NUTRITIONAL and CLINICAL MANAGEMENT of CHRONIC CONDITIONS and DISEASES

Edited by
Felix Bronner

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Preface

Nutritional status is now recognized as a major determinant in health and disease. The course of virtually all chronic diseases is affected by the nutritional status of the ill person, and treatment and outcome of a disease can be markedly improved if the patient complies with recommended diet changes. This book and its predecessor, *Nutritional Aspects and Clinical Management of Chronic Disorders and Diseases* (CRC Press, 2003) are intended to help clinicians integrate nutritional management into overall clinical management. Whereas the earlier book deals largely with diseases of major organs, the current book discusses broader topics, such as obesity, pregnancy, and errors of metabolism, as well as diseases of organs not previously covered, the skin, and the oral cavity.

The first chapter, "Childhood Obesity," by Peebles and Hammer, deals with what is fast becoming a major public health issue in the United States and other developed countries. After introductory statistics that call attention to the fact that nearly half of U.S. children and youth aged 6 to 19 years are overweight, the authors discuss measures for determining adiposity; review critical growth periods; define and indicate the importance of the glycemic index; and then describe the effects of decreased physical activity, genetics, family, social situation, and hormonal factors. After discussing the relationship of obesity to specific diseases and conditions, including hypertension and sleep apnea, the authors proceed to a discussion of treatment, emphasizing the need for exercise, and review the various dietary and medical approaches to effective weight loss and maintenance of the loss. This chapter, similar to all that follow, has an extensive list of bibliographic references.

Keith and Rowell, in the second chapter, deal with weight control in the adult. They too begin by emphasizing that in the past generation or so obesity has become an epidemic in both the developed and developing worlds, due in part to the ready availability of high-energy foods and the marked increase in sedentary living. Keith and Rowell recognize that proper weight control depends on a realistic definition of what constitutes success. They then discuss the genetics of obesity, pointing out that genetic influences, while important, do not account for 60% of weight variance. Indeed, genetic influences alone cannot account for the dramatic increase in weight, with decrease in physical activity, consumption of energy-dense food, increased stress levels, and sleep disturbances contributing significantly to energy balance. An important part of the chapter describes the approach to the overweight patient, including the use of the tools WAVE and REAP, which are defined and explained in tables that describe how to use them, depending on the amount of time available to the clinician. The chapter summarizes pharmacologic advances that may help control obesity and concludes with an outlook to future advances.

In the third chapter, Sharma, Calleo-Cross, and Aronne discuss in detail the indication for bariatric surgery in very obese adults who have not responded to the kind of medical intervention described in the preceding chapter. These authors point

out that the burden placed on patients and society by severe obesity makes surgery a viable option, provided the surgeon selects the patients with great care. Gastric bypass surgery can make patients euglycemic long before they attain their ultimate, typically very profound weight loss. It can also improve cardiovascular status, respiratory insufficiency, and the sleep apnea syndrome. The chapter discusses contraindications to surgery, details preoperative screening, and describes the various operative procedures, including the Roux-en-Y bypass, the vertical banded gastroplasty, laparoscopic adjustable gastric banding, and the biliopancreatic diversion with duodenal switch.

The elderly constitute an increasing proportion of the population, and their nutritional management is an important part of their care, particularly since practices appropriate to the middle-aged adult may be inappropriate for the elderly. A striking example cited by Young and Apovian in Chapter 4 is the observation that some obesity in the elderly may in fact be protective and that excessive thinness may be undesirable for the very old. The chapter describes the physiologic changes that occur with aging and what they mean for nutrition of the elderly in terms of a modified food guide. It then proceeds to screening and assessment, evaluates over- and undernutrition in this population, and discusses in some detail the sarcopenia of aging. Even though nutritional approaches are important in the attempt to overcome the frailty and muscle loss so typical of the elderly in assisted living and nursing facilities, Young and Apovian emphasize that the as yet best approach to sarcopenia is resistance training.

Food allergy, a topic of interest to otherwise healthy individuals, is a condition that can lead to severe allergic reactions, even anaphylactic death. In the fifth chapter, Abba Terr discusses the normal immune response, allergic responses, and mechanisms of allergy. He describes the three types of reactions, based on the particular immune pathway involved in the disease, and enumerates and details the various allergic diseases and their clinical manifestations. Terr then discusses nonallergic immunologic diseases associated with food intolerance, such as celiac sprue, nonimmunological reactions to foods, and reactions to food additives. An extensive section of the chapter deals with diagnosis and treatment. While the only sure way to overcome food allergy is to eliminate the responsible food allergen, other methods of treatment are available, such as immunotherapy. Terr also calls attention to controversial practices and inappropriate diagnostic procedures, as well as unproven therapies, thereby strengthening the informed clinician's hand.

In Chapter 6, Brenner and Bhatia deal with nutritional management of pregnancy and lactation. Starting with recommendations for women of all childbearing ages, they tabulate recommended dietary allowances, adequate intakes, and calorie requirements with respect to body index and deal with specific nutrients, such as folic acid, calcium, and iron. They then outline specific recommendations for the pregnant woman, including a discussion of weight gain, specific nutrients, and dietary environmental hazards, such as mercury. The second half of the chapter deals with the management of lactation. Lactating mothers' concerns regarding quality and volume of milk are discussed, as is the topic of weight loss during the lactation period and the effects of alcohol, caffeine, and peanut consumption.

For appropriate nutritional advice to become an integral part of clinical management, the advice must be repeated often, in different ways, and adherence to the recommended dietary pattern must be monitored. This is another way of stating the need for persistent behavior change. In Chapter 7, Fleming, Curtin, and Bandini address this general topic, outlining the way behavior change can be altered and retained. In their introduction, the authors point out that nutritional adherence to a particular regimen not only demands personal commitment by the patient and family, but is also greatly influenced by the environment and its "pull." For example, weight control is more difficult when a person is surrounded by the ready availability of energy-dense foods. The authors then discuss the three basic psychological theories — applied behavior analysis, social cognitive theory, and the transtheoretical model — that govern behavioral interventions. This is followed by detailed descriptions of how advice, counseling, and education can reinforce a patient's change in behavior. A section on comprehensive intervention programs is followed by a practical model for promoting patient adherence, which is also outlined in a table. The chapter concludes with suggestions for future research.

In Chapter 8, Kimberlee and Reuben Matalon discuss inborn errors of metabolism, with phenylketonuria (PKU) the classic example of a genetic disease that can be treated by dietary intervention. They review the disease, discuss NIH treatment guidelines, and refer to the response to tetrahydrobiopterin (BH_4). The chapter then discusses maternal PKU, galactosemia (where lactose restriction can lead to dramatic improvement), biotinidase deficiency, isovaleric academia, maple syrup urine disease, and urea cycle defects.

In a compact chapter, R.K. Chandra discusses the relationship between malnutrition and the immune system. Malnutrition has long been known to aggravate the risk of infection, but nutrient excess can also impair the immune response. Impaired immune response is in fact the key pathogenic factor in the interaction between malnutrition and infection. Although nutrition plays an important role in the development and maintenance of immunity at all ages, Chandra discusses persons of three periods of life in detail: low birth weight infants, adolescents, and the elderly. He cites a number of diseases where nutrition plays an important role in enhancing immunity, including AIDS, the human immunodeficiency virus infection, a disease that has spread over the globe in but two decades. The chapter concludes with advice for the treating physician, with special reference to children and the elderly.

By now dental caries and periodontal disease are recognized to be chronic infections of the oral cavity that are markedly influenced by diet. In Chapter 10, Tanzer and Livingston consider diet and nutrition as they affect oral mucosal disease, gingival/periodontal disease, and dental caries. They also explore the consequences of tooth loss and review gaps in overall knowledge concerning the management of patients with nutritional problems. A notable aspect of the chapter is the detailed discussion of dental caries, a disease that arises as a result of infection, largely by *Streptococcus mutans*, provided the host consumes a diet high in fermentable carbohydrates. Caries may therefore be termed an opportunistic infection. Various strategies to inhibit caries are discussed, including the use of nonfermentable carbohydrates like xylitol. The chapter concludes by calling attention to the needs of

special patients, including those who have Sjögren's syndrome or gallbladder disease or who are edentulous.

In Chapter 11, McCusker, Marcy, Rothe, and Grant-Kels treat the relationship between skin and nutrition. Dermatitis herpetiformis and its relationship to gluten, acrodermatitis enterohepatica and its relationship to zinc, and erythropoietic porphyria and beta-carotene are dealt with first, as diseases with a known, nutrition-related epidemiology. Yet, the epidemiology of the most common skin disorder in the United States, acne vulgaris, is not fully known. The role of sugar in acne vulgaris has long been discussed, and the authors cite new evidence of a potential glycemic role, but their discussion of the nutritional aspects of this disease is much broader, including the role of macro- and micronutrients. Other skin diseases that receive detailed and extensive discussion are acne rosacea, acne dermatitis, psoriasis, melanoma, and nonmelanoma skin cancer. Treatment for each of these diseases is detailed in an extensive table that lists topical and oral agents, light and nutritional therapy, structure and function of a given agent, and comments thereon.

Proper function of the esophagus, stomach, and pancreas is clearly essential for food intake and adequate nutrition. For this reason, the prognosis for persons with upper gastrointestinal cancer is poor, and nutrition support for these patients assumes major importance in their care. In Chapter 12, Ferrone and Scolapio describe dietary issues that are linked to cancer incidence, such as the consumption of foods that contain N-nitroso compounds and the chewing of betel nuts, a widespread custom in India and other Asian countries. Almost three-quarters of people with esophageal cancer have dysphagia. The authors describe various procedures to minimize this condition, with emphasis on a properly designed nutritional regimen. Although the incidence of gastric cancer has declined in the United States, its fatality rate is very high, and there is much interest in exploring ways to improve treatment by adjuvant or neoadjuvant therapy. Diet may play a role in the risk for gastric cancer, and nutritional management of the gastric cancer patient is essential. Similarly, nutritional management of the pancreatic cancer patient following a Whipple procedure (pancreaticoduodenectomy) is essential and can help the patient lead a near-normal life after surgery. In patients with advanced pancreatic cancer, various dietary approaches have been explored, but data are insufficient for firm recommendations.

The last chapter, by Frankenfield and Smith, deals with the nutritional management of body wasting that occurs as a result of disease, a condition known as cachexia. Although there is commonality between simple malnutrition and cachexia, the latter is driven by an inflammatory response. In malnutrition the body adapts by sparing body protein, but this is not true in cachexia. The authors describe the inflammatory response in detail and then proceed to discuss monitoring and treatment of the condition. Ideally treatment includes controlling the infection or healing the injury. This may not be possible in chronic illness, but a balance of n-6 and n-3 fatty acids, with a ratio of between 2:1 and 4:1 in n-6 to n-3 fatty acids, appears to be a promising nutritional agent that promotes an anti-inflammatory milieu. This can be achieved by dietary means, albeit with difficulty. Yet, as Frankenfield and Smith point out, the dietary approach here may be more desirable than using pharmaceuticals to inhibit enzyme activity.

It is reassuring that nutritional recommendations in the various chapters, even though they treat different diseases and conditions, are essentially similar: Eat moderately but with variety, make vegetables and fruit an important part of your diet, be sure to consume appropriate amounts of micronutrients, have a low fat intake, but make sure the diet includes certain fatty acids. Clearly, then, nutrition has become important in all aspects of life.

My thanks to the contributors for sharing their clinical knowledge and their willingness, even insistence, on making nutritional management an integral part of patient management. I also thank CRC Press/Taylor and Francis for their support in making this book a reality.

Felix Bronner
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The Editor

Felix Bronner, Ph.D., physiologist and nutritionist, is professor emeritus at the University of Connecticut Health Center. A doctoral thesis at MIT on calcium metabolism in adolescent boys was the beginning of a long research career in bone and calcium metabolism and nutrition. A major aspect of Dr. Bronner's research has been the quantitative elucidation of active and passive calcium absorption in humans and experimental animals and of renal calcium movement, and a kinetic analysis of plasma calcium homeostasis.

Author of 114 refereed research papers and 76 book chapters, and editor of 53 books, treatises, and book series, Dr. Bronner has organized many scientific meetings and symposia and has trained graduate students and many postdoctoral fellows. He is the recipient of the 1975 Andre Lichtwitz prize awarded by the French National Institute for Health and Medical Research (INSERM) for excellence in calcium and phosphate research. In 1996 he was awarded an honorary doctorate by the École Pratique des Hautes Études, Paris, under the auspices of the French Ministry of Higher Education. He has been a visiting professor at the universities of Cape Town, Tel Aviv, Vienna, and Lyon and a visiting scientist at the Pasteur Institute in Paris, at the Weizmann Institute for Science in Rehovot, Israel, and at INSERM U 45, Lyon. He is a fellow of the American Association for the Advancement of Science and of the American Society for Nutritional Science and an honorary member of the Austrian Society for Bone and Mineral Research. A member of numerous professional societies, Dr. Bronner has served on the editorial boards of the *American Journal of Physiology, The Journal of Nutrition,* and *The American Journal of Clinical Nutrition*. He was the founder and first chair of the Gordon Research Conference on Bones and Teeth.

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Rebecka Peebles and Lawrence D. Hammer

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1.1 INTRODUCTION

Childhood overweight is quickly emerging as the most important public health issue facing young people. Among U.S. children ages 6 to 19 years in 1999 to 2002, 31.0% were at or above the 85th percentile for body mass index, and 16.0% were at or above the 95th percentile for body mass index (74). According to the NHANES III data collected between 1999 and 2000, the prevalence of overweight doubled among children 6 to 11 years of age and tripled among those 12 to 17 years of age. Of these, African American and Hispanic children are disproportionately affected (40). In the most recent Youth Risk Behavior Survey, 8% of American youth had not eaten the minimum recommended servings of fruits and vegetables during the 7 days preceding the survey, and 33.4% had engaged in an insufficient amount of physical activity (67). These figures also project disturbing economic consequences. From 1979–1981 to 1997–1999, the percentage of U.S. discharges for diabetes, gallbladder disease, sleep apnea, and obesity increased between twofold and fivefold. Obesity-associated annual hospital costs (based on 2001 constant U.S. dollar value) increased from $35 million during 1979–1981 to $127 million during 1997–1999 (150). From a socioeconomic standpoint, studies have shown that women who have been overweight complete fewer years of school, are 20% less likely to be married, and have a 10% higher rate of household poverty than women who have never been overweight, independent of baseline socioeconomic status and aptitude-test scores. In contrast, people with other chronic conditions show no socioeconomic differences from controls (66). Obese children and adolescents have been found to have significantly lower health-related quality of life scores across all domains, equal to those of children diagnosed with cancer, compared with normal-weight peers (129).

Childhood obesity is an important predictor of adult obesity (154), and children who suffer from overweight are at high risk for multiple medical complications during childhood and later in life (39). Multiple studies have documented the increased risk of mortality for adults associated with poor diet, physical inactivity, and an excessive body mass index (34,105). Overweight and obesity in adulthood are associated with diabetes, high blood pressure, high cholesterol, asthma, arthritis, and poor health status (104).

It is critical that physicians work to better understand, treat, and prevent childhood overweight. This chapter attempts to define etiologies, comorbidities, examination, and treatment of pediatric obesity and to outline future directions for public health advocacy.

1.2 DEFINITIONS OF OVERWEIGHT IN CHILDHOOD

The pediatric literature describes multiple measures of adiposity. These include skin-fold thickness measurements by calipers, electrical impedance techniques, and waist circumference, all of which have no pediatric norms and a high degree of variability in measurement. Dual energy x-ray absorptiometry (DEXA), densitometry, and magnetic resonance imaging are expensive and not accessible on a widespread basis.

Body mass index (BMI), or the Quetelet index, has been proposed in multiple position statements and by expert committees to be the measure of choice for defining childhood weight norms. The U.S. Centers for Disease Control currently recommends using BMI to classify a child's weight status in the following way: Children are defined as clinically *overweight* if their BMI exceeds the 95th percentile for age and as "at risk for overweight" if their BMI exceeds the 85th percentile for age (41,45,72,92; http://www.cdc.gov/nccdphp/dnpa/bmi/bmi-for-age.htm). BMI is calculated as the body weight in kilograms divided by the height in meters squared. Some authors use the BMI at the 95th percentile to define obesity, leading to some inconsistencies from one report to another. BMI measurements have some inherent limitations, in that they are not a direct measure of adiposity and some patients with a high BMI may not have excess adiposity, but rather a high degree of lean body mass. However, BMI measurements have correlated reasonably well with adiposity in numerous studies across different ethnic groups (41).

1.3 ETIOLOGIES

1.3.1 Critical Growth Periods

Children may be especially vulnerable metabolically to developing obesity during certain critical growth periods. These include the prenatal period, the period of "adiposity rebound," and early puberty (40,76). High birth weights have been shown to correlate positively with rates of obesity later in life. However, no studies have corrected birth weight for gestational age or birth height; they therefore need to be interpreted with caution. Multiple studies have shown that infants whose mothers

were energy deprived during the first two trimesters are at significantly increased risk for hypertension, diabetes, and obesity later in life. Evidence is strongest that maternal gestational diabetes is a major risk factor for the development of obesity in offspring (153).

The period of adiposity rebound has been defined as the age at which body fatness reaches a postinfancy low point (typically 4 to 6 years) and then begins to increase. Early adiposity rebound is inversely associated with BMI later in life. A recent study showed that children's BMI at 8 years of age was negatively predicted by age of adiposity rebound and positively predicted by their BMI at 2 years of age (135). Adult subjects with impaired glucose tolerance or diabetes have been found to have a low BMI up to the age of 2 years, followed by an early adiposity rebound and an accelerated increase in BMI until adulthood (22). Early menarche has also been shown to increase the risk of later developing obesity and the metabolic syndrome (55,59).

1.3.2 Impact of Food and Diet

Clearly, excessive calorie intake contributes to the development and maintenance of obesity. The modern proliferation of fast food and prepackaged foods is thought to contribute significantly to the current epidemic of childhood obesity. On a typical day, 30.3% of a sample of children reported consuming fast food. Fast-food consumption occurs in both genders, all ethnic groups, and all regions of the country. Children who eat fast food, compared with those who do not, consume more total energy, more energy per gram of food, more total fat, more total carbohydrate, more added sugars, more sugar-sweetened beverages, less fiber, less milk, and fewer nonstarchy vegetables and fruits (28). Adolescents have been shown to overconsume fast food regardless of body weight, although overweight teens show a heightened intake. Moreover, overweight adolescents are less likely to compensate for the energy in fast food by adjusting their energy intake throughout the day, when compared with normal weight peers (45). Strong data suggest that the high prevalence of soda machines in schools is positively linked to adolescent soda consumption, with soda providing a large proportion of caloric intake (155).

Some have hypothesized that carbohydrate intake and glycemic load have a major impact on childhood BMI. There is little controversy that diets restricted in sweetened drinks and containing whole grains and produce could benefit youth (136). Much work has been done to examine the glycemic index (GI) of different carbohydrate-containing foods and its possible effect on BMI, insulin regulation, and hunger cues.

The glycemic index describes the propensity of a carbohydrate-containing food to cause a rise in blood sugar after a meal. High GI foods are rapidly transformed into serum glucose. Obese teenage boys have been shown to display a significant increase in voluntary food intake after a high-GI meal, as compared with the effects of the consumption of medium-GI (53% greater) and low-GI (81% greater) meals (94). In addition, compared with the low-GI meal, the high-GI meal resulted in higher serum insulin levels, lower plasma glucagon levels, and lower postabsorptive plasma glucose (96–98).

Many studies have shown that dairy foods have a protective influence on body weight. The intake of calcium from dairy foods correlates negatively with 2-year changes in total body weight and body fat in young women, even when exercise level and energy intake are taken into account (93). Dairy food intake has also been found to be inversely correlated with the development of insulin resistance (115).

1.3.3 Decreased Physical Activity

The benefits of physical activity for long-term health status are well established, and a looming concern is that children in Western countries are engaging in less physical activity than in earlier decades. A recent report by the Centers for Disease Control reveals that 61.5% of children 9 to 13 years of age in the United States do not participate in any organized physical activity during their nonschool hours and that 22.6% do not engage in any free-time physical activity (117). The current decrease in funding for physical education classes in the United States has ominous health implications. Non-Hispanic Black and Hispanic children are significantly less likely than non-Hispanic White children to report involvement in organized activities. This is also true for children with parents of low income and low education levels. Overall, parents with low income and low education levels report that there are more barriers to physical activity for their children than for children from families with higher education and income (117).

When 11- to 15-year-old children were studied in San Diego, boys and girls with a BMI over the 85th percentile did significantly less vigorous exercise than those with a BMI under the 85th percentile. This study also showed that overweight boys, but not girls, were found to engage in exercise that was significantly more moderate and more sedentary than that of their normal-weight peers. When multiple diet, sedentary, and activity behaviors were studied, the only factor shown to be predictive of a higher BMI in adolescent boys was decreased physical activity (113).

1.3.4 Increased Sedentary Behaviors

Patterns of inactivity and an unhealthy lifestyle are often established in adolescence (6). Multiple studies have examined the effect of television viewing on health in young children and adolescents, with television viewing providing a model of the effects of sedentary behaviors. As much as 25% of children's waking hours are spent watching television or playing video games. Increased television time has been correlated with increased risk of the development of Type 2 diabetes (75). Many studies have shown a positive correlation between time spent watching television and an increase in BMI (75,119–123). This may be because television viewing displaces physical activity, lowers resting energy expenditure, and may be associated with increased intake of energy-rich foods. One randomized, controlled, school-based trial that manipulated television viewing in elementary school children showed that children who reduced their time spent watching television increased their BMI at a slower rate than did children who did not reduce their television viewing. These results suggest that reducing television viewing is a promising strategy for preventing childhood obesity (122).

Television constitutes a predominant source of media influence on food choices and obesity. Even brief exposures to televised food commercials have been found to influence preschool children's food preferences. It is possible that limiting exposure to food advertisements in media would positively impact body composition in children (27).

1.3.5 Genetics

Obesity is indeed a disease with multifactor etiologies, most of them exogenous. A number of endocrine disorders and some genetic syndromes can be the cause of childhood obesity. Of note is that these disorders are generally accompanied by poor linear growth relative to an excessive body weight and that mental deficiency and hypogonadism are frequent features. See Table 1.1 for a list of the more common clinical syndromes associated with obesity in childhood.

Many genetic loci that appear to be promising markers for the disease in some patient subgroups have been studied in recent years. One genetic locus found to be relatively common in obese populations is that which encodes for the melanocortin

TABLE 1.1
Clinical Syndromes That Include Obesity

Name	Common Features
Cushing's syndrome	Delayed growth, moon facies, buffalo hump, truncal obesity, hirsutism, clitoromegaly, striae, and hypertension
Hypothyroidism	Short stature, enlargement of the tongue, temperature dysregulation, anemia, hypotonia, enlarged fontanelles, delayed dentition, and delayed development
Turner syndrome (1 per 2,000 to 5,000 births)	Short stature, pubertal delay, lymphedema during infancy, ptosis, widely spaced nipples, and webbing of the neck
Growth hormone deficiency (1 per 4,000 to 10,000 births)	Growth failure, commonly appearing after the second year of life
Pseudohypoparathyroidism	Short stature, short neck, short extremities, brachydactyly, and a round face
Polycystic ovary syndrome	Amenorrhea, acanthosis nigricans
Prader–Willi syndrome (1 per 25,000 births)	Early feeding difficulty with increasingly severe obesity after the first year of life, mental retardation, growth delay, and hypogonadism, small hands and feet, a narrow forehead, almond-shaped eyes, and a triangular mouth
Bardet–Biedl syndrome (1 per 160,000 births)	Mental retardation; hypogonadism; polydactyly; and eye abnormalities, including retinitis pigmentosa, optic atrophy, cataracts, microphthalmia, and colobomata (previously referred to as Laurence–Moon–Bardet–Biedl)
Cohen syndrome (frequency unknown)	Short stature, mental retardation, hypotonia, obesity, short philtrum, microcephaly, hand or foot anomalies, high narrow palate, antimongoloid slant of the palpebral fissures, narrow hands and feet, with long slender fingers and toes, and occasional syndactyly

4 receptor. Alterations in this receptor have been shown to lead to binge eating and obesity phenotypes (29,50,161).

1.3.6 Family Risk Factors

One of the strongest predictors of childhood obesity is parental weight. A prospective study of 150 children from birth to 9.5 years of age found the strongest risk factor for childhood obesity to be parent overweight, which was mediated by child temperament (4). After the age of 7 years, children with two overweight parents had consistently elevated BMI, compared to children with either no overweight parents or one overweight parent (125). Parental obesity also more than doubles the risk of adult obesity among both obese and nonobese children under 10 years of age (154).

Much work has also been done examining maternal and parental interactions with children surrounding food and eating. In one study, maternal food offers, food presentations, and total prompts were all significantly related to children's intake. Children who ate the fastest had mothers who delivered eating prompts at a higher frequency, raising concerns that maternal interactions may cause rapid eating or poor self-regulation during eating (43).

Data have also suggested that disordered eating patterns can emerge during early childhood, possibly as a result of parental characteristics. One study showed the risk for emergence of inhibited eating, secretive eating, overeating, and vomiting increases annually through age 5. Maternal body dissatisfaction, internalization of the thin-ideal, dieting, bulimic symptoms, and maternal and paternal body mass prospectively predicted the emergence of childhood eating disturbances (142). These disordered eating patterns could progress to a disregulated pattern of binge eating and obesity in adolescence.

1.3.7 Psychologic Factors

Disordered eating behaviors have been shown to be associated with greater weight gain. Patients who report feelings of loss of control over eating weigh more and have higher depression scores than do patients who feel in control of eating (107). Weight control practices are relatively common in late childhood and adolescence. Dietary restraint, self-labeled dieting, exercise for weight-control purposes, and appetite suppressant or laxative use predict an increased risk for obesity onset in female adolescents. In fact, self-reported weight reduction practices are more likely to result in weight gain than in weight loss in adolescent girls; this suggests the need for ongoing research to find effective weight loss techniques for this population (143).

Adolescents who suffer from major depression are likely to have a higher BMI in adult life than would be true for adolescents free of depression. Among women, some studies have linked obesity to major depression; this relationship becomes more positive among those of high socioeconomic status (SES). However, among men, there appears to be an inverse relationship between depression and obesity, and no correlation with SES (145).

Binge eating has a significant effect on glucose and insulin metabolism, even in lean women. Eating an entire day's worth of calories in a single sitting more than

doubled insulin levels in healthy volunteers, even when glucose was corrected for. This suggests that bingeing may lead to insulin resistance and predispose to obesity (146).

1.3.8 Hormonal/Physiology

Increasing evidence points to the hypothalamic-pituitary-adrenal (HPA) axis and the arousal/sympathetic system as being major mediators in the development of obesity. Principal hormones implicated are corticotropin-releasing hormone (CRH), arginine vasopressin, melanocyte-stimulating hormone, glucocorticoids, neuropeptide Y (NPY), and the catecholamines, norepinephrine and epinephrine.

Glucocorticoids promote food consumption directly through stimulation of NPY and inhibition of CRH and of melanocortin release. CRH and NPY are also functionally linked by mutual regulation. Sustained stimulation of the HPA axis by CRH seems to promote weight gain. Furthermore, glucocorticoids may increase visceral abdominal fat stores (35), as well as metabolic abnormalities. Hypertension is probably due to a parallel activation of the central sympathetic nervous system and catecholamines (24).

Insulin regulation also plays a large role in the hormonal cycle contributing to obesity. Insulin resistance has been shown to increase weight gain. Fasting plasma insulin levels were significantly greater in obese adolescents than in lean controls (8). Sex differences in insulin resistance exist, even in early childhood, with girls at 5 years of age exhibiting 35% higher insulin resistance than boys, even when corrections are made for differences in body composition (108). Disturbances in pathways of insulin-mediated lipolysis also play a role in the origin of obesity and in Type 2 diabetes mellitus (25).

Obesity is clearly associated with increased levels of the recently discovered hormone leptin. Leptin is a hormone secreted from adipocytes that moderates food intake and energy expenditure. Circulating levels correlate with body fat and BMI (106). Leptin increases in boys and girls from 5 to 15 years of age, before the appearance of other pubertal hormones. Leptin levels are lower in boys than girls, and they decrease in males coinciding with a pubertal rise in testosterone. Leptin is therefore implicated as being a hormone that interplays closely with the initiation of puberty (63).

Ghrelin is a gastric hormone that has received much attention for its effect on appetite and weight regulation. Ghrelin has adipogenic properties, and increased levels are thought to contribute to hyperphagia. It has been shown to modulate pituitary hormones. It has also been found to be negatively correlated with androstenedione production in women (112). In fact, androgens are independent modulators of circulating ghrelin concentrations (60).

