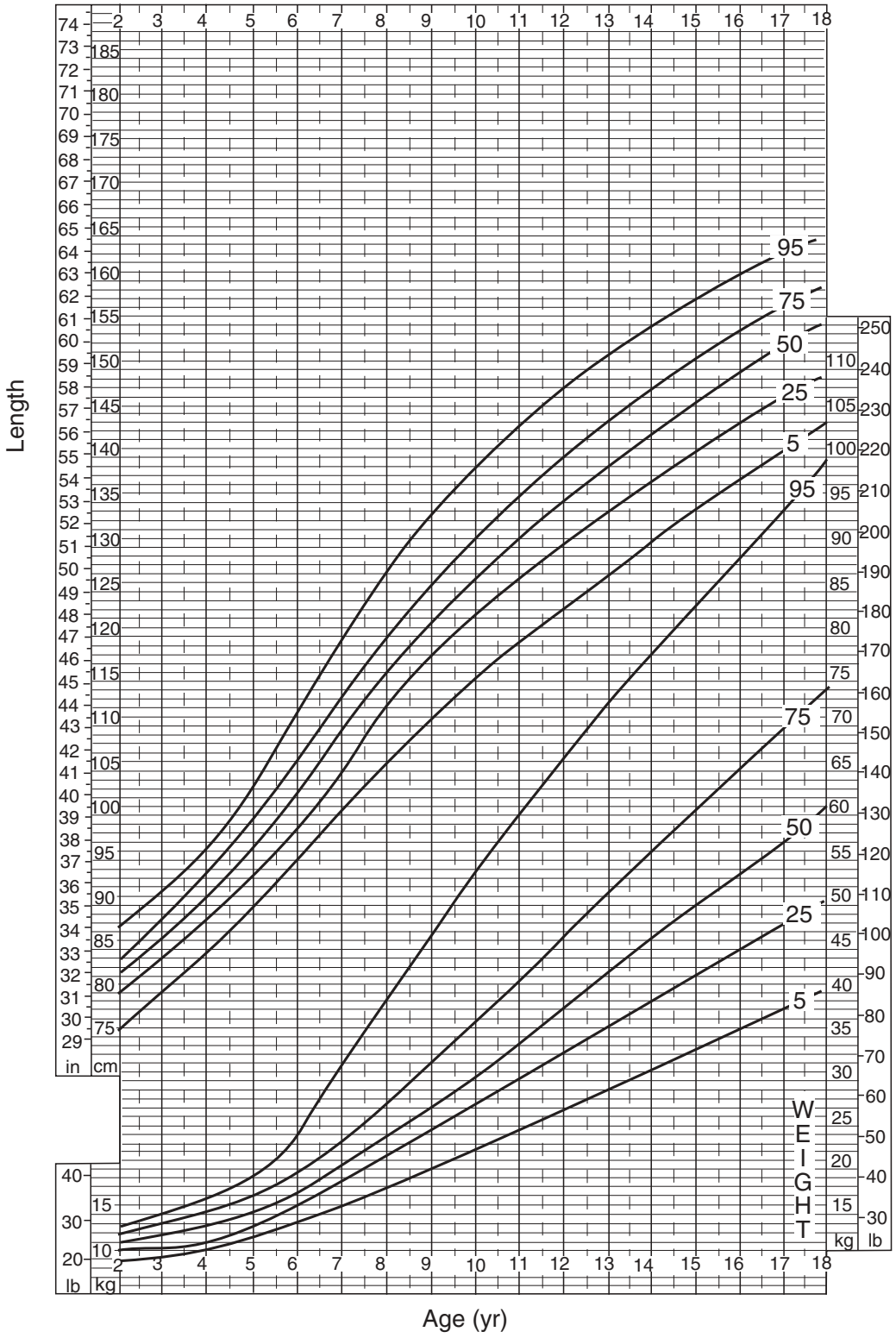


FIGURE A-23 Physical growth of males with Down syndrome (2 to 18 years).

TABLE A-13 Growth Charts for Specific Syndromes*

Condition	*Reference(s)*
Achondroplasia	Horton WA, et al. J Pediatr 1978;93:435. Stature, growth velocity, head circumference, upper and lower segments
Brachmann-de Lange syndrome	Kline AD, et al. Am J Med Genet 1993;47:1042. Length and weight for age, birth to 36 mo; height and weight for age, 2–18 yr; head circumference for age, birth to 18 yr
Cerebral palsy (quadriplegia)	Krick J, et al. J Am Diet Assoc 1996;96:680. Stature and weight for age and weight for stature, age birth to 10 yr
Down syndrome	Cronk CE, et al. Pediatrics 1978;61:564; Pediatrics 1988;81:102. Length for age and weight for age, birth to 36 mo; stature for age and weight for age, 2–18 yr
Marfan's syndrome	Pyeritz RE. In: Emery AH, Rimoirn DL, editors. Principles and practice of medical genetics. New York: Churchill Livingstone; 1983; Pyeritz RE, Papadatas CJ, Bartsocas CD, editors. In: Endocrine genetics and genetics of growth (Prog Clin Biol Res v200). Alan R. Liss; 1985. Stature and weight for age, 2–18 yr, 20–24 yr, and > 24 yr Upper and lower segment ratios 2–20 yr and adult
Myelomeningocele	Appendix 2. In: Ekvall S, editor. Pediatric nutrition in chronic disease and development disorders: prevention, assessment, and treatment. New York: Oxford University Press; 1993. Preliminary charts, height and weight for age, 2–18 yr
Noonan's syndrome*	Ranke MB, Heidemann P, Knupfer C, et al. Eur J Pediatr 1988;148:220–7 Height for age
	Witt DR, et al. Clin Genet 1985;30:150. Stature for age, birth to 18
Prader-Willi syndrome	Holm VA, Appendix A. In: Greeway LR, Alexander PC, editors. Management of Prader-Willi syndrome. New York: Springer Verlag; 1988. p. 317. Height for age, 3–25 yr
	Butler MG, et al. Pediatrics 1991;88:853. Weight, height, sitting height, head circumference, triceps and subscapular skinfold (plus other measure) for age 2–22 yr
Sickle cell disease	Phebus CK, et al. J Pediatr 1984;105:28. Height and weight for age, birth to 18 yr
	Tanner JM, et al. J Pediatr 1985;107:317–29. Height velocity (cm/yr), age 2½ –19 yr
Silver-Russell syndrome	Tanner JM, et al. Pediatr Res 1975;9:611. Height and height velocity for age, 2–19 years (includes periods of treatment with human growth hormone)
Turner's syndrome*	Lyon AJ, et al. Arch Dis Child 1985;60:932. Height for age, birth to 18 yr (girls)
	Ranke MB, Pfluger H, Rosendahl W, et al. Eur J Pediatr 1983;141:81–8. Height for age, height velocity
Williams syndrome*	Morris CA, et al. J Pediatr 1988;113:318. Stature for age, birth to 24 mo and birth to 18 yr; weight for age, birth to 18 yr; head circumference for age, birth to 36 mo and 2–18 yr
	Pankau R, Tartsch CJ, Gosch A, et al. Eur J Pediatr 1992;151:751–5. Height for age, head circumference

Anthropometric assessment of the nutritional status of patients with genetic and other medical conditions can be difficult using the National Center for Health Statistics data. To help evaluate the growth patterns of these patients, special weight and height curves for several syndromes have been published.
*Unless otherwise specified, charts are available for both girls and boys.

APPENDIX 2

Nutritional Requirements

Gina Hardiman, RD, LD

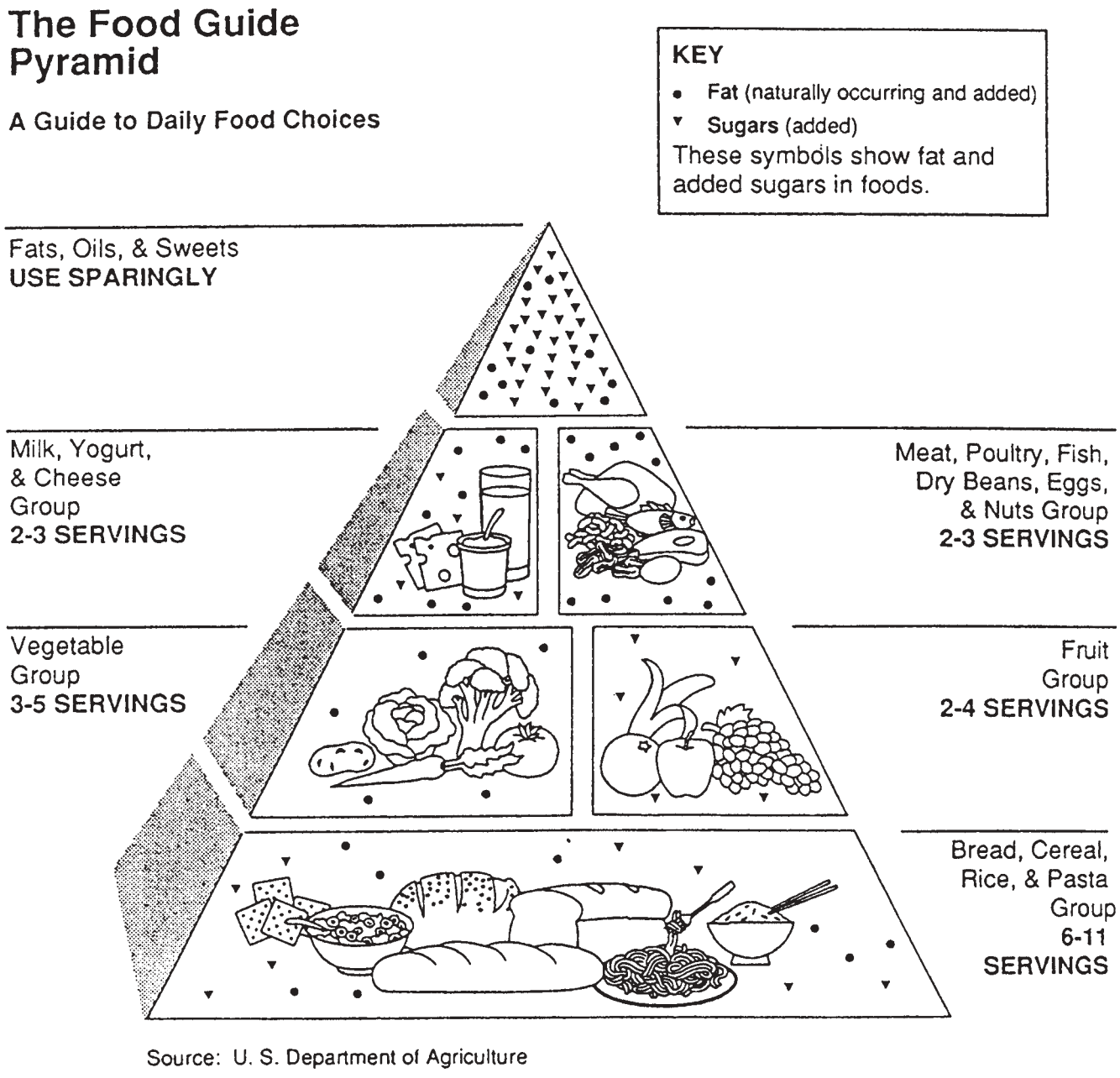


FIGURE A-24 The Food Guide Pyramid (from the US Department of Agriculture).