1.4 COMORBIDITIES

1.4.1 Hyperlipidemia/Cardiac Risk

Hyperlipidemia is a common complication of obesity in childhood. It is thought also to be related to insulin resistance. In obese adolescents, the degree of insulin resis-

tance explains a significant portion of the variance in the levels of triglycerides, LDL-C, and HDL-C (141). Studies have shown the occurrence of atherosclerotic lesions in the vasculature by late adolescence and have also shown that hyperlipidemias are a common factor in the development of these lesions. Because coronary artery disease is a leading cause of death in adulthood, it is critical to screen for early-onset hyperlipidemia. How to screen for lipid disorders and cardiovascular risk is well described in several position papers (82,84,157).

The National Cholesterol Education Program guidelines suggest that all children with obesity undergo testing for lipid abnormalities, usually with a fasting lipid profile. LDL-C cholesterol levels less than 110 mg/dl are considered acceptable, and levels greater than 130 mg/dl are considered elevated. LDL-C levels of 110 to 130 mg/dl are considered borderline and necessitate repeat measurement in 1 year. The finding of elevated LDL-C values should trigger an individualized treatment plan, including dietary advice (16).

Increases in BMI have been shown to be correlated with increases in future cardiovascular risk (56,57,19). They also correlate with increased left ventricular size and relative wall thickness, both thought to be risk factors for future cardiovascular disease (77,103). Unfavorable levels of fitness and adiposity in obese children have been associated with higher levels of hemostatic and inflammatory markers, possibly putting children with this profile at greater risk for future cardiovascular disease (12,71).

There are also known ethnic differences in cardiovascular risk, with higher BMIs in Black and Mexican American girls than in White girls, evident by the age of 6 to 9 years. Blood pressure levels are higher in Black than White girls in every age group, and glycosylated hemoglobin levels are highest for Black and Mexican American girls and boys in every age group (158).

1.4.2 Type 2 Diabetes/Glucose Intolerance

The incidence of Type 2 diabetes in childhood is rising dramatically, now representing up to 45% of all diabetes reported among children and adolescents (9,38,111,124). Impaired glucose tolerance is also found in large numbers in young obese cohorts. A recent study examined a multiethnic cohort of 167 obese children and adolescents. All subjects underwent a 2-h oral glucose-tolerance test (1.75 mg of glucose per kilogram of body weight), with analyses for glucose, insulin, proinsulin, and C-peptide levels. Impaired glucose tolerance was detected in 25% of the 55 obese children (4 to 10 years of age) and in 21% of the 112 obese adolescents (11 to 18 years of age). 4% of the obese adolescents were diagnosed with Type 2 diabetes after testing. Insulin resistance was the best predictor of impaired glucose tolerance in this cohort (134).

Obesity is a known contributor to the development of Type 2 diabetes and cardiovascular risk in youths. Other risk factors include increased body fat and abdominal fat, insulin resistance, ethnicity (with greater risk in African American, Hispanic, and Native American children), and onset of puberty. These risk factors appear to be cumulative in their interactions and may be even more problematic during early adolescence, with changes in body fat stores and hormonal signaling

(64). A final risk factor is a family history of non–insulin-dependent diabetes mellitus (NIDDM). Because NIDDM leads to long-term morbidity, the prevention of obesity, as well as early identification of overt disease, is critical (116).

1.4.3 Polycystic Ovary Syndrome and Menstrual Irregularities

The polycystic ovary syndrome (PCOS) is a condition characterized by menstrual irregularity, usually oligomenorrhea or amenorrhea, in a setting of chronic hyperandrogenism. The name, originating from Stein and Leventhal's original autopsy studies, is a misnomer, as many patients with PCOS do not have polycystic ovaries on ultrasound, and many patients with multiple cysts on their ovaries do not have PCOS. Ovarian cysts can be a normative finding in pubertal girls. Approximately 50 to 75% of women with PCOS are obese, most of them characterized by visceral abdominal obesity. Obesity may play a causative role in the development of PCOS in susceptible individuals. It certainly seems to contribute to the insulin resistance experienced by many women with PCOS (54,61,65).

1.4.4 Hypertension

Childhood hypertension is an increasingly common complication of obesity. Other risk factors include a family history of hypertension and an ethnic predisposition to hypertensive disease. Obese children have three times the risk for hypertension of nonobese children. In addition, the risk of hypertension in children increases as BMI increases. Overactivity of the sympathetic nervous system in response to stress and insulin resistance contribute to the development of hypertension in children, as in adults. Similarly, weight loss can produce dramatic improvements in blood pressure (110,138).

1.4.5 Metabolic Syndrome

The metabolic syndrome is a newly described clustering of metabolic risk factors known to have a significant and negative impact on cardiac outcome and thrombotic and inflammatory risk. The factors include abdominal obesity, decreased HDL, elevated triglycerides, insulin resistance or diabetes, and elevated blood pressure. Please see Table 1.2 for the definition of metabolic syndrome in adults using ATP III guidelines. No age-specific guidelines for diagnosis have been published for children, although most specialists adapt these guidelines for pediatric patients (68).

The metabolic syndrome prototype has been found to be shockingly prevalent in obese children. In 439 obese, 31 overweight, and 20 nonobese children and adolescents studied, the prevalence of the metabolic syndrome increased with the severity of obesity and reached 50% in severely obese youth. Each half-unit increase in BMI (converted to an age-appropriate Z-score) was associated with an increase in the risk of the metabolic syndrome among overweight and obese subjects. The

TABLE 1.2
Characteristics of the Metabolic Syndrome

- Abdominal obesity
- Hypertriglyceridemia
- Low HDL cholesterol
- Hypertension
- Impaired glucose tolerance

Source: Adapted and modified from (68).

prevalence of the metabolic syndrome increased significantly with increasing insulin resistance, even after the data were normalized for ethnic group and the degree of obesity. C-reactive protein levels increased and adiponectin levels decreased with increasing obesity (151).

1.4.6 Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is currently the most common cause of elevated liver enzymes in the United States. It is commonly seen in association with obesity, diabetes, hypertension, and hypertriglyceridemia. Most patients are asymptomatic and usually present with mild elevations in aminotransferases. The natural history of NAFLD is not clearly defined, but it can progress to cirrhosis and end-stage liver disease. Insulin-resistant states lead to altered glucose and lipid metabolism, culminating in hepatic steatosis. This can then progress to nonalcoholic steatohepatitis (NASH) or cirrhosis through mechanisms that are not yet well elucidated (1,73). In one study examining morbidly obese adults undergoing gastric bypass, 65% of the patients had moderate to severe steatosis, 12% had advanced fibrosis, and 33% had NASH on liver biopsy preoperatively. The factor that most correlated with abnormal liver biopsy findings in these patients was the presence of Type 2 diabetes, not BMI. This observation adds support to the concept that insulin resistance plays a critical role (21). It is as yet unknown how common this disorder is in obese children and adolescents.

1.4.7 Sleep Apnea

Obstructive sleep apnea (OSA) is also growing more and more common in the setting of extreme childhood obesity. This condition has a known link to future cardiovascular disease (2,131).

Current recommendations state that all children should be screened for snoring, and those who snore should be tested by polysomnography to determine if they have OSA (2,100).

1.4.8 Orthopedic Complications

Overweight children are at increased risk for a number of weight-related orthopedic complications. Chronic excess weight can lead to a bowing of the tibia and femur, causing an overgrowth on the medial aspect of the proximal tibial metaphysis called Blount's Disease. Slipped capital femoral epiphysis (SCFE) can also result from excess weight and is considered an orthopedic emergency. Finally, many overweight patients have degenerative disease of the spine, leading to discomfort and decreased mobility due to excess pressure on the lower spine from their body mass (39).

1.4.9 Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Idiopathic intracranial hypertension (IIH) is a rare disorder in children, although up to 59% of children and 91% of late adolescents with IIH are also obese (10,86). It is characterized by increased intracranial pressure in the absence of other intracranial pathology. It often presents with headaches and can sometimes lead to severe visual impairment or blindness. Papilledema is often found in a physical examination. To diagnose IIH, the following criteria must be present: symptoms of increased intracranial pressure (ICP), a normal neurologic exam and mental status, normal brain-imaging results, evidence of increased ICP on exam and by lumbar puncture opening pressure, normal CSF findings, and no identifiable cause of increased ICP. These criteria, also called the Dandy criteria, must be met to diagnose IIH. Once diagnosed, IIH requires prompt treatment, with weight reduction paramount to reduce the risk of further complications (23).

1.4.10 Gallbladder Disease

Nearly 50% of cases of cholecystitis are associated with obesity. Weight reduction can also be complicated by cholelithiasis. A sharp index of suspicion for this condition coupled with a family history of gallbladder disease can help with early diagnosis and treatment (39).

1.4.11 Psychiatric Conditions

Overweight children and adolescents appear to be at risk of disordered eating, most commonly overeating and binge eating disorder. Overweight adolescents tend to engage in significantly more unhealthy behaviors and to experience more psychosocial distress than their nonoverweight peers. Among the overweight youth, high levels of family connectedness and modest parental monitoring constitute factors that can reduce psychosocial pathology (101).

Overeating appears to be quite common in young people, with 17.3% of girls and 7.8% of boys reporting such behavior. Youth who overeat are more likely to be overweight or obese, to have dieted in the past year, to be trying to lose weight currently, and to report that weight and shape are very important to their overall feelings about self. In the study by Ackard et al. (3), children and adolescents who met the criteria for binge eating syndrome demonstrated lower satisfaction with their

body, lower self-esteem, and higher measures of depressive mood than those who reported either subclinical or no binge eating. Of those who met criteria for binge eating syndrome, 28.6% of the girls and 27.8% of the boys reported that they had attempted suicide (3).

Another study shows a relationship between depressive symptoms and BMI in preadolescent girls, mediated by overweight concerns, but this was not true for boys of the same age (49). Other studies have demonstrated increased victimization and bullying behaviors with increased BMI (80).

1.5 EVALUATION OF THE OVERWEIGHT CHILD

1.5.1 Screening

Multiple position papers have been published to help guide the complex evaluation of the overweight child. A committee of pediatric obesity experts developed streamlined recommendations for clinicians (13). They recommended that the BMI be calculated and assessed at every visit. Thus every visit provides an opportunity to identify children at risk. All children with a BMI greater than or equal to the 85th percentile who have complications due to obesity, or with a BMI greater than or equal to the 95th percentile, with or without complications, should undergo evaluation and possible treatment (13). Figure 1.1 provides a chart of recommended overweight screening procedures.

1.5.2 Nutrition Assessment

A separate nutrition evaluation conducted by a licensed dietician experienced in obesity is a critical component of the evaluation of the overweight child. A full dietary history can be elicited, with calorie counts. Food frequency checklists, with special attention to sugared drinks and juice consumption, convenience and fast foods, and the content of school lunches, should be completed (37). Food diaries should be interpreted with caution, as self-reporting of food intake has known limitations (99). If the validity of food journals or the diet intake history seems questionable, indirect calorimetry can be a helpful adjunct to determining resting energy expenditure levels (128). Practitioners need not worry that asking questions about risky eating behaviors, such as purging or diet pill usage, leads to an increase in risky eating behaviors in children and adolescents (36).

1.5.3 History and Physical Examination

When children meet overweight criteria, they should be subjected to a thorough medical and nutritional assessment. Clinicians should examine and screen clinically for signs of rare exogenous causes of obesity, including genetic syndromes, endocrinologic diseases, and psychologic disorders. However, these are rarely seen and can often be ruled out on physical exam. If a child is not experiencing delayed linear growth, an endocrinologic cause is unlikely. If no developmental delay and no dysmorphisms are present, genetic conditions are unlikely. It is recognized that parents are often seeking a medical cause. Frequently, parents require reassurance

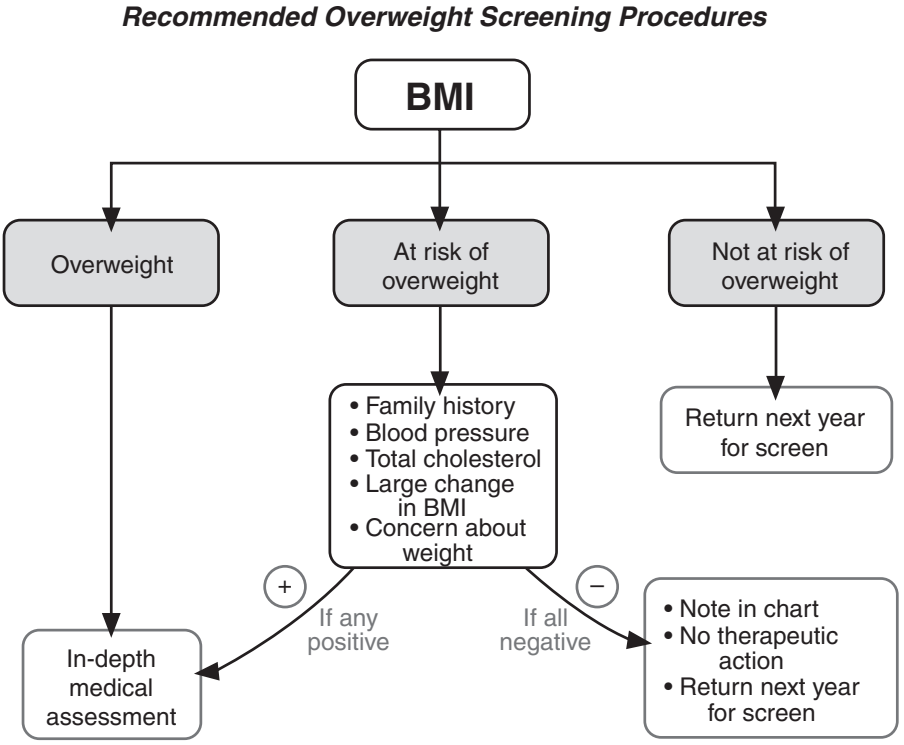


FIGURE 1.1 Screening guidelines. (From Barlow, S., Dietz, W.H. *Pediatrics 102:* e29, 1998. With permission.)

that no further workup is necessary, but that screening for comorbidities and treatment should be initiated without delay. Specific features that should be included in the history and physical exam are listed in Table 1.3.

The American Academy of Pediatrics (AAP) committee recommends screening for hypertension, hyperlipidemia, orthopedic difficulties, OSA, gallbladder disease, and insulin resistance. Pseudotumor cerebri should be screened for by conducting a fundoscopic exam. It is desirable to screen adolescent females for PCOS, as the condition is extremely common in this population and can increase future diabetes and lipid risk levels. Many people with obesity are diagnosed with asthma, when their breathing difficulties are due more to thoracic restriction from their increased BMI and undertraining. Therefore, it is important to elicit a history of breathing difficulties, along with a family history of asthma and allergies. Prior to starting chronic long-term anti-inflammatory agents, a full round of pulmonary function tests should be undertaken, including an exercise challenge, if the diagnosis of exercise-induced asthma is being considered. Screening for binge eating and purging behaviors, along with body image dysmorphisms and dietary supplement usage, is also wise, as these issues frequently coexist with difficulties in regulating weight. Table 1.4 lists laboratory and clinical tests and gives contexts in which they would be appropriate.

TABLE 1.3
History and Exam Findings

Exam Portion	Findings	Conditions
History	Developmental delay	Genetic disorder
	Poor linear growth	Endocrine disorder
	Headaches	Pseudotumor cerebri
	Snoring, difficulty breathing	Sleep apnea
	Abdominal pain	Gallbladder disease
	Hip or knee pain	SCFE
	Menstrual irregularity	PCOS
Family History	Obesity	
	NIDDM	
	Cardiovascular disease	
	Hypertension	
	Hyperlipidemia	
	Gallbladder disease	
Social/Psychological History	Full physical activity and sedentary behavior history: computer, television, game use	
	Tobacco use	
	Drug use	
	Dietary supplement use	
	Bingeing	
	Purging	
	Depressive symptoms	
Physical Examination	Height, weight, BMI	Hypertension
	Blood pressure > 95th percentile for age	NIDDM, insulin resistance
	Acanthosis nigricans	Androgen excess, PCOS
	Hirsutism	Androgen excess, PCOS
	Acne	Cushing's Syndrome
	Violaceous striae	Pseudotumor cerebri
	Fundoscopic exam	Gallbladder disease
	Abdominal tenderness	Prader–Willi Syndrome
	Undescended testicle	SCFE
	Limited hip range of motion	Blount's Disease
	Lower leg bowing	

Note: For abbreviations, see Note in Table 1.4.

Source: Adapted from Barlow, S., Dietz, W.H. *Pediatrics 102:* e29, 1998. With permission.

1.5.4 Referral Considerations

Occasionally, a child suffers from severe obesity or is particularly difficult to manage in the primary care setting. Clearly, every practitioner develops his or her own comfort level in this management. If a child is found to have a significant comorbidity, a referral to a relevant subspecialist is appropriate. AAP guidelines for further referral to a pediatric obesity specialist include:

TABLE 1.4
Laboratory and Other Testing Considerations

Laboratory/Clinical Test	Reason
CBC, plus differential chemistries	General screen
Fasting lipid panel	Hyperlipidemia screen, yearly
Fasting glucose and insulin	Insulin resistance, NIDDM, yearly
	Criteria for NIDDM include (see Nesmith, 2001): • Random blood glucose > 199 • Fasting blood glucose > 125 • 2-h postprandial glucose > 199 during 2-h oral glucose tolerance testing
Two-hour oral glucose tolerance testing	NIDDM, as necessary
LH, FSH, free and total testosterone, DHEA-S, androstenedione	PCOS: indicated with obesity and menstrual irregularity with or without signs of androgen excess
Hepatic function tests	NAFLD, yearly
Ultrasound of right upper quadrant	NASH, gallbladder disease
MRI brain	Pseudotumor cerebri: when fundoscopic exam shows blurring of optic disc margins
Polysomnogram	OSA: with history of snoring
X-rays: AP and frog leg of hips	SCFE: with limitation of hip range of motion
Pulmonary function testing with exercise challenge, if indicated	With difficulty breathing
EKG, echocardiogram	With difficulty breathing, in severe obesity
Calorimetry	More accurate estimation of baseline caloric requirements

Note: NIDDM = non–insulin-dependent diabetes mellitus; LH = lutenizing hormone; FSH = follicle stimulating hormone; DHEA-S = dehydroepiandrosterone sulfate; PCOS = polycystic ovary syndrome; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OSA = obstructive sleep apnea; SCFE = slipped capital femoral epiphysis; EKG = electrocardiogram.

Pseudotumor cerebri
Obesity-related sleep disorders
Orthopedic problems
Massive obesity
Obesity in children younger than 2 years of age (13)

1.6 TREATMENT

1.6.1 General Considerations

Primary objectives in obesity treatment in pediatrics always involve teaching healthy behaviors, increasing activity, and teaching about sound nutritional practices. Treatment of the overweight child first depends on the age of the child and the severity of disease. Unless a child 2 to 7 years of age suffers from a weight-related medical complication (e.g., sleep apnea) and has a BMI above the 95th percentile for age,

the treatment recommended consists of a program of weight maintenance. For the rare patient in this age range who is truly suffering a significant medical comorbidity, careful, medically supervised weight loss is the recommended course.

If the patient is 7 years of age or older, with a BMI between the 85th and 94th percentiles, and has no complications, weight maintenance should still be the focus of treatment. However, if patients this age have medical complications, or if their BMI is greater than the 95th percentile for age, medically supervised weight loss is recommended. Once the severity of the disease is categorized, an assessment of patient and family readiness to engage in treatment must take place. Most successful long-term weight treatment programs for children include a significant family component, and parents must be committed to behavior change if improvement is to occur. Helping with appropriate teaching of parenting skills and family support is a foundation of any weight maintenance or weight loss program for children (13).

1.6.2 Behavior Change

Ten-year follow-up of children participating in four different family-based group behavior change studies that used the Traffic Light Diet showed a significantly larger decrease in the percentage of overweight patients if their parents had also been targeted, as compared to controls whose families were not involved. In one of the studies, a larger decrease was seen in children of nonobese parents than in patients whose parents were obese. All in all, 30% of patients were not obese at their 10-year follow-up. All four studies targeted children aged 6 to 12 years who weighed from 20 to 100% above their ideal body weight and where at least one parent was willing to participate (48). Another study showed that in a family-based behavior change program for overweight Black adolescent females, patients lost more weight with each increase in maternal session attendance (149). Regression analysis of 142 parent–child pairs in Traffic Light Diet programs showed that parental weight change is a significant predictor of the child's weight change (159). Additionally, in one family-based program, as maternal psychopathology was reduced in the course of treatment of the child, the psychological symptoms improved as well. Therefore, family-based treatment programs for obesity lead to both medical and psychiatric benefits (109).

In addition to structured parental involvement where parent groups meet separately from the children groups, features of behavioral treatment programs that have been found helpful include frequent sessions, longer treatment, and the inclusion of individualized counseling with the group sessions. Clear and simple diets, physical activity programs, emphasis on reduction of sedentary behaviors and teaching skills for high-risk situations, and relapse prevention are important components of a well-structured pediatric weight program (118).

1.6.3 Physical Activity

The majority of studies confirm that physical activity has protective health effects at any weight (26). In a recent study of women, physical fitness levels were more predictive of cardiac risk factors and coronary artery disease than was body mass

index (152). Most weight loss experts advocate a combination of aerobic and strength exercises, combined with behavioral modifications and calorie reduction, for optimal results in weight reduction (6). A referral to physical therapy can be helpful in establishing such a program.

In the pediatric population, exercise has shown similar benefits. Youths with poor fitness levels and high adiposity have higher levels of hemostatic markers; this may increase their risk of future cardiovascular disease (12). Becque et al. (15) examined multiple risk factors in 36 obese adolescents, including serum triglycerides, total cholesterol, HDL, maximum work capacity, obesity, and family history of coronary heart disease. Youths were randomly assigned to control, diet intervention, and diet and exercise intervention groups. Youths assigned to the diet and exercise group had a 41% multiple risk reduction compared to controls, with no significant differences observed between the diet-alone group and controls (15). Plasma triglyceride, insulin, and percentage body fat were all improved after 4 months of structured exercise in obese children; these benefits were lost when the children became less active (51). High-intensity exercise has been shown to be more effective than moderate activity in improving lipoprotein profiles and diastolic blood pressure in obese teens (83). Exercise interventions have also produced favorable changes in body composition of obese youth, their visceral adipose tissue, insulin levels, triacylglycerol levels, and cardiac parasympathetic activity; these were achieved without additional dietary interventions (70). Finally, cardiovascular fitness significantly improves in obese youth with physical training, especially with high-intensity exercise (69).

1.6.4 Decreasing Sedentary Behaviors

Given the increasing prevalence of sedentary behaviors, such as television viewing, video-game playing, and computer use, among children and adolescents, much attention has been paid to the question of how to reduce these behaviors, so as to be able to bring about weight loss. Identifying these behaviors is as helpful as increasing physical activity in the adolescent population (46). A school-based study involving a 6-month classroom curriculum to reduce television, videotape, and video game usage in 3rd and 4th graders showed statistically significant decreases in BMI, triceps skinfold thickness, waist circumference, and waist-to-hip ratio in the intervention group as compared with controls. Studies such as this highlight the importance of reducing sedentary behaviors to achieve effective weight control in the pediatric population (121).

1.6.5 Nutrition

No weight program can be successful without some ordered approach to improved nutrition. However, the many diets advertised in today's culture present a dizzying array of options and make an evidence-based approach difficult. The most commonly used nutritional interventions, involving caloric reduction, are reviewed below. Liquid diets have not been well studied in children and therefore are not reviewed.

1.6.5.1 Increased Dairy Consumption

The Coronary Artery Risk Development in Young Adults (CARDIA) study showed that in overweight subjects, increased dairy consumption was strongly and inversely associated with obesity, glucose intolerance, hypertension, and hyperlipidemia. Risk of developing the metabolic syndrome involving these conditions was 72% lower among individuals in the highest dairy consumption category (115). Numerous studies have shown the impact of calcium and dairy intake on weight loss. Dairy food intake, when combined with caloric reduction, has been shown to be more helpful than simple calcium supplementation with regard to weight loss and metabolism. The reason for this effect of dairy products is not clear (147,148).

1.6.5.2 Low-Fat Diet

Low-fat diets are often based on the U.S. Department of Agriculture (USDA) food guide pyramid, a commonly used tool for weight reduction. These diets usually suggest that approximately 20 to 30% of daily caloric intake should come from dietary fats. These diets focus on increasing servings in the lower part of the food pyramid (grains, fruits, vegetables) and decreasing saturated fat and sweet consumption (130). This provides a safe approach to the reduction of serum lipids as well. The American Heart Association recommends a diet that is also low in trans-fats to help with combating atherosclerosis. Jenkins et al. have shown that a low-fat diet that includes additional supplementation with plant sterols, soy proteins, and extra fiber led to impressive reductions in serum LDL and total cholesterol (7,81). The food guide pyramid has undergone extensive revision and can now be individualized to specific patient needs, based on age and gender (www.mypyramid.gov).

1.6.5.3 Increased Fiber

Increased fiber is an important addition to a healthy diet. Overweight children and adolescents have been shown to consume significantly less fiber than do their normal-weight peers (130). Fiber intake is a stronger predictor of weight gain and insulin levels than is saturated fat intake. Fiber intake varies inversely with both variables (95). It is also independently and inversely associated with serum CRP concentrations and appears to be a predictor of future cardiovascular risk (5). Multiple studies have shown benefits when weight loss regimens include attention to increased fiber intake (90).

1.6.5.4 Moderate-Fat Diet

In this diet, approximately 35% of daily calories are derived from fat. Low-fat diets have traditionally been recommended for weight loss, but not much research has focused on simply moderating fat intake until recently, when the health benefits of including omega-3 and omega-6 essential fatty acids in the diet became known (17,32,133). Overweight and obese men and women achieved similar weight loss when assigned to a moderate-fat compared with a low-fat regimen, and their lipoprotein profiles improved (114).

1.6.5.5 Traffic Light or Stop Light Diet

Originally designed by Epstein et al. (47,48), this diet has been studied extensively in young children and has shown good outcomes. It is a low-calorie eating plan that categorizes foods into green, yellow, and red groups. Green foods are low-calorie items that may be consumed in unlimited quantities. Daily intake of yellow foods must be limited, but they provide good nutrient density. Red foods should be eaten infrequently, as they are high in fat and refined sugars (47,48).

1.6.5.6 Low-Carbohydrate Diet

Low-carbohydrate approaches have been the subject of many recent studies. A low-carbohydrate diet seems to be safe in adolescent subjects with morbid obesity, as it leads to overall weight loss. Loss of lean body mass is blunted, but consumption of the diet improves sleep abnormalities (156). One 12-week study in overweight adolescents showed significantly greater weight loss with a low-carbohydrate diet compared with a low-fat diet, with no adverse effects on lipid profiles in either group (137). In another study of severely obese subjects with a high prevalence of insulin resistance, patients lost more weight and had greater improvement in insulin and triglyceride levels on a low-carbohydrate diet than on a low-fat diet. This was true even after the amount of weight lost was taken into account (126). Longer-term trials of low-carbohydrate and conventional diet approaches have not, however, shown significant differences in weight reduction by 1 year (53). A recent meta-analysis concluded there was no evidence for or against the use of low-carbohydrate diets for the purpose of weight loss (30).

1.6.5.7 Low–Glycemic Index Diet

The glycemic index is an evolving area of interest for obesity researchers, as a diet focusing on foods with a low to moderate GI may be helpful in achieving meaningful weight loss (37,97,140). In one small study of 14 adolescents, those on a low- to moderate-GI diet lost significantly more weight and showed less of an increase in insulin resistance over a 12-month period than did the youth assigned to a low-fat diet (25 to 30% of energy from fat; 44). Meals with low GI prolong satiety; this may increase their efficacy as a means to lose weight (11).

1.6.5.8 Protein-Sparing Modified Fast

The protein-sparing modified fast (PSMF) approach is generally reserved for adolescents and adults suffering from severe obesity, and it is often prescribed for patients hospitalized for obesity. If used on an outpatient basis, it requires very close medical monitoring, daily supplements, adequate water intake, and the frequent measurement of electrolyte levels in order to ensure safety. The diet typically allows for 600 to 900 kcal daily, with 1.5 to 2.5 g/kg/d of protein, with intakes of carbohydrate (20 to 40 g/d) and fat very restricted. These diets are usually not used for periods longer than 12 weeks. Described complications of the PSMF include cholelithiasis, hyperuricemia, orthostatic hypotension, halitosis, and diarrhea.

Because of high dropout rates due to this regimen, studies have been difficult to interpret (37,160). One study showed greater weight loss at 10 weeks in children taking the PSMF, but at 1 year the weight loss was not significantly different from that of controls on a standard low-calorie diet (52).

1.6.6 Pharmacotherapy

Because obesity frequently becomes a chronic condition that progresses from childhood to adulthood, the use of medications to help with metabolic and weight control is alluring. Multiple weight loss medications and supplements are targeted at adults with obesity. Very few weight loss medications have been studied in the pediatric population, and usually such medications are indicated only for severe obesity that has not responded to other measures (37). To date, no studies have been conducted that have examined these medications in a long-term, randomized, double-blind, placebo-controlled trial and compared them with a program that involves diet, exercise, and behavior modification. The findings in children and adolescents of certain currently used weight loss medications are reviewed below, but the results should be interpreted with caution, as the studies are limited and the medications carry risk (160,162).

1.6.6.1 Sibutramine

Sibutramine is an inhibitor of the synaptic reuptake of norepinephrine, serotonin, and dopamine. It has been shown to decrease weight in adults in a 6-month to 1-year randomized, double-blind, placebo-controlled study (31). Side effects usually include mild hypertension and tachycardia. Other common adverse reactions include dry mouth, headache, insomnia, and constipation. Sibutramine should not be administered in conjunction with monoamine oxidase inhibitors or other serotonin reuptake inhibitors (160,162). In a recent trial involving 82 adolescents that compared sibutramine combined with behavior therapy with behavior therapy alone, the sibutramine-treated group lost significantly more weight and reported less hunger than the control group over a period of 6 months (20).

1.6.6.2 Orlistat

Orlistat is a gastrointestinal lipase inhibitor and can have modest efficacy in adults attempting weight loss for up to 2 years. To date, there are no published randomized, placebo-controlled trials of orlistat in children or adolescents, although such studies are currently ongoing. Common side effects of orlistat include flatulence, fecal incontinence, steatorrhea, and a decrease in the levels of fat-soluble vitamins (160,162).

1.6.6.3 Octreotide

Octreotide, or somatostatin, is a suppressor of pancreatic insulin secretion. Hyperinsulinemia that may be mediated by the ventromedial hypothalamus may be a stimulus for overeating in children who sustain damage to that area of the brain. Lustig et al. reported that children with intractable obesity due to intracranial therapy

for cancer experienced significant weight reductions as a result of using octreotide. Octreotide is injected and can cause pain at the injection site. Side effects include gallstones, diarrhea, abdominal pain, nausea, cardiac abnormalities, vitamin B_{12} deficiency, hypothyroidism, suppression of growth hormone secretion, and Type 1 diabetes. Octreotide is being studied as a treatment of hypothalamic obesity, but it clearly requires more study before it can be used more widely (160,162).

1.6.6.4 Metformin

Metformin, which inhibits hepatic glucose production, is indicated in the treatment of Type 2 diabetes and can cause weight loss in adults. In a randomized, placebo-controlled trial of 29 obese adolescents with hyperinsulinemia, Freemark and Bursey (58) showed there occurred significant decreases in BMI in the treated group, compared with the placebo group. Metformin also had favorable effects on leptin, insulin, and glucose in treated subjects (58). Another randomized, double-blind, placebo-controlled trial in obese adolescents with hyperinsulinemia on a low-calorie diet showed greater weight loss, greater decrease in body fat, and enhanced insulin sensitivity when the subjects were given metformin in conjunction with the reducing diet than when on the diet only. The treatment group also showed significant reductions in plasma leptin, cholesterol, triglycerides, and free fatty acid (FFA) levels, compared with the placebo group (85). By and large, metformin is well tolerated, although it can cause nausea, flatulence, bloating, and diarrhea. On rare occasions, metformin causes lactic acidosis. The estimated rate is 3 per 100,000 patient-exposure years, and it affects primarily patients with renal insufficiency, decreased perfusion, cardiac or pulmonary insufficiency, or liver disease. Clearly the use of metformin is contraindicated in those conditions (160,162).

1.6.7 Weight Loss Surgery

Recently, guidelines have been published to elucidate when weight loss surgery might be considered for treatment of severe refractory obesity in the pediatric population, as this procedure is becoming more common (79,62). Weight loss surgery has been shown to be curative for diabetes mellitus in adult subjects (127). It also lowers insulin resistance and raises glucose tolerance (18,102). Weight loss surgery in adults leads to significant improvement in clinical signs of the metabolic syndrome and of hepatic cirrhosis (91). Initial results published in the adolescent population are promising, with case series showing weight reductions in excess of 30 kg. These studies are too small adequately to assess long-term success and risks, but they have shown few unanticipated complications in the initial postoperative periods (78,144). Criteria for bariatric surgery in the pediatric population are listed in Table 1.5.

Contraindications to surgery include a medically correctable cause of obesity, recent history of substance abuse, any condition that would impair adherence to postoperative dietary or medication regimens, current lactation or pregnancy, or planned pregnancy within 2 years postoperatively. The currently recommended pro-

TABLE 1.5
Criteria for Bariatric Surgery in Adolescents

BMI 40 and at least one of the following:
- Diabetes mellitus type 2
- Sleep apnea
- Pseudotumor cerebri

or

BMI ≥ 50 with less serious comorbidities:
- Hypertension
- Dyslipidemia
- Nonalcoholic steatohepatitis (NASH)
- Venous stasis
- Impaired activities of daily living (ADL)
- Intertriginous infection
- Stress incontinence
- Gastroesophageal reflux disease (GERD)
- Weight-related arthropathies
- Obesity-related psychosocial disease

Additional criteria:
- Skeletal maturation
  - Girls ≥ 13 years old
  - Boys ≥ 15 years old
- Psychiatric evaluation
- Participation in at least 6 months of organized attempts at weight management

Source: Adapted from information in (79).

cedure in the adolescent population is the laparoscopic Roux-en-Y gastric bypass. Potential postoperative complications may include intestinal leakage, strictures, small bowel obstruction, infection, cholelithiasis, nutritional deficiencies, thromboembolism, and even death (33,62,79).

For a discussion of bariatric surgery in adults, see Chapter 3.

1.6.8 Hazards of Weight Loss

Rapid and profound weight loss is associated with dangers of its own. When obese subjects are placed on very low calorie diets, they experience a loss of myocardial muscle mass. Ventricular tachyarrhythmias, prolongation of the QT interval, syncope, and sudden death are known complications of such regimens (42,132,139). It is clearly important, therefore, not to endorse a regimen that is dangerously low in calories or that causes extremely rapid weight loss.

Studies that have examined the risk of developing eating disorders after efforts at weight loss have shown that girls who have great concern about their weight are more likely to develop eating disorders (88,89). In another study, girls at high risk for symptomatology of bulimia nervosa had significantly heavier body weights and

greater fear of weight gain. They also had greater dissatisfaction with their bodies than did others without such symptoms (87). There are no long-term prospective studies of treatment outcomes with respect to the development of disordered eating. Therefore, even though it may be intuitively obvious that this population is at risk when undergoing supervised weight loss, caution is indicated before excluding potential subjects from treatment.

1.7 CONCLUSIONS AND FUTURE DIRECTIONS

In summary, obesity is affecting children in developed countries in epidemic proportions. Body mass index for age is the measure of choice to define obesity in a pediatric patient. Thorough evaluations should screen for all related comorbidities, as they are becoming more common. Therapy rests on behavior change, increased activity, decreased sedentary activities, and diet modifications. However, in extreme cases, pharmacotherapy and even bariatric surgery may be considered in the therapeutic plan.

Health care providers need more education and support to be able to care adequately for this population. Continuing education, Web-based resources, and structured questionnaires are examples of supports that providers have found helpful. Improved techniques for addressing poorly motivated or noncompliant patients and families are also needed (cf. Chapter 7). National media and local advocacy initiatives may prove to be helpful in this regard (14). Physicians and other professionals concerned with the growing problem of obesity should play a leadership role in pressing for improved insurance coverage for overweight children, in urban planning initiatives for active recreational facilities, and in monitoring media advertising. Providers should continue to educate schools and local city planning commissions about the dangers of dietary fats, trans-fats, and sweetened beverages, and they should emphasize the importance of physical activity in schools and communities. Table 1.6 provides a list of Web sites that provide further information on the topics discussed in this article.

TABLE 1.6
Helpful Web Sites

Centers for Disease Control	www.cdc.gov
Office of the Surgeon General	www.surgeongeneral.gov
President's Council on Physical Fitness and Sports	www.fitness.gov
American Academy of Pediatrics	www.aap.org
American Heart Association	www.americanheart.org
Steps to a Healthier U.S. Initiative	www.healthierus.gov/steps
North American Association for the Study of Obesity	www.naaso.org
Food guide pyramid	www.mypyramid.com

REFERENCES

1. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. (2002). *Gastroenterology 123:* 1702–1704.
2. AAP Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. (2002). Clinical practice guideline: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics 109:* 704–712.
3. Ackard, D, Neumark-Sztainer, D, Story, M, & Perry, C. (2003). Overeating among adolescents: Prevalence and associations with weight-related characteristics and psychological health. *Pediatrics 111:* 67–74.
4. Agras, WS, Hammer, LD, McNicholas, F, & Kraemer, HC. (2004). Risk factors for childhood overweight: A prospective study from birth to 9.5 years. *J. Pediatr. 145:* 20–25.
5. Ajani, UA, Ford, ES, & Mokdad, AH. (2004). Dietary fiber and C-reactive protein: Findings from national health and nutrition examination survey data. *J. Nutr. 134:* 1181–1185.
6. Amisola, R, & Jacobson, M. (2003). Physical activity, exercise, and sedentary activity: Relationship to the causes and treatment of obesity. *Adolescent Medicine: State of the Art Reviews 14:* 23–33.
7. Anderson, J. (2003). Diet first, then medication for hypercholesterolemia. *JAMA 290:* 531–533.
8. Attia, N, Tamborlane, WV, Heptulla, R, Maggs, D, Grozman, A, Sherwin, RS, & Caprio, S. (1998). The metabolic syndrome and insulin-like growth factor I regulation in adolescent obesity. *J. Clin. Endocrinol. Metab. 83:* 1467–1471.
9. Aye, T, & Levitsky, LL. (2003). Type 2 diabetes: An epidemic disease in childhood. *Curr. Opin. Pediatr. 15:* 411–415.
10. Balcer, L, Liu, GT, Forman, S, Pun, K, Volpe, NJ, Galetta, SL, & Maguire, M.G. (1999). Idiopathic intracranial hypertension: Relation of age and obesity in children. *Neurology 52:* 870–872.
11. Ball, S, Keller, KR, Moyer-Mileur, LJ, Ding, Y, Donaldson, D, & Jackson, WD. (2003). Prolongation of satiety after low versus moderately high glycemic index meals in obese adolescents. *Pediatrics 111:* 488–494.
12. Barbeau, P, Litaker, M, Woods, KF, Lemmon, CR, Humphries, MC, Owens, S, Riggs, S, & Gutin, B. (2002). Hemostatic and inflammatory markers in obese youths: Effects of exercise and adiposity. *J. Pediatr. 141:* 415–420.
13. Barlow, S, & Dietz, WH. (1998). Obesity evaluation and treatment: Expert committee recommendations. *Pediatrics 102:* e29.
14. Barlow, S, Dietz, WH, Klish, WJ, & Trowbridge, FL. (2002). Medical evaluation of overweight children and adolescents: Reports from pediatricians, pediatric nurse practitioners, and registered dietitians. *Pediatrics 110:* 222–228.
15. Becque, M, Katch, VL, Rocchini, AP, Marks, CR, & Moorehead, C. (1988). Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. *Pediatrics 81:* 605–612.
16. Belay, B, Belamarich, P, & Racine, AD. (2004). Pediatric precursors of adult atherosclerosis. *Pediatrics in Review 25:* 4–16.
17. Belury, M, Mahon, A, & Banni, S. (2003). The conjugated linoleic acid (CLA) isomer, t10c12–CLA, is inversely associated with changes in body weight and serum leptin in subjects with type 2 diabetes mellitus. *J. Nutr. 133:* 257S–260S.

18. Benedetti, G, Mingrone, G, Marococcia, S, Benedetti, M, Giancaterini, A, Greco, AV, Castagneto, M, & Gasbarrini, G. (2000). Body composition and energy expenditure after weight loss following bariatric surgery. *J. Am. Coll. Nutr. 19:* 270–274.
19. Berenson, G, Srinivasan, SR, Bao, W, Newman, III, WP, Tracy, RE, & Wattigney, WA. (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *New England Journal of Medicine 338:* 1650–1656.
20. Berkowitz, R, Wadden, TA, Tershakovec, AM, & Cronquist, JL. (2003). Behavior therapy and sibutramine for the treatment of adolescent obesity: A randomized controlled trial. *JAMA 289:* 1805–1812.
21. Beymer, C, Kowdley, KV, Larson, A, Edmonson, P, Dellinger, EP, & Flum, D.R. (2003). Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. *Arch. Surg. 138:* 1240–1244.
22. Bhargava, SK, Sachdev, HS, Fall, CHD, Osmond, C, Lakshmy, R, Barker, DJP, Biswas, SKD, Ramji, S, Prabhakaran, D, & Reddy, KS. (2004). Relation of serial changes in childhood body mass index to impaired glucose tolerance in young adulthood. *New England Journal of Medicine 350:* 865–875.
23. Binder, D, Horton, JC, Lawton, MT, & McDermott, MW. (2004). Idiopathic intracranial hypertension. *Neurosurgery 54:* 538–552.
24. Bjorntorp, P. (2001). Do stress reactions cause abdominal obesity and comorbidities? *Obesity Reviews 2:* 73–86.
25. Blaak, E. (2003). Fatty acid metabolism in obesity and type 2 diabetes mellitus. *Proc. Nutrition Soc. 62:* 753–760.
26. Blair, S, & Church, TS. (2004). The fitness, obesity, and health equation: Is physical activity the common denominator? *JAMA 292:* 1232–1234.
27. Borzekowski, DL, & Robinson, TN. (2001). The 30-second effect: An experiment revealing the impact of television commercials on food preferences of preschoolers. *J. Am. Diet. Assoc. 101:* 42–46.
28. Bowman, SA, Gortmaker, SL, Ebbeling, CB, Pereira, MA, & Ludwig, DS. (2004). Effects of fast-food consumption on energy intake and diet quality among children in a national household survey. *Pediatrics 113:* 112–118.
29. Branson, R, Potoczna, N, Kral, JG, Lentes, K, Hoehe, MR, & Horber, FF. (2003). Binge eating as a major phenotype of melanocortin 4 receptor gene mutations. *New England Journal of Medicine 348:* 1096–1103.
30. Bravata, D, Sanders, L, Huang, J, Krumholz, HM, Olkin, I, Gardner, CD, & Bravata, DM. (2003). Efficacy and safety of low-carbohydrate diets: A systematic review. *JAMA 289:* 1837–1850.
31. Bray, G, Blackburn, GL, Ferguson, JM, Greenway, JL, Jain, AK, Mendel, CM, Mendels, J, Ryan, DH, Schwartz, SL, Scheinbaum, ML, & Seaton, TB. (1999). Sibutramine produces dose-related weight loss. *Obes. Res. 7:* 189–198.
32. Brown, J, & McIntosh, MK. (2003). Conjugated linoleic acid in humans: Regulation of adiposity and insulin sensitivity. *J. Nutr. 133:* 3041–3046.
33. Byrne, T. (2001). Complications of surgery for obesity. *Surgical Clinics of North America 81:* 1181–1193.
34. Calle, E, Thun, MJ, Petrelli, JM, Rodriguez, C, & Heath, CW. (1999). Body mass index and mortality in a prospective cohort of U.S. adults. *New England Journal of Medicine 341:* 1097–1105.
35. Cavagnini, F, Croci, M, Putignano, P, Petroni, ML, & Invitti, C. (2000). Glucocorticoids and neuroendocrine function. *Int. J. Obesity 24:* S77–S79.

36. Celio, AA, Bryson, S, Killen, JD, & Taylor, CB. (2003). Are adolescents harmed when asked risky weight control behavior and attitude questions? Implications for consent procedures. *Int. J. Eat. Disord. 34:* 251–254.
37. Copperman, N, & Jacobson, M. (2003). Medical nutrition therapy of overweight adolescents. *Adolescent Medicine: State of the Art Reviews 14:* 11–20.
38. Daaboul, JJ, & Siverstein, JH. (2004). The management of type 2 diabetes in children and adolescents. *Minerva Pediatr. 56:* 255–264.
39. Dietz, WH. (1998). Health consequences of obesity in youth: Childhood predictors of adult disease. *Pediatrics 101:* 518–525.
40. Dietz, WH. (2004). Overweight in childhood and adolescence. *New England Journal of Medicine 350:* 855–857.
41. Dietz, WH, & Robinson, TN. (1998). Use of the body mass index (BMI) as a measure of overweight in children and adolescents. *J. Pediatr. 132:* 191–193.
42. Drott, C, & Lundholm, K. (1992). Cardiac effects of caloric restriction — mechanisms and potential hazards. *Int. J. Obes. Relat. Metab. Disord. 16:* 481–486.
43. Drucker, RR, Hammer, LD, Agras, WS, & Bryson, S. (1999). Can mothers influence their child's eating behavior? *J. Dev. Behav. Pediatr. 20:* 88–92.
44. Ebbeling, CB, Leidig, MM, Sinclair, KB, Hangen, JP, & Ludwig, DS. (2003). A reduced–glycemic load diet in the treatment of adolescent obesity. *Arch. Pediatr. Adolesc. Med. 157:* 773–779.
45. Ebbeling, CB, Sinclair, KB, Pereira, MA, Garcia-Lago, E, Feldman, HA, & Ludwig, DS. (2004). Compensation for energy intake from fast food among overweight and lean adolescents. *JAMA 291:* 2828–2833.
46. Epstein, L, Paluch, RA, Gordy, CC, & Dorn, J. (2000). Decreasing sedentary behaviors in treating pediatric obesity. *Arch. Pediatr. Adolesc. Med. 154:* 220–226.
47. Epstein, L, Valoski, A, Koeske, R, & Wing, RR. (1986). Family-based behavioral weight control in obese young children. *J. Am. Diet. Assoc. 86:* 481–484.
48. Epstein, L, Valoski, A, Wing, RR, & McCurley, J. (1994). Ten-year outcomes of behavioral family based treatment for childhood obesity. *Health Psychology 13:* 373–383.
49. Erickson, SJ, Robinson, TN, Haydel, KF, & Killen, JD. (2000). Are overweight children unhappy? Body mass index, depressive symptoms, and overweight concerns in elementary school children. *Arch. Pediatr. Adolesc. Med. 154:* 931–935.
50. Farooqi, I, Keogh, JM, Yeo, GSH, Lank, EJ, Cheetham, T, & O'Rahilly, S. (2003). Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *New England Journal of Medicine 348:* 1085–1095.
51. Ferguson, M, Gutin, B, Le, NA, Karp, W, Litaker, M, Humphries, M, Okuyama, T, Riggs, S, & Owens, S. (1999). Effects of exercise training and its cessation on components of the insulin resistance syndrome in obese children. *Int. J. Obes. Relat. Metab. Disord. 23:* 889–895.
52. Figueroa-Colon, R, von Almen, TK, Franklin, FA, Schuftan, C, & Suskind, RM. (1993). Comparison of two hypocaloric diets in obese children. *Am. J. Dis. Child. 147:* 160–166.
53. Foster, G, Wyatt, HR, Hill, JO, McGuckin, BG, Brill, C, Mohammed, BS, Szapary, PO, Rader, DJ, Edman, JS, & Klein, S. (2003). A randomized trial of a low-carbohydrate diet for obesity. *New England Journal of Medicine 348:* 2082–2090.
54. Franks, S. (1995). Polycystic ovary syndrome. *New England Journal of Medicine 333:* 853–861.

55. Freedman, DK, Khan, LK, Serdula, MK, Dietz, WH, Srinivasan, SR, & Berenson, GS. (2003). The relation of menarcheal age to obesity in childhood and adulthood: The Bogalusa heart study. *BMC Pediatrics 3:* 3.
56. Freedman, DS, Dietz, WH, Srinivasan, SR, & Berenson, GS. (1999). The relation of overweight to cardiovascular risk factors among children and adolescents: The Bogalusa heart study. *Pediatrics 103:* 1175–1182.
57. Freedman, DS, Khan, LK, Dietz, WH, Srinivasan, SR, & Berenson, GS. (2001). Relationship of childhood obesity to coronary heart disease risk factors in adulthood: The Bogalusa heart study. *Pediatrics 108:* 712–718.
58. Freemark, M, & Bursey, D. (2001). The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics 107:* e55.
59. Frontini, M, Srinivasan, SR, & Berenson, GS. (2003). Longitudinal changes in risk variables underlying metabolic Syndrome X from childhood to young adulthood in female subjects with a history of early menarche: The Bogalusa heart study. *Int. J. Obesity 27:* 1398–1404.
60. Gambineri, A, Pagotto, U, Tschop, M, Vicennati, V, Manicardi, E, Carcello, A, Cacciari, M, De Iasio, R, & Pasquali, R. (2003). Anti-androgen treatment increases circulating ghrelin levels in obese women with polycystic ovary syndrome. *J. Endocrinol. Invest. 26:* 629–634.
61. Gambineri, A, Pelusi, C, Vicennati, V, Pagotto, U, & Pasquali, R. (2002). Obesity and the polycystic ovary syndrome. *Int. J. Obes. Relat. Metab. Disord. 26:* 883–896.
62. Garcia, VF, Langford, L, & Inge, TH. (2003). Application of laparoscopy for bariatric surgery in adolescents. *Curr. Opin. Pediatr. 15:* 248–255.
63. Garcia-Mayor, R, Andrade, MA, Rios, M, Lage, M, Dieguez, C, & Casanueva, FF. (1997). Serum leptin levels in normal children: Relationship to age, gender, body mass index, pituitary–gonadal hormones, and pubertal stage. *J. Clin. Endocrinol. Metab. 82:* 2849–2855.
64. Goran, M, Ball, GDC, & Cruz, ML. (2003). Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J. Clin. Endocrinol. Metab. 88:* 1417–1427.
65. Gordon, C. (1999). Menstrual disorders in adolescents: Excess androgens and the polycystic ovary syndrome. *Pediatr. Clin. North Am. 46:* 519–543.
66. Gortmaker, S, Must, A, Perrin, JM, Sobol, AM, & Dietz, WH. (1993). Social and economic consequences of overweight in adolescence and young adulthood. *New England Journal of Medicine 329:* 1008–1012.
67. Grunbaum, J, Kann, L, Kinchen, S, Ross, J, Hawkins, J, Lowry, R, Harris, WA, McManus, T, Chyen, D, & Collins, J. (2004). Youth risk behavior surveillance: United States, 2003. *MMWR 53:* 1–96.
68. Grundy, S, Brewer, Jr, B, Cleeman, JI, Smith, SC, & Lenfant, C. (2004). Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation 109:* 433–438.
69. Gutin, B, Barbeau, P, Owens, S, Lemmon, CR, Bauman, M, Allison, J, Kang, H, & Litaker, MS. (2002). Effects of exercise intensity on cardiovascular fitness, total body composition, and visceral adiposity of obese adolescents. *Am. J. Clin. Nutr. 75:* 818–826.
70. Gutin, B, & Owens, S. (1999). Role of exercise intervention in improving body fat distribution and risk profile in children. *Am. J. Hum. Biol. 11:* 237–247.

71. Hackam, D, & Anand, S.S. (2003). Emerging risk factors for atherosclerotic vascular disease: A critical review of the evidence. *JAMA 290:* 932–940.
72. Hammer, L, Kraemer, HC, Wilson, DM, Ritter, PL, & Dornbusch, S.M. (1991). Standardized percentile curves of body-mass index for children and adolescents. *Am. J. Dis. Child. 145:* 259–263.
73. Harrison, SA, & Di Bisceglie, AM. (2003). Advances in the understanding and treatment of nonalcoholic fatty liver disease. *Drugs 63:* 2379–2394.
74. Hedley, AA, Ogden, CL, Johnson, CL, Carroll, MD, Curtin, LR, & Flegal, KM. (2004). Prevalence of overweight and obesity among U.S. children, adolescents, and adults, 1999–2002. *JAMA 291:* 2847–2850.
75. Hu, F, Li, TY, Colditz, GA, Willett, WC, & Manson, JE. (2003). Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA 289:* 1785–1791.
76. Hulman, S, Kushner, H, Katz, S, & Falkner, B. (1998). Can cardiovascular risk be predicted by newborn, childhood, and adolescent body size? An examination of longitudinal data in urban African Americans. *J. Pediatr. 132:* 90–97.
77. Humphries, M, Gutin, B, Barbeau, P, Vemulapalli, S, Allison, J, & Owens, S. (2002). Relations of adiposity and effects of training on the left ventricle in obese youths. *Med. Sci. Sports Exerc. 34:* 1428–1435.
78. Inge, TH, Garcia, V, Daniels, S, Langford, L, Kirk, S, Roehrig, H, Amin, R, Zeller, M, & Higa, K. (2004). A multidisciplinary approach to the adolescent bariatric surgical patient. *J. Pediatr. Surg. 39:* 442–447; discussion 446–447.
79. Inge, TH, Krebs, NF, Garcia, VF, Skelton, JA, Guice, KS, Strauss, RS, Albanese, CT, Brandt, ML, Hammer, LD, Harmon, CM, Kane, TD, Klish, WJ, Oldham, KT, Rudolph, CD, Helmrath, MA, Donovan, E, & Daniels, SR. (2004). Bariatric surgery for severely overweight adolescents: Concerns and recommendations. *Pediatrics 114:* 217–223.
80. Janssen, I, Craig, WM, Boyce, WF, & Pickett, W. (2004). Associations between overweight and obesity with bullying behaviors in school-aged children. *Pediatrics 113:* 1187–1194.
81. Jenkins, D, Kendall, CWC, Marchie, A, Faulkner, DA, Wong, JMW, de Souza, R, Emam, A, Parker, TL, Vidgen, E, Lapsley, KG, Trautwein, EA, Josse, RG, Leiter, LA, & Connelly, PW. (2003). Effects of a dietary portfolio of cholesterol-lowering foods vs. lovastatin on serum lipids and c-reactive protein. *JAMA 290:* 502–510.
82. Kanani, PM, & Sperling MA. (2002). Hyperlipidemia in adolescents. *Adolesc. Med. 13:* 37–52, v–vi.
83. Kang, H, Gutin, B, Barbeau, P, Owens, S, Lemmon, CR, Allison, J, Litaker, MS, & Le, N. (2002). Physical training improves insulin resistance syndrome markers in obese adolescents. *Med. Sci. Sports Exerc. 34:* 1920–1927.
84. Kavey, R, Daniels, SR, Lauer, RM, Atkins, DL, Hayman, LL, & Taubert, K. (2003). American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation 107:* 1562–1566.
85. Kay, J, Alemzadeh, R, Langley, G, D'Angelo, L, Smith, P, & Holshouser, S. (2001). Beneficial effects of metformin in normoglycemic morbidly obese adolescents. *Metabolism 50:* 1457–1461.
86. Kesler, A, & Fattal-Valevski, A. (2002). Idiopathic intracranial hypertension in the pediatric population. *J. Child Neurol. 17:* 745–748.
87. Killen, JD, Hayward, C, Wilson, DM, Taylor, CB, Hammer, LD, Litt, I, Simmonds, B, & Haydel, F. (1994). Factors associated with eating disorder symptoms in a community sample of 6th and 7th grade girls. *Int. J. Eat. Disord. 15:* 357–367.