TABLE A-14 Dietary Reference Intakes: Recommended Intakes for Individuals, Elements (Food and Nutrition Board, Institute of Medicine, National Academies of Sciences)

Life Stage Group	*Calcium (mg/d)*	*Chromium (µg/d)*	*Copper (µg/d)*	*Fluoride (mg/d)*	*Iodine (µg/d)*	*Iron (mg/d)*	*Magnesium (mg/d)*	*Manganese (mg/d)*	*Molybdenum (µg/d)*	*Phosphorus (mg/d)*	*Selenium (µg/d)*	*Zinc (mg/d)*
Infants												
0–6 mo	210*	0.2*	200*	0.01*	110*	0.27*	30*	0.003*	2*	100*	15*	2*
7–12 mo	270*	5.5*	220*	0.5*	130*	11*	75*	0.6*	3*	275*	20*	3
Children												
1–3 yr	500*	11*	**340**	0.7*	**90**	**7**	**80**	1.2*	**17**	**460**	**20**	**3**
4–8 y	800*	15*	**440**	1*	**90**	**10**	**130**	1.5*	**22**	**500**	**30**	**5**
Males												
9–13 yr	1,300*	25*	**700**	2*	**120**	**8**	**240**	1.9*	**34**	**1,250**	**40**	**8**
14–18 yr	1,300*	35*	**890**	3*	**150**	**11**	**410**	2.2*	**43**	**1,250**	**55**	**11**
19–30 yr	1,000*	35*	**900**	4*	**150**	**8**	**400**	2.3*	**45**	**700**	**55**	**11**
31–50 yr	1,000*	35*	**900**	4*	**150**	**8**	**420**	2.3*	**45**	**700**	**55**	**11**
51–70 yr	1,200*	30*	**900**	4*	**150**	**8**	**420**	2.3*	**45**	**700**	**55**	**11**
> 70 yr	1,200*	30*	**900**	4*	**150**	**8**	**420**	2.3*	**45**	**700**	**55**	**11**
Females												
9–13 yr	1,300*	21*	**700**	2*	**120**	**8**	**240**	1.6*	**34**	**1,250**	**40**	**8**
14–18 yr	1,300*	24*	**890**	3*	**150**	**15**	**360**	1.6*	**43**	**1,250**	**55**	**9**
19–30 yr	1,000*	25*	**900**	3*	**150**	**18**	**310**	1.8*	**45**	**700**	**55**	**8**
31–50 yr	1,000*	25*	**900**	3*	**150**	**18**	**320**	1.8*	**45**	**700**	**5**	**8**
51–70 yr	1,200*	20*	**900**	3*	**150**	**8**	**320**	1.8*	**45**	**700**	**55**	**8**
> 70 yr	1,200*	20*	**900**	3*	**150**	**8**	**320**	1.8*	**45**	**700**	**55**	**8**
Pregnancy												
≤ 18 yr	1,300*	29*	**1,000**	3*	**220**	**27**	**400**	2.0*	**50**	**1,250**	**60**	**13**
19–30 yr	1,000*	30*	**1,000**	3*	**220**	**27**	**350**	2.0*	**50**	**700**	**60**	**11**
31–50 yr	1,000*	30*	**1,000**	3*	**220**	**27**	**360**	2.0*	**50**	**700**	**60**	**11**
Lactation												
≤ 18 yr	1,300*	44*	**1,300**	3*	**290**	**10**	**360**	2.6*	**50**	**1,250**	**70**	**14**
19–30 yr	1,000*	45*	**1,300**	3*	**290**	**9**	**310**	2.6*	**50**	**700**	**70**	**12**
31–50 yr	1,000*	45*	**1,300**	3*	**290**	**9**	**320**	2.6*	**50**	**700**	**70**	**12**

This table presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data or uncertainty in the data prevents being able to specify with confidence the percentage of individuals covered by this intake.

Adapted from Dietary Reference Intakes for calcium, phosphorous, magnesium, vitamin D, and fluoride (1997); Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline (1998); Dietary Reference Intakes for vitamin C, vitamin E, selenium, and carotenoids (2000); and Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (2001). These reports may be accessed at <www.nap.edu>.

TABLE A-15 Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Vitamins

Life Stage Group	*Vitamin A* (μg/d)[a]	*Vitamin C* (mg/d)	*Vitamin D* (μg/d)[b,c]	*Vitamin E* (mg/d)[d]	*Vitamin K* (μg/d)	*Thiamin* (mg/d)	*Riboflavin* (mg/d)	*Niacin* (mg/d)[e]	*Vitamin B_6* (mg/d)	*Folate* (μg/d)[f]	*Vitamin B_{12}* (μg/d)	*Pantothenic Acid* (mg/d)	*Biotin* (μg/d)	*Choline*[g] (mg/d)
Infants														
0–6 mo	400*	40*	5*	4*	2.0*	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
7–12 mo	500*	50*	5*	5*	2.5*	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
Children														
1–3 yr	**300**	**15**	5*	**6**	30*	**0.5**	**0.5**	**6**	**0.5**	**150**	**0.9**	2*	8*	200*
4-8 yr	**400**	**25**	5*	**7**	55*	**0.6**	**0.6**	**8**	**0.6**	**200**	**1.2**	3*	12*	250*
Males														
9–13 yr	**600**	**45**	5*	**11**	60*	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
14–18 yr	**900**	**75**	5*	**15**	75*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	5*	25*	550*
19–30 yr	**900**	**90**	5*	**15**	120*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
31–50 yr	**900**	**90**	5*	**15**	120*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
51–70 yr	**900**	**90**	10*	**15**	120*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**[h]	5*	30*	550*
> 70 yr	**900**	**90**	15*	**15**	120*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**[h]	5*	30*	550*
Females														
9–13 yr	**600**	**45**	5*	**11**	60*	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
14–18 yr	**700**	**65**	5*	**15**	75*	**1.0**	**1.0**	**14**	**1.2**	**400**	**2.4**	5*	25*	400*
19–30 yr	**700**	**75**	5*	**15**	90*	**1.1**	**1.1**	**14**	**1.3**	**400**	**2.4**	5*	30*	425*
31–50 yr	**700**	**75**	5*	**15**	90*	**1.1**	**1.1**	**14**	**1.3**	**400**	**2.4**	5*	30*	425*
51–70 yr	**700**	**75**	10*	**15**	90*	**1.1**	**1.1**	**14**	**1.5**	**400**[i]	**2.4**	5*	30*	425*
> 70 yr	**700**	**75**	15*	**15**	90*	**1.1**	**1.1**	**14**	**1.5**	**400**[i]	**2.4**	5*	30*	425*
Pregnancy														
≤ 18 yr	**750**	**80**	5*	**15**	75*	**1.4**	**1.4**	**18**	**1.9**	**600**[f]	**2.6**	6*	30*	450*
19–30 yr	**770**	**85**	5*	**15**	90*	**1.4**	**1.4**	**18**	**1.9**	**600**[f]	**2.6**	6*	30*	450*
31–50 yr	**750**	**85**	5*	**15**	90*	**1.4**	**1.4**	**18**	**1.9**	**600**[f]	**2.6**	6*	30*	450*
Lactation														
≤ 18 yr	**1,200**	**115**	5*	**19**	75*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
19–30 yr	**1,300**	**120**	5*	**19**	90*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
31–50 yr	**1,300**	**120**	5*	**19**	90*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*

This table (taken from the Dietary Reference Intake reports (see <www.nap.edu>) presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data or uncertainty in the data prevents being able to specify with confidence the percentage of individuals covered by this intake.

[a]As retinol activity equivalents (RAEs). 1 RAE = 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalent (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b]Cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D.

[c]In the absence of adequate exposure to sunlight.

[d]As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2*R*-stereoisomeric forms of α-tocopherol (*RRR-, RSR-, RRS-,* and *RRS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2S-stereoisomeric forms of α-tocopherol (*SRR-, SSR, SRS-*, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

[e]As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 mo = preformed niacin (not NE).

[f]As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

[g]Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

[h]Because 10 to 30% of older people may malabsorb food-bound vitamin B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}.

[i]In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet.

[j]It is assumed that women will continue consuming 400 μg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube.

TABLE A-16a Criteria and Dietary Reference Intake Values for Energy by Active Individuals by Life Stage Group*

		Active PAL† EER (kcal/d)	
Life Stage Group	*Criterion*	*Male*	*Female*
0–6 mo	Average consumption of protein from human milk	570	520 (3 mo)
7–12 mo	Nitrogen equilibrium + protein deposition	743	676 (9 mo)
1–2 yr	Nitrogen equilibrium + protein deposition	1,046	992 (24 mo)
3–8 yr	Nitrogen equilibrium + protein deposition	1,742	1,642 (6 yr)
9–13 yr	Nitrogen equilibrium + protein deposition	2,279	2,071 (11 yr)
14–18 yr	Nitrogen equilibrium + protein deposition	3,152	2,368 (16 yr)
> 18 yr	Nitrogen equilibrium	3,067‡	2,403‡ (19 yr)
Pregnancy			
14–18 yr	Adolescent female EER plus change in TEE plus pregnancy energy deposition		
1st trimester	2,368 (16 yr)		
2nd trimester	2,708 (16 yr)		
3rd trimester	2,820 (16 yr)		
19–50 yr	Adult female EER plus change in TEE plus pregnancy energy deposition		
1st trimester	2,403‡ (19 yr)		
2nd trimester	2,743‡ (19 yr)		
3rd trimester	2,855‡ (19 yr)		
Lactation			
14–18 yr	Adolescent female EER plus milk energy output minus weight loss		
1st 6 mo	2,698 (16 yr)		
2nd 6 mo	2,768 (16 yr)		

*For healthy, moderately active Americans and Canadians.
†EER = estimated energy requirement; PAL = physical activity level; TEE = total energy expenditure. The intake that meets the average energy expenditure of individuals at the reference height, weight, and age (see Table 1-1).
‡Subtract 10 kcal/day for males and 7 kcal/day for females for each year of age above 19 years.

TABLE A-16b Criteria and Dietary Reference Intake Values for Carbohydrate by Life Stage Group

		*EAR (g/kg/d)**		*RDA (g/kg/d)†*		
Life Stage Group	*Criterion*	*Male*	*Female*	*Male*	*Female*	*AI (g/kg/d)‡*
0–6 mo	Average content of human milk					60
7–12 mo	Average intake from human milk plus complementary foods					95
1–3 yr	Extrapolation from adult data	100	100	130	130	
4–8 yr	Extrapolation from adult data	100	100	130	130	
9–13 yr	Extrapolation from adult data	100	100	130	130	
14–18 yr	Extrapolation from adult data	100	100	130	130	
> 18 yr	Brain glucose use	100	100	0.80	130	
Pregnancy						
14–18 yr	Adolescent female EAR plus fetal brain glucose use	135	175			
19–50 yr	Adult female EAR plus fetal brain glucose use	135	175			
Lactation						
14–18 yr	Adolescent female EAR plus average human milk content of carbohydrate	160	210			
19–50 yr	Adult female EAR plus average human milk content of carbohydrate	160	210			

*EAR = Estimated Average Requirement. The intake that meets the estimated nutrient needs of half of the individuals in a group.
†RDA = Recommended Dietary Allowance. The intake that meets the nutrient need of almost all (97–98%) of individuals in a group.
‡AI - Adequate Intakes. The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal. circulatory nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an EAR. For healthy infants receiving human milk, the AI is the mean intake. *The AI is not equivalent to an RDA.*

TABLE A-16c Criteria and Dietary Reference Intake Values for Protein by Life Stage Group

		AI or RDA for Reference Individual (g/d)		*EAR (g/kg/d)**		*RDA (g/kg/d)†*		
Life Stage Group	*Criterion*	*Males*	*Females*	*Males*	*Females*	*Males*	*Females*	*AI (g/kg/d)‡*
0– 6 mo	Average consumption of protein from human milk	9.1 (AI)	9.1 (AI)					1.52
7–12 mo	Nitrogen equilibrium + protein deposition	13.5	13.5	1.1	1.1	1.5	1.5	
1–3 yr	Nitrogen equilibrium + protein deposition	13	13	0.88	0.88	1.10	1.10	
4–8 yr	Nitrogen equilibrium + protein deposition	19	19	0.76	0.76	0.95	0.95	
9–13 yr	Nitrogen equilibrium + protein deposition	34	34	0.76	0.76	0.95	0.95	
14–18 yr	Nitrogen equilibrium + protein deposition	52	46	0.73	0.71	0.85	0.85	
> 18 yr	Nitrogen equilibrium	56	46	0.66	0.66	0.80	0.80	

*EAR = Estimated Average Requirement. The intake that meets the estimated nutrient needs of half of the individuals in a group.
†RDA = Recommended Dietary Allowance. The intake that meets the nutrient need of almost all (97–98%) of individuals in a group.
‡AI - Adequate Intakes. The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal. circulatory nutrient values, or other functional indicators of health. The AI is used if sufficient scientific evidence is not available to derive an EAR. For healthy infants receiving human milk, the AI is the mean intake. *The AI is not equivalent to an RDA.*
The EAR and RDA for pregnancy are only for the second half of pregnancy. For the first half of pregnancy, the protein requirements are the same as those of the nonpregnant woman.
In addition to the EAR and RDA of the nonlactating adolescent or women.