88. Killen, JD, Taylor, CB, Hayward, C, Haydel, KF, Wilson, DM, Hammer, L, Kraemer, H, Blair-Greiner, A, & Strachowski, D. (1996). Weight concerns influence the development of eating disorders: A 4-year prospective study. *J. Consult. Clin. Psychol. 64:* 936–940.
89. Killen, JD, Taylor, CB, Hayward, C, Wilson, DM, Haydel, KF, Hammer, LD, Simmonds, B, Robinson, TN., Litt, I, & Varady, A. (1994). Pursuit of thinness and onset of eating disorder symptoms in a community sample of adolescent girls: A three-year prospective analysis. *Int. J. Eat. Disord. 16:* 227–238.
90. Kimm, SYS. (1995). The role of dietary fiber in the development and treatment of childhood obesity. *Pediatrics 96:* 1010–1014.
91. Kral, J, Thung, SN, Biron, S, Hould, F, Lebel, S, Marceau, S, Simard, S, & Marceau, P. (2004). Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. *Surgery 135:* 48–58.
92. Krebs, N, Jacobson, MS, & AAP Committee on Nutrition. (2003). Prevention of pediatric overweight and obesity. *Pediatrics 112:* 424–430.
93. Lin, YC, Lyle, RM, McCabe, LD, McCabe, GP, Weaver, CM, & Teegarden, D. (2000). Dairy calcium is related to changes in body composition during a two-year exercise intervention in young women. *J. Am. Coll. Nutr. 19:* 754–760.
94. Ludwig, D, Majzoub, JA, Al-Zahrani, A, Dallal, GE, Blanco, I, & Roberts, SB. (1999). High glycemic index foods, overeating, and obesity. *Pediatrics 103:* e26.
95. Ludwig, D, Pereira, MA, Kroenke, CH, Hilner, JE, Van Horn, L, Slattery, ML, & Jacobs, DR. (1999). Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA 282:* 1539–1546.
96. Ludwig, DS. (2000). Dietary glycemic index and obesity. *J. Nutr. 130:* 280S–283S.
97. Ludwig, DS. (2003). Dietary glycemic index and the regulation of body weight. *Lipids 38:* 117–121.
98. Ludwig, DS, & Gortmaker, SL. (2004). Programming obesity in childhood. *Lancet 364:* 226–227.
99. Matheson, DM, Hanson, KA, McDonald, TE, & Robinson, TN. (2002). Validity of children's food portion estimates: A comparison of two measurement aids. *Arch. Pediatr. Adolesc. Med. 156:* 867–871.
100. Matiz, A, & Roman, EA. (2003). In Brief: Apnea. *Pediatrics in Review 24:* 32–34.
101. Mellin, A, Neumark-Sztainer, D, Story, M, Ireland, M, & Resnick, MD. (2002). Unhealthy behaviors and psychosocial difficulties among overweight adolescents: The potential impact of familial factors. *J. Adolesc. Health 31:* 145–153.
102. Mingrone, G, DeGaetano, A, Greco, AV, Capristo, E, Benedetti, G, Castagneto, M, & Gasbarrini, G. (1997). Reversibility of insulin resistance in obese diabetic patients: Role of plasma lipids. *Diabetalogia 40:* 599–605.
103. Mitchell, B, Gutin, B, Kapuku, G, Barbeau, P, Humphries, MC, Owens, S, Vemulapalli, S, & Allison, J. (2002). Left ventricular structure and function in obese adolescents: Relations to cardiovascular fitness, percent body fat, and visceral adiposity, and effects of physical training. *Pediatrics 109:* e73.
104. Mokdad, AH, Ford, ES, Bowman, BA, Dietz, WH, Vinicor, F, Bales, VS, & Marks, JS. (2003). Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA 289:* 76–79.
105. Mokdad, AH, Marks, JS, Stroup, DF, & Gerberding, JL. (2004). Actual causes of death in the United States, 2000. *JAMA 291:* 1238–1245.
106. Moran, O, & Phillip, M. (2003). Leptin: Obesity, diabetes and other peripheral effects — a review. *Pediatr. Diabetes 4:* 101–109.

107. Morgan, C, Yanovski, SZ, Nguyen, TT, McDuffie, J, Sebring, NG, Jorge, MR, Keil, M, & Yanovski, JA. (2002). Loss of control over eating, adiposity, and psychopathology in overweight children. *Int. J. Eat. Disord. 31:* 430–441.
108. Murphy, M, Metcalf, BS, Voss, LD, Jeffery, AN, Kirkby, J, Mallam, KM, & Wilkin, TJ. (2004). Girls at five are intrinsically more insulin resistant than boys: The programming hypotheses revisited — the EarlyBird Study. *Pediatrics 113:* 82–86.
109. Myers, M, Raynor, HA, & Epstein, LH. (1998). Predictors of child psychological changes during family-based treatment for obesity. *Arch. Pediatr. Adolesc. Med. 152:* 855–861.
110. Narkiewicz, K. (2002). Obesity-related hypertension: Relevance of vascular responses to mental stress. *J. Hypertension 20:* 1277–1278.
111. Nesmith, J. (2001). Type 2 diabetes mellitus in children and adolescents. *Pediatrics in Review 22:* 147–152.
112. Pagotto, U, Gambineri, A, Vicennati, V, Heiman, ML, Tschop, M, & Pasquali, R. (2002). Plasma ghrelin, obesity, and the polycystic ovary syndrome: Correlation with insulin resistance and androgen levels. *J. Clin. Endocrinol. Metab. 87:* 5625–5629.
113. Patrick, K, Norman, GJ, Calfas, KJ, Sallis, JF, Zabinski, MF, Rupp, J, & Cella, J. (2004). Diet, physical activity, and sedentary behaviors as risk factors for overweight in adolescence. *Arch. Pediatr. Adolesc. Med. 158:* 385–390.
114. Pelkman, C, Fishell, VK, Maddox, DH, Pearson, TA, Mauger, DT, & Kris-Etherton, PM. (2004). Effects of moderate fat (from monounsaturated fat) and low-fat weight-loss diets on the serum lipid profile in overweight and obese men and women. *Am. J. Clin. Nutr. 79:* 204–212.
115. Pereira, MA, Jacobs, DR, Jr, Van Horn, L, Slattery, ML, Kartashov, AI, & Ludwig, DS. (2002). Dairy consumption, obesity, and the insulin resistance syndrome in young adults: The CARDIA Study. *JAMA 287:* 2081–2089.
116. Pinhas-Hamiel, O, Dolan, LM, Daniels, SR, Standiford, D, Khoury, PR, & Zeitler, P. (1996). Increased incidence of non–insulin-dependent diabetes mellitus among adolescents. *J. Pediatr. 128:* 608–615.
117. Centers for Disease Control and Prevention (CDC). (2003). Physical activity levels among children aged 9–13 years — United States, 2002. *MMWR 52:* 785–788.
118. Robinson, TN. (1999). Behavioural treatment of childhood and adolescent obesity. *Int. J. Obes. Relat. Metab. Disord. 23* Suppl 2: S52–S57.
119. Robinson, TN. (2000). Can a school-based intervention to reduce television use decrease adiposity in children in grades 3 and 4? *West. J. Med. 173:* 40.
120. Robinson, TN. (1998). Does television cause childhood obesity? *JAMA 279:* 959–960.
121. Robinson, TN. (1999). Reducing children's television viewing to prevent obesity: A randomized controlled trial. *JAMA 282:* 1561–1567.
122. Robinson, TN. (2001). Television viewing and childhood obesity. *Pediatr. Clin. North Am. 48:* 1017–1025.
123. Robinson, TN, Hammer, LD, Killen, JD, Kraemer, HC, Wilson, DM, Hayward, C, & Taylor, CB. (1993). Does television viewing increase obesity and reduce physical activity? Cross-sectional and longitudinal analyses among adolescent girls. *Pediatrics 91:* 273–280.
124. Rowell, HA, Evans, BJ, Quarry-Horn, JL, & Kerrigan, JR. (2002). Type 2 diabetes mellitus in adolescents. *Adolesc. Med. 13:* 1–12.
125. Safer, DL, Agras, WS, Bryson, S, & Hammer, LD. (2001). Early body mass index and other anthropometric relationships between parents and children. *Int. J. Obes. Relat. Metab. Disord. 25:* 1532–1536.

126. Samaha, FF, Iqbal, N, Seshadri, P, Chicano, KL, Daily, DA, McGrory, J, Williams, T, Williams, M, Gracely, EJ, & Stern, L. (2003). A low-carbohydrate as compared with a low-fat diet in severe obesity. *New England Journal of Medicine 348:* 2074–2081.
127. Schauer, P, Burguera, B, Ikramuddin, S, Cottam, D, Gourash, W, Hamad, G, Eid, GM, Mattar, S, Ramanthan, R, Barinas-Mitchel, E, Rao, RH, Kuller, L, & Kelley, D. (2003). Effect of laparoscopic roux-en-y gastric bypass on type 2 diabetes mellitus. *Annals of Surgery 238:* 467–485.
128. Schebendach, J. (2003). The use of indirect calorimetry in the clinical management of adolescents with nutritional disorders. *Adolesc. Med. 14:* 77–85.
129. Schwimmer, J, Burwinkle, TM, & Varni, JW. (2003). Health-related quality of life of severely obese children and adolescents. *JAMA 289:* 1813–1819.
130. U.S. Department of Agriculture and Health and Human Services (2000). *Nutrition and Your Health: Dietary Guidelines for Americans.*
131. Shamsuzzaman, A, Gersh, BJ, & Somers, VK. (2003). Obstructive sleep apnea: Implications for cardiac and vascular disease. *JAMA 290:* 1906–1914.
132. Siegel, RJ, Cabeen, Jr, WR, & Roberts, WC. (1981). Prolonged QT interval-ventricular tachycardia syndrome from massive rapid weight loss utilizing the liquid-protein-modified-fast diet: Sudden death with sinus node ganglionitis and neuritis. *Am. Heart J. 102:* 121–122.
133. Simopoulos, A. (2002). Omega-3 fatty acids in inflammation and autoimmune diseases. *J. Am. Coll. Nutr. 21:* 495–505.
134. Sinha, R, Fisch, G, Teague, B, Tamborlane, WV, Banyas, B, Allen, K, Savoye, M, Rieger, V, Taksali, S, Barbetta, G, Sherwin, RS, & Caprio, S. (2002). Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *New England Journal of Medicine 346:* 802–810.
135. Skinner, JD, Bounds, W, Carruth, BR, Morris, M, & Ziegler, P. (2004). Predictors of children's body mass index: A longitudinal study of diet and growth in children aged 2–8 years. *Int. J. Obes. Relat. Metab. Disord. 28:* 476–482.
136. Slyper, AH. (2004). The pediatric obesity epidemic: Causes and controversies. *J. Clin. Endocrinol. Metab. 89:* 2540–2547.
137. Sondike, S, Copperman, N, & Jacobson, MS. (2003). Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factors in overweight adolescents. *J. Pediatr. 142:* 253–258.
138. Sorof, J, & Daniels, S. (2002). Obesity hypertension in children: A problem of epidemic proportions. *Hypertension 40:* 441–447.
139. Sours, HE, Frattali, VP, Brand, CD, Feldman, RA, Forbes, AL, Swanson, RC, & Paris, AL. (1981). Sudden death associated with very low calorie weight reduction regimens. *Am. J. Clin. Nutr. 34:* 453–461.
140. Spieth, L, Harnish, JD, Lenders, CM, Raezer, LB, Pereira, MA, Hangen, SJ, & Ludwig, DS. (2000). A low-glycemic index diet in the treatment of pediatric obesity. *Arch. Pediatr. Adolesc. Med. 154:* 947–951.
141. Steinberger, J, Moorehead, C, Katch, V, & Rocchini, AP. (1995). Relationship between insulin resistance and abnormal lipid profile in obese adolescents. *J. Pediatr. 126:* 690–695.
142. Stice, E, Agras, WS, & Hammer, LD. (1999). Risk factors for the emergence of childhood eating disturbances: A five-year prospective study. *Int. J. Eat. Disord. 25:* 375–387.
143. Stice, E, Cameron, RP, Killen, JD, Hayward, C, & Taylor, CB. (1999). Naturalistic weight-reduction efforts prospectively predict growth in relative weight and onset of obesity among female adolescents. *J. Consult. Clin. Psychol. 67:* 967–974.

144. Strauss, R, Bradley, LJ, & Brolin, RE. (2001). Gastric bypass surgery in adolescents with morbid obesity. *J. Pediatr. 138:* 499–504.
145. Stunkard, A, Faith, MS, & Allison, KC. (2003). Depression and obesity. *Biological Psychiatry 54:* 330–337.
146. Taylor, A, Hubbard, J, & Anderson, EJ. (1999). Impact of binge eating on metabolic and leptin dynamics in normal young women. *J. Clin. Endocrinol. Metab. 84:* 428–434.
147. Teegarden, D. (2003). Calcium intake and reduction in weight or fat mass. *J. Nutr. 133:* 249S–251S.
148. Teegarden, D, & Zemel, MB. (2003). Dairy product components and weight regulation: Symposium overview. *J. Nutr. 133:* 243S–244S.
149. Wadden, T, Stunkard, AJ, Rich, L, Rubin, CJ, Sweidel, G, & McKinney, S. (1990). Obesity in black adolescent girls: A controlled clinical trial of treatment by diet, behavior modification, and parental support. *Pediatrics 85:* 345–352.
150. Wang, G, & Dietz, WH. (2002). Economic burden of obesity in youths aged 6 to 17 years: 1979–1999. *Pediatrics 109:* e81.
151. Weiss, R, Dziura, J, Burgert, TS, Tamborlane, WV, Taksali, SE, Yeckel, CW, Allen, K, Lopes, M, Savoye, M, Morrison, J, Sherwin, RS, & Caprio, S. (2004). Obesity and the metabolic syndrome in children and adolescents. *New England Journal of Medicine 350:* 2362–2374.
152. Wessel, T, Arant, CB, Olson, MB, Johnson, BD, Reis, SE, Sharaf, BL, Shaw, LJ, Handberg, E, Sopko, G, Kelsey, SF, Pepine, CJ, & Merz, CNB. (2004). Relationship of physical fitness vs. body mass index with coronary artery disease and cardiovascular events in women. *JAMA 292:* 1179–1187.
153. Whitaker, R, & Dietz, WH. (1998). Role of the prenatal environment in the development of obesity. *J. Pediatr. 132:* 768–776.
154. Whitaker, R, Wright, JA, Pepe, MS, Seidel, KD, & Dietz, WH. (1997). Predicting obesity in young adulthood from childhood and parental obesity. *New England Journal of Medicine 337:* 869–873.
155. Wiehe, S. (2004). Sugar high. *Arch. Pediatr. Adolesc. Med. 158:* 209–211.
156. Willi, S, Oexmann, MJ, Wright, NM, Collop, NA, & Key, Jr, LL. (1998). The effects of a high-protein, low-fat ketogenic diet on adolescents with morbid obesity: Body composition, blood chemistries, and sleep abnormalities. *Pediatrics 101:* 61–67.
157. Williams, CL, Hayman, LL, Daniels, SR, Robinson, TN, Steinberger, J, Paridon, S, & Bazzarre, T. (2002). Cardiovascular health in childhood: A statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation 106:* 143–160.
158. Winkleby, MA, Robinson, TN, Sundquist, J, & Kraemer, HC. (1999). Ethnic variation in cardiovascular disease risk factors among children and young adults: Findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *JAMA 281:* 1006–1013.
159. Wrotniak, BH, Epstein, LH, Paluch, RA, & Roemmich, JN. (2004). Parent weight change as a predictor of child weight change in family-based behavioral obesity treatment. *Arch. Pediatr. Adolesc. Med. 158:* 342–347.
160. Yanovski, J. (2001). Intensive therapies for pediatric obesity. *Pediatr. Clin. North Am. 48:* 1041–1053.
161. Yanovski, J, & Yanovski, SZ. (1999). Recent advances in basic obesity research. *JAMA 282:* 1504–1506.
162. Yanovski, SZ, & Yanovski, JA. (2002). Drug therapy: Obesity. *New England Journal of Medicine 346:* 591–602.

2 Medical Weight Control in the Adult Patient

Jeanette Newton Keith and Lori Rowell

CONTENTS

2.1 INTRODUCTION

Over the past 30 years, obesity has emerged as the latest epidemic to adversely impact the health of people of all ages and races, mandating the need to address health and nutrition in every medical practice from pediatrics to geriatrics. To highlight the significance of the obesity epidemic, as of 2002, the CDC reports that between 300,000 and 400,000 obesity-related deaths in the United States have occurred, making obesity the number two preventable cause of death in the United States (70). It is projected that obesity will soon surpass smoking as the number one cause of preventable deaths in the United States.

When defining obesity, actual body weight and percent total body fat are important, but these do not indicate body composition or build. The body mass index (BMI) is a surrogate marker of body fat and correlates with mortality as well

as risk of developing obesity-related complications. Adult obesity is defined as having a BMI greater than 30 or greater than 27 with weight-related complication (12). The primary limitation of the BMI is its inability to discriminate between total body fat or body fat distribution versus lean tissue. It also has decreased accuracy in the setting of excess muscle mass, short stature, or loss of significant muscle mass. In spite of these limitations, the BMI remains the best clinical tool for defining the risk of obesity-related mortality. The BMI is determined by dividing the weight in kilograms by the height in meters squared. NHLBI BMI tables are widely available for clinical use (110). Worldwide, obesity is the latest epidemic to take its toll on developing nations. Reports from international surveys reveal that Europe and third world nations have not been spared in this epidemic, highlighting the need for a systematic approach to this devastating disease. In Hungary, it is reported that the number of people with a BMI of greater than 35 has doubled since 1989. In addition, 80% of Latvian women and 75% of Czech men are reported to have a BMI above 25. In Prague, it is estimated by researchers that 60% of middle-aged Czechs are overweight and 22 to 25% of all Czechs are obese. According to the Bulgarian Association for the Study of Obesity, nearly 56% of Bulgarians are overweight. This figure compares with the nearly 50% of Serbians, Slovakians, and residents of Montenegro who are also overweight (109). There are even case reports of obesity and obesity-related complications affecting pediatric populations in sub-Saharan African nations such as Senegal (25). These findings underscore the need for culturally appropriate, multidisciplinary interventions on a worldwide scale.

While recognition and identification of the problem have been easy, finding a cure remains an enigma, as do research efforts such as to determine the etiology of obesity. In the face of the current obesity epidemic, every health care practitioner is challenged with caring for medically complex overweight and obese patients. Current treatment includes both medical and surgical interventions, with success rates for surgical approaches to weight loss at 5 years being superior to that of medical management (cf. Chapter 3). Yet in clinical practice, surgical interventions are not appropriate for every patient; therefore, medical management should be the foundation of any approach to weight control.

Because obesity is a chronic disease like diabetes or hypertension, it requires a systematic approach with clearly defined treatment goals and lifelong management. The incorporation of medical management of obesity into a busy practice can, however, present an overwhelming challenge to any practitioner. The goal of this review is to empower health care providers in the trenches by providing clinically relevant and useful tools from evidence-based data for clinical practice. This chapter will provide a limited overview of emerging science relative to the genetics of obesity, discuss the neurohormonal mechanisms that influence food intake, and review approaches to medical weight management in clinical programs. In addition, environmental and dietary influences on obesity, as well as FDA approved pharmacologic interventions, will be discussed. Emerging data regarding the role of endoscopic therapies and minimally invasive devices will be briefly addressed. Surgical interventions are presented in Chapter 3.

2.2 DEFINING SUCCESS

Moderate weight loss of 5 to 10% maintained for 1 year is now the benchmark of success for modern medical weight management programs. Historically, traditional weight loss programs sought to achieve tremendous weight loss, with attaining the ideal body weight as the mark of success. Early studies found significant reduction in obesity-related mortality and improvement in metabolic parameters when very low calorie diets (98) and gastric bypass surgery were used to induce significant weight loss (55). Long-term follow-up, however, revealed high levels of recidivism with weight regain when medical management was the primary mechanism of weight loss (121). With weight regain, there is reestablishment of the disease-associated risks (121). Not only does obesity lead to debilitating medical complications in nearly every biologic system (41), but there are financial consequences in excess of billions of dollars per year (82). These findings underscore that obesity is a chronic disease, necessitating lifelong intervention. This understanding led to efforts to determine how much weight loss is required to reduce obesity-related complications and associated mortality (35). One prospective study of intentional weight loss and mortality in nonsmoking overweight women found a 20 to 25% reduction in all-cause mortality with modest weight loss. The reduction in overall mortality in women with obesity-related health conditions following an intentional weight loss of any amount was attributed to decreased premature mortality as evidenced by a 40 to 50% reduction in obesity-related cancer deaths and a 30 to 40% reduction in diabetes-associated mortality. Of note, in overweight women with no preexisting medical illnesses, intentional weight loss equal to or greater than 20 pounds within the previous year reduced all-cause, cardiovascular and cancer mortality by 25% (127).

The findings of this study and others led to a report by the Institute of Medicine titled "Weighing the Options," in which clinicians were challenged to refocus the goal of obesity treatment in order to achieve and maintain good health. The definition of success was

> broadened and made more realistic based on the research findings that small weight losses can reduce risks of developing chronic diseases. Specifically, the goal of obesity treatment should be refocused from weight loss alone, which is often aimed at appearance, to *weight management*, achieving the best weight possible in the context of overall health (113).

Successful weight management programs are defined by their ability to stop weight gain, achieve a 5 to 10% weight loss with reduction in disease-associated morbidity and mortality, prevent weight regain, improve lifestyle habits that include increased physical activity, and improve health care practices (113).

To help guide clinical practice in obesity medicine, the NHLBI released *The Practical Guide* outlining the identification, evaluation, and treatment of overweight and obesity in adults (81). The NHLBI stated that "the initial goal of weight loss therapy for overweight patients is a reduction in body weight of about 10%. Moderate weight loss of this magnitude can significantly decrease the severity of obesity

associated risk factors." With an intentional weight loss of 5 to 10%, there is improvement in glycemic control, reduction of triglycerides levels, increases in HDL cholesterol, and a reduction of blood pressure. Of note, blood pressure will return to baseline by 4 to 6 years even when weight loss is maintained. In contrast, a 20% weight loss is needed for a reduction in total cholesterol and LDL cholesterol (12). Therefore, according to the NHLBI, "if the goal of 10% weight loss is achieved, further weight loss can be attempted through further evaluation" (81).

For most individuals, it is reasonable to expect a 10% reduction in body weight over a 6-month period when a multidisciplinary approach is utilized. However, patients may have an expectation or a desire for greater weight loss. In a scientific review of popular diets by Freedman et al. (36) it was noted that many obese women desire, on average, a 32% reduction in body weight. Even in the setting of optimal medical management, these goals are unrealistic and may contribute to failure of medical weight management (37). Surgical intervention, in many cases, does reach a weight loss in the range of expected and desired weight loss. However, the decision to pursue surgery as a treatment for severe morbid obesity should be weighed against the risk–benefit profile for an individual patient (121).

For practitioners, it is therefore critical to partner with patients to set realistic goals when defining success for each patient. The primary objective should include the loss and maintenance of 5 to 10% weight loss. Thus, even during the initial 6 months of medical weight loss, efforts to prevent weight regain should be put into place in order to increase the likelihood of sustained success. Weight-control programs should therefore include dietary therapy, physical activity, and behavioral therapy for a lifetime of change. Any therapeutic intervention requires understanding and appreciating the genetic, environmental, and dietary influences that affect clinical management of these patients. More recent work by Schwartz, Bray, and others has illuminated the role of neurobiochemical factors and toxic environmental elements that appear to be key in improving clinical outcomes in medical weight management and provide targets for pharmacologic therapy (13). These recent advances will shape the future management of obesity.

2.3 THE GENETICS OF OBESITY

When multiple randomized controlled studies were summarized, approximately 40% of the heritability of human obesity is due to genetic influences (107). In the 1980s, a study of twins reared apart found a closer correlation of body weight with the biologic parent versus the adopted parent, suggesting a role for genetic influences in weight control. Genetics was thought to account for 50% of the heritability of body weight in dizygotic twins and 90% of the heritability in monozygotic twins (115). Other studies examining family groups suggested that genetics accounted for 30 to 50% of the weight variance; studies of adopted children found that genetics accounted for 10 to 30% of the weight variance. Therefore, in human obesity, genetic influences are significant but do not account for 60% of the weight variance. Historically, there were few models of human obesity, and, therefore, the study of obesity was primarily limited to the five animal models with single gene defects, such as

the db/db mice, ob/ob mice, the tubby mice, the agouti mice, and the zucker fatty (fa/fa) rat (19). In these animal models, mutations of the gene coding for the protein product leptin and its receptor were identified.

Leptin is a hormone secreted by adipocytes in direct proportion to their size, and when deficient results in hyperphagia and obesity (107). However, it was not until 1994, when Dr. Jeffrey Friedman identified human leptin and its gene mutation, that the study of human obesity was revolutionized and legitimized. In contrast to the mouse model, leptin resistance was found to be more common in humans, whereas leptin deficiency was noted in the animal models (107). However, there are rare genetic deficiencies of leptin in humans that result in hyperphagia and severe morbid obesity. Patients with this genetic condition respond to leptin replacement with weight loss and regain control of their appetite.

This landmark discovery led to the recognition of the adipocyte as an endocrine organ and furthered the development of hormonal regulatory pathways to explain the physiology of human obesity. Genetic studies were also undertaken in an effort to identify an "obesity gene" that might lead to a cure for this debilitating and costly disease. A few well-described clinical syndromes, such as Prader–Willi syndrome, follow Mendelian distribution and show phenotypic expression of obesity (34). The syndromes that result from single gene defects are rare and noteworthy when they occur in clinical practice. For most causes of obesity, no single obesity gene has been identified.

As of October 2003, there are 41 Mendelian syndromes relevant to human obesity with maps to a genomic region, 183 animal and 208 quantitative trait loci, and 35 chromosomal regions that have been implicated as causative agents resulting in human obesity (106). Causative gene defects leading to a deficiency state that results in rare cases of human obesity include but are not limited to leptin deficiency, melanocortin-4 receptor deficiency, proopiomelanocortin derived protein (POMC) deficiency, and α-melanocyte stimulating hormone deficiency (105). Variations in chromosomes containing obesity-related genes have also been implicated as genetic causes of obesity based on quantitative genetic studies. For example, in Mexican Americans and African Americans, studies have linked serum leptin levels to chromosome 2 at band 21 (2p21), which is the same chromosome that codes for proopiomelanocortin or the POMC gene. The loss of POMC function causes monogenic obesity in mice and humans (19). Other studies in French sibling pedigree pairs with a BMI > 27 did not find such linkage (31). More recently, obesity has been linked to chromosome 1 at bands 22–32 (1p22–32), which contain the region that codes for the leptin receptor (16). Other investigators have identified sequence variation in the leptin receptor exons that are not associated with body fat, suggesting that genetics alone does not explain human obesity (18).

When the data are summarized, single gene defects do cause human obesity but are rare and do not explain human obesity in most cases. Unlike rodent models, human obesity represents a polygenic disease with dietary and environmental influences, as well as neurobiologic and hormonal regulation. Overall, as one examines the current obesity epidemic, it is unlikely that genetic influences alone would account for the dramatic changes in body weight.

2.4 ENVIRONMENTAL AND DIETARY INFLUENCES

Key environmental factors that contribute to obesity include decreased physical activity (66), excess total caloric consumption through larger portion sizes (112), increased consumption of high-fat or calorie-dense foods (69), and increased stress levels and sleep disturbances that increase serum cortisol levels, which have been associated with hyperphagia (106). Dietary considerations also include micronutrient deficiencies that occur in addition to over-consumption of macronutrients such as carbohydrates or fat. Specifically, inadequate intake of dietary calcium and vitamin D has been associated with increased central body fat and obesity, a particular concern for dark-skinned populations (129).

With regard to physical activity, as modern technology has advanced, the nation has become more sedentary. In 1995, Weighing the Options reported that approximately 25% of men and women were inactive, and less than 20% of adults could be considered vigorously physically active (111). By 1996, the U.S. Department of Health and Human Services reported that nearly 60% of the U.S. population does not participate in regular physical activity and 25% is almost entirely sedentary. The youth are also more sedentary; nearly 50% of Americans between ages 12 and 21 years are not involved in vigorous activity on a regular basis (29).

In lieu of physical activity, watching television, working on computers, playing video games, and other sedentary behaviors have become the norm (114). Other factors that may be contributing to decreased physical activity include technological advances that reduce energy demands (e.g., elevators, escalators, people movers), safety concerns related to playing or being outdoors (104), urban sprawl that necessitates increased automobile travel (63), the loss of many physical education programs in the school systems, and increasing time demands that limit leisure activity. Within a given community, there may also be a lack of sidewalks, absence of bike paths, and limited playground areas that are safe.

This behavior pattern has resulted in an exponential increase in both adult and pediatric obesity. For example, in Chicago, there are neighborhoods where 50 to 60% of 2- to 5-year-old children already have a BMI above the 95th percentile, versus 15% nationally (Mount Sinai report, CLOCC). Community organizations such as the Coalition to Lower Obesity in Chicago Children (CLOCC) are strategizing to develop and implement programs to address these concerns. Therefore, as clinicians, it will be essential to discuss leisure-time activities and to work with individuals to reduce sedentary behaviors as part of their medical weight management care plan.