Table A-17 Estimated Safe and Adequate Daily Dietary Intakes of Selected Minerals

		*Trace Elements**				
Category	*Age (yr)*	*Copper (mg)*	*Manganese (mg)*	*Fluoride (mg)*	*Chromium (µg)*	*Molybdenum (µg)*
Infants	0–0.5	0.4–0.6	0.3–0.6	0.1–0.5	10–40	15–30
	0.5–1	0.6–0.7	0.6–1.0	0.2–1.0	20–60	20–40
Children and adolescents	1–3	0.7–1.0	1.0–1.5	0.5–1.5	20–80	25–50
	4–6	1.0–1.5	1.5–2.0	1.0–2.5	30–120	30–75
	7–10	1.0–2.0	2.0–3.0	1.5–2.5	50–200	50–150
	11+	1.5–2.5	2.0–5.0	1.5–2.5	50–200	75–250
Adults		1.5–3.0	2.0–5.0	1.5–4.0	50–200	75–250

*Because the toxic levels for many trace elements may be only several times usual intakes, the upper levels for the trace elements given in this table should not be habitually exceeded.

Table A-18 Normal Electrolyte Requirements

Electrolyte	*Daily Requirement*
Sodium	2–4 mEq/kg
Potassium	2–3 mEq/kg
Chloride	2–3 mEq/kg
Magnesium	0.25–0.5 mEq/kg
Calcium	
Infants	300–400 mg/kg
Children	100–200 mg/kg
Adolescents	50–100 mg/kg
Phosphorus	
Infants	1–1.5 mmol/kg
Children	1 mmol/kg
Adolescents	0.5–1 mmol/kg

Adapted from Handbook of parenteral nutrition, Boston: Children's Hospital;

TABLE A-19 Fluid Requirement

Holliday-Segar Method	
1st 10 kg body weight	100 mL/kg
2nd 10 kg body weight	1,000 mL + 50 mL/kg > 10 kg
Each additional kg	1,500 mL + 20 mL/kg > 20 kg
Body Surface Area Method	
1,500 mL/m^2 24 hr	

Adapted data from Finberg L, et al. Water and electrolytes in pediatrics. Philadelphia: WB Saunders; 1982; and from Behrman R, et al. Nelson textbook of pediatrics. 13th ed. Philadelphia: WB Saunders; 1987.

TABLE A-20 Milliequivalent-Milligram Conversion Table

Mineral Element	*Chemical Symbol*	*Atomic Weight*	*Valence*
Calcium	Ca	40	2
Chlorine	Cl	35.4	1
Magnesium	Mg	24.3	2
Phosphorus	P	31	2
Potassium	K	39	1
Sodium	Na	23	1
Sulfur	S	32	2
Zinc	Zn	65.4	2
Sulfate	SO_4	96	2

$$\text{Milliequivalents} = \frac{\text{milligrams}}{\text{atomic weight}} \times \text{valence}$$

Example: Convert 2,000 mg sodium to mEq of sodium

$$\frac{2{,}000}{23} \times 1 = 87 \text{ mEq sodium}$$

To change milliequivalents back to milligrams, multiply the milliequivalents by the atomic weight and divide by the valence.

Example: Convert 20 mEq sodium to mg sodium

$$\frac{20 \times 23}{1} = 460 \text{ mg sodium}$$

Adapted from Hendricks KM, Duggan C, Walker WA. Manual of pediatric nutrition. Hamilton (ON): BC Decker; 2000.

TABLE A-21 Definitions of Nutritional Requirements*

Term		*Abbreviation*	*Year Introduced*	*Definition/Use*
Old	Recommended Dietary Allowances	RDAs	1943	Average daily dietary intake value sufficient to meet the requirement of nearly all (97–98%) healthy individuals in a group; more recently, the term has been calculated as EAR plus 2 SD of the EAR (see below)
New	Dietary Reference Intakes	DRIs	1994	Umbrella term including RDA, EAR, AI, and UL (see below)
	Estimated Average Requirement	EAR	1994	A nutrient intake value estimated to meet the requirement of half the individuals in a group
	Adequate Intake	AI	1994	(Used when no EAR is available and no RDA can therefore be calculated) Nutrient intake value based on observed or experimentally determined approximations of nutrient intakes in a group or groups of healthy people
	Tolerable Upper Intake level	UI	1994	The highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population

Adapted from Duggan C. Nutritional requirements. In: Walker WA, Durie PR, Hamilton JR, et al, editors. Pediatric gastrointestinal disease: pathophysiology, diagnosis, management. Hamilton (ON): BC Decker; 2000.
*Set by the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences.

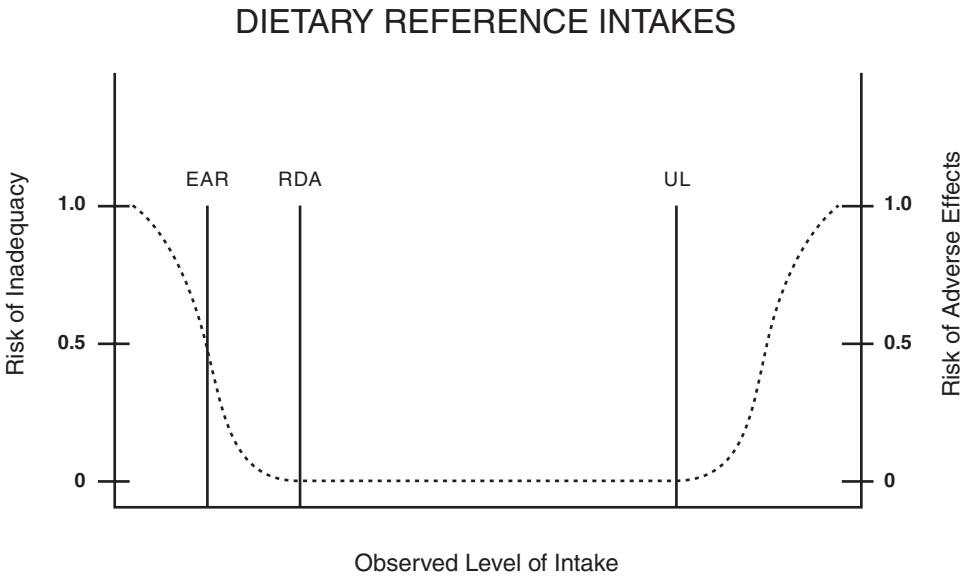


FIGURE A-25 The relationship between estimated average requirement (EAR), Recommended Dietary Allowance (RDA), and tolerable upper intake level (UL). The risk of inadequate intake is 50% at the EAR, 2 to 3% at the RDA, and close to 0% at the UL. Risks of adverse effects are close to 0% at the UL but increase with increasing intake. Reproduced with permission from the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington (DC): National Academy Press; 1997.

Table A-22 Median Heights and Weights and Recommended Energy Intake

Category	Age (yr) or Condition	Weight (kg)	Weight (lb)	Height (cm)	Height (in)	REE* (kcal/d)	Average Energy Allowance (kcal)† Multiples of REE	Average Energy Allowance (kcal)† Per kg	Average Energy Allowance (kcal)† Per day‡
Infants	0.0–0.5	6	13	60	24	320		108	650
	0.5–1.0	9	20	71	28	500		98	850
Children	1–3	13	29	90	35	740		102	1,300
	4–6	20	44	112	44	950		90	1,800
	7–10	28	62	132	52	1,130		70	2,000
Males	11–14	45	99	157	62	1,440	1.70	55	2,500
	15–18	66	145	176	69	1,760	1.67	45	3,000
	19–24	72	160	177	70	1,780	1.67	40	2,900
	25–50	79	174	176	70	1,800	1.60	37	2,900
	51+	77	170	173	68	1,530	1.50	30	2,300
Females	11–14	46	101	157	62	1,310	1.67	47	2,200
	15–18	55	120	163	64	1,370	1.60	40	2,200
	19–24	58	128	164	65	1,350	1.60	38	2,200
	25–50	63	138	163	64	1,380	1.55	36	2,200
	51+	65	143	160	63	1,280	1.50	30	1,900
Pregnant	1st trimester								+0
	2nd trimester								+300
	3rd trimester								+300
Lactating	1st 6 mo								+500
	2nd 6 mo								+500

*Calculation based on FAO equations and then rounded.
†In the range of light to moderate activity, the coefficient of variation is ± 20%.
‡Figure is rounded.
REE = resting energy expenditure.
Reproduced with permission from National Academy of Science. Recommended Dietary Allowances. 10th ed. Washington (DC): National Academy Press; 1989.

Table A-23 Schofield Equations for Calculating Basal Metabolic Rate in Children

Males	
0–3 yr	REE = 0.167W + 15.174H – 617.6
3–10 yr	REE = 19.59W + 1.303H + 414.9
10–18 yr	REE = 16.25W + 1.372H + 515.5
> 18 yr	REE = 15.057W + 1.004H + 705.8
Females	
0–3 yr	REE = 16.252W + 10.232H – 413.5
3–10 yr	REE = 16.969W + 1.618H + 371.2
10–18 yr	REE = 8.365W + 4.65H + 200
> 18 yr	REE = 13.623W + 23.8H + 98.2

Adapted from Schofield W. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39C Suppl 1:5–41.
Resting energy expenditure (REE) = kcal/day; W = weight (kg); H = height (cm).

TABLE A-24 Equations for Predicting Basal Metabolic Rate from Body Weight in Kilograms

Age Range (yr)	Kcal/kg per day
Males	
0–3	60.9 W – 54
3–10	22.7 W + 495
10–18	17.5 W + 651
18–30	15.3 W + 679
30–60	11.6 W + 879
> 60	13.5 W + 487
Females	
0–3	61.0 W – 51
3–10	22.5 W + 499
10–18	22.2 W + 746
18–30	14.7 W + 496
30–60	8.7 W + 829
> 60	10.5 W + 596

Adapted from World Health Organization. Energy and protein requirements. Report of a Joint FAO/WHO/UNU Expert Consultation. Geneva: WHO; 1985. Technical Report Series 724.

Table A-25 Assessment of Energy Requirements in Hospitalized Pediatric Patients: Step 1. Estimating Basal Metabolic Requirements

	Kcal/d			*Kcal/d*	
Body Wt (kg)	*Male*	*Female*	*Body Wt (kg)*	*Male*	*Female*
3.0	120	144	36.0	1,270	1,173
4.0	191	191	38.0	1,305	1,207
5.0	270	274	40.0	1,340	1,241
6.0	330	336	42.0	1,370	1,274
7.0	390	395	44.0	1,400	1,306
8.0	445	448	46.0	1,430	1,338
9.0	495	496	48.0	1,460	1,369
10.0	545	541	50.0	1,485	1,399
11.0	590	582	52.0	1,505	1,429
12.0	625	620	54.0	1555	1,458
13.0	665	655	56.0	1,580	1,487
14.0	700	687	58.0	1,600	1,516
15.0	725	718	60.0	1,630	1,544
16.0	750	747	62.0	1,660	1,572
17.0	780	775	64.0	1,690	1,599
18.0	810	802	66.0	1,725	1,626
19.0	840	827	68.0	1,765	1,653
20.0	870	852	70.0	1,785	1,679
22.0	910	898	72.0	1,815	1,705
24.0	980	942	74.0	1,845	1,731
26.0	1,070	984	76.0	1,870	1,756
28.0	1,100	1,025	78.0	1,900	1,781
30.0	1,140	1,063	80.0	1,935	1,805
32.0	1,190	1,101	82.0	1,970	1,830
34.0	1,230	1,137	84.0	2,000	1,855

Adapted from Schofield W. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39C Suppl 1:5–41.