In addition to physical activity levels, health care professionals must address caloric intake in terms of portion sizes, fat content, and total caloric density. Since the 1970s, serving sizes have increased, leading to increased caloric consumption (112). For example, if one considers a serving of cola from Burger King, the original Coke was a 6.75-oz beverage containing approximately 75 kcal. Currently available serving sizes contain from 10 oz or 120 kcal for the “child” size to 36 oz or 450 kcal for the “king” size. A 52-oz soda offered by a convenience store contains, in “one serving,” 650 kcal. This is not to mention the 64-oz beverages that are available or the additional calories present in fruit-flavored beverages. Our clinical practice

sees patients who are in their 20s and morbidly obese, who believe that these larger beverages are normal serving sizes. For many, these are the only portions they have been exposed to during their youth, leading us to the conclusion that we are victims of "portion distortion" (112).

If one considers calories in terms of fat intake and caloric density, the larger portion sizes have led to increased caloric consumption. If one considers the portion of French fries available from McDonald's in 1950, it was 2 oz, which represents 210 kcal. In contrast, a large serving of fries in 2000 contained 540 kcal, and the more economically priced super-size portion of fries contained 610 kcal. It becomes essential to recognize that according to the U.S. Department of Agriculture (USDA), a standard serving size of French fries is 1 oz or 80 kcal. Therefore, one super-size serving of fries is equivalent to 7.6 "recommended servings" of fries, highlighting the challenge of portion control when there is limited understanding of how a recommended serving size or portion is defined. Unfortunately, people tend to eat according to the amount of food present, not its caloric density, leading to passive or active over-consumption (111).

Conversely, small changes in net energy intake can have a significant impact on body weight over time. Over-consumption, regardless of food source, leads to weight gain. For example, whether you consume extra calories from protein (4 kcal/g), fat (9 kcal/g), carbohydrates (4 kcal/g), or alcohol (7 kcal/g), it is stored as an energy reserve in the form of adipose fat. Equally, small reductions in caloric intake can lead to weight loss over time. If one reduces caloric intake by 100 kcal/d, this results in a net energy deficit of 36,500 kcal over a year, leading to a 10-lb weight loss. (One pound of body fat corresponds to 3500 kcal.) Simple dietary modifications such as eliminating a serving of butter per day or reducing mayonnaise from 2 to 1 tablespoon per sandwich can have a tremendous impact in terms of net energy balance (111). Ideally, a caloric deficit of 500 kcal/d (i.e., the calorie equivalent of a 12-oz can of soda and a candy bar) should be advised to obtain a net weight loss of 1 to 1.5 lb/week or 50 to 70 lb/year. This will meet for most and exceed for some the goal of a 5 to 10% total weight loss in 6 months.

However, life is not that simple. Stressful life events, sleep deprivation, and dietary micronutrients also influence energy balance. Data from the 1980s implicate chronic subclinical depression as a risk factor in the development of Type 2 diabetes mellitus, but no mechanism was identified (123). Recent data suggest that chronic stress, such as depression or sleep deprivation, has an adverse effect on several endocrine pathways. Serum cortisol levels increase with stress, leading to increased visceral fat deposition, a known risk factor for Type 2 diabetes, dyslipidemia, and other changes seen in Syndrome X or the so-called metabolic syndrome (32). Elevated levels of serum cortisol have been associated with uncontrolled hyperphagia and nocturnal eating in animal models, suggesting a possible mechanism for caloric over-consumption during stress. Work by Spiegel et al. (107) suggests that chronic sleep deprivation (approximately 4 h/night sleep) can elevate leptin and serum cortisol levels. Interestingly, the cortisol levels change in direct proportion to leptin levels, indicating that physiologic stress such as chronic sleep deprivation is an important regulator in weight control and food intake operating through a leptin-mediated pathway (107).

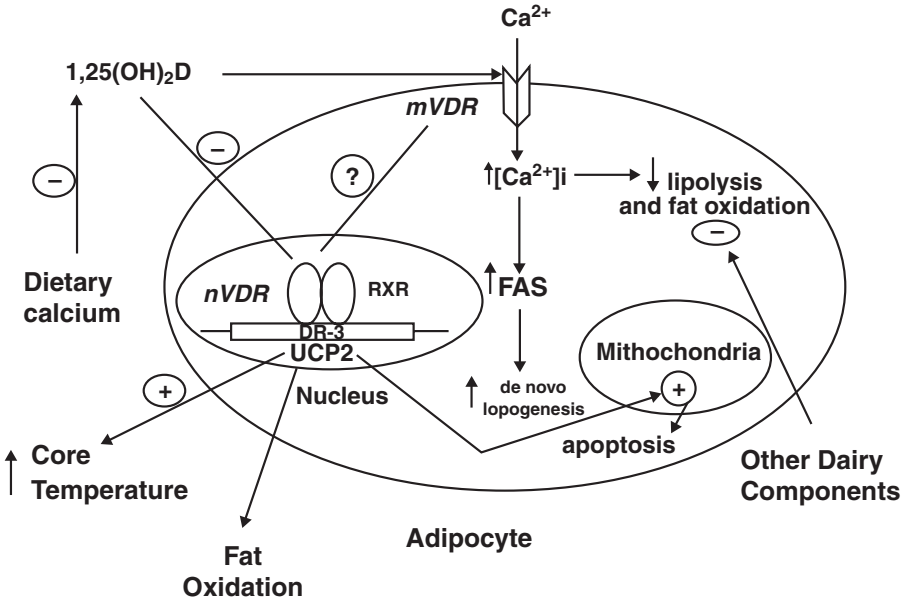


FIGURE 2.1 Mechanisms of dietary calcium and dairy modulation of adiposity. $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; $[Ca^{2+}]i$ = intracellular Ca^{2+} concentration; *mVDR* and *nVDR* = mouse and nuclear vitamin D receptors, respectively; RXR = retinoic acid receptor; UCP2 = uncoupling protein 2; FAS = fatty acid synthase; DR-3 = D response element-3. (From Zemel, M. *Amer. J. Clin. Nutr. 79* (5): 907S–912S, 2004. With permission.)

With regard to dietary influences, data from Zemel et al. (131) suggest a role for calcium and vitamin D in the regulation of adipocyte function and size. In work published in 2000, Zemel et al. reported that hypertensive African American men consuming 2 servings/d of yogurt as part of an effort to increase calcium for blood pressure control lost and maintained a significant amount of weight compared to the control group. Further study in the agouti mouse model revealed that increasing dietary calcium from dairy foods resulted in less weight gain due to less fat synthesis (lipogenesis) and increased fat breakdown (lipolysis). Doubling the amount of calcium present did not double the effect, suggesting a role for other dairy nutrients in the regulation of the adipocyte. Additionally, supplements were effective in decreasing body fat but only half as effective as dairy foods.

Work by Melanson et al. (75) has further explained Zemel's findings by showing that dietary calcium increased 24-h fat oxidation in humans when consumed acutely. This beneficial effect was not maintained chronically in the absence of calcium consumption (75). Mechanistically, it appears that nutrients from dairy foods, calcium in particular, stimulate fatty acid synthase, inhibit lipolysis, and increase lipid storage, as noted in Figure 2.1. These effects are dose-dependent in the physiological concentration range, result from calcium signaling, and are mediated by vitamin D1, $25\text{-}(OH)_2\text{-}D_3$ (131). Relative to the obesity epidemic, dietary food intake trends of

adolescents from 1965 to 1996 reveal that 90% of teen females consume less than 100% of the recommended daily intake (RDI) for calcium (1). Minority populations, especially African Americans, also have decreased intake of calcium and vitamin D. As dairy foods provide 70% of the calcium and vitamin D in most U.S. diets, lactose intolerance, perceived or real, is a major barrier to increased consumption. Perception of tolerance to dairy foods also limits intake. When 50 African American women with objective lactose maldigestion on breath hydrogen testing were surveyed, those who perceived tolerance consumed more total calcium through dairy foods than those who were self-described as lactose intolerant. However, the women failed to meet the RDI for calcium, even for the dairy consumers (15). The clinical significance of these data lies in the knowledge that individuals with low intake of dietary calcium have a higher BMI (15).

Obesity disproportionately affects African Americans and an increasing number of children, the same populations with suboptimal intake of dietary calcium (NHANES data). There are also vitamin D receptor differences in dark-skinned individuals such that it takes longer sun exposure to generate the same level of vitamin D as seen in fair-skinned people (78). Especially in temperate climates, dark-skinned individuals may limit sun exposure for cosmetic reasons, impairing the formation of skin-derived vitamin D. Increased consumption of a diet containing low-fat dairy foods, fruits, vegetables, and reduced total and saturated fats has been associated with a 72% risk reduction in the development of the insulin resistance syndrome when a calorie appropriate diet is consumed (89). Onset of Type 2 diabetes mellitus is reduced by 58% when combined with increased physical activity and modest weight loss (101). These studies suggest that efforts to increase consumption of dietary calcium and vitamin D through consumption of whole foods and a modest increase in sun exposure may be important clinical interventions for health care providers.

In summary, there are modifiable and nonmodifiable risk factors for the development of obesity, with genetics accounting for 40% of obesity and environment accounting for the remaining 60%. According to Dr. Judith Stern, "Genetics loads the gun, but environment pulls the trigger!" (quoted in *Washington Post,* August 12, 1997). However, that does not appear to be the end of the story.

2.5 THE NEUROBIOLOGY OF FOOD INTAKE AND WEIGHT CONTROL

Food intake and weight are under an active regulatory process, termed energy homeostasis. In 1953, Kennedy postulated that there was an inhibitory signal generated in proportion to body fat stores, which acted at the level of the brain to reduce food intake. Weight loss by caloric restriction was thought to decrease the level of this inhibitory signal. When the signals dropped beyond a certain level, food intake would increase until the energy deficit was corrected. However, this theory did not explain how energy intake was controlled during a meal. In 1973, Gibbs and Smith suggested that satiety factors or signals were generated from the gut in response to a meal and provide information to the brain that results in meal termination. Chole-

cystokinin (CCK) was identified as the first meal-induced satiety factor that influences food intake (102).

These two discoveries are now linked by recent data advancing our knowledge of energy balance and food intake. Friedman (37) and Schwartz et al. (102) have described models to delineate the roles of various hormonal and neuropeptide-signaling pathways in the control of food intake. It is the integration of these signals in the hindbrain that ultimately determines food intake, satiety, meal termination, and weight. Friedman's work highlights the role of leptin in the regulation of adiposity by its effect on food intake and energy expenditure in humans, as noted in Figure 2.2 (37). The schematic in Figure 2.3 suggests that the long-term mediators or adiposity signals, such as leptin and insulin, as well as more acute mediators or meal-related satiety factors, such as ghrelin, peptide YY, glucagon-like peptide-1 (GLP-1), and cholecystokinin, regulate food intake and meal termination. Further, central nervous system peptides such as neuropeptide Y, agouti-related protein, melanocortins, and serotonin also influence the regulation of appetite and satiety through mediation of leptin and insulin signals. Derangement of this system, for example, in response to toxic stimuli, has been proposed as the mechanism that results in human obesity (13). Understanding these pathways will be important as new drug therapies are being developed to specifically target these peptides and other signals of food intake in the battle to treat and perhaps cure obesity.

2.6 APPROACH TO THE PATIENT

Incorporating weight management into an already busy and at times overwhelming practice can be a daunting task, and yet is a necessity. To aid the primary care provider, two tools have been developed to provide a user-friendly approach to weight management, which allow physicians to address nutritional counseling as part of their general practice. The innovative teaching strategy for training physicians in clinical nutrition is presented in full in articles by Barner et al. (5) and by Gans et al. (39). To summarize, the tools are known as WAVE (Weight, Activity, Variety, Exercise) and REAP (Rapid Eating and Activity Assessment for Patients).

WAVE, as noted in Figure 2.4 and Figure 2.5, allows the physician and the patient to discuss the pros and cons of the patient's current weight. It is designed to help the health care provider identify weight, nutrition, and physical activity issues during the office visit, as well as to reveal concerns that may be best addressed with the assistance of a dietitian. The two-sided WAVE pocket card is divided into four sections on the front side. In the first box, entitled "Weight," the provider is instructed to obtain the BMI and is provided with body weight ranges for a given height to determine if the BMI is greater than 25. The physician is directed to perform an additional assessment if there has been unintentional weight loss in overweight patients. The second box, "Activity," asks about physical activity and evaluates for potential sedentary behaviors. Specifically, it addresses the need to have a dedicated increase in physical activity for 30 min on most days. It also attempts to identify sedentary patterns such as watching TV more than 2 h/d or avoiding stair climbing. Under "Variety," the third box, one is able to obtain a global assessment of the patient's eating pattern through a one-day dietary recall. This is an efficient way to

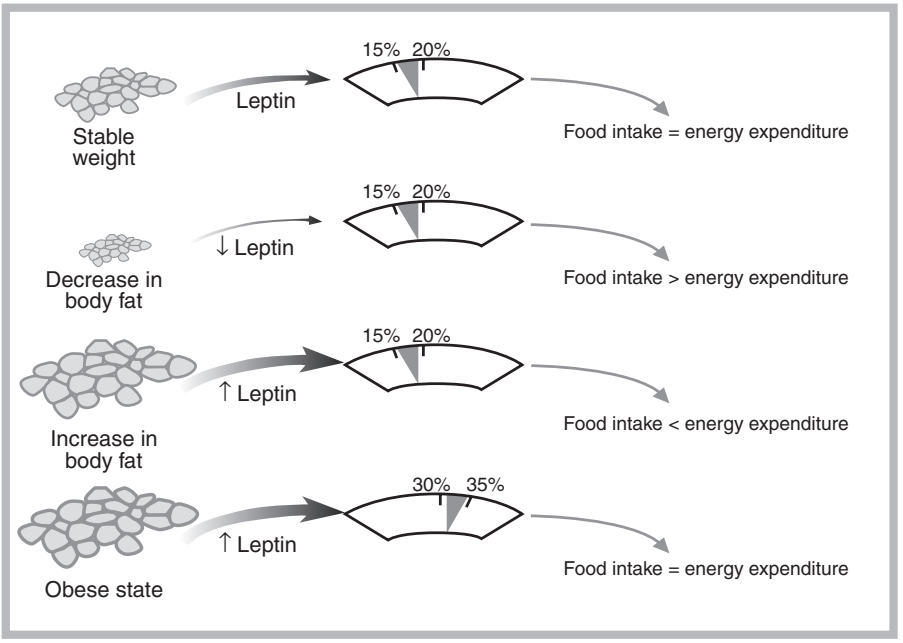


FIGURE 2.2 Leptin and the regulation of adipose tissue mass. The cloning of the *ob* gene and the characterization of leptin have indicated that body fat content is under homeostatic control. The available data suggest that leptin is the afferent signal in a feedback loop regulating adipose tissue mass. At an individual's stable weight (shown as 15 to 20% body fat in this figure, which is the typical fat content of a nonobese subject) the amount of circulating leptin elicits a state in which food intake equals energy expenditure. Increasing leptin levels result in negative energy balance (energy expenditure > food intake), whereas decreasing levels lead to positive energy balance (food intake > energy expenditure). These effects maintain constancy of fat cell mass within a relatively narrow range. Evidence further suggests that the intrinsic sensitivity to leptin is reduced among the obese and that the set point for body fat content is thus increased (designated as 30 to 35% in the bottom panel). Most obese individuals have high leptin levels and thus enter a state of negative energy balance when weight is reduced and leptin levels fall. (From Friedman, JM. *Nature 404:* 632–634, 2000. With permission.)

look for worrisome eating trends that predispose to more severe forms of obesity. With the information from the dietary recall, patterns of dietary "Excess" can be identified using questions from the fourth box. Key areas to assess for excess include total fat, saturated fats, total calories, sugar, and salt. The best part of this assessment tool for the busy practitioner is that the reverse side of the card provides answers for each of the questions as well as suggested interventions. The primary limitations of this tool are the lack of objective measure of body fat distribution, such as waist circumference, and that it does not factor in modifiers such as cholesterol that influence total risks.

The Rapid Eating and Activity Assessment for Patients (REAP) is a tool designed to assess the diet by comparing intake to the Food Guide Pyramid and the 2000

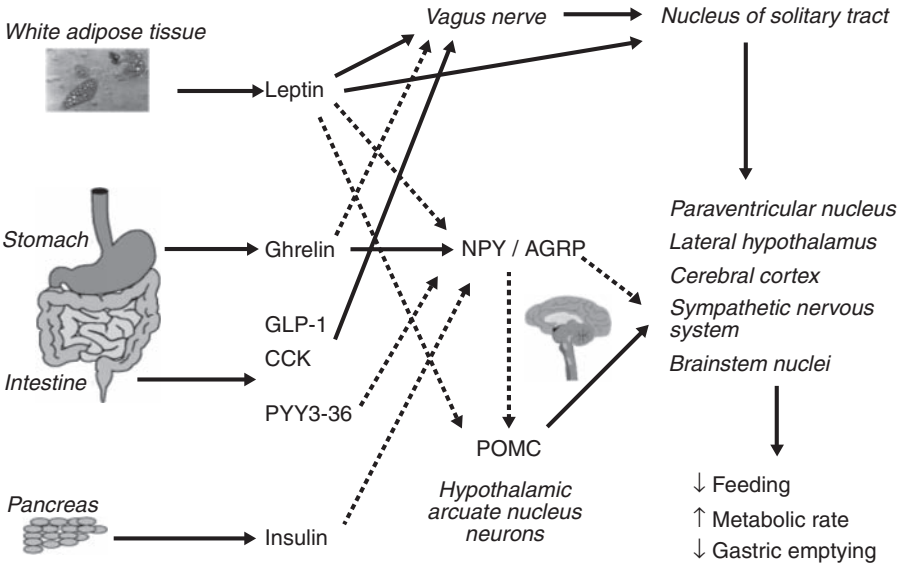


FIGURE 2.3 Circulating gastrointestinal and adipocyte hormones and neuronal circuits involved in energy homeostasis. Solid lines represent net stimulatory effect; dashed lines represent net inhibitory effect. (From Neary, NM, Goldstone, AP, & Bloom, SR. *Clin. End. 60:* 153–160, 2003. With permission.)

U.S. Dietary Guidelines. Although the "gold standards" are slightly outdated, this tool, described in Table 2.1 and Table 2.2, provides an assessment of intake of whole grains, calcium-rich foods, fruits and vegetables, total fat, saturated fat and cholesterol, sugary beverages and foods, sodium, and alcohol, as well as an assessment of physical activity. It also allows for determining whether patients shop for and prepare their own food, ever have trouble being able to shop or cook for themselves, follow a special diet, eat or limit certain foods for health or other reasons, and are willing to make changes to eat healthier. This survey, written at a 5th-grade level, takes approximately 10 min to complete and may be done while the patient is in the waiting area. In addition to the survey, health care providers are supplied with a key to aid in discussions based on the patient's answers. Updated versions of this tool are available online at www.biomed.brown.edu/course/nutrition.

Both tools allow the health care provider to determine which tool to use based on the time available for counseling, and both can be performed in less than 10 min, as outlined in Table 2.3.

Being armed with the proper tools to perform a nutrition assessment and select a possible intervention is important and requires a preliminary evaluation of psychological readiness. Vallis et al. (114a) have addressed the issue of stages of change in a model specific to weight management. The patient's current level of readiness determines the intervention, as patients rarely move more than two stages unless they are self-motivated. If the patient presents as unaware of the problem or has no interest in change, he or she is at the precontemplation stage. An appropriate action would be to provide information focusing on health and positive changes. Individuals

WAVE Assessment

Weight

Assess patient's Body Mass Index.*
Patient is overweight if BMI>25.

Height	Body Weight lbs.	Height	Body Weight lbs.
4'10"	≥119	5'8"	≥164
4'11"	≥124	5'9"	≥169
5'0"	≥128	5'10"	≥174
5'1"	≥132	5'11"	≥179
5'2"	≥136	6'0"	≥184
5'3"	≥141	6'1"	≥189
5'4"	≥145	6'2"	≥194
5'5"	≥150	6'3"	≥200
5'6"	≥155	6'4"	≥205
5'7"	≥159		

* Certain patients may require assessment for underweight and/or unintentional weight loss

Activity

Ask patient about any physical activity in the past week: walking briskly, jogging, gardening, swimming, biking, dancing, golf, etc.

1. Does patient do **30 minutes** of moderate activity on **most days/wk.?**
2. Does patient do "lifestyle" activity like taking the **stairs** instead of elevators, etc.?
3. Does patient usually watch less than **2 hours of TV or videos/day?**

If patient answers **NO** to above questions, assess whether patient is willing to increase physical activity.

Variety

Is patient eating a variety of foods from important sections of the food pyramid?

Grains (6-11 servings)
Fruits (2-4 servings)
Vegetables (3-5 servings)
Protein (2-3 servings)
Dairy (2-3 servings)

Determine **Variety** and **Excess** using one of the following methods:

- Do a quick one-day recall.
- Ask patient to complete a self-administered eating pattern questionnaire.

Excess

Is patient eating too much:
Fat? Saturated fat?
Calories?
Salt?
Sugar?
Alcohol?

- Ask about serving/portion sizes, preparation methods and added fats like butter, mayonnaise, sour cream, salad dressing, etc.
- Does patient eat 4 or more meals from sit-down or take-out restaurants per week?
- Does patient indulge on the weekends?

- *What does patient think are pros/cons of his/her eating pattern?*
- *If patient needs to improve eating habits, assess willingness to make changes.*

FIGURE 2.4 WAVE assessment. (From Gans, KM, Ross, E, Barner, CW, Wylie-Rossett, J, McMurray, J, & Eaton, C. *J. Nutr., 133* (2): 556S–562S, 2003. With permission.)

who are aware of the problem and may be considering change are in the contemplation stage and would benefit from assistance to resolve their ambivalence. For all patients, regardless of stage, establishing understanding and reinforcing their "why" for participating in the program helps to guide therapy and will provide motivation. Individuals who present with a clear realization that there are benefits to change and who are thinking about ways to change are in the preparation phase (120). The best option is to begin teaching them about behavior modification and to customize the intervention to meet their specific clinical needs. Individuals already making positive health changes are in the action phase and primarily need guidance with support. Given the overwhelming amount of lay press and literature regarding

WAVE Recommendations

Weight

If patient is overweight:

1. **State concern** for the patient, e.g., "I am concerned that your weight is affecting your health."
2. Give the patient **specific advice**, i.e.,
   a) Make 1 or 2 changes in eating habits to reduce calorie intake as identified by diet assessment.
   b) Gradually increase activity/decrease inactivity.
   c) Enroll in a weight management program and/or consult a dietitian.
3. If patient is ready to make behavior changes, jointly **set goals** for a plan of action and arrange for follow-up.
4. Give patient education materials/ resources.

Activity

Examples of moderate amounts of physical activity:

- Walking 2 miles in 30 minutes
- Stair walking for 15 minutes
- Washing and waxing a car for 45-60 minutes
- Washing windows or floors for 45-60 minutes
- Gardening for 30-45 minutes
- Pushing a stroller 1½ miles in 30 minutes
- Raking leaves for 30 minutes
- Shoveling snow for 15 minutes

1. If patient is ready to increase physical activity, jointly **set specific activity goals** and arrange for a follow-up
2. **Give patient education materials/ resources.**

Variety

What is a serving?

Grains (6-11 servings)
1 slice bread or tortilla, ½ bagel, ½ roll, 1 oz. ready-to-eat cereal, ½ cup rice, pasta, or cooked cereal, 3-4 plain crackers.
Is patient eating whole grains?

Fruits (2-4 servings)
1 medium fresh fruit, ½ cup chopped or canned fruit, ¾ cup fruit juice

Vegetables (3-5 servings)
1 cup raw leafy vegetables, ½ cup cooked or chopped raw vegetables, ¾ cup vegetable juice

Protein (2-3 servings)
2-3 oz. poultry, fish, or lean meat, 1-1½ cup cooked dry beans, 1 egg equals 1 oz. meat, 4 oz. or ½ cup tofu

Dairy (2-3 servings)
1 cup milk or yogurt, 1½ oz. cheese

See instructions 1-4 under Excess.

Excess

How much is too much?

Too much fat, saturated fat, calories
- > 6 oz/day of meat
- Ice cream, high fat dairy products
- Fried foods
- High fat snacks and desserts
- Eating out > 4 meals/wk

Too much sugar, calories
- High sugar beverages
- Sugary snacks/desserts

Too much salt
- Processed meats, canned/frozen meals, salty snacks, added salt

1. **Discuss pros and cons** of patient's eating pattern keeping in mind Variety and Excess.
2. If patient is ready, jointly **set specific dietary goals** and arrange for follow-up.
3. **Give patient education materials/ resources.**
4. **Consider referral** to a dietitian for more extensive counseling and support.

FIGURE 2.5 WAVE recommendations. (From Gans, KM, Ross, E, Barner, CW, Wylie-Rossett, J, McMurray, J, & Eaton, C. *J. Nutr. 133* (2): 556S–562S, 2003. With permission.)

TABLE 2.1
Rapid Eating Assessment for Patients, Part 1

Topic	In an Average Week, How Often Do You:	Usually/ Often	Sometimes	Rarely/ Never	Does Not Apply to Me
	Please check the box that best describes your habits.				
Meals	1. Skip breakfast?	☐	☐	☐	☐
	2. Eat 4 or more meals from sit-down or take out restaurants?	☐	☐	☐	☐
Grains	3. Eat less than 3 servings of whole grain products a day? Serving = 1 slice of 100% whole grain bread; 1 cup whole grain cereal like Shredded Wheat, Wheaties, Grape Nuts, high fiber cereals, oatmeal, 3–4 whole grain crackers, 1/2 cup brown rice or whole wheat pasta	☐	☐	☐	☐
Fruits and Vegetables	4. Eat less than 2–3 servings of fruit a day? Serving = 1/2 cup or 1 med. fruit or 4 oz. 100% fruit juice	☐	☐	☐	☐
	5. Eat less than 3–4 servings of vegetables/potatoes a day? Serving = 1/2 cup vegetables/potatoes, or 1 cup leafy raw vegetables	☐	☐	☐	☐
Dairy	6. Eat or drink less than 2–3 servings of milk, yogurt, or cheese a day? Serving = 1 cup milk or yogurt; $1\frac{1}{2}$–2 ounces cheese	☐	☐	☐	☐
	7. Use 2% (reduced fat) or whole milk instead of skim (non-fat) or 1% (low-fat) milk?	☐	☐	☐	☐
	8. Use regular cheese (like American, cheddar, Swiss, Monterey jack) instead of low-fat or part-skim cheeses as a snack, on sandwiches, pizza, etc.?	☐	☐	☐	☐

Source: From Gans, KM, Ross, E, Barner, CW, Wylie-Rossett, J, McMurray, J, & Eaton, C. *J. Nutr. 133* (2): 556S–562S, 2003. With permission.

TABLE 2.2
Rapid Eating Assessment for Patients, Part 2

Question(s)	Patients at Risk	Further Evaluation and Treatment	Counseling Points/Further Information
Meal pattern Q #1	Patient skipping breakfast	Consider risk for undernutrition Explore etiology including medical and psychiatric conditions, socioeconomic issues, shopping and cooking capabilities, degree of life stress Further workup, treatment, referral as appropriate	If skipped meals are due to poverty or lack of facilities, refer patient to community resources, i.e., congregate meal probrams, Meals on Wheels, food bank and pantries Skipping breakfast is correlated with obesity as well as a higher fat overall diet Normalizing meal pattern may help with weight management
Dining out Q #2	Patient eating out often	Query reasons for frequent restaurant meals If lack of shopping/cooking knowledge and skills, or time are a barrier, patient may benefit from referral to a dietitian	Restaurant portions are often larger than necessary contributing to obesity Restaurant meals are often high in saturated fat, sodium, and calories contributing to hypercholesterolemia, hypertension, and obesity
Grains Q #3	Patient eating <3 servings whole grains a day	Inquire into reasons for low intake or avoidance of whole grains Counsel appropriately (suggest easy ways to incorporate whole grains such as high fiber breakfast cereal, sprinkling wheat germ on yogurt, eating cereals as a snack)	Fortified or whole grain products are a good source of folate and other vitamins and minerals Adequate folate intake may decrease the risk for coronary heart disease (CHD) and colon cancer and decreases the risk for fetal neural tube defects Whole grain products are also a good source of fiber and vitamin E Adequate fiber intake may decrease the risk of hypercholesterolemia and certain cancers Higher vitamin E intakes may prevent the development of CHD, and higher intakes of vitamin E from foods are associated with lower CHD mortality

Source: From Gans, KM, Ross, E, Barner, CW, Wylie-Rossett, J, McMurray, J, & Eaton, C. *J. Nutr. 133* (2): 556S–562S, 2003. With permission.

TABLE 2.3
Tool Recommendation Based on Time Available for Counseling

Time Available	Action
8–9 min	WAVE protocol with 1-d recall
6–7 min	WAVE protocol with self-assessment (REAP)
3–5 min	REAP only with goal setting
1–2 min	Discuss the importance of nutrition and assess readiness to change; give patient REAP to take home and set personal goals; provide handouts/Web resources and/or refer to appropriate staff person

Source: Bray, GA. *End. Metab. Clin. North Am. 25* (4): 907–919, 1996. With permission.

weight loss and weight control, emphasizing evidence-based data helps patients take action that is clinically sound. Patients are in the maintenance phase when their initial goals have been met; they are best served by the prevention of relapse. In all cases, there should be ongoing assessment of stages, as well as of overall progress.

While having tools available and performing a psychological assessment are important, neither can substitute for an accurate medical history. Factors that are additive to the measured BMI result in increased risk of obesity-related complications. As noted in Table 2.4, Bray has developed a tool that adjusts the BMI based on key metabolic variables so that an absolute risk or risked adjusted index can be determined. This value reflects one's risk of complication and death more accurately than does the BMI. It is particularly important in assessing those with a normal or borderline BMI but with multiple metabolic risks, as their risks may be equal to or greater than those of their more obese counterparts. Table 2.5 lists key questions that should be asked of the patient as part of the initial assessment. Table 2.6 reviews treatment algorithms, and Table 2.7 identifies obesity-related risks based on BMI and waist circumference.

At the bedside, the chart for each patient should contain a measured height, an objective weight, and a waist circumference obtained at the initial visit. This height and weight information is used to generate the BMI, which is determined by dividing the weight in kilograms by height in meters squared. In our clinical program, the waist circumference is identified as the point of maximal protuberance, especially in severe obesity (BMI > 40), where landmarks are often mobile. When the BMI is combined with the waist circumference, one is able to perform a risk assessment and rank individuals by their risk of developing obesity-related complications. As per the NHLBI/NIH guidelines, interventions should be performed in a stepwise fashion based on BMI. See the algorithm for assessment and intervention guidelines (80).

2.7 SPECIAL CONSIDERATIONS

Several barriers that limit health care providers' effectiveness in caring for obese patients are noted in Table 2.8. One of the most challenging barriers is limited access

TABLE 2.4
REAP and WAVE Protocols

Score	Adjustment Scores 0	+2	+4	Adjustment Score
BMI				_____
Weight gain since age 18 (kg)	<5	5–15	>15	_____
Triglyceride/HDL cholesterol (mg/dL)	<5	5–8	>8	_____
Blood pressure (mm Hg)	<140/<90	140–160/90–100	>160/>100	_____
Fasting glucose (mg/dL)	<95	96–126	>126	_____
Waist circumference, inches (cm)	(f) <32 (81) (m) <37 (94)	32–35 (81–89) 37–40 (94–102)	>35 (89) >40 (102)	_____
Sleep apnea	Absent		Present	_____
Physical activity	Regular activity	Sedentary		_____

Note: Risk-adjusted BMI achieved by adding points to the measured BMI to determine the adjustment score.

Source: Bray, GA. *End. Metab. Clin. North Am. 25* (4): 907–919, 1996. With permission.

to health care services, either real or perceived. Patients participating in our program and others report difficulty in finding transportation services that have vehicles large enough for them and that are willing to provide transportation. Upon arriving at a given clinic, obese patients have reported being further challenged by finding inadequate seating, receiving stares from insensitive fellow patients and staff, encountering negative or anti-obese comments, sometimes being unable to pass through the clinic doorjambs into the examination area, a lack of bathroom facilities that accommodate their size, being measured with blood pressure cuffs that do not fit (leading to inaccurate blood pressure readings and potential misdiagnosis of disease), encountering insensitivity to weighing concerns (for example, being weighed on a freight or large-animal scale), being prevented from weighing due to scale limitations, or being weighed in public. Further, once they enter the examination room, the tables may be either too small or too high to accommodate their weight, the gowns may be too small, and, if there is any body odor, the exam may be less optimal or too brief.

After the examination, the ideal treatment plan may be recommended. Unfortunately, the cost of treatment may be prohibitive for many people. A growing number of studies show that healthier food choices, such as fruits and vegetables, are limited in many underserved neighborhoods and are priced above the means of the people who need these dietary items the most. In low-income neighborhoods, there are more fast-food chains and often a paucity of grocery stores that maintain a good selection of healthier food choices (71). The cost of pharmacologic therapy is typically $110 to $120/month for a 30-d supply of brand-name anti-obesity therapies such as Meridia or Orlistat. Most insurances and medical cards do not cover the

TABLE 2.5
Key Questions for Initial Assessment

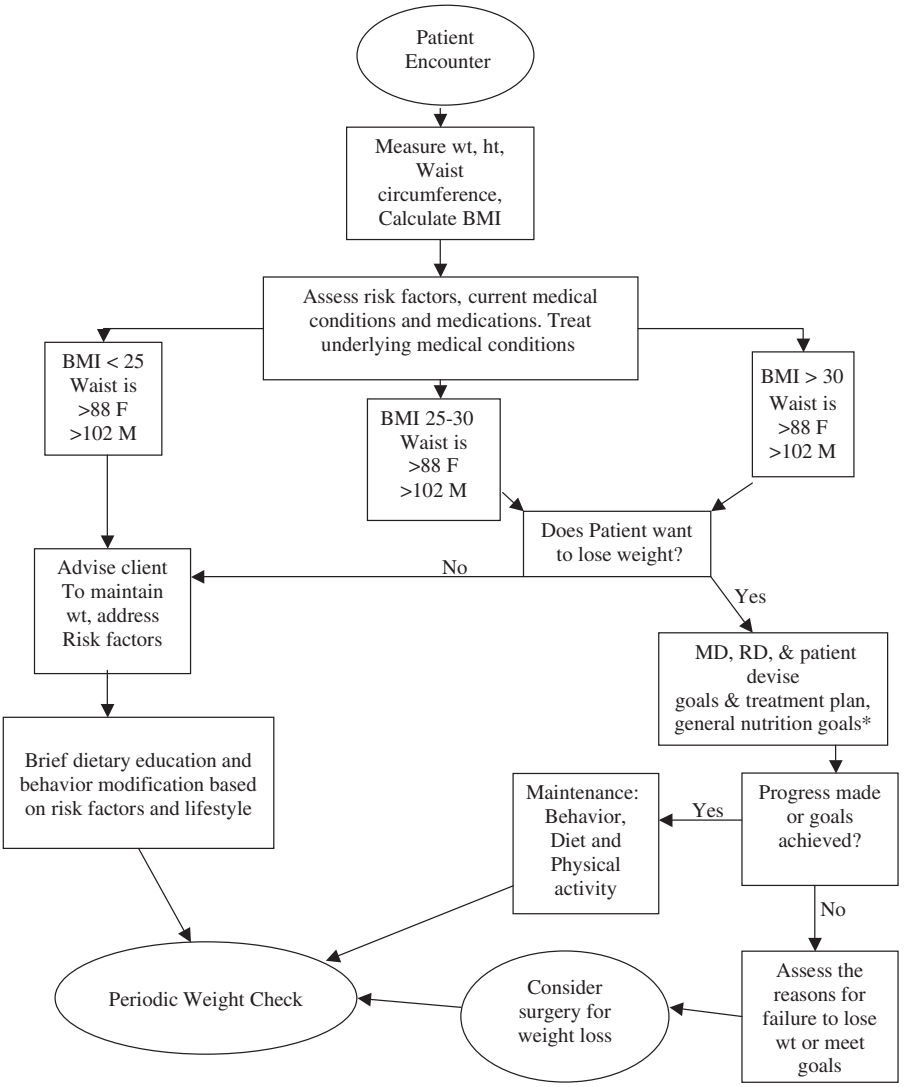
The History
Weight during childhood
Weight at age 18 years if female or 21 years if male
Weight pattern of gains and losses for each decade
Maximal weight
Weight loss attempts: most successful method, duration of loss
Current exercise level; identify potential limitations
Current diet efforts
Inquire about use of herbal or over-the-counter medications
Inquire about diet pills or shots
Ask why they desire weight loss
Identify potential triggers for overeating, the precipitating factor for weight gain (e.g., pregnancy, death in family, job change, stress, medications)
Screening for Obesity-Related Complications
Do they have chest pain? Are they short of breath? (CAD)
Do they have insomnia? Are they well rested in the morning? Do they snore? (sleep apnea)
Do they have muscle cramps? (magnesium deficiency)
Do they have polyuria, polydipsia, or polyphagia? (diabetes mellitus)
Key Food-Related Questions
Perform a 24-h dietary recall to identify eating patterns
Identify the primary cook and the primary shopper
Typical meal location
Frequency of meals eaten outside of the home
Frequency of skipped meals and snacks
Frequency of binge eating or overeating episodes

Source: Copyright Keith 2004.

cost of these drugs. For individuals on a fixed or limited income, this is cost-prohibitive therapy, rendering this modality ineffective in their treatment. In some cases, surgical interventions are covered by Medicare and third-party payers such as Blue Cross Blue Shield. However, stringent criteria and risk–benefit requirements are such that this option is not available to all individuals.

According to the patients we have cared for in our practice, the number one barrier that limits the effectiveness of health care providers is our own feelings regarding obesity. For years, patients have suggested that some health care providers are biased against the morbidly obese patient. However, it is only recently that a prospective study documented these findings, noting that providers who routinely care for this population of patients often have an anti-obesity bias that is readily perceived by patients. If a patient feels a sense of bias from the physician, it impairs the doctor–patient relationship in an already hostile environment. Therefore, for physicians who are caring for obese patients, it becomes important to provide a safe environment that lends itself to the care of these patients. The importance of

TABLE 2.6
Medical Weight Management Treatment Algorithm



* Refer to Table 2.10.

Source: Adapted from National Institutes of Health, National Heart Lung and Blood Institute. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. NIH Publication 00-4084, 2000.

TABLE 2.7
Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risk

	BMI (kg/m²)	Obesity Class	Men 102 cm (40 in.) Women 88 cm (35 in.)	Men > 102 cm (> 40 in.) Women > 88 cm (> 35 in.)
Underweight	< 18.5	N/A	N/A	
Normal	18.5–24.9	+	+	
Overweight	25.0–29.9	Increased	High	
Obese	30.0–34.9	I	High	Very High
	35.0–39.9	II	Very High	Very High
Extreme Obese	> 40	III	Extremely High	Extremely High

Note: Disease risk for Type 2 diabetes, hypertension, and CVD. + indicates that increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Source: Adapted from National Institutes of Health, National Heart Lung and Blood Institute. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. NIH Publication 00-4084, 2000.

TABLE 2.8
Barriers to Effective Treatment of Obese Patients

- Access to health care and the health care system
- Costs of treatment
- Lack of size-appropriate equipment
- Lack of nursing care expertise
- Discrimination
- Perception of the provider

Source: Copyright Keith 2004.

size-appropriate facilities and equipment cannot be overstated. Equally important, we should seek to understand our own perceptions of obesity and obese patients. A review of the current literature shows that obesity is a chronic debilitating disease with a pathophysiologic mechanism that is being increasingly better understood and that moves the diagnosis out of the realm of a pure psychological eating disorder (13).

2.8 DIETARY OPTIONS

A vast array of diets has been developed over the past decade, aimed at decreasing the rates of obesity. Unfortunately, many of the diets offer entirely different approaches with regard to the amounts of macronutrients. Although a specific diet

may work for one patient, it may not work as well for another. It is suggested that the effect of diet on fatty-acid metabolism varies between those with upper-body and lower-body obesity, causing the responses to low-fat or low-carbohydrate diets to vary (51). Prior to assessing a patient, it is essential that the physician and dietitian recognize that the simple word "diet" has a negative connotation. Through past experiences, the word often suggests a restriction of food choices, and it may create barriers to and limitations of patient adherence (84). Therefore, when communicating with patients, using terms such as "healthy lifestyle" and "healthful eating" is more appropriate — just as "physical activity" connotes a more positive tone to an obese individual than does the term "exercise." When assessing a patient, it is important to consider the individual's motivation, his or her time availability, any barriers to dietary changes, and whether the patient typically does the grocery shopping or cooking for the household. These social factors are essential in determining which diet is appropriate for the patient to be successful in weight loss therapy.

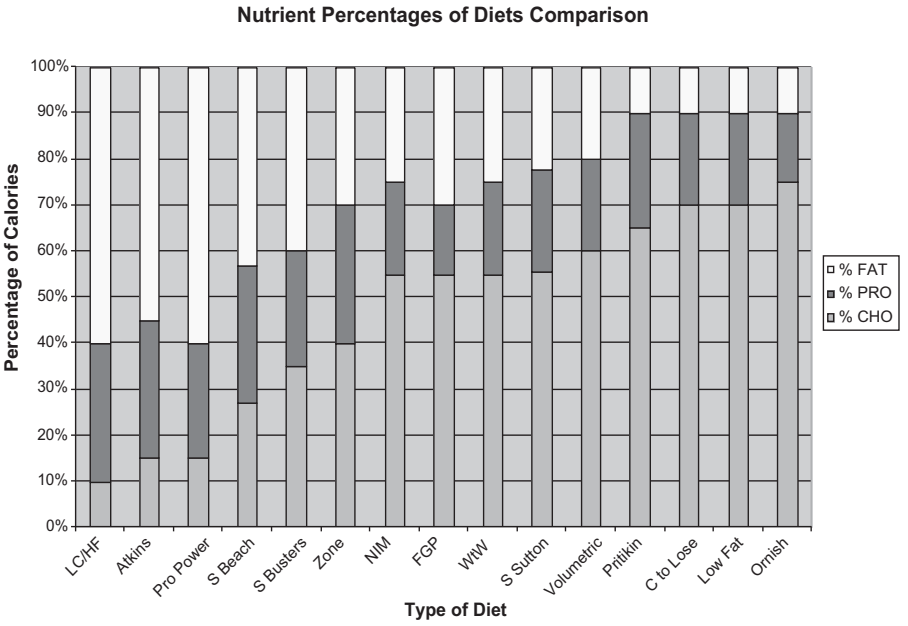
Decreasing caloric intake by 500 to 1000 kcal/d can generate the recommended weight loss of 1 to 2 lb/week (80). Prescribing a decrease in fat or carbohydrate intake, along with a total decrease in caloric consumption, is typically considered as dietary therapy. Reducing total caloric intake is key, regardless of what macronutrient is compromised to cause weight loss (111). It is crucial to recognize the dangers and negative consequences of over-restricting dietary intake to less than 15 kcal/kg/d in relation to adjusted body weight. Any diet should not be lower than 800 kcal/d, taking into account that very low caloric diets have not been shown to be more effective in weight loss (80). A major decrease in caloric intake induces conservation of energy and places the body in survival mode, as the body perceives the change as starvation (46). Patients who consume only one meal per day are placing themselves at risk of gaining weight due to the body's compensating for its needs in calories by conserving energy and by slowing down metabolically (67). It is important to educate patients on eating four to six small meals a day to allow the metabolism to become more controlled. It is vital that patients reduce the amount of high-fat and high-calorie foods in their diet, while decreasing portion sizes and improving the types of snacks they consume.

The variety of diets that promote weight loss can be categorized with respect to the proportion of macronutrients that promote weight loss. Table 2.9 displays the amounts of macronutrients that are suggested for each popular diet. For greater success with each patient, dietary recommendations should be highly individualized. It may be helpful to include a variety of dietary strategies that accommodate the type of lifestyle the patient leads. Table 2.10 provides general guidelines for nutrition goals to assist in weight loss. The following diets are categorized as high protein, low carbohydrate, low fat, and moderate, and there is a separate category for prepared and convenience diets.

2.8.1 High-Protein Diets

The high-protein, low-carbohydrate diets include Dr. Atkins' New Diet Revolution, Protein Power, and South Beach. Although these diets are very similar, they have significant differences. One of the main reasons that these diets are easy to adhere

TABLE 2.9
Nutrient Percentages of Diets Comparison



Note: Nutrient percentages of diet give comparison of percent fat, protein, and carbohydrates when calories are equalized. From left to right, the diets are as follows: a classic low-carbohydrate, high-fat eating plan, the Atkins Diet, Protein Power, South Beach, Sugar Busters, The Zone, Recommended Dietary Intake from the National Institute of Medicine, Food Guide Pyramid, Weight Watchers, Seattle Sutton Healthy Eating plan, Volumetric, Pritikin, Choose to Lose, a typical low-fat eating plan, and the Ornish Diet. The current recommended dietary intake for weight reduction is the National Institute of Medicine eating plan, which contains 55% carbohydrates, 20% protein, and 25% fat.

Source: Adapted from Freedman, MR, King, J, & Kennedy, E. *Obes. Res. 9* (Suppl. 1): 1S–40S, 2001; adapted from Dechelbaum RJ et al. *Circulation 100:* 450–456, 1999; Copyright Keith 2004.

to is that protein is the macronutrient associated with increased satiety (52). The amount of fat varies among the diets, with Atkins' being considerably higher in saturated fat, due to the increase in animal fat in proportion to vegetable fats. The Atkins approach is sometimes easier for patients to adhere to due to the satiety that the high fat and protein content of the diet provides. The Atkins approach disregards dietary fiber as an important factor, with fruits or vegetables rarely allowed in any of the phases, and is low in calcium (87). The Protein Power diet suggests the same percentage of calories from carbohydrates as Atkins', with a 5% decrease in protein and a 5% increase in total fat calories. The Protein Power diet offers more fruits and vegetables, but it still restricts healthful foods such as whole grains and beans, and it is lacking in calcium. South Beach is not considered

TABLE 2.10
General Nutrition Goals

- Fresh fruits and vegetables
- Low-fat or fat-free dairy
- Lean sources of protein
- Reduced saturated fats
- Minimum of 150 min/week of physical activity
- Low-fat diet deficit of 500 kcal/d
- 15 to 20 kcal/kg of body weight (avoid restricting to < 15 kcal/kg of body weight)

Source: Copyright Keith 2004.

to be as restrictive a low-carbohydrate diet as Atkins', although the first 2 weeks are restrictive in terms of carbohydrate intake. The South Beach diet relies on consuming the right carbohydrates and the right fats, while eliminating the bad carbohydrates and fats from the diet. Good fats include polyunsaturated fats (omega-3 and omega-6), as well as monounsaturated fats, found in olive oil, nuts, and avocados. Good carbohydrates include those found in vegetables, as well as in foods that are not highly processed or refined, with an emphasis on dietary fiber. The diet also follows the glycemic index, which is a scale that ranks carbohydrate-rich foods by how much they raise blood glucose levels compared to a standard food (glucose or white bread). Foods that have a lower glycemic index may control appetite, cholesterol levels, and blood glucose levels and may help to maintain a healthy weight. Although most diets consider a calorie as just a calorie, no matter what the source, the glycemic index suggests that, from a hormonal standpoint, not all calories are alike (66). South Beach has a leaner approach regarding overall calories, as well as fat calories, and allows the patient to consume fruits and vegetables in the second phase.

2.8.2 Low-Fat Diets

Low-fat diets are popular in weight loss programs. The Pritikin Principle and the Dean Ornish: Eat More, Weigh Less diets are the most widely used low-fat diets. The "Pritikin Principle" is the claim that cutting calorie density is the key to weight loss. Fruits, vegetables, pasta, oatmeal, soups, salads, and low-fat dairy are considered less dense items and favored, while poultry, seafood, meat, and dry foods such as crackers, popcorn, and pretzels are restricted, as are other fatty foods. Saturated fat is limited to about 1% of the total caloric consumption, while total fat intake is less than 10% of total calories. While the Pritikin Principle diet is a fairly adequate diet, especially for patients with heart disease and other comorbidities, it may not be easy to comply with on a long-term basis due to the stringent guidelines. Dean Ornish's Eat More, Weigh Less diet is a low-fat, nearly vegetarian diet, with recommendations categorized in three groups: "Eat Freely," "Eat Moderately," and "Banned" foods. Although the banned foods contain nutritiously dense items including nuts, seeds, and avocados, this approach is advantageous in that it steers away

from counting calories or paying attention to portion sizes. Many patients may enjoy the approach, considering it does not require them to measure foods, consider portion sizes, or count caloric consumption.

2.8.3 Moderate Diets

Moderate diets are the most conventionally recognized diets, and they are most likely the easiest for patients to comply with on a daily basis. Moderate diets include The Zone, Volumetrics, Institute of Medicine guidelines, Weight Watchers, and the current Food Guide Pyramid recommendations.

The Zone is recognized as a moderate carbohydrate, protein, and dietary fat approach, with consideration of high sugar levels. While fruits and vegetables are recommended, bananas, figs, prunes, raisins, and grapes, as well as peas, potatoes, corn, and carrots, are restricted due to their high sugar content. One of the main goals of The Zone is to maintain the hormonal balance of insulin and glucagons levels through limiting the amounts of various food groups. Low-fat protein is eaten at each meal, with carbohydrates doubling the portion of protein. Carbohydrates that are acceptable in The Zone consist of whole grains, vegetables (low sugar), and beans. This ratio of carbohydrates to protein is claimed to promote weight loss and to keep insulin in "the Zone." While this is nutritiously sound advice, the diet still lacks in calcium and whole grains. Taking into account the fact that this is a more moderate diet, there is still not enough evidence to claim that it is easy for patients to comply with for the long term (61).

The Volumetrics diet is based on cutting calorie density to induce weight loss. Protein and fat each make up 20% of the total calories, with carbohydrates consisting of the other 60% of total calories. This diet is in line with many of the principles of the Pritikin Principle diet, with the exception that carbohydrates and protein are slightly lower in the proportion to total calories, and the Volumetrics diet allows slightly more fat. In contrast to the Pritikin Principle approach, Volumetrics allows more variety, with a more liberal allowance of low-fat poultry and meat, which may increase the likelihood that a patient can adhere to a diet that decreases total caloric consumption.

The Institute of Medicine developed its most recent Dietary Reference Intakes in September of 2002. The goal of the Dietary Reference Intakes is to provide a basis from which a healthy diet can be developed, through the ranges that are proposed for each macronutrient. These ranges allow flexibility for each individual and stress the importance of "calories in, calories out" for maintaining a healthy weight (49). Total caloric intake is recommended with respect to the amount of physical activity and energy expended. Although there is a vast range within the fat intake recommendations, this allows for an increase in unsaturated fats, while discouraging excess saturated fat consumption. Carbohydrates are regarded as a vast range as well, ranging from 45 to 65%, with consideration given to the amount of refined and added sugars, which make up less than 25% of the total caloric consumption. The diet stresses the importance of getting essential nutrients from foods rather than relying on supplements for vitamins and minerals. For the first time, intakes of fiber are suggested, with consideration given to age and total caloric

consumption, as well as the amounts necessary for each of the nine indispensable amino acids available in protein (49).

Weight Watchers recommends a diet that has a very similar content to the Institute of Medicine guidelines, but this diet does not provide a range for each of the macronutrients. Instead, 20% protein, 55% carbohydrate, and 25% fat are allowed, with the aim of losing weight and adhering to the diet plan. Weight Watchers is an excellent choice for patients who want to lose weight but would benefit from balance and moderation with regard to portion sizes. The plan follows "flex points," whose amount is determined for the patient with consideration given to weight after the initial meeting. There is a full range of food options that may be consumed, with regard to portion sizes and flex points. Each week, the patient attends a meeting where he or she may be weighed and is educated on nutritious, healthy habits and choices that can be incorporated into his or her life.

The Food Guide Pyramid illustrates the USDA's dietary guidelines. In 1992, it became a tool for communicating concepts of a healthy diet to the American population. The Food Guide Pyramid allows a range for each of the macronutrients and calories, taking into account a variety of body types and physical activity levels within the population. The calorie recommendation, which ranges from 1600 to 2800 kcal/d, allows individuals to choose how much energy is necessary based on current age, weight, and activity status. The macronutrient recommendations are within ranges that are very similar to those of the Institute of Medicines Dietary Reference Intakes. The ranges for the Food Guide Pyramid are less liberal, spanning 5% for both protein and carbohydrate. The pyramid recommends intake for each of the five major food groups, along with fats, oils, and sweets sparingly. As for the total amount of each food group recommended, flexibility is allowed, with consideration given to the amount of calories consumed. Consumers who are not educated regarding healthy choices of carbohydrate could be confused by the depiction of servings recommended by the pyramid. The updated 2005 food guide pyramid is now available at www.healthierus.gov/dietaryguidelines. For the first time, the recommended servings of dairy foods have been increased, a specific number of whole grains servings are suggested, and trans fatty acids are mentioned. Likewise, a focus on weight, population and age-specific guidelines, healthy eating patterns and the relationship of food groups to disease prevention were noted.

2.8.4 Convenience Diets

For patients who are busy and do not typically cook, meal replacement diets, including Slim-Fast, may be the best option, considering the quick initial weight loss and convenience. The nutritional adequacy of these weight loss plans is sound, and it is easy for patients to comply with these diets on a daily basis (84). For patients who are looking for a low-fat, low-calorie diet and can afford to purchase three meals a day, Seattle Sutton's Healthy Eating is appropriate. The plan offers three healthy meals a day, with the option of purchasing a plan with either 1200 kcal/d or 2000 kcal/d. This option is great for most diabetics, those with heart conditions or high blood pressure, or those who want to lose weight and do not enjoy shopping, cooking, or planning meals. The generous carbohydrate intake

(approximately 55% of total calories) limits its use for all diabetics. In spite of this concern, the Seattle Sutton Healthy Eating plan has worked well for patients in our clinical practice, including many diabetics.

2.9 PHARMACOLOGIC THERAPY

Currently two FDA-approved drugs are on the market that are used for long-term treatment of obesity along with diet and physical activity. Orlistat (trade name: Xenical, Roche Pharmaceuticals) and sibutramine (trade name: Meridia, Merck Pharmaceuticals) are currently indicated for use by patients with a BMI of at least 30 or a BMI of 27 combined with medical comorbidities. These drugs may reduce the health risks of obese patients, but they should not be utilized as substitutes for proper diet or physical activity. Sibutramine and orlistat have been shown to induce weight loss in obese patients, as well as to improve HgbA1c levels (38). The benefits of pharmacologic therapy are typically maximized within 6 months from initial treatment, as weight tends to level off during the remainder of treatment (92). Phentermine is also approved by the FDA for short-term treatment of obesity, with a maximum treatment period of 12 weeks.

When determining the type of therapy that is appropriate for a patient, the physician should consider the patient's current medications and past medical history, behavior therapy, and possible adverse effects of each drug. Physicians should pay attention to how patients' weight responds to prescribed medications. Some medications do not alter weight, and if a patient presents with less than 4 lb of weight loss after 8 weeks of continued drug therapy, alternatives to the current treatment should be considered (38). However, in clinical practice, if the medications are successful in preventing continued weight gain, we may continue their use, even in the absence of weight loss. This practice is in line with the Institute of Medicine recommendations to prevent weight gain as a goal for medical weight management programs.

Orlistat was approved for weight loss management in 1999. Orlistat inhibits the activity of pancreatic and gastric lipases, preventing the breakdown, digestion, and absorption of about 30% of the dietary fat that is consumed (24). The recommended dosage is one 120-mg capsule, up to three times daily, taken with meals that contain fat. If no fat is consumed, dosage should be avoided. Fat-soluble vitamins are recommended at least 2 h before or after taking orlistat to ensure adequate nutrient absorption (103). The side effects consist of uncomfortable gastric disturbances, steatorrhea, and oily stools and discharge with excess intake of fat, though side effects generally improve with continued use (2). Orlistat may enhance dietary adherence to a lower-fat diet, taking into account the common gastrointestinal side effects of consuming high-fat meals (2). In clinical trials, orlistat decreased total cholesterol levels, LDL levels, and diastolic blood pressure, in long-term treatment compared with placebo (38). Orlistat is not significantly absorbed by the body but may interfere with the absorption of fat-soluble vitamins, which should be monitored during therapy. It does not require an extensive laboratory follow-up, as does Meridia (103). Orlistat is contraindicated for patients with chronic malabsorption syndrome or cholestasis.

Meridia was the first reuptake inhibitor of norepinephrine and serotonin to be approved by the FDA for long-term treatment in 1997. It is an adrenergic and serotonergic agent that works to suppress appetite while possibly stimulating metabolic rate, and it creates a thermogenic effect (8). Although maximum weight loss occurs within the first 6 months of treatment, studies have shown possible weight loss and patients' ability to maintain weight for up to 1 year while taking sibutramine (38). Patients are generally prescribed 10 mg initially, increasing up to a maximum dose of 20 mg daily (2). Weight loss attributed to Meridia typically results in beneficial effects on triglyceride, HDL cholesterol, and HgbA1c levels (93). It is necessary to monitor blood pressure due to the possible increase in both diastolic and systolic blood pressure. Sibutramine should be avoided or prescribed with caution for patients with uncontrolled high blood pressure and those with a medical history of any other heart-related conditions, due to the increase it causes in pulse rate and blood pressure (103).