TABLE A-26 Factors Used in the Calculation of Total Energy Expenditure

Factor	
Activity	
Bedridden	1.20
Ambulatory	1.30
Fever	
Per degree Fahrenheit deviation from	1.07
Injury	
Starvation	0.70
Minor surgery	1.00–1.20
Peritonitis	1.20–1.50
Soft tissue trauma	1.14–1.37
Skeletal trauma	1.35
Major sepsis	1.40–1.60
Thermal injury	2.00

Adapted with permission from Long C, Schaffel N, Geiger J, et al. Response to injury and illness: estimation of energy and protein needs from indirect calorimetric and nitrogen balance. JPEN J Parenter Enteral Nutr 1979;3:452.

APPENDIX 3

Enteral Products

Gina Hardiman, RD, LD

TABLE A-27 Cow's Milk–Based Infant Formulas (per L)

	Enfamil Lipil (Mead Johnson, Evansville, IN)	*Enfamil/Enfamil with Iron (Mead Johnson*)*	*Enfamil/AR Liquid Only (Mead Johnson)*	*Enfamil Lacto-Free* (Mead Johnson)*	*Good Start* (Nestle, Glendale, CA)*	*Similac Low Iron/ with Iron* (Ross Products, Abbott Laboratories, Columbus, OH)†*	*Similac Lactose Free (Ross)*	*Similac PM 60/40 Powder Only (Ross)*	*Store Brand Milk-Based Formula† (Wyeth Nutritionals)*	*Similac with Iron 24* Liquid Only (Ross)*
Energy, kcal/100 mL	680	680	680	680	676	676	676	676	672	806
Protein, g	14.5	14.5	16.9	14.3	16.2	14	14	15	15	21.9
Casein, % of total protein	40	40	82	82	0	52	18	40	40	18
Whey, % of total protein	60	60	18	18	100‡	48	82	60	60	82
Fat, g	36	36	35	36	34.5	36.5	36.5	37.8	36	42.5
Polyunsaturated, %	20	19	19	19	32	24	37	39	17.7	37
Monounsaturated %	37	38	38	38	26	39	17	18	37.3	17
Saturated, %	43	43	43	43	43	37	46	43	45	46
Oils	Palm olein, high-oleic sunflower, soy and coconut DHA, ARA	Palm olein, high-oleic sunflower coconut, and soy	Palm olein, high-oleic sunflower, coconut, and soy	Palm olein, soy, coconut, and high-oleic sunflower	Palm olein, coconut, and high-oleic safflower	High-oleic safflower, coconut, and soy	Soy and coconut	Corn, coconut, and soy	Palm, high oleic, coconut and soybean, safflower or sunflower	Soy and coconut
Carbohydrate, g	73 Lactose	73 Lactose	74 Lactose, rice starch, and maltodextrin	74 Corn syrup solids	73 Lactose, corn maltodextrins	73 Lactose	72.3 Corn syrup solids and sucrose	68.9 Lactose	72 Lactose	85 Lactose
Monounsaturated %	37	38	38	38	26	39	17	18	37.3	17
Minerals										
Calcium, mg	530	530	530	550	433	527	568	378	420	726
Phosphorus, mg	360	360	360	370	243	284	378	189	280	565
Magnesium, mg	54	54	54	54	45.3	41	41	40.5	45	56.5
Iron, mg	12.2	4.7/12.2§	12.2	12.2	10.1	4.7/12.2§	12.2	4.7	12	14.5
Zinc, mg	6.8	6.8	6.8	6.8	5.1	5.1	5.1	5.07	5	6.05
Manganese, µg	100	101	101	101	47	34	34	34	100	40
Copper, µg	510	510	510	510	541	608	608	608	470	726
Iodine, µg	68	68	68	101	54	41	61	41	60	73
Sodium, mEq	8	8	11.7	8.7	7	7.1	8.8	7.1	6.4	11.9
Potassium, mEq	18.7	18.7	18.7	18.9	17	18.1	18.5	14.9	14.4	27.2
Chloride, mEq	12.1	12.1	14.4	12.7	11.2	12.4	12.4	11.2	10.7	18.4
Vitamins										
A, IU	2,000	2,000	2,000	2,000	2,027	2,027	2,027	2,027	2,000	2,419
D, IU	410	410	410	410	405	405	405	405	400	484
E, IU	13.5	13.5	13.5	13.5	8	10.1	20.3	16.9	10.0	24.2
K, µg	54	54	54	54	55	54	54	54	55	65
Thiamin (B_1), µg	540	540	540	540	405	676	676	676	670	806
Riboflavin (B_2), µg	950	950	950	950	912	1,014	1,014	1,014	1,000	1,210
Pyridoxine, µg	410	410	410	410	507	405	405	405	420	484
B_{12}, µg	2.0	2.0	2.0	2.0	1.5	1.7	1.7	1.69	1.0	1.69
Niacin, mg	6.8	6.8	6.8	6.8	5.1	7.1	7.1	7.1	5.0	8.5
Folic acid, µg	108	108	108	108	61	101	101	101	50	101
Pantothenic acid, mg	3.4	3.4	3.4	3.4	3	3.04	3.04	3.0	2.1	3.6
Biotin, µg	20	20	20	20	14.9	29.7	29.7	30.4	15.0	30.4
C (ascorbic acid), mg	81	81	81	81	54.1	61	61	61	55	61
Choline, mg	81	81	81	81	81	108	108	81	100	129
Inositol, mg	41	41	41	41	122	32	29	162.2	27	37.9

*Liquid and powder; †with nucleotides; ‡partially hydrolyzed; §high iron.
ARA = arachidonic acid; DHA = docosahexaenoic acid.

TABLE A-28 Soy-Based Infant Formulas (per L)

	Isomil (Ross Products, Abbott Laboratories, Columbus, OH)	*Isomil DF* (Ross)*	*Alsoy (Nestle, Glendale, CA)*	*Prosobee (Mead Johnson Evansville, IN)*
Energy, kcal	676	676	680	680
Protein, g	16.55	17.97	18.8	17.3
Carbohydrate, g	69.6	68.2	74.4	73.0
Fat, g	36.89	36.89	33.3	37.0
Mineral				
Calcium, mg	709	709	704	710
Phosphorus, mg	507	507	409	560
Magnesium, mg	50.7	50.7	74.0	74.0
Iron, mg	12.2	12.2	12.1	12.2
Zinc, mg	5.07	5.07	6.0	8.1
Manganese, µg	169	203	228	169
Copper, µg	507	507	804	510
Iodine, µg	101	101	80.4	101
Selenium, µg	14.2	14.2	13.0	18.9
Sodium, mEq	12.9	12.9	9.6	10.4
Potassium, mEq	18.7	18.7	19.9	21.0
Chloride, mEq	11.8	11.8	13.6	15.2
Vitamin				
A, IU	2,027	2,027	2,077	2,000
D, IU	405	405	402	410
E, IU	10.1	20.3	20.1	13.5
K, µg	74	74	52.3	54
Thiamin (B_1), µg	405	405	402	540
Riboflavin (B_2), µg	608	608	630	610
Pyridoxine, µg	405	405	402	410
B_{12}, µg	3.04	3.04	2.1	2.0
Niacin, µg	9,122	9,122	8,710	6,800
Folic acid, µg	101	101	107	108
Pantothenic acid, µg	5,068	5,068	3,149	3,400
Biotin, mcg	30.4	30.4	52.0	20.0
C (ascorbic acid), mg	61	61	107	81
Choline, mg	54	54	80	81
Inositol, mg	33.8	33.8	121.0	41.0

*Isomil DF contains 6 g of added dietary fiber per L.

TABLE A-29 Follow-up Formulas for Infant Feeding (per L)

	*Similac 2** *(Ross, Columbus, OH)*	*Follow-Up (Nestle, Glendale, CA)*[#]	*Enfamil Next-Step (Mead Johnson, Evansville, IN)*	*Store Brand Formula for Older Infants (Wyeth Nutritionals)*[†]	*Enfamil Next-Step Soy Powder (Mead Johnson)*	*Isomil 2 Powder Only (Ross)*
Energy, kcal	676	680	680	680	680	676
Protein	14*	17.6	17.6	18	22[‡]	16[‡]
Casein, % of total calories	52	82	82	50	—	NA
Whey, %	48	18	18	50	—	NA
Fat, g	37	27	34	6	30	37
Polyunsaturated, %	24	22.2	19	14.5	19	24
Monounsaturated, %	39	33.2	38	41.3	38	39
Saturated, %	37	44.6	40	44.2	40	37
Predominant oil	High-oleic safflower, coconut, and soy	Palm, soy, coconut, and high-oleic safflower	Palm olein, soy, coconut, and high-oleic sunflower	Oleo, coconut, high oleic, and soy	Palm olein, soy, coconut, high-oleic sunflower	High-oleic safflower, coconut, and soy
Carbohydrate, g	72[§]	89[§]	75[§]	69[§]	80[‖]	70[‖]
Osmolality, mOsm/kg	300	200	270	280	260	200
Minerals						
Calcium, mg	797	912	810	816	780	912
Phosphorus, mg	432	608	570	571	610	608
Magnesium, mg	40.5	43	54	67	54	50.7
Iron, mg	12.2	12.8	12.2	12.0	12.2	12.2
Zinc, mg	5.1	4.3	6.1	6.0	8.1	5.1
Manganese, µg	34	47	47	40	169	169
Copper, µg	608	813	610	580	510	507
Iodine, µg	41	223	54	69	101	101
Sodium, mEq	7.1	12	12.2	9.6	13	12.9
Potassium, mEq	18.1	20	23	21.5	26	18.7
Chloride, mEq	12.4	15.0	16.3	15.7	19.2	11.8
Vitamins						
A, IU	2,027	1,541	2,000	2,500	2,000	2,027
D, IU	405	445	410	440	410	405
E, IU	20.3	13.5	13.5	13.6	13.5	10.1
K, µg	54	54.7	54	67	54	74
Thiamin (B_1), µg	676	540.8	680	1,000	540	405
Riboflavin (B_2), µg	1,014	648.9	1,010	1,500	610	608
Pyridoxine, µg	405	446	410	600	610	405
B_{12}, µg	1.7	2.2	1.7	2.0	2.0	3.04
Niacin, mg	7.1	8.7	7.1	6.9	6.8	9.1
Folic acid, µg	101	108	101	10.2	108	101
Pantothenic acid, mg	3	3	3	3	3.4	5.1
Biotin, µg	29.7	13.5	30	20	20	30.4
C (ascorbic acid), mg	61	54	61	90	81	61
Choline, mg	108	81.1	108	100	81	54
Inositol, mg	31.8	121.6	32	27	115	33.8

*Cow's milk and soy isolate; [†]for infants 4–6 months and older; [‡]soy protein isolate; [§]lactose and corn syrups; corn syrup solids and sucrose; [‖]powder only.

TABLE A-30 Formulas for Low Birth Weight and Prematurely Born Infants (per L)

	Similac Special Care 24 (Ross Products, Abbott Laboratories, Columbus, OH)*	*Enfamil Premature 24* (Mead Johnson, Evansville, IN)*	*Neosure 22 Cal (Ross)*	*Enfacare 22 Cal (Mead Johnson)*
Energy, kcal	806	810	746	740
Protein, g	22*	24*	19.4	21
Fat, g	43.8†	41‡	41	39
Polyunsaturated, g	8.3	10.3	—	—
Monounsaturated, g	3.5	4.6	—	—
Saturated, g	32	26.2§	—	—
Linoleic acid, g	5.7	9	5.6	7.8
Carbohydrate, g	86.1‖	90#	76.9	79
Mineral				
Calcium, mg	1,460	1,340	784	890
Phosphorus, mg	730	670	463	490
Magnesium, mg	100	55	67.2	59
Iron, mg	3.0	2	13.4	13.3
Zinc, mg	12.2	12.2	9.0	9.2
Manganese, µg	100	51	75	111
Copper, µg	2,030	1,010	896	890
Iodine, µg	50	200	112	111
Sodium, mEq	15	13.9	10.7	11.3
Potassium, mEq	27	21	27.1	20
Chloride, mEq	19	19.4	15.8	16.3
Vitamin				
A, USP Units	10,081	10,100	3,433	3,330
D, USP Units	1,210	2,200	522	590
E, USP Units	32.3	51	27	30
K, µg	97	65	82	59
Thiamin (B_1), µg	2,016	1,620	1,642	1,480
Riboflavin (B_2), µg	5,000	2,400	1,119	1,480
Pyridoxine, µg	2,016	1,220	746	740
B_{12}, µg	4.4	2	3.0	2.2
Niacin, mg	40.3	32.0	14.5	14.8
Folic acid, µg	298	280	187	192
Pantothenic acid, mg	15.3	9.7	6.0	6.3
Biotin, µg	298	32	67	44
C (ascorbic acid), mg	298	162	112	118
Choline, mg	81	97	119	111
Inositol, mg	48.4	138	45	220

*24 cal/oz; 81 cal/dL; †medium-chain triglyceride (MCT) oil, 50%; soy oil, 30%; coconut oil, 20%; ‡MCT oil, 40%; soy oil, 40%; coconut oil, 20%; §included 17.4 g MCT oils; ‖lactose, 50%; glucose polymers, 50%; #glucose polymers, 60%; lactose, 40%.
‡Nonfat milk, whey protein concentrate.

TABLE A-31 Human Milk Fortifiers for Premature Infants Fed Human Milk: Nutrients Provided When Added to 100 mL of Human Milk

Nutrient	*Enfamil Human Milk Fortifier (4 pkt) (Mead Johnson, Evansville, IN)*	*Similac Human Milk Fortifier (4 pkt) (Ross Laboratories, Columbus, OH)*	*Similac Natural Care Fortifier (Liquid, 100 mL)* (Ross Laboratories)*
Energy, kcal	14	14	80
Protein, g	1.1	1.0	2.2
Fat, g	0.65	0.36	4.4
Linoleic acid, mg	90	0	565
µ-Linolenic acid, mg	11	0	
Carbohydrate, g	1.1	1.8	8.5
Vitamin A, IU	950	620	1,008
Vitamin D, IU	150	120	121
Vitamin E, IU	4.6	3.2	3.2
Vitamin K, µg	4.4	8.3	9.7
Vitamin C (ascorbate), mg	12	25	30
Thiamin, µg	150	233	202
Riboflavin, µg	220	417	500
Pyridoxine, µg	115	211	202
Niacin, mg	3	3.57	4
Pantothenate, mg	0.73	1.5	1.5
Biotin, µg	2.7	26	30
Folate, µg	25	23	30
Vitamin B_{12}, µg	0.18	0.64	0.44
Calcium, mg	90	117	169
Phosphorus, mg	45	67	94
Magnesium, mg	1	7	9.7
Iron, mg	1.44	0.35	0.32
Zinc, mg	0.72	1	1.2
Manganese, µg	10	7.2	9.7
Copper, µg	44	170	202
Sodium, mEq	0.48	0.65	1.50
Potassium, mEq	0.51	1.6	2.7
Chloride, mEq	0.25	1.1	1.8

*Similac Natural Care is to be diluted 1:1 with human milk.

TABLE A-32 Increasing the Caloric Density of Human Milk and Infant Formula

kcal/oz	*Human Milk Milk Volume*	*Powdered Standard Infant Formula*
24	4 oz	1¼ tsp
30	4 oz	1 T
	Infant Formula (Powdered)	
kcal/oz	*Amount Powder*	*Volume Water*
24	1¼ cup	29 oz (32/3 cups)
30	1½ cup	29 oz (32/3 cups)
	Infant Formula (Liquid Concentrate)	
kcal/oz	*Volume Concentrate*	*Volume Water*
24	13 oz (1 can)	8 oz (1 cup)
28	13 oz (1 can)	5.5 oz (1 cup)
30	13 oz (1 can)	4 oz (½ cup)

Other Additives

Medium-chain triglyceride oil contains 7.7 kcal/mL; 1 tsp contains 39 kcal
Vegetable oil contains 40 kcal/tsp
Polycose liquid contains 60 kcal/oz; polycose powder contains 8 kcal/tsp

TABLE A-33 Composition of Special Infant Formulas

Formula	*Protein g/dL*	*Protein Source*	*Fat g/dL*	*Fat Source*	*Carbohydrate g/dL*	*Carbohydrate Source*	*Na mg/L*	*K mg/L*	*Ca mg/L*	*P Mg/L*	*Indications*	*Manufacturer*
Alimentum	1.9	Casein hydrolysate	3.7	50% MCT, 50% LCFA	6.9	Sucrose, modified tapioca starch	297	797	709	507	Multiple food allergies, impaired GI function	Ross
Pregestimil	1.9	Casein hydrolysate	3.8	55% MCT, 45% LCFA	6.9	Corn syrup solids, modified cornstarch, dextrose	264	736	635	426	Multiple food allergies, impaired GI function	Mead Johnson
Portagen	2.4	Na caseinate	3.2	85% MCT, 15% LCFA*	7.8	Corn syrup solids, sucrose	372	845	635	473	Fat malabsorption	Mead Johnson
Neocate Infant	2.5	Amino acids	3	Safflower, coconut, soy	7.8	Corn syrup solids	249	1,034	827	621	Multiple food allergies	SHS North America
Nutramigen	1.9	Casein hydrolysate + added amino acids	3.4	Palm olein, soy, coconut, high-oleic safflower oil	7.5	Corn syrup solids, modified cornstarch	320	740	640	430	Protein/ malabsorption problems	Mead Johnson

*Only 3.5% of calories are derived from linoleic acid. Supplementation with essential fatty acid mixture may be required.
GI = gastrointestinal; LCFA = long-chain fatty acid; MCT = medium-chain triglyceride.

TABLE A-34 Enteral Products Grouped by Usage Indication

Standard adult oral	Boost, Ensure High Calcium, Ensure, Ensure Light, NuBasics, ReSource Standard
Standard adult tube feeding	FiberSource Standard, Isocal, Isosource Standard, Jevity, Nutren 1.0, Osmolite, Ultracal
High-protein oral	Boost High Protein, Ensure High Protein, Ensure Plus HN, Meritene, NuBasics VHP
High-protein tube feeding	FiberSource HN, Isocal HN, Isosource HN, Jevity Plus, Osmolite HN, Osmolite HN Plus, ProBalance, Promote, Ultracal HN Plus
1.5 calorie/mL	Boost Plus, Comply, Ensure Plus, NuBasics Plus, Nutren 1.5, ReSource Plus
2.0 calorie/mL	Deliver 2.0, NovaSource 2.0, NuBasics 2.0, Nutren 2.0, ReSource 2.0, TwoCal HN
Standard Pediatric (> 1 yr of age)	Kindercal, Kindercal TF, Nutren Jr., Pediasure, ReSource Just For Kids
Blenderized	Compleat, Compleat Pediatric
Clear fortified liquid	Citrotein, Enlive, ReSource Fruit Beverage
Peptide-based adult	Alitraq, Criticare HN, Peptamen, Peptamen 1.5, Peptamen VHP, Perative, SandoSource Peptide, Vital High Nitrogen
Peptide-based pediatric	Pepdite One+, Peptamen Jr.
Free amino acid adult	EO28 Extra, Tolerex, Vivonex T.E.N., Vivonex Plus, Vivonex RTF
Free amino acid pediatric (> 1 yr of age)	Elecare, Neocate Junior, Neocate One+, Pediatric EO28, Vivonex Pediatric
Immune enhancing	Immun-Aid, Impact, Impact 1.5, Impact Glutamine
Wound healing	Crucial, Intensical, Isosource VHN, NutriFocus, Protain XL, Reabilan, Reabilan HN, Replete, Traumacal
Diabetes	Choice dm beverage, Choice dm TF, DiabetiSource, Glucerna, Glytrol, ReSource Diabetic
Kidney disease	Amin-Aid, Magnacal Renal, Nepro, NovaSource Renal, NutriRenal, Renalcal Diet, Suplena
Liver disease	Hepatic-Aid, NutriHep
Pulmonary disease	Isosource 1.5, NovaSource Pulmonary, NutriVent, Oxepa, Pulmocare, Respalor
HIV/AIDS	Advera
Inflammatory bowel disease	Modulen, Optimental, Subdue, Subdue Plus
Fat malabsorption	Lipisorb, Portagen
Carbohydrate modulars	Moducal, Polycose
Protein modulars	Casec, ProMod
Calorie enhancers	Additions, Duocal, PFD2, Product 3232A, Product 80056
Fat modulars	MCT oil, Microlipid

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; MCT = medium-chain triglyceride.

TABLE A-35 Selected Enteral Products for Special Indications

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
Advera*	1,280	Soy protein hydrolysate, Na caseinate, 60	Maltodextrin, sucrose, soy fiber, 215.8	Canola, MCT (19%) and sardine oils, 22.8	8.9	High-calorie, high-protein complete formula, designed for people with HIV or AIDS
Additions	526/ 100 g	Na caseinate, whey protein isolate, 31.6/100 g	Corn syrup solids, 47.4/100 g	Canola oil, soy lecithin, 26.3/100 g		Neutral-flavored powdered blend of protein, carbohydrate, and fat used to supplement regular food
Alitraq*	1,000	Soy hydrolysate, amino acids, whey protein concentrate, lactalbumin hydrolysate, 52.5	Maltodextrin, sucrose, fructose, 165	Safflower and MCT (53%) oils, 15.5		Elemental formula with added glutamine, designed for patients with impaired GI function
Amin-aid‡	1,956	Essential amino acids + histidine, 19.4	Maltodextrin, sucrose, 366	Partially hydrogenated soybean oil, lecithin, 46.2		Essential amino acid and calorie supplement for patients with renal failure; contains no vitamins or minerals
Boost (with fiber)§	1,010	Milk protein concentrate, 43	Corn syrup solids, sucrose (soy fiber, acacia, microcrystalline cellulose), 173 (178)	Canola, high-oleic sunflower, and corn oils, 18	(11.1)	Nutritionally complete liquid food, lactose free
Boost High Protein§	1,010	Milk protein concentrate, Na and Ca caseinate, 61	Corn syrup solids, sucrose, 139	Canola, high-oleic sunflower, and corn oils, 23		High-protein, nutritionally complete oral supplement
Boost Plus§	1,520	Na and Ca caseinate, 59	Corn syrup solids, sucrose, 200	Canola, high-oleic sunflower and corn oils, 58		High-calorie nutritionally complete oral supplement
Casec§	380/ 100 g	Ca caseinate, 90/100 g	0	Soy lecithin, 2/100 g		Concentrated, intact, powdered protein supplement
Choice dm beverage§	930	Ca and Na caseinate, milk protein concentrate, 39	Maltodextrin, sucrose, soy fiber, acacia, microcrystalline cellulose, 93	Canola, high-oleic sunflower, and corn oils, 43	11	Fiber-containing oral supplement, designed for people with diabetes
Choice dm TF§	1,060	Milk protein concentrate, casein, 45	Maltodextrin, micro-crystalline cellulose, soy fiber, acacia, 119	Canola, high-oleic sunflower, corn, and MCT (10%) oils, 51	14.4	Nutritionally complete tube feeding with fiber for patients with abnormal glucose tolerance
Citrotein‖	730	Pasteurized egg white solids, 41	Sucrose, maltodextrins, 120	Mono- and diglycerides, soybean oil, 1.6		Clear, fruit-flavored liquid nutrition, low in fat, lactose and gluten free
Compleat‖	1,070	Beef, Ca caseinate, 43	Hydrolyzed cornstarch, fruits, vegetables, 140	Canola oil, beef, 37	4.3	Blenderized tube feed formulated from traditional foods
Compleat Pediatric‖	1,000	Beef, Na and Ca caseinate, 38	Hydrolyzed cornstarch, fruits, vegetables, apple juice, 130	High-oleic sunflower, soybean, MCT (18%) oils, 39	4.4	Intact protein, formulated from traditional foods including meats, vegetables, and fruit
Comply§	1,500	Na and Ca caseinate, 60	Maltodextrin, 180	Canola, high-oleic sunflower, MCT (20%), and corn oils, 61		Nutritionally complete, high calorie formula for tube feeding
Criticare HN§	1,060	Casein hydrolysate, amino acids, 38	Maltodextrin, modified cornstarch, 220	Safflower oil, emulsifiers, 5.3		Ready-to-use elemental formula—50% small peptides, 50% amino acids
Crucial	1,500	Hydrolyzed casein, L-arginine, 94	Maltodextrin, 135	MCT oil (50%), deodorized fish oil, soy oil, soy lecithin, 68		High-calorie and protein peptide-based formula designed for critically ill patients
Deliver 2.0§	2,000	Na and Ca caseinate, 75	Corn syrup, 200	Soy and MCT (30%) oils, 101		High-calorie and high-nitrogen complete liquid diet