Phentermine is currently approved by the FDA for short-term pharmacological management of obesity (up to 3 months). Phentermine stimulates the hypothalamus gland and affects neurotransmitters to suppress appetite, resulting in significant weight loss over a short trial period (24). Dosages range from 30 to 37.5 mg daily. Phentermine should be taken on an empty stomach to achieve optimal weight loss effects. Phentermine is typically well tolerated, although some patients may experience insomnia or have other stimulant reactions (38). Common adverse reactions consist of tachycardia, increased blood pressure, hyperthyroidism, and possible addiction due to the stimulant effect of Phentermine.

2.10 FUTURE ADVANCES

Novel approaches to weight management are rapidly emerging in an effort to address this epidemic. The mechanisms discovered and discussed in the section titled "The Neurobiology of Obesity" form the backbone for targeted pharmacologic interventions. Recent recognition of central nervous system (CNS) receptors and peptides that play a major role in the regulation of food intake has led to the identification of a new receptor, termed endocannabinoid-1 or CB1, that is widely distributed in the CNS and is normally inactive. When the system becomes activated, it stimulates relaxation, rest, forgetfulness, protectiveness, and appetite and is the site of reward-reinforcing effects. It is also the site of action for the active ingredient in marijuana, cannabis, as well as the receptor involved in nicotine addiction. Blockage of this receptor with an antagonist or genetic deletion in animal models resulted in leaner animals that are resistant to diet-induced obesity and insulin resistance. These animals also had a smaller fat mass and a lower level of food intake (91).

In animal models, the CB1 receptor antagonist, SR141716, inhibits neuropeptide Y-induced hyperphagia and reverses hyperphagia that is induced by increased ghrelin levels. The antagonist also prevents the increase in food intake normally stimulated by the orexigenic melanocortin antagonist, JKC-363, that binds to the melanocortin-4 receptor. Anorexigenic neuropeptides of the melanocortin-4 receptor, such as α-MSH, cannot prevent food intake when the CB1 receptor is stimulated. CB1 receptor stimulation also increases the level of adiponectin, a protein produced in

adipose tissue that is a key regulator of fat and glucose metabolism (71). The level of this protein is decreased in obese subjects and in subjects with Type 2 diabetes. Low levels of adiponectin are associated with reduced HDL-C, hypertriglyceridemia, and the presence of small LDL particles. In contrast, increased levels are associated with reduced insulin levels and increased insulin sensitivity.

Human trials are in progress with the CB1 receptor antagonist, rimonabant. Preliminary studies suggest that the drug reduces the rate of metabolic syndrome by 53%. At the 2004 annual meeting of the North American Association for the Study of Obesity (NAASO), Pi-Sunyer reported significant decreases in total body weight and waist circumference in individuals on the highest dose of rimonabant. This report from the Rimonabant in Obesity — Europe (RIO-Europe) trial is a welcome indication of a renewed interest in developing therapeutic interventions that can lead to enhanced patient care. Other drug therapies now under study include methylphenidate (a dopamine reuptake inhibitor that increases levels of brain synaptic dopamine, a compound that in turn produces anorexia), intranasal peptide YY (a CNS peptide) and pramlintide (an amylin analog) to treat obesity and Type 1 diabetes. Protocols that evaluate the roles of exogenous leptin and AYT, a histamine-1 receptor agonist, in treatment of obesity have been reported.

Beyond drug therapy, gastric pacing has emerged as a potential intervention in the treatment of morbid obesity. Gastric pacing resulted in significant weight loss and a decrease in neuropeptide levels such as leptin. These novel approaches to the treatment of obesity are promising, but they require rigorous testing to ensure safety and appropriate use, in the hope of avoiding the adverse events associated with therapy with the combination drug fenfluramine/phentermine, also known as Fen-Phen (24).

2.11 SUMMARY

Obesity remains the number one public health challenge of this decade. Effective interventions that lead to permanent lifestyle changes require a multidisciplinary approach. Integration of medical weight management into clinical practice, regardless of discipline, is critical to reversing the current tide. Recent advances in the neurobiology of obesity allow for targeted interventions. Most important, however, are lifestyle changes that lead to small, but sustained weight changes. Such changes have a major impact on weight management and therefore on health.

REFERENCES

1. Albertson, AM, Tobelmann, RC, & Marquert, J. (1997). Preventing osteoporosis: Starting in childhood. *J. Adol. Health* 20: 20–22.
2. Aronne, LJ. (1998). Modern medical management of obesity: The role of pharmaceutical intervention. *JADA 98* (10) suppl.: 23–26.
3. Aude, YW, Agaston, AS, Lopez-Jimenez, F, Lieberman, EH, Almon, M, Hansen, M, Rojas, G, Lamas, GA, & Hennekens, CH. (2004). The national cholesterol education program diet vs. a diet lower in carbohydrates and higher in protein and monounsaturated fat. *Arch. Intern. Med. 164:* 2141–2146.

4. Barak, N. (2004). AYT as a weight managing agent: A randomized double-blinded placebo controlled trial. NAASO Annual Meeting Oral Presentation, Las Vegas, NV.
5. Barner, CW, Wylie-Rossett, J, & Gans, KM. (2001). WAVE: A pocket guide for a brief nutrition dialogue in primary care. *Diabetes Educ. 27:* 352–362.
6. Barsh, GS, Farooqi, S, & O'Rahilly, S. (2000). Genetics of body-weight regulation. *Nature 404:* 644–651.
7. Bays, HE. (2004). Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes. Res. 12:* 1197–1211.
8. Berke, EM, & Morden, NE. (2000). Medical management of obesity. *Am. Fam. Phys. 62:* 419–428.
9. Bonow, RO, & Eckel, RH. (2003). Diet, obesity, and cardiovascular risk. *N. Eng. J. Med. 348* (21): 2057–2058.
10. Brandt, G, Sileno, A, & Quay, S. (2004). Intranasal peptide YY; phase 1 dose ranging and dose sequencing studies. NAASO Annual Meeting Oral Presentation, Las Vegas, NV.
11. Bray, GA. (1996). Health hazards of obesity. *End. Metab. Clin. North Am. 25* (4): 907–919.
12. Bray, GA. (2004). Medical consequences of obesity. *J. Clin. End. 89* (6): 2583–2589.
13. Bray, GA. (2004). Obesity is a chronic, relapsing neurochemical disease. *Int. J. Obes. 28:* 34–38.
14. Breitkopf, CR, & Berenson, AB. (2004). Correlates of weight loss behaviors among low-income African-American, Caucasian, and Latina women. *Am. Coll. Obstr. Gyn. 103* (2): 231–239.
15. Buchowski, MS. (2002). Dietary calcium intake in lactose maldigesting intolerant and tolerant African American women. *J. Am. Coll. Nutr. 21* (1): 47–54.
16. Busetto, L, Sergi, G, Enzi, G, Segato, G, De Marchi, F, Foletto, M, De Luca, M, Pigozzo, S, & Favretti, F. (2004). Short-term effects of weight loss on the cardiovascular risk factors in morbidly obese patients. *Obes. Res. 12* (8): 1256–1263.
17. Chagnon, YC, Perusse, L, & Lamothe, M. (1997). Suggestive linkages between markers on human body fat and insulin levels in the Quebec Family Study. *Obes. Res. 5:* 115–121.
18. Cigaina, V, & Hirschberg, AL. (2003). Gastric placing for morbid obesity: Plasma levels of gastrointestinal peptides and leptin. *Obes. Res. 11:* 1456–1462.
19. Considine, RV, Considine EL, Williams, CJ, Hyde, TM, & Caro, JF. (1996). The hypothalamic receptor in humans: Identification of incidental sequence polymorphisms and absence of the ob/ob mouse and fa/fa rat mutations. *Diabetes 45:* 992–994.
20. Cossrow, N, & Falkner, B. (2004). Race/ethnic issues in obesity and obesity-related comorbidies. *J. Clin. End. Metab. 89* (6): 2590–2594.
21. Cummings, DE, & Schwartz, MW. (2000). Melanocortins and body weight: A tale of two receptors. *Nature Genetics 26:* 8–9.
22. Danielzik, S, Czerwinski-Mast, M, Langnase, K, Dilba, B, & Muller, MJ. (2004). Parental overweight, socionomic status and high birth weight are the major determinants of overweight and obesity in 5–7 year-old children: Baseline data of the Kiel Obesity Prevention Study (KOPS). *Int. J. Obes. 28:* 1494–1502.
23. Daviglus, ML, Stamler, J, Pirzada, A, Yan, LL, Garside, DB, Liu, K, Wang, R, Dyer, AR, Lloyd-Lones, DM, & Greenland, P. (2004). Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *JAMA, 292* (13): 1588–1592.
24. Dickerson, LM, Sloan, RW, & Carek, PJ. (2000). Drug therapy for obesity. *Am. Fam. Phys. 61:* 2131–2138.

25. Diouf, S, Outtara, A, Sylla, A, Sarr, M, & Kuakuvi, N. (2004). P1058 The obesity: An emergent disease at the Senegalese child. Epidemiological aspects and managements. *J. Ped. G.I. Nutr. 39* (1): S459–S460.
26. Ditschuneit, HH, & Flechtner-Mors, M. (2001). Value of structured meals for weight management: Risk factors and long-term weight maintenance. *Obes. Res. 9* (4): 284S–289S.
27. Ditschuneit, HH, Flechtner-Mors, M, Johnson, TD, & Adler, G. (1999). Metabolic and weight-loss effects of a long-term dietary intervention in obese patients. *Am. J. Clin. Nutr. 69:* 198–204.
28. Drewnowski, A, Damon, N, & Briend, A. (2004). Replacing fats and sweets with vegetables and fruits — a question of cost. *Am. J. Publ. Health 94* (9): 1555–1559.
29. Dyer, AR, Stamler, J, & Greenland, P. (2000). Associations of weight change and weight variability with cardiovascular and all-cause mortality in the Chicago western electric company study. *Am. J. Epidemiol. 152:* 324–333.
30. Epstein, LH, Paluch, RA, Kilanowski, CK, & Raynor, HA. (2004). The effect of reinforcement or stimulus control to reduce sedentary behavior in the treatment of pediatric obesity. *Health Psychology 23* (4): 371–380.
31. Faraj, M, Havel, PJ, Phelis, S, Blank, D, Sniderman, AD, & Clanflone, K. (2003). Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J. Clin. Endocrinol. Metab. 88:* 1594–1602.
32. Farrell, SW, Braun, LA, Barlow, CE, Cheng, YJ, & Blair, SN. (2002). The relation of body mass index, cardiovascular fitness, and all-cause mortality in women. *Obes. Res. 10* (6): 417–423.
33. Ford, ES, Giles, WH, & Mokdad, AH. (2004). Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care 27* (10), 2444–2449.
34. Foster, GD, Phelan, S, Wadden, TA, Gill, D, Ermold, J, & Didie, E. (2004). Promoting more modest weight losses: A pilot study. *Obes. Res. 12:* 1271–1277.
35. Foster, GD, Wyatt, HR, Hill, JO, McGuckin, BG, Brill, C, Mohammed, S, Szapary, PO, Rader, DJ, Edman, JS, & Klein, S. (2003). A randomized trial of a low-carbohydrate diet for obesity. *N. Eng. J. Med. 348* (21): 2082–2090.
36. Freedman, MR, King, J, & Kennedy, E. (2001). Popular diets: A scientific review. *Obes. Res. 9* (1): 1S–40S.
37. Friedman, JM. (2000). Obesity in the new millennium. *Nature 404:* 632–634.
38. Fujioka, K. (2002). Management of obesity as a chronic disease: Nonpharmacologic, pharmacologic, and surgical options. *Obes. Res. 10* (2): 116–123.
39. Gans, KM, Ross, E, Barner, CW, Wylie-Rosett, J, McMurray, J, & Eaton, C. (2003). REAP and WAVE: New tools to rapidly assess/discuss nutrition. *J. Nutr. 133:* 556S–562S.
40. Goldthwaite, CA. (2002). Management of overweight and obese patients by primary care clinicians. *Illinois Acad. Fam. Phys. 3* (4): 1–16.
41. Gregg, EW, Gerzoff, RB, Thompson, TJ, & Williamson, DF (2003). Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older. *Ann. Int. Med. 138* (5): 383–390.
42. Gregg, EW, Gerzoff, RB, Thompson, TJ, & Williamson, DF. (2004). Trying to lose weight, losing weight, and 9-year mortality in overweight U.S. adults with diabetes. *Diabetes Care 27* (3): 657–662.
43. Hamilton, M, & Greenway, F. (2004). Evaluating commercial weight loss programmes: An evolution in outcomes research. *Obes. Rev. 5:* 217–232.

44. Hampl, JS, Wharton, CM, Tayor, CA, Winham, DM, Block, JL, & Hall, R. (2004). Primetime television impacts on adolescents' impressions of bodyweight, sex appeal, and food and beverage consumption. *Brit. Nutr. Found. Bull. 29:* 92–98.
45. Hauptman, J, Lucas, C, Boldrin, MN, Collins, H, & Segal, KR. (2000). Orlistat in the long-term treatment of obesity in primary care settings. *Arch. Fam. Med. 9:* 160–167.
46. Horwitz, BA. (2001). Introduction: Physiology, pathophysiology, and genetics of body weight/adiposity regulation. *Exp. Biol. Med. 226:* 961–962.
47. Hu, FB. (2003). The Mediterranean diet and mortality: Olive oil and beyond. *N. Eng. J. Med. 348* (26): 2595–2596.
48. Hu, FB, Li, TY, Colditz, GA, Wilett, WC, & Manson, JE. (2003). Television watching and other sedentary behaviors in relation of obesity and type 2 diabetes mellitus in women. *JAMA 289* (14): 1785–1791.
49. Institutes of Medicine (2002). *Shaping the Future for Health: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*.
50. Jago, R, Baranowski, T, Yoo, S, Cullen, KW, Zakeri, I, Watson, K, Himes, JH, Pratt, C, Wanjie, P, Pruitt, LA, & Matheson, DM. (2004). Relationship between physical activity and diet among African-American girls. *Obes. Res. 12:* 55S–63S.
51. Jenkins, DJA, Kendal, CWC, Augustin, LSA, Franceschi, S, Hamidi, M, Marchie, A, Jenkins, AL, & Axelsen, M. (2002). Glycemic index: Overview of implications in health and disease. *Am. J. Clin. Nutr. 76:* 266S–273S.
52. Johnston, CS, Tjonn, SL, & Swan, PD. (2004). High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults. *J. Nutr. 134:* 586–591.
53. Kennedy, ET, Shanthy, BT, Spence, JT, Freedman, M, & King, J. (2001). Popular diets: Correlation to health, nutrition, and obesity. *JADA 101* (4): 411–420.
54. Klein, S. (2001). Outcome success in obesity. *Obes. Res. 9* (4): 354S–358S.
55. Klein, S, Burke, LE, Bray, GA, Blair, S, Allison, DB, Pi-Sunyer, X, Hong, Y, & Eckel, RH. (2004). Clinical implications of obesity with specific focus on cardiovascular disease: A statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. *Circulation 110:* 2952–2967.
56. Knoops, KTB, de Groot, LCP, Kromhout, D, Perrin, AE, Moreiras-Varela, O, Menotti, A, & van Staveren, WA. (2004). Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women. *JAMA 292* (12): 1433–1446.
57. Kopelman, PG. (2000). Obesity as a medical problem. *Nature 404:* 635–643.
58. Kopelman, PG, & Grace, C. (2004). New thoughts on managing obesity. *Gut 53:* 1044–1053.
59. Korner, J, & Aronne, LJ. (2003). The emerging science of body weight regulation and its impact on obesity treatment. *J. Clin. Invest. 111* (5): 565–570.
60. Krebs, NF, Jacobson, MS, & Kanda, P. (2003). Prevention of pediatric overweight and obesity. *Pediatrics 112* (2): 424–430.
61. Landers, PS, & Landers, TL. (2004). Survival analysis of dropout patterns of dieting clinical trials. *JADA 104* (10): 1586–1588.
62. Lara-Castro, C, & Garvey, WT. (2004). Diet, insulin resistance, and obesity: Zoning in on data for Atkins dieters living in South Beach. *J. Clin. End. Metab. 89* (9): 4197–4205.
63. Leddy, JJ, Epstein, LH, Jaroni, JL, Roemmich, JN, Paluch, RA, Goldfield, GS, & Lerman, C. (2004). Influence of methylphenidate on eating in obese men. *Obes. Res. 12:* 224–232.

64. Lopez, R. (2004). Urban sprawl and risk for being overweight or obese. *Am. J. Publ. Health 94* (9): 1574–1579.
65. Lowell, BB, & Spiegelman, BM. (2000). Towards a molecular understanding of adaptive thermogenesis. *Nature 404* (6): 652–660.
66. Ludwig, DS. (2000). Dietary glycemic index and obesity. *J. Nutr. 130:* 280–283.
67. Manson, JE, Skerrett, PJ, Greenland, P, & VanItallie, TB. (2004). The escalating pandemics of obesity and sedentary lifestyle: A call to action for clinicians. *Arch. Intern. Med. 164:* 249–258.
68. Marshall, SJ, Biddle, SJH, Gorely, T, Cameron, N, & Murdey, I. (2004). Relationships between media use, body fatness and physical activity in children and youth: A meta-analysis. *Int. J. Obes. 28:* 1239–1246.
69. Maru, S, van Der Schouw, Y, Gimbrere, CHR, Grobbee, DE, & Peeters, PM. (2004). Body mass index and short-term weight change in relation to mortality in Dutch women after age 50. *Am. J. Clin. Nutr. 80:* 231–236.
70. Matheson, DM, Wang, Y, Klesges, LM, Beech, BM, Kraemer, HC, & Robinson, TN. (2004). African-American girls' dietary intake while watching television. *Obes. Res. 12:* 32S–37S.
71. McDuffie, J, Eliforal, KC, Depaoli, A, & Yanovski, J. (2004). Effects of exogenous leptin on ghrelin and meal characteristics in patients with lipodystrophy. NAASO Annual Meeting Oral Presentation, Las Vegas, NV.
72. McGarvey, E, Keller, A, Forrester, M, Williams, E, Seward, D, & Suttle, DE. (2004). Feasibility and benefits of a parent-focused preschool child obesity intervention. *Am. J. Publ. Health 94* (9): 1490–1495.
73. McTigue, KM, Harris, R, Hemphill, B, Lux, L, Sutton, S, Bunton, AJ, & Lohr, KN. (2003). Screening and interventions for obesity in adults: Summary of the evidence for the U.S. preventative services task force. *Ann. Int. Med. 139* (11): 933–949.
74. McVeigh, JA, Norris, SA, & de Wet, T (2004). The relationship between socio-economic status and physical activity patterns in South African children. *Acta Paediatr. 93:* 982–988.
75. Melanson, EL, Sharp, TA, Schneider, J, Donahoo, WT, Grunwald, GK, & Hill, JO. (2003). Relation between calcium intake and fat oxidation in adult humans. *Int. J. Obes. 27:* 196–203.
76. Melzer, K, Kayser, B, & Pichard, C. (2004). Physical activity: The health benefits outweigh the risks. *Curr. Opin. Clin. Nutr. Metab. Care* 7: 641–647.
77. Mertens, HL, & Van Gaal, LF. (2000). Overweight, obesity, and blood pressure: The effects of modest weight reduction. *Obes. Res. 8* (3): 270–278.
78. Meyer, C. (2004). Scientists probe role of vitamin D. *JAMA 292* (12): 1416–1418.
79. Mullis, RM, Blair, SN, Aronne, LJ, Bier, DM, Denke, MA, Dietz, W, Donato, KA, Drewnowski, A, French, SA, Howard, BV, Robinson, TN, Swinburn, B, & Wechsler, H. (2004). Obesity, a worldwide epidemic related to heart disease and stroke group IV: Prevention/treatment. *Circulation 110:* e484–e488.
80. National Institutes of Health, National Heart Lung and Blood Institute. (2000). *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. NIH Publication 00-4084.
81. National Institutes of Health, National Heart Lung and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of obesity in adults: Executive summary. [Online]. Available: www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm.
82. Neary, NM, Goldstone, AP, & Bloom, SR. (2003). Appetite regulation: From the gut to the hypothalamus. *Clin. End. 60* (2): 153–160.
83. Newman, C. (Aug. 2004). The heavy cost of fat. *National Geographic* 47–62.

84. Nonas, CA. (1998). A model for chronic care of obesity through dietary treatment. *JADA 98* (10), Suppl. 2: 16–22.
85. Norris, SL, Zhang, X, Avenell, A, Gregg, E, Schmid, CH, Kim, C, & Lau, J. (2004). Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Arch. Int. Med. 164:* 1395–1404.
86. Olson, MB, Kelsey, SF, Bittner, V, Reis, SE, Reichek, N, Handberg, EM, & Merz, NB. (2000). Weight cycling and high-density lipoprotein cholesterol in women: Evidence of an adverse effect. *J. Am. Coll. Cardiol. 36* (5): 1565–1571.
87. Ornish, D. (2004). Was Dr. Atkins right? *JADA 104* (4): 537–542.
88. Orzano, AJ, & Scott, JG. (2004). Diagnosis and treatment of obesity in adults: An applied evidence-based review. *JABFP 17* (5): 359–369.
89. Pereira, MA, Jacobs, DR, Van Horn, L, Slattery, ML, Kartashov, AI, & Ludwig, DS. (2002). The CARDIA study. *JAMA 287:* 2081–2089.
90. Pischon, T, Hankinson, SE, Hotamisligil, GS, Rifai, N, & Rimm, EB. (2003). Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obes. Res. 11* (9): 1055–1064.
91. Pi-Sunyer, X. (2004). Clinical design of the studies of weight reduction and metabolic effects with rimonabant: The RIO (rimonabant in obesity) program. NAASO Annual Meeting Oral Presentation, Las Vegas, NV.
92. Pittler, MH, & Ernst, E. (2004). Dietary supplements for body-weight reduction: A systematic review. *Am. J. Clin. Nutr. 79:* 529–536.
93. Poston, WS, & Foreyt, JP. (2000). Successful management of the obese patient. *Am. Fam. Phys. 61:* 3615–3625.
94. Punjabi, NM, Shahar, E, Redline, S, Gottlieb, DJ, Givelber, R, & Resnick, HE. (2004). Sleep-disordered breathing, glucose intolerance, and insulin resistance. *Am. J. Epidemiol. 160:* 521–530.
95. Rimm, EB, & Stampfer, MJ. (2004). Diet, lifestyle, and longevity — the next steps? *JAMA 292* (12): 1490–1492.
96. Rippe, JM, McInnis, KJ, & Melanson, KJ. (2001). Physician involvement in the management of obesity as a primary medical condition. *Obes. Res. 9* (4), Suppl.: 302–311.
97. Ryan, DH, & Stewart, TH. (2004). Medical management of obesity in women: Office based approaches to weight management. *Clin. Obst. Gyn. 47* (4): 914–927.
98. Schulze, MB, Manson, JE, Ludwig, DS, Colditz, GA, Stampfer, MJ, Willett, WC, & Hu, FB. (2004). Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA 292* (8): 927–934.
99. Schwartz, MB, & Puhl, R. (2003). Childhood obesity: A societal problem to solve. *Obes. Rev. 4:* 57–71.
100. Schwartz, MW. (2001). Brain pathways controlling food intake and body weight. *Exp. Biol. Med. 226* (11): 978–981.
101. Schwartz, MW, O'Neal-Chambliss, H, Brownell, KD, Blair, SN, & Billington, C. (2003). Weight bias among health professionals specializing in obesity. *Obes. Res. 11* (9): 1033–1039.
102. Schwartz, MW, Woods, SC, Porte, D, Seeley, RJ, & Baskin, DG. (2000). Central nervous system control of food intake. *Nature 404:* 661–671.
103. Sheperd, TM. (2003). Effective management of obesity — research findings that are changing clinical practice. *J. Fam. Pract. 52* (1), 57–72.
104. Slentz, CA, Duscha, BD, Johnson, JL, Ketchum, K, Aiken, LB, Samsa, GP, Houmard, JA, Bales, CW, & Kraus, WE. (2004). Effects of the amount of exercise on body weight, body composition, and measures of central obesity. *Arch. Intern. Med. 164:* 31–39.

105. Snyder, EE, Walts, B, Perusse, L, Chagnon, YC, Weisnagel, J, Rankinen, T, & Bouchard, C. (2004). The human obesity gene map: The 2003 update. *Obes. Res. 12:* 369–439.
106. Sorensen, TI, & Stunkard, AJ. (1993). Does obesity run in families because of genes? An adoption study using silhouettes as a measure of obesity. *Acta Psychiat. Scant. Suppl. 370:* 67–72.
107. Spiegel, K, Leproult, R, L'Hermite-Baleriaux, M, Copinschi, G, Pnev, PD, & Van Cauter, E. (2004). Leptin levels are dependent on sleep duration: Relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thryrotropin. *Am. J. End. Metab. 89* (1): 5762–5771.
108. Spritzer, DA. (2004). Obesity epidemic migrates east. *CMAJ 171* (10): 1159.
109. Stein, CJ, & Colditz, GA. (2004). The epidemic of obesity. *J. Clin. End. Metab. 88* (6): 2522–2525.
110. Steinbeck, KS. (2004). The future of obesity management. *Clin. Obstr. Gyn. 47* (4): 942–956.
111. Stephenson, J. (2003). Low-Carb, Low-Fat Diet Gurus Face Off. *JAMA 289* (14): 1767–1773.
112. Stern, JS. (1995). "Preface." In: *Weighing the Options: Criteria for Evaluating Weight Management Programs,* Ed. P. Thomas. Washington DC: Institutes of Medicine, NH Acad. Press, pp. vii–x.
113. Stern, JS. (2004). Obesity: Food intake. In: *Office Management of Obesity,* Ed. G.A. Bray. Philadelphia, PA: Elsevier Press, pp. 91–106.
114. Stunkard, AJ, Sorensen, TI, Hanis, C, Chakraborty, R, Schull, WJ, & Schulsinger, F. (1986). An adoption study of human obesity. *N. Eng. J. Med. 314* (4): 193–198.
114a. Vallis, M, Ruggiero, L, Greene, G, Jones, H, Zinman, B, Rossi, S. Edwards, L, Rissi, J, & Prochaska, J. (2003). Stages of change for healthy eating diabetes. *Diabetes Care 26*(5): 1468–1474.
115. Van Baak, MA, van Mil, E, Astrup, AV, Finer, N, Van Gaal, LF, Hilsted, J, Kopelman, PG, Rossner, S, James, WP, & Saris, WH. (2003). Leisure-time activity is an important determinant of long-term weight maintenance after weight loss in the sibutramine trial on obesity reduction and maintenance (STORM trial). *Am. J. Clin. Nutr. 78:* 209–214.
116. Vastag, B. (2003). Experimental drugs take aim at obesity. *JAMA 289* (14): 1763–1764.
117. Velicer, WF, Hughes, SL, Fava, JL, Prochaska, JO, & DiClemente, CC. (1995). An emprirical typology of subject within stage of change. *Addict. Behav. 20* (3): 299–320.
118. Vgontzas, AN, Zoumakis, M, Bixler, EO, Lin, HM, Prolo, P, Bela-Bueno, A, Kales, A, & Chrousos, GP. (2003). Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: Physiologic and therapeutic implications. *J. Clin. End. Metab. 88* (5): 2087–2095.
119. Voderholzer, U, Hohagen, F, Klein, T, Jungnickel, J, Kirschbaum, C, Berger, M, & Riemann, D. (2004). Impact of sleep deprivation and subsequent recovery sleep on cortisol in unmedicated depressed patients. *Am. J. Psychiatry 161* (8): 1404–1410.
120. Wadden, TA, Foster, GD, & Brownell, KD. (2002). Obesity: Responding to the global epidemic. *J. Cons. Clin. Psych. 70* (3): 510–525.
121. Wannamethee, SG, Shaper, G, & Walker, M. (2002). Weight change, weight fluctuation, and mortality. *Arch. Int. Med. 162:* 2575–2580.
122. Warren, E, Brennan, A, & Akehurst, R. (2004). Cost-effectiveness of sibutramine in the treatment of obesity. *Med. Decision Making 24:* 9–19.