Continues

TABLE A-35 Selected Enteral Products for Special Indications (Continued)

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
DiabetiSource[‖]	1,000	Ca caseinate, beef, 50	Maltodextrin, fructose, vegetables, fruits, 90	High-oleic sunflower, canola, and beef oils, 49	4.3	Traditional food ingredients, designed for abnormal glucose tolerance
Duocal[#]	490/ 100 g	0	Hydrolyzed cornstarch, 73	Corn, coconut, MCT (35%) oils, 22		Powdered carbohydrate and fat supplement
Elecare*	1,000	Free L-amino acids, 30	Corn syrup solids, 107	High-oleic safflower, MCT (33%) and soy oils, 48		Complete amino acid–based diet for children > 1 yr of age with intact protein intolerance
EO28 Extra (flavored)[#]	886 (854)	Free amino acids, 25	Dried glucose syrup (sugar, sodium saccharin, dried glucose syrup), 118 (110)	MCT (35%), canola, hybrid safflower oils, 35		Nutritionally complete elemental diet for adults and children > 5 yr of age with GI impairment
Enlive*	1,250	Whey protein isolate, 41	Maltodextrin, sucrose, 267	0		High-calorie, fat-free clear liquid oral supplement
Ensure Fiber with FOS*	1,060	Na and Ca caseinate, soy protein isolate, 38	Maltodextrin, sucrose, soy fiber, oat fiber, fructo-oligosaccharides, 177	High-oleic safflower, canola, and corn oils, 26	11.8	Complete or supplemental nutrition with fiber and FOS
Ensure*	1,060	Ca caseinate, soy protein isolate, whey protein concentrate, 37.2	Corn syrup, sucrose, maltodextrin, 167	Corn, high-oleic safflower, and canola oils, 25		Nutritionally complete oral supplement
Ensure High Calcium*	950	Ca and Na caseinates, soy protein isolate, 51	Sucrose, maltodextrin, 131	High-oleic safflower, canola, and soy oils, 25		Supplemental high-protein oral nutrition with 1,688 mg Ca/L
Ensure High Protein*	950	Ca and Na caseinates, soy protein isolate, 51	Sucrose, maltodextrin, 131	High-oleic safflower, canola, and soy oils, 25		High-protein complete oral nutritional supplement
Ensure Light*	850	Ca caseinate, 42	Sucrose, maltodextrin, 141	High-oleic safflower and canola oils, 13		Lower-calorie, lower-fat nutritionally complete oral supplement
Ensure Plus*	1,500	Na and Ca caseinate, soy protein isolate, 55	Corn syrup, maltodextrin, sucrose, 211	High-oleic safflower, canola, and corn oils, 48		High-calorie, complete oral supplement
Ensure Plus HN*, flavored (unflavored RTH)	1,500	Na and Ca caseinate, soy protein isolate, 62 (63)	Maltodextrin, sucrose (maltodextrin), 200 (204)	Corn oil (high-oleic safflower, canola, and MCT [20%] oils), 50 (49)		High-calorie, high-nitrogen nutritionally complete liquid for oral supplementation or tube feeding
f.a.a.	1,000	Free amino acids, 50	Maltodextrin, cornstarch, 176	Soybean and MCT (25%) oils, 11.2		Low-fat elemental diet with 20% of calories from free amino acids
FiberSource Standard II	1,200	Soy concentrate, soy isolate, 43	Corn syrup, hydrolyzed cornstarch, 170	Canola and MCT (20%) oils, 39	10	Higher calories, contains soluble and insoluble fiber
FiberSource HN[‖]	1,200	Soy isolate, soy concentrate, 53	Corn syrup, hydrolyzed cornstarch, 160	Canola and MCT (20%) oils, 39	10	Higher calories and protein; contains soluble and insoluble fiber
Glucerna*	1,000	Na and Ca caseinate, 41.8	Maltodextrin, fructose, soy fiber, 95.6	High-oleic safflower and canola oils, soy lecithin, 54.4	14.1	Supplemental or complete tube feeding or oral nutrition for patients with abnormal glucose tolerance
Glytrol	1,000	Ca and K caseinate, 45	Maltodextrin, corn starch, fructose, gum arabic, pectin, soy polysaccharides, 100	Canola, high-oleic safflower, and MCT (20%) oils, soy lecithin, 47.5	15	Fiber containing, fat and CHO designed for better glucose control
HepaticAid[‡]	1,176	L-Amino acids, 44	Maltodextrin, sucrose, 169	Partially hydrogenated soybean oil, lecithin, mono- and diglycerides, 36		High BAA and calorie supplement for patients with chronic liver disease; contains no vitamins or minerals
Immun-Aid[‡]	1,000	Lactalbumin, supplemental amino acids, 80	Maltodextrin, 120	MCT (50%) and canola oils, 22		High-nitrogen nutritionally complete feeding for immunocompromised patients

Continues

TABLE A-35 Selected Enteral Products for Special Indications (Continued)

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
Impact (with fiber)[‖]	1,000	Na and Ca caseinate, L-arginine, 56	Hydrolyzed cornstarch, 130 (140)	Palm kernel, sunflower, and menhaden oils, 28 (10)		High protein; designed for critically ill patients
Impact Glutamine[‖]	1,300	Wheat protein hydrolysate, free amino acids, sodium caseinate, 78	Maltodextrin, 150	Palm kernel, menhaden, and sunflower oils, 43		High-glutamine (15 g/L), immune-enhancing enteral formula for critically ill patients
Intensical[§]	1,300	Casein hydrolysate, L-arginine, 81	Maltodextrin, modified cornstarch, 150	Canola, MCT (25%), high-oleic sunflower, corn, refined menhaden oils, 42		Complete elemental nutrition for highly metabolically stressed patients
Impact 1.5[‖]	1,500	Na and Ca caseinate, L-arginine, 84	Hydrolyzed cornstarch, 140	Palm kernel and sunflower oils, menhaden and MCT (55%) oils, 69		High calorie and high protein; designed for critically ill patients
Isocal[§]	1,060	Ca and Na caseinate, soy protein isolate, 34	Maltodextrin, 135	Soy and MCT (20%) oils, 44		Nutritionally complete, isotonic, tube feeding formula
Isocal HN[§]	1,060	Na and Ca caseinate, soy protein isolate, 44	Maltodextrin, 124	Soy and MCT (40%) oils, 45		Moderately high-nitrogen, isotonic, nutritionally complete tube feeding
Isocal HN Plus[§]	1,200	Milk protein concentrate, casein, 54	Maltodextrin, 156	Canola, MCT (30%), high-oleic sunflower and corn oils, 40		Moderately high-nitrogen, 1.2 calorie/mL, nutritionally complete tube feeding
Isosource Standard[‖]	1,200	Soy isolate, 43	Corn syrup, hydrolyzed cornstarch, 170	Canola and MCT (20%) oils, 39		High-calorie soy protein formula
Isosource 1.5 Cal[‖]	1,500	Na and Ca caseinate, 68	Hydrolyzed cornstarch, sugar, 170	Canola, MCT (30%), and soybean oils, 65	8	High calorie, high nitrogen; contains soluble and insoluble soy fiber
Isosource HN[‖]	1,200	Soy isolate, 53	Corn syrup, hydrolyzed cornstarch, 160	Canola and MCT (20%) oils, 39		High-nitrogen, high-calorie soy protein formula
Isosource VHN[‖]	1,000	Na and Ca caseinate, 62	Hydrolyzed cornstarch, 130	Canola and MCT (50%) oils, 29	10	High nitrogen, isotonic; contains soluble and insoluble fiber
Jevity*	1,060	Na and Ca caseinate, 44.3	Maltodextrin, soy fiber, corn syrup, 155	High-oleic safflower, canola, and MCT (20%) oils, 34.7	14.4	Isotonic fiber-containing nutritionally complete tube feeding formula
Jevity Plus*	1,200	Na and Ca caseinate, 56	Corn syrup, maltodextrin, fructo-oligosaccharides, fiber blend, 173	High-oleic safflower, canola, and MCT (19%) oils, 39.3	12	Higher-calorie, high-protein, fiber-containing tube feeding
Kindercal (with fiber)[§]	1,060	Milk protein concentrate, 30	Maltodextrin, sucrose, 135	Canola, high-oleic sunflower, corn, and MCT (20%) oils, 44 (6.3)		Nutritionally complete, lactose-free oral beverage for children 1–10 yr
Kindercal TF (with fiber)[§]	1,060	Milk protein concentrate, 30	Sugar, maltodextrin, 135	Canola, high-oleic sunflower, MCT (20%), and corn oils, 44 (6.3)		Nutritionally complete, isotonic, lactose-free tube feeding for children 1–10 yr of age
Lipisorb Liquid[§]	1,350	Na and Ca caseinate, 57	Maltodextrin, sucrose, 161	MCT (85%) and soy oils, 57		Nutritionally complete MCT formulation for patients with fat malabsorption
MCT oil[§]	115 kcal/tbsp, 8.3 kcal/g	—	—	Fractionated coconut oil, 934		Fat supplement or substitute for patients with long-chain fatty acid malabsorption; directly absorbed into portal vein
Magnacal Renal[§]	2,000	Na and Ca caseinate, 75	Maltodextrins, sucrose, 200	Canola, high-oleic sunflower, MCT (20%), and corn oils, 101		Very-high-calorie, complete oral or tube feeding formula designed for patients on hemodialysis

Continues

TABLE A-35 Selected Enteral Products for Special Indications (Continued)

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
Meritene[‖] (mixed with whole milk)	1,080	Nonfat and whole milk, 69	Lactose, corn syrup solids, sucrose, 120	Milk fat, 34		High-protein oral supplement, concentrated with vitamins and minerals, low in fat and cholesterol, high calcium, gluten free; mix with whole or skim milk
Microlipid[§]	4,500	—	—	Safflower oil, 506		50% fat emulsion for special dietary use in oral or tube feeding formulas
Moducal[§]	375 kcal/ 100 g	—	—	Maltodextrin, 95 g/100 g		Powdered, low-osmolality calorie supplement consisting of glucose polymers
Modulen IBD[†]	1,000	Acid casein, 36	Sugar, 108	Milk fat, MCT (25%), and corn oils, 46		Oral intact protein formula designed for people with Crohn's disease
Neocate Jr.[#]	1,000	Free amino acids, 30	Corn syrup solids, 104	MCT (35%), canola, hybrid safflower oils, 50		Nutritionally complete elemental formula for children > 1 yr with severe GI impairment; more vitamins and minerals than Neocate 1+
Neocate 1+[#]	1,000	Free amino acids, 25	Corn syrup solids, 146	MCT (35%), canola, hybrid safflower oils, 35		Elemental diet suitable for children > 1 yr with protein hypersensitivity or allergy
Nepro*	2,000	Ca, Mg, and Na caseinate, milk protein isolate, 70	Corn syrup, sucrose, fructo-oligosaccharides, 222.3	High-oleic safflower and canola oils, 95.6		Very-high-calorie, complete oral or tube feeding designed for dialysis patients
NovaSource Pulmonary[‖]	1,500	Na and Ca caseinates, 75	Corn syrup, sugar, 150	Canola and MCT (20%) oils, 68	8	High-calorie and nitrogen formula, designed for pulmonary patients
NovaSource Renal[‖]	2,000	Na and Ca caseinate, L-arginine, 74	Corn syrup, frucrose, 200	High-oleic sunflower corn, and MCT (14%) oils, 100		Very high calorie; vitamin and mineral profile specifically formulated for dialysis patients, TetraBrik Pak
NovaSource 2.0[‖]	2,000	Ca and Na caseinate, 90	Corn syrup, sucrose, maltodextrin, 220	Canola and MCT (20%) oils, 87.5		Very high calorie, high nitrogen, reduced level of sodium, TetraBrik Pak
NuBasics[†]	1,000	Ca caseinate, 35	Corn syrup solids, sucrose, 132.4	Canola and corn oils, soy lecithin, 36.8		Oral supplement, lactose free, gluten free
NuBasics Plus[†]	1,500	Ca caseinate, 52.4	Corn syrup solids, sucrose, 176.4	Canola and corn oils, soy lecithin, 64.8		High-calorie, lactose-free, oral supplement
NuBasics 2.0[†]	2,000	Ca and K caseinate, 80	Corn syrup solids, maltodextrin, sucrose, 196	MCT oil (75%), canola, soy lecithin, corn oils, 106		Very high calorie; 75% of fat from MCT
NuBasics VHP[†]	1,000	Ca and K caseinate, 62.4	Corn syrup solids, sucrose, 112.8	Canola and corn oils, soy lecithin, 33.2		High-protein, lactose-free, oral supplement
Nutren 1.0 (fiber)	1000	Ca and K caseinate, 40	Maltodextrin, corn syrup solids (soy polysaccharides), 127	Canola, MCT (25%), corn oils, soy lecithin, 38 (14)		Complete liquid nutrition, fiber for management of diarrhea or constipation
Nutren 1.5[†]	1,500	Ca and K caseinate, 60	Maltodextrin, 169.2	MCT (50%), canola, corn oils, soy lecithin, 67.6		High calorie for fluid restriction; 50% MCT oil
Nutren 2.0[†]	2,000	Ca and K caseinate, 80	Corn syrup solids, maltodextrin, sucrose, 196	MCT (75%), canola, soy lecithin, corn oils, 106		Very high calorie; severe fluid restriction; 75% MCT oil
Nutren Jr[†] (fiber)	1,000	Casein, whey, 30	Maltodextrin, sucrose (soy polysaccharides), 127.5	MCT (25%), canola, and soybean oils, soy lecithin, 42 (6)		Balanced formula designed to meet needs of children ages 1–10 yr

Continues

TABLE A-35 Selected Enteral Products for Special Indications (Continued)

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
NutriFocus	1,500	Na caseinate, milk protein isolate, soy protein isolate, arginine, 62	Corn syrup, sucrose, fiber blend, fructo-oligosaccharides, 215	Canola, corn, and high-oleic safflower oils, 49	10.5	High-calorie, high-protein oral supplement used for wound healing
NutriHep†	1,500	L-Amino acids, whey protein (50% BCAAs), 40	Maltodextrin, modified corn starch, 290	MCT (66%), canola, soy lecithin, and corn oils, 21.2		High BCAAs, low aromatic and ammonogenic amino acids
NutriRenal†	2,000	Ca and K caseinate, 70	Corn syrup solids, maltodextrin, sucrose, 205	MCT (50%), canola, corn oils, 104		High calorie, high biologic protein; designed for the dialyzed patient
NutriVent†	1,500	Ca and K caseinate, 67.5	Maltodextrin, 100	Canola, MCT (40%), corn oils, soy lecithin, 94		High fat content; designed to reduce CO_2 production
Optimental*	1,000	Soy protein hydrolysate, partially hydrolyzed Na caseinate, free arginine, 51	Maltodextrin, sucrose, fructo-oligosaccharides, 139	Sardine oil/MCT structured lipid, canola, and soybean oils, 28		Complete elemental oral or tube feeding formula designed for patients with malabsorptive conditions
Osmolite*	1,060	Na and Ca caseinates, soy protein isolate, 37	Maltodextrin, 151	High-oleic safflower, canola, and MCT (20%) oils, 35		Isotonic, low residue, complete nutrition for oral or tube feeding use
Osmolite HN*	1,060	Na and Ca caseinates, soy protein isolate, 44	Maltodextrin, 144	High-oleic safflower, canola, and MCT (20%) oils, 35		Isotonic, nutritionally complete, high-nitrogen, mild-flavored liquid for oral or tube feeding
Osmolite HN Plus*	1,200	Na and Ca caseinates, 56	Maltodextrin, 158	High-oleic safflower, canola, MCT (19%) oils, 39		High calorie, high nitrogen, complete oral or tube feeding
Oxepa	1,500	Na and Ca caseinates, 63	Sucrose, maltodextrin, 106	Canola, MCT (25%), borage and refined, deodorized sardine oils, 94		High-calorie complete tube feeding formula for patients with lung injury
Pediasure and Pediasure Enteral* (with fiber)	1,000	Na caseinate, whey protein concentrate, 30	Maltodextrin, sucrose, 110 (114)	High-oleic safflower, soy, and MCT (20%) oils, 50 (5)		Complete oral or tube feeding designed for patients ages 1–10 yr
Pediatric EO28#	1,000	Free amino acids, 25	Maltodextrin, sucrose, 146	MCT (33%), canola, high-oleic safflower oils, 35		Ready-to-feed, flavored elemental liquid for children > 1 yr old with severe GI impairment
Pepdite One+# (banana flavored)	1,000	Soy and pork hydrolysates, free amino acids, 31	Corn syrup solids (sucrose, aspartame), 106	MCT (35%), canola, safflower oils, 50		Semielemental formula for children > 1 yr old with severe GI impairment
Peptamen† (oral)	1,000	Enzymatically hydrolyzed whey, 40	Maltodextrin, cornstarch (sucrose), 127	MCT (70%), soybean, soy lecithin, 39		Peptide based, isotonic; designed for general malabsorption
Peptamen 1.5 (oral)	1,500	Enzymatically hydrolyzed whey, 60	Maltodextrin, cornstarch (sucrose), 191	MCT (70%), soybean, soy lecithin, 58.5		High calorie, peptide based, high percentage MCT oil designed for malabsorption
Peptamen VHP† (oral)	1,000	Enzymatically hydrolyzed whey, 62.5	Maltodextrin, cornstarch (sucrose), 104.5	MCT (70%), soybean, soy lecithin, 39.2		High protein, peptide based, high percentage MCT oil designed for general malabsorption
Peptamen Jr.† (oral)	1,000	Enzymatically hydrolyzed whey, 30	Maltodextrin, cornstarch (sucrose), 137.6	MCT (60%), soybean, and canola oils, soy lecithin, 38.5		Designed for children ages 1–10 yr, peptide based, 60% of fat from MCT oil
Perative*	1,300	Partially hydrolyzed Na caseinate, lactalbumin hydrolysate, L-arginine, 66.6	Maltodextrin, 177.2	Canola, MCT (40%), and corn oils, 37.4		Higher calorie; 40% of fat from MCT oil; designed for metabolically stressed patients
PFD 2§	400/100 g powder	26 mg taurine/100 g powder, 0	Corn syrup solids, sugar, modified cornstarch, 88/100 g	Soy oil, 4.8/100 g		Protein-free powdered supplement providing calories, vitamins, and minerals

Continues

TABLE A-35 Selected Enteral Products for Special Indications (Continued)

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
Polycose*	380/100 g powder, 2,000/L liquid	—	Glucose polymers from cornstarch, 94/100 g, 500/L	—		CHO calorie supplement, available in powder or liquid
Portagen (20 kcal/oz. dilution)[§]	67.6/ 100 mL	Sodium caseinate, 2.3 g/100 mL	Corn syrup solids, sucrose, 7.7 g/100 mL	MCT (86%) and corn oils, 3.2 g/100 mL		Nutritionally complete for infants and children < 2 yr; with inefficient conventional fat digestion or malabsorption, 3.6% kcal from linoleic acid
ProBalance[†]	1,200	Ca and K caseinate, 54	Maltodextrin, corn syrup solids, polysaccharides, gum arabic, 156	Canola, MCT (20%), and corn oils, soy lecithin, 40.8	10	Higher calorie, fiber containing for the mature adult
Product 3232A[§]	500/ 100 g powder	Casein hydrolysate, 22 g/100 g	Modified tapioca starch, 33 g/100 g	MCT (85%) and corn oils, 33 g/100 g		Protein hydrolysate formula free of mono- and disaccharides for use with added carbohydrate
Product 80056[§]	500/ 100 g powder	Taurine added, 0	Corn syrup solids, modified tapioca starch, 72/100 g	Corn oil, 23/100 g		Protein-free formula base for use with added protein, sodium, potassium, and chloride
ProMod*	4.2/g	Whey protein concentrate with lecithin, 75/100 g	—, < 10/100 g	—, < 9/100 g		Powdered protein supplement
Promote* (with fiber)	1,000	Sodium and calcium caseinate, soy protein isolate, 62.5	Maltodextrin, sucrose (oat and soy fiber), 130 (138)	High-oleic safflower, canola, MCT (19%) oil, soy lecithin, 26 (28)	(14.4)	High protein complete oral or tube feeding
Protain XL[§]	1,000	Na and Ca caseinate, 57	Maltodextrin, soy fiber, 145	Canola, high-oleic sunflower, MCT (20%) and corn oils, 30	9.1	Nutritionally complete, high protein, fiber containing; designed to aid with wound healing
Pulmocare*	1,500	Na and Ca caseinates, 62.6	Sucrose, maltodextrin, 106	Canola, MCT (20%), high-oleic safflower and corn oils, 93.3		High fat, low carbohydrate, complete oral or tube feeding; designed for pulmonary patients
Reabilan[†]	1,000	Enzymatically hydrolyzed casein and whey, 31.5	Corn syrup solids, cornstarch, 131.5	MCT (50%), soybean, and canola oils; soy lecithin; glyceryl monostearate, 40.5		Peptide based, low nitrogen, 50% of oil from MCT
Reabilan HN[†]	1,333	Enzymatically hydrolyzed casein and whey, 57.9	Corn syrup solids, cornstarch, 158	MCT (50%), soybean, and canola oils; soy lecithin; glyceryl monostearate, 54		Higher calorie, peptide based, 50% of oil from MCT; designed for GI impairment
Renalcal Diet[†]	2,000	Essential and select non-essential amino acids, whey protein, 34.4	Maltodextrin, modified cornstarch, 290.4	MCT (70%), canola, and corn oils; soy lecithin, 82.4		Very high calorie, low protein; designed to maintain positive nitrogen balance, added histidine for renal failure, negligible electrolytes
Replete[†] (with fiber)	1,000	Ca and K caseinate, 62.4	Maltodextrin, corn syrup solids (soy polysaccharides), 113.2	Canola and MCT (25%) oils, soy lecithin, 34 (14)		High protein, elevated vitamin and mineral profile; designed for wound healing
ReSource Diabetic[‖]	1,060	Na and Ca caseinates, soy protein isolates, 63	Hydrolyzed cornstarch, 100	High-oleic sunflower and soybean oils, 47	13	Fiber containing; designed for diabetics; TetraBrik Pak
ReSource Fruit Beverage[‖]	1,060	Whey protein isolate, 38	Sugar, corn syrup, 230	0		Fat-free clear liquid nutritional supplement
ReSource Just For Kids[‖] (with fiber)	1,000	Na and Ca caseinate, whey protein concentrate, 30	Hydrolyzed cornstarch, sucrose, fructose (chocolate only), 110	High-oleic sunflower, soybean, and MCT (20%) oils, 50	(6)	Complete formula designed for children ages 1–10 yr, available with fiber, TetraBrik Pak

Continues

TABLE A-35 Selected Enteral Products for Special Indications (Continued)

Product	*Energy, kcal/L*	*Protein Source, g/L*	*Carbohydrate Source, g/L*	*Fat Source, g/L*	*Fiber g/L*	*Purpose*
ReSource Plus‖	1,520	Na and Ca caseinates, soy protein isolate, 55	Corn syrup solids, sugar, 220	High-oleic sunflower and corn oils, 46		High calorie, lactose and gluten free; TetraBrik Pak
ReSource Standard‖	1,060	Na and Ca caseinates, soy protein isolates, 38	Corn syrup, sugar, 170	High-oleic sunflower and corn oils, 25		Nutritionally balanced, lactose and gluten free; TetraBrik Pak
ReSource 2.0‖	2,000	Ca and Na caseinates, 89	Corn syrup, sucrose, maltodextrin, 215	Canola and MCT (20%) oils, 89		Very high calorie; designed for medication pass supplement programs, pouch pak
Respalor§	1,500	Na and Ca caseinates, 75	Maltodextrin, sugar, 146	Canola, high-oleic sunflower, corn, and MCT (30%) oils, 68		High calorie; designed for patients with limited respiratory function, COPD
SandoSource Peptide‖	1,000	Casein hydrolysate, free amino acids, Na caseinate, 50	Hydrolyzed cornstarch, 160	MCT (54%) and soybean oils, hydroxylated lecithin, 17		High-protein, semielemental, low-fat formula
Subdue§	1,000	Hydrolyzed whey protein concentrate or casein hydrolysate, 50	Maltodextrin, modified cornstarch, sugar, 130	MCT (52%), canola, high-oleic sunflower, and corn oils, 34		Ready-to-use liquid peptide-based formula designed for malabsorption problems
Subdue Plus§	1,500	Hydrolyzed whey protein concentrate, 76	Maltodextrin, modified cornstarch, 186	MCT (47%), canola, high-oleic sunflower, and corn oils, 51		High-calorie, peptide-based liquid designed for impaired GI function
Suplena*	2,000	Na and Ca caseinates, 30	Maltodextrin, sucrose, 255.2	High-oleic safflower and soy oils, 95.6		Very-high-calorie, low-protein, complete formula for renal failure
Tolerex‖	1,000	Free amino acids, 21	Maltodextrin, modified cornstarch, 230	Safflower oil, 1.5		Nutritionally complete, truly elemental diet, low fat
Traumacal§	1,500	Na and Ca caseinates, 82	Corn syrup, sucrose, 142	Soy and MCT (30%) oils, 68		High calorie, high nitrogen for metabolically stressed patients
TwoCal HN*	2,000	Na and Ca caseinates, 84	Maltodextrin, sucrose, fructo-oligosaccharides, 219	High-oleic safflower, MCT (19%), and canola oils, 91		Complete very-high-calorie feeding with fructo-oligosaccharides
Ultracal§	1,060	Milk protein concentrate, casein, 45	Maltodextrin, microcrystalline cellulose, soy fiber, acacia, 142	Canola, MCT (40%), high-oleic sunflower, and corn oils, 39	14.4	Nutritionally complete tube feeding formula with dietary fiber
Ultracal HN Plus§	1,200	Milk protein concentrate, casein, 54	Maltodextrin, microcrystalline cellulose, soy fiber, acacia, 156	Canola, MCT (30%), high-oleic sunflower, and corn oils, 40	10.5	Moderately high-nitrogen, nutritionally complete tube feeding formula with dietary fiber
Vital High Nitrogen*	1,000	Partially hydrolyzed whey, meat, soy, free essential amino acids, 41.7	Maltodextrin, sucrose, 185	Safflower and MCT (45%) oils, 10.8		Nutritionally complete, peptide-based formula for patients with impaired GI function
Vivonex T.E.N.‖	1,000	Free amino acids, 38	Maltodextrin, modified cornstarch, 210	Safflower oil, 2.8		Free amino acids plus, additional glutamine; designed for GI impairment
Vivonex Plus‖	1,000	Free amino acids, 45	Maltodextrin, modified cornstarch, 190	Soybean oil, 6.7		High-nitrogen, very-low-fat elemental diet; additional glutamine arginine and BCAAs
Vivonex Pediatric‖	800	Free amino acids, 24	Maltodextrin, modified cornstarch, 130	MCT (68%) and soybean oils, 24		Nutritionally complete, elemental formula for children; can be flavored with Vivonex Flavor Packets
Vivonex RTF‖	1,000	Free amino acids, 50	Maltodextrin, modified cornstarch, 175	Soybean and MCT (40%) oils, 12		Ready-to-use high-nitrogen, low-fat elemental diet for use in stressed, catabolic patients

*Ross Products Division, Abbott Laboratories, Columbus, OH; †Nestle Clinical Nutrition, Deerfield, IL; ‡B. Braun, Irvine, CA; §Mead Johnson Nutritionals, Evansville, IN; ‖Novartis Nutrition Corp, Minneapolis, MN; #Scientific Hospital Supplies North America, Gaithersburg, MD.

AIDS = acquired immune deficiency syndrome; BCAA = branched-chain amino acid; CHO = choline; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; HIV = human immunodeficiency virus; MCT = medium-chain triglyceride.

TABLE A-36 Selected Modular Formulas Used in Pediatrics

	Source			
Supplements	*Protein*	*Fat*	*Carbohydrate*	*Manufacturer*
Promod	Whey	—	—	Ross
Casec	Ca caseinate	—	—	Mead Johnson
Microlipid	—	Safflower oil	—	Mead Johnson
MCT oil	—	Fractionated coconut oil	—	Mead Johnson
Polycose	—	—	Glucose polymers	Ross
Moducal	—	—	Maltodextrin	Mead Johnson
Duocal	—	Blend of refined vegetable oil (corn + coconut) and MCT oil (fractionated coconut)	Hydrolyzed cornstarch	SHS North America

Information from manufacturers.
MCT = medium-chain triglyceride.

TABLE A-37 Selected Modular Formulas Used in Pediatrics: Miscellaneous

Other Modular Supplements	*Caloric Sources*	*Indications*	*Manufacturer*
Ross Carbohydrate Free	Protein and fat	Intolerance to type or amount of carbohydrate in standard solutions; carbohydrate added prior to use	Ross
Protein-Free Diet Powder (Product 80056)	Carbohydrate and fat	Use in children with specific amino acid requirements; protein added prior to use	Mead Johnson
Mono- and Disaccharide-Free Powder (Product 3232A)	Protein and carbohydrate	Supplement to breast milk in the premature infant	Mead Johnson

TABLE A-38 Selected Metabolic Disorders for Which Nutritional Therapy is Used

Disorder	*Nutritional Therapy*	*Enteral Products Used*
β-Ketothiolase deficiency	Low protein High carbohydrate	
Biotinidase deficiency	Biotin supplementation	
Galactosemia	Galactose restriction ± calcium supplementation	Soy based (Prosobee,* Isomil†)
Glutaricaciduria type 1	Lysine and tryptophan restriction Riboflavin supplementation Carnitine supplementation	Analog XLys XTrypt† Maxamaid XLys XTrypt‡ Glutarex-1,† Glutarex-2†
Glycogen storage disease types I and III	High carbohydrate (50–60% of kcal) Low fat (15–30%) Protein (5–10% of kcal) Regular feeding regimen Low cholesterol	Cornstarch
Hereditary fructose intolerance	Fructose restriction Vitamin C supplementation	Fructose, sucrose free
Homocystinuria (cystathionine β-synthase deficiency)	Methionine restriction Cystine supplementation ± vitamin B_6 supplementation ± betaine supplementation	HOM-1,* HOM-2,* Analog XMet,‡ Maxamaid XMet‡ Hominex-1,* Hominex-2†
Isovaleric acidemia	Leucine restriction Glycine supplementation ± carnitine supplementation	Analog XLeu, Maxamaid XLeu‡
Long-chain acyl-CoA dehydrogenase (LCAD) deficiency	Low fat MCT acceptable Avoid prolonged fasting ± carnitine supplementation	Portagen* ProViMin† (add fat and carbohydrate) Tolerex, Vivonex§ as overnight glucose source
Long-chain hydroxy acyl-CoA dehydrogenase (LCHAD) deficiency	Low fat Avoid MCT Avoid prolonged fasting ± carnitine supplementation	ProViMin† (add fat and carbohydrate) Tolerex, Vivonex§ as overnight glucose source
Maple syrup urine disease	Valine, isoleucine, and leucine restriction Thiamin supplementation	Analog MSUD‡ Maxamaid MSUD,‡ MSUD-1,* MSUD-2* Murex-1,† Murex-2†
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Low fat Avoid MCT ± carnitine supplementation Avoid prolonged fasting	
Methylmalonicacidemia	Methionine, valine, threonine, and isoleucine restriction ± vitamin B_{12} supplementation	Analog XMTVI,‡ Maxamaid XMVTI‡ OS-1,† OS-2* Propimex-1,† Propimex-2†
Multiple acyl-CoA dehydrogenase deficiency (glutaricaciduria type II)	Fat restriction ± protein restriction Riboflavin supplementation Carnitine supplementation	
Phenylketonuria	Phenylalanine restriction Tyrosine supplementation	Analog XP,‡ Maxamaid XP,‡ Maxamum XP‡ Lofenalac,* Phenyl-Free,* PKU-1,* PKU-2,* PKU-3,* Phenex-1,† Phenex-2†
Propionic acidemia	Valine, isoleucine, methionine, and threonine restriction Carnitine supplementation ± biotin supplementation	Analog XMTVI,‡ Maxamaid XMTVI,‡ OS-1,* OS-2* Propimex-1,† Propimex-2†
Pyruvate dehydrogenase deficiency	High fat (60 + % of kcal) Low carbohydrate (20–30% of kcal) Thiamin supplementation	Mono- and Disaccharide-Free Diet Powder* Ross Carbohydrate Free (RCF)†
Tyrosinemia	Phenylalanine and tyrosine restriction ± methionine restriction Regular feeding regimen	Analog XPXT,‡ Analog XPTM,‡ Maxamaid XPXT,‡ Maxamaid XPTM,‡ Low Phe/Tyr Powder* TYR-1,* TYR-2* Tyromex-1,† Tyromex-2†
Urea cycle disorders	Protein restriction Essential amino acid supplementation Arginine or citrulline supplementation Sodium benzoate and sodium phenylacetate (or sodium phenylbutyrate)	Cyclinex-1,† Cyclinex-2† Protein-Free Diet Powder* UCD-1,* UCD-2*

Adapted from Baker S. Chapman & Hall.
MCT = medium-chain triglyceride.
*Mead Johnson Nutritional Division, Evansville, IN.
†Ross Laboratories, Columbus, OH.
‡Scientific Hospital Supplies, Gaithersburg, MD.
§Sandoz Nutrition Corporation, Minneapolis, MN.

INDEX