123. Weinstein, AR, Sesso, HD, Lee, IM, Cook, NR, Manson, JE, Buring, JE, & Gaziano, JM. (2004). Relationship of physical activity vs. body mass index with type 2 diabetes in women. *JAMA 292* (10): 1188–1194.
124. Weyer, C, Chapman, I, Parker, B, Doran, S, Feinle-Bisset, C, Wang, Y, Burns, C, Lush, C, & Horowitz, M. (2004). Effect of pramlintide on ad-libitum food intake in obese subjects and subjects with type 2 diabetes: A randomized double-blind, placebo-controlled, crossover study. NAASO Annual Meeting Oral Presentation, Las Vegas, NV.
125. Wessel, TR, Arant, CB, Olson, MB, Johnson, BD, Reis, SE, Sharaf, BL, Shaw, LF, Handberg, E, Sopko, G, Kelsey, SF, Pepine, CJ, & Bairey Merz, CN. (2004). Relationship of physical fitness vs. body mass index with coronary artery disease and cardiovascular events in women. *JAMA 292* (10): 1179–1187.
126. Williamson, DF, Pamuk, E, Thun, M, Flanders, D, Byers, T, & Hath, C. (1995). Prospective study of intentional weight loss and mortality in never-smoking overweight U.S. white women aged 40–64 years. *Am. J. Epidemiol. 141* (12): 1128–1141.
127. Wirth, A, & Krause, J. (2001). Long-term weight loss with sibutramine. *JAMA 286* (11): 1331–1339.
128. Yanovski, SZ, & Yanovski, JA. (2002). Obesity. *N. Eng. J. Med. 346* (8): 591–602.
129. Young-Hyman, D, Schlundt, DG, Herman-Wenderoth, L, & Bozylinski, K. (2003). Obesity, appearance, and psychological adaptation in young African American children. *J. Ped. Psych. 28* (7): 463–472.
130. Zemel, MB, & Miller, SL. (2004). Dietary calcium and dairy modulation of adiposity and obesity risk. *Nutr. Rev. 62* (4): 125–131.
131. Zemel, M, Shi, H, Greer, B, Direnzo, D, & Zemel, P. (2000). Regulation of adiposity by dietary calcium. *FASJEB J. 14:* 1132–1138.
132. Zemel, MB, Thompson, W, Milstead, A, Morris, A, Morris, K, & Campbell, P. (2004). Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. *Obes. Res. 12* (4): 582–589.
133. Zemel, M. (2004). Role of calcium and dairy products in energy partitioning and weight management. *Am. J. Clin. Nutr. 79* (5): 907S–912S.

3 Adult Obesity, with Special Reference to Bariatric Surgery

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CONTENTS

3.1 INTRODUCTION

The prevalence of overweight and obesity has increased to epidemic proportions throughout the world, currently affecting over two-thirds of adults in the United States. Approximately 23 million Americans are extremely or morbidly obese (34). The rate of extreme obesity, defined as more than 100 lb or 100% above ideal body weight (IBW), is as high as 2 to 5% in men and 6 to 7% in women (54). This degree of obesity carries with it a marked increase in morbidity and as much as a 6- to 12-fold increase in mortality (54).

Some of the more conservative treatment options for obese patients include a low-calorie diet, exercise, behavioral modification, and, if indicated, pharmacotherapy. Despite this multipronged approach, some severely obese patients are unable to achieve healthy weights. Because of the failures of conservative methods and limited medical treatment, surgery provides the greatest degree of sustained weight loss and weight maintenance for the extremely obese patient. The National Institutes of Health (NIH) Technology Assessment Conference in 1992 concluded that an unacceptable number of morbidly obese (BMI > 40) individuals failed to achieve long-term weight loss with or without behavioral modification or drug therapy, and gastric bypass was recommended as the best treatment option (41). It is important to emphasize that while bariatric surgery is clearly invasive and requires ongoing medical and nutritional monitoring, the burden that severe obesity places on patients and society makes this surgery a viable option in eligible patients refractory to conservative measures.

In the past few years, the number of patients undergoing bariatric surgery has increased dramatically. This has resulted from an increase in the number of people who are extremely obese, the failure of more conservative measures, and the advent of laparoscopic procedures. The number of gastrointestinal surgeries performed annually for severe obesity has increased from about 16,000 in the early 1990s to about 103,000 in 2003 (53). The number of practicing surgeons who are members of the American Society for Bariatric Surgery (ASBS) increased from 258 in 1998 to 1070 in 2003 (53). Currently there are several surgical procedures that have been proven effective in achieving long-term weight reduction. These procedures include the Roux-en-Y gastric bypass (RYGB), vertical banded gastroplasty (VBG), laparoscopic adjustable silicone gastric band (LASGB), and biliopancreatic diversion with duodenal switch (BPDS).

The main goal of surgery is safely to achieve and maintain a significant loss of excess weight and to resolve many of the comorbid conditions associated with obesity in order to improve the patient's overall quality of life. A multidisciplinary team capable of providing all aspects of preoperative and postoperative care is crucial in the care of these complex patients. Ideally the team should include surgeons, internists, psychiatrists/psychologists, dietitians, and nurses.

3.2 HOW SURGERY WORKS IN ACHIEVING WEIGHT LOSS

Obesity results from a failure of the body's normal weight and energy regulatory mechanisms. Surgery essentially affects this complex weight regulatory system at multiple levels and blunts the body's defense system against starvation in the obese individual. For example, certain neuroendocrine hormones are altered after gastric bypass surgery. Ghrelin, a 28 amino acid neuroendocrine peptide that is secreted by the stomach, is one of the most potent endocrine stimulators of appetite and food intake (17). Weight loss from reduced caloric intake is associated with an increase in fasting plasma concentration of ghrelin. Ghrelin is part of the body's defense mechanism to maintain the weight "set point." Recent studies have shown that weight

loss from gastric bypass surgery is associated with low ghrelin levels that may be responsible for the reduced appetite associated with the procedure (17). Similarly, peptide YY (PYY), a gut hormone, is released in proportion to the calories ingested and signals food intake to the appetite-regulating circuits of the brain. PYY levels were elevated in patients after gastric bypass surgery. This result in turn causes greater satiety in these individuals (6).

3.3 OUTCOMES FOR OBESITY SURGERY

Current surgical procedures have proven to be successful in achieving significant weight reduction for most patients. Success is largely a result of patient selection, education, and, most important, long-term follow-up. Weight loss achieved with surgery improves or resolves many of the obesity-associated comorbidities. A study performed by Schauer et al. (49) showed that there was roughly an 80% "cure" rate or improvement in most obesity-related conditions.

The outcomes of specific comorbid conditions postoperatively have been described in several studies. Pories et al. (48) demonstrated that in 608 patients who underwent gastric bypass surgery, 271 (91%) of the 298 diabetic or glucose-intolerant patients became euglycemic (48). This correction of NIDDM occurred within days of surgery and long before profound weight loss occurred. Thus, it is evident that bariatric surgery causes an improvement in serum glucose levels, a decrease in fasting insulin, and a decrease in glycosylated hemoglobin. This improves or cures diabetes and decreases the likelihood of developing Type 2 diabetes in individuals with glucose intolerance (26,27).

Cardiovascular disease and hypertension also have favorable postsurgical outcomes. Over 90% of hypertensive patients improve with surgery, but long-term data have not shown a permanent effect (Swedish Obese Subjects trial, 14). In addition to improvements in blood pressure, glucose, and lipid profiles, there are also notable improvements in left ventricular ejection fraction, chamber size, and wall thickness, thereby minimizing cardiomyopathy (2). It is important to note that successful improvements in cardiac function and hypertension by bariatric surgery correlate with the amount of weight loss and not the final weight (25).

Respiratory insufficiency caused by sleep apnea syndrome (SAS) and obesity hypoventilation syndrome (OHS) are two other obesity-related conditions that are improved after surgery. Sugerman et al. (58), in a study of patients with OHS and/or SAS, demonstrated a marked improvement of both conditions as evidenced by lower sleep apnea indices and improvements in arterial blood gases and pulmonary artery and pulmonary capillary wedge pressures. Long-term follow-up after gastric bypass surgery has shown that 93% of patients with SAS had improved indices (12).

3.4 CANDIDATES FOR SURGERY

Criteria for selecting appropriate patients for bariatric surgery were established by the 1991 NIH Consensus Development Conference Panel. Appropriate patients

include those with BMI greater than 40, or BMI greater than 35 with serious coexisting conditions such as severe sleep apnea, diabetes, cardiopulmonary problems, and so forth (40). In addition, patients must have tried and failed nonsurgical weight loss methods (39). It is crucial for potential candidates to understand the risks of the procedure and the way in which surgery can affect their lives in the postoperative period; these changes can range from long-term vitamin supplementation to ongoing gastrointestinal problems. The age range for patients eligible for surgery can vary but is generally between 16 and 65 years of age. Advances in perioperative management and surgical techniques have dramatically decreased complication and mortality rates in younger and older patients (36).

3.5 CONTRAINDICATIONS

Contraindications to bariatric surgery include conditions that can cause an unacceptable medical risk, such as uncontrolled cardiovascular disease, gastric varices, active IBD, and active peptic ulcer. Illnesses that greatly reduce life expectancy, such as cancer and end-stage renal, lung, or heart disease also constitute contraindications (54). Active substance abuse and serious uncontrolled psychiatric illnesses, such as untreated schizophrenia, depression, or psychotic disorders, are other contraindications to surgery (4,60). Patients with these disorders may be unable to comprehend the physical and behavioral changes associated with bariatric surgery. It is important to emphasize that psychiatric illness, as a general category, is not always a contraindication to surgery, as long as the patient is being adequately managed (54). Finally, women who are lactating or pregnant or who are planning pregnancy within 18 months of surgery are not optimal surgery candidates (9).

3.6 PREOPERATIVE ASSESSMENT AND MANAGEMENT OF COMORBIDITIES

Most patients undergoing bariatric surgery have multiple comorbidities associated with their obesity (54). In order to reduce perioperative morbidity and mortality, these conditions must be evaluated and optimally managed prior to referral for surgery. During the preoperative screening period, it is also important to diagnose previously unrecognized comorbidities. Schauer et al. (49) have identified an average of 6.8 comorbidities per patient. The six most common conditions are degenerative joint disease, hypercholesterolemia, hypertension, gastroesophageal reflux disease, depression, and hypertriglyceridemia (in descending order). Their finding of a high rate of depression among those seeking bariatric surgery adds support to the need for careful screening for depression to ensure a favorable postsurgical outcome (49). See Table 3.1 for a list of comorbidities associated with obesity.

It is also important to screen for medically treatable causes of obesity, such as thyroid disease and Cushing's Syndrome. If hypothyroidism is diagnosed preoperatively, treatment should be initiated, since patients may benefit from some weight loss. However, because it is unlikely to be the sole cause of an individual's obesity,

TABLE 3.1
Comorbidities Associated with Obesity

Hypertension
Dyslipidemia
Type 2 diabetes mellitus
Coronary heart disease
Congestive heart failure
Stroke
Gallstones
Osteoarthritis
Sleep apnea
Cancer
Amenorrhea
Menstrual irregularity
Infertility
Psychosocial disorders
Impaired quality of life

Source: From *NHLBI Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. NIH Publication No. 98-4083.

surgery may still be an option for further weight reduction. Patients with Cushing's Syndrome, on the other hand, may experience substantial weight loss with treatment of the disease and should not undergo bariatric surgery until the disease is adequately managed (54).

3.7 PREOPERATIVE SCREENING

Screening should begin with a thorough history and physical examination. All patients should also be up to date with health maintenance screening, including pap smear, mammogram, colonoscopy, and PSA as appropriate. Preoperative laboratory evaluation should include a complete baseline blood count (CBC), urinalysis, chemistries, liver function tests (LFTs), and renal function. Other needed tests include hemoglobin A1c (HbA1c), insulin, iron/TIBC/ferritin, B_{12}, folate, vitamin D, PTH, calcium, TSH, hypercoagulability screen, PT/PTT, and *H. pylori* antibody (9). Patients should also receive a chest radiogram and electrocardiogram (9).

Given the high incidence of cardiovascular disease in the severely obese, a cardiovascular evaluation is often indicated, particularly in patients over 50 years of age (54). This would include an echocardiogram and/or a stress test. In addition, if pulmonary hypertension is suspected clinically or by chest radiogram or electrocardiogram, an echocardiogram should be performed.

Patients with rapid weight loss following surgery have a high incidence of gallstone formation. Hence, gallbladder function should be explored by ultrasound

in patients who have not already had a cholecystectomy (9). Any patient who has gallstones or evidence of other gallbladder pathology should undergo a cholecystectomy at the time of bariatric surgery. Whether prophylactic cholecystectomy should be performed is somewhat controversial. In general, prophylactic cholecystectomies are performed for extensive malabsorptive procedures and occasionally for the RYGB, at the discretion of the surgeon (31). Prophylactic cholecystectomies should not be performed for purely restrictive procedures, such as the laparoscopic adjustable silicone gastric band.

As mentioned above, obstructive sleep apnea (OSA) occurs frequently in morbidly obese patients (12). Because OSA may be associated with pulmonary hypertension and CO_2 retention, it should be screened for, and, if OSA is found, the patient should be referred to a pulmonologist. Patients or their partners will often report any of the following: snoring, gasping for air, morning headache, and daytime hypersomnolence. On physical exam, clinicians should measure neck circumference. In males with OSA, the neck circumference tends be greater than 17 in., and, in females, greater than 15 in. The diagnosis of OSA is confirmed by a sleep study.

Other disease entities worth mentioning are infection from *H. pylori* and GERD. Some studies have shown that patients who were tested and treated for *H. pylori* have a lower incidence of postoperative marginal ulcer (50). The test most commonly used to screen for *H. pylori* infection is the *H. pylori* serum antibody (50). If a patient tests positive for *H. pylori*, treatment with antibiotics and a proton pump inhibitor or an H_2 blocker should be initiated. Patients may also require further GI evaluation, particularly endoscopy, if they complain of dysphagia or epigastric pain.

In order to know whether patients will be motivated sufficiently to adapt to changes that result from surgery (9), they should be referred to a psychiatrist or psychologist with a particular focus in this area (54).

3.8 PERIOPERATIVE USE OF MEDICATION

Medications often have to be discontinued temporarily around the time of surgery. For example, oral contraceptive (OCP) use is associated with a three- to fourfold increased risk of venous thromboembolism (VTE), a condition higher in incidence in the obese population (3). OCPs should therefore be discontinued 4 to 6 weeks prior to surgery and restarted no less than 90 d postoperatively (43). Aspirin and NSAIDS are another category of drugs that could increase perioperative morbidity and mortality by causing increased risk of bleeding and ulcer formation. Patients are advised to stop this class of medications prior to surgery and restart them later, if necessary. Special conditions warrant early resumption of aspirin, as in patients who have coronary artery disease (CAD) or stroke. Diuretics should also be discontinued, mainly because of complications from dehydration that can result from surgery. Aspirin and diuretics should be discontinued at the time of surgery and, if indicated, restarted 1 month postoperatively. In cases of moderate to severe congestive heart failure and severe venous insufficiency, diuretics may be restarted earlier, but the patients then require close observation.

The prophylactic use of anticoagulation for venous thromboembolism postoperatively remains controversial. Some clinicians prescribe either subcutaneous hep-

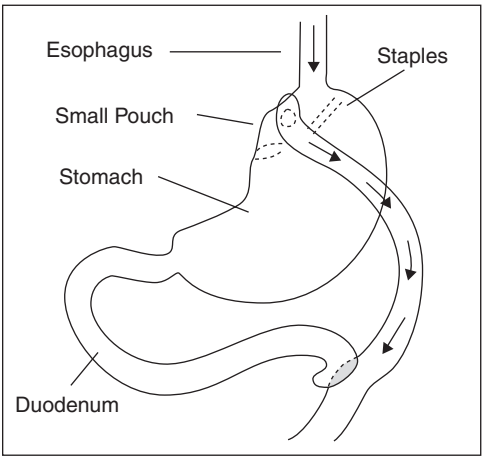

FIGURE 3.1 Roux-en-Y gastric bypass. (From http://www.niddk.nih.gov/health/nutrit/pubs/gastric/gastricsurgery.htm.)

arin or low molecular weight heparin or recommend inferior vena cava filter placement in their patients if the risk of thromboembolic disease is high. The optimal time course for postoperative prophylaxis has not yet been determined (64).

3.9 SURGICAL THERAPIES

3.9.1 Roux-en-Y Gastric Bypass

Mason and Ito, based on their observation that patients experienced significant weight loss after subtotal gastrectomies, first used gastric bypass (GBP) surgery to treat obesity in 1969 (32). There have been modifications to the procedure since then. The most commonly used variation, the Roux-en-Y gastrojejunostomy (RNYGP) (Figure 3.1), utilizes both restrictive and malabsorptive physiology to induce weight loss. The procedure is mainly restrictive in that a small gastric pouch and narrow stoma prevent ingestion of a large meal. The malabsorption due to the gastrojejunostomy produces a negative conditioning response to the dumping syndrome if a high-carbohydrate meal is ingested. Nausea, lightheadedness, palpitations, diaphoresis, and/or abdominal pain and diarrhea characterize the dumping syndrome (55). Eaters of sweets who have undergone a purely restrictive vertical banded gastroplasty (VBG) and who remain resistant to weight loss due to overeating may lose significant weight if their procedure is converted to a RNYGBP (48). Dumping symptoms in response to oral glucose occur specifically in GBP but not in VBG patients. These are closely associated with an elevated serum enteroglucagon level (33).

The NIH Consensus Development Panel endorses both the VBG and GBP, but the GBP has been shown to be superior to VBG in weight reduction in several randomized, prospective comparisons (57,61). One long-term study reported a series with 58%, 55%, and 49% excess weight loss at 5, 10, and 14 years from surgery, respectively (15). A more recent study reported a loss of 62% excess weight at 10

years (23). Long-term maintenance of weight loss after RNYGP is excellent, and modifications to the length of the Roux limb may achieve better weight loss in superobese (BMI 50) patients, although the potential for nutrition deficiencies increases as well (48). "Long-limb RNYGP," in which the Roux limb is 150 cm long compared to the standard 50 to 75 cm, shortens the distal common digestive channel and thereby enhances the malabsorptive effects (10). The procedure may be performed both by open surgery and laparoscopic methods. A study by Nguyen et al. (37) compared the two procedures, concluding that the laparoscopic procedure caused patients to lose less blood and led to a shorter hospital stay and to faster convalescence. Patients operated on laparoscopically lost the same amount of weight in the year as those on whom open surgery was performed but had a more rapid improvement in quality of life (37).

The mortality associated with RNYGP is approximately 1%, and the risk of early postoperative complications is approximately 10% (35). Sepsis and pulmonary embolus are the most common causes of perioperative mortality. Early postoperative complications include wound infection and seromas, marginal ulcers, anastomosis stenosis (managed through endoscopic dilation), small bowel obstruction, splenic laceration, gastrointestinal hemorrhage, and wound dehiscence (48). The development of an anastomotic leak (risk of 1.5 to 5%) can lead to peritonitis, abscess formation, and sepsis. Laparoscopic techniques have decreased the incidence of hernias and wound infections but are associated with an increase in anastomotic strictures and leaks (61).

The development of symptomatic gallstones is the most common late complication following RYGB. The use of ursodiol in the first 6 months postoperatively reduced the incidence of symptomatic gallstones from 32% to 2% in a placebo-controlled trial by Sugerman et al. (56). The potential micronutrient deficiencies of vitamins (vitamin B_{12}, folic acid, vitamin D, and thiamine) and minerals (iron, calcium) are of primary concern and require long-term management. Vitamin B_{12} deficiency is most likely in patients who do not take their multivitamin medication. Thiamine is primarily absorbed in the jejunum. Thiamine deficiency in the postsurgical patient, the "bariatric beriberi" syndrome, may manifest as encephalopathy, opthalmoplegia, and neuropathy. Thiamine deficiency–induced neurologic disorders occur almost always in patients with protracted vomiting and impaired intake (18). Iron is the most commonly deficient micronutrient after GBP, and one third of iron-deficient patients do not have microcytosis. Calcium and vitamin D absorption are decreased after GBP. This requires adequate supplementation and periodic monitoring of serum levels and dual energy x-ray absorptiometry (DEXA) scans in postmenopausal women and patients at increased risk.

3.9.2 Vertical Banded Gastroplasty

A purely restrictive procedure, gastroplasty involves decreasing the storage capacity of the stomach to diminish consumption of solid foods. This procedure is commonly referred to as "stomach stapling," because surgical staples are used (19). Initially this procedure involved the horizontal division of the stomach into a small proximal pouch connected via a narrow channel (stoma) to a large distal remnant (Figure 3.2;

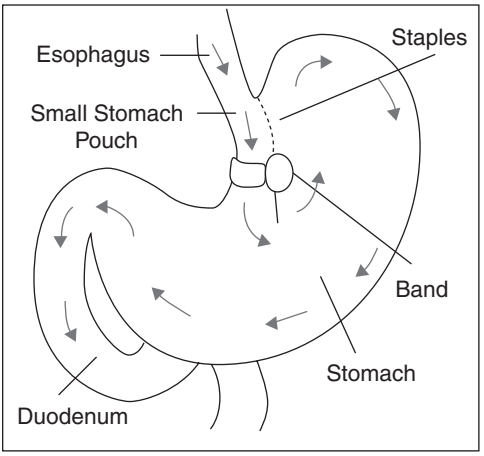

FIGURE 3.2 Vertical banded gastroplasty. (From http://www.niddk.nih.gov/health/nutrit/pubs/gastric/gastricsurgery.htm.)

45). In the 1980s, Mason, using a mesh-band reinforcement of the stoma, modified the procedure to a vertical banded gastroplasty with an upward extension of the staple line. The vertical staple line excludes the fundus, which is thought to dilate easily, and the prosthetic mesh is used to prevent stomal dilation (30). The VBG can be performed either open or laparoscopically.

In gastroplasty, notwithstanding the reinforcement of the staples and the use of mesh, the incidence of staple line dehiscence and stomal stenosis is high. In addition, patients tend to develop esophagitis and gastroesophageal reflux disease (28). Complications after a VBG are often serious and include gastric perforation (2%), enterocutaneous fistula (1%), severe esophagitis (12%), and intestinal obstruction (2%; 46).

The ingestion of food is minimized by the small (50 cc) pouch and stoma. However, many patients learn to eat high-calorie liquid foods such as ice cream and milk shakes (48). Even though there is rapid weight loss in the first 12 to 24 months following VBG, long-term weight maintenance has been disappointing. One study found that at 3 years only 38% of patients were able to maintain at least 50% of the excess weight loss (38). Another study found that at 3 years the mean loss of excess weight after VBG was only about 38% (57). Because these randomized prospective trials demonstrated that weight loss after VBG was inferior to that after RNYGP, many bariatric surgeons use RNYGP as the gold standard for anti-obesity surgery (48).

3.9.3 Laparoscopic Adjustable Gastric Banding

The use of a prosthetic surgical band, which encircles the proximal stomach, dividing it into a small pouch and large remnant, is another pure restrictive weight loss procedure (Figure 3.3; 7). Fixed silicone gastric banding was first performed in 1983, and banding became adjustable in 1986 (20). Advantages of this procedure over the VGB include absence of a staple line and the associated risk of staple line dehiscence. Laparoscopic adjustable gastric banding (LAGB), first used extensively in Europe,

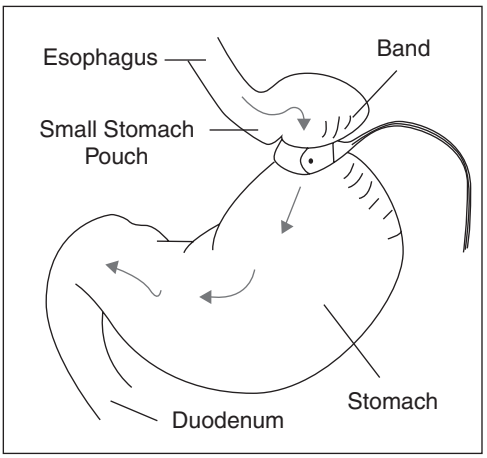

FIGURE 3.3 Adjustable gastric banding. (From http://www.niddk.nih.gov/health/nutrit/pubs/gastric/gastricsurgery.htm.)

is the most common weight loss surgery worldwide (39). The silicone band is placed laparoscopically, and the small stomach pouch diameter can be changed by infusing or withdrawing saline from a subcutaneous saline port (24). The silicone band is left empty for at least 1 month following surgery to help decrease early postoperative band slippage. Postoperative follow-up involves fluoroscopic guidance to inject or remove saline from the band reservoir to change the outlet size according to the patient's weight loss and satiety (44).

The LAGB is an appealing weight loss surgery because it is minimally invasive and reversible. The mortality risk is low, 0.5 to 1%, and nutritional deficiencies are not common. Common complications include pouch dilation and band migration, which manifest as nausea, vomiting, dysphagia, and anorexia (1). Both conditions require operation and repositioning of the band if conservative measures of nasogastric decompression and gastric band deflation fail (49). Esophageal dysfunction has been linked to the LAGB; manometric studies have demonstrated diminished esophageal motility, with the development of esophageal dilatation in some patients (62). The follow-up for the LAGB is intensive and expensive, requiring frequent office visits at regular intervals (35).

The weight loss associated with LAGB is similar to that for VBG. Westling and Gustafson have reported that by 2 years there was a 56% loss of excess weight in 90 patients, but with a disappointing 35% conversion to RNYGP (63). One study reported that 50% of patients required LAGB removal within 42 months after surgery, and only 11% of patients achieved a BMI < 35 and/or at least 50% reduction in excess weight without complications (16).

3.9.4 Biliopancreatic Diversion with Duodenal Switch

In 1979 Scopinaro described biliopancreatic diversion (BPD) as a mixed malabsorptive and restrictive surgical procedure that consists of a functional shortening of the

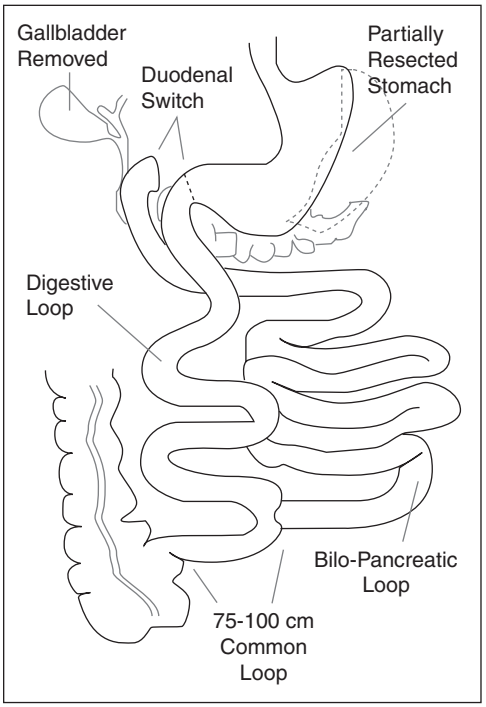

FIGURE 3.4 Duodenal switch.

small intestine and a partial gastrectomy (48). The surgery is highly effective in the supermorbidly obese (BMI > 50). The principal weight-loss mechanism of malabsorption is caused by the diversion of biliary and pancreatic secretions to the distal 50 cm of the ileum. The distal gastrectomy adds to the restrictive weight loss by reducing the stomach to a 200- to 500-cc pouch (51). Food and nutrient digestion is limited to a 100-cm "common channel" of terminal ileum. The BPD causes marked weight loss, but it can lead to significant nutritional deficiencies (52). Hess, in 1998, modified the BPD with a pylorus-preserving gastrectomy and added the duodenal switch (DS) that connects the jejunum (rather than the ileum) to the proximal duodenum (Figure 3.4; 5,21). The preservation of the pylorus avoids the dumping syndrome that occurs after a gastrojejunostomy, and the DS prevents duodenal-gastric reflux, decreasing the risk of stomal ulcer formation (35).

Experienced surgeons can perform BPD and BPDDS either by open surgery or laparoscopically. The procedure carries a perioperative mortality rate of 0.5 to 2%, most commonly due to pulmonary embolism, respiratory failure, and gastrointestinal leaks (39). BPDDS is the most effective weight loss operation. One study demonstrated the percentage of excess weight loss (%EWL) was >70% at 1 year and reached 81.4% at 5 years, when 97% of the patients had a %EWL >50% (5). The beneficial effects of BPDDS include an improvement of the metabolism of insulin and lipids, a decrease in blood glucose and blood pressure, an improvement in preexisting liver inflammation, and an increase in fertility and improvement in pregnancy outcome (59).

The most common complaints reported by patients undergoing this procedure include foul-smelling diarrhea, abdominal bloating and pain, and more than three stools per day (61). The malabsorption can lead to fat-soluble vitamin A, D, K, and E deficiency. Vitamin A deficiency can lead to ocular complications. Calcium metabolism is severely affected by this operation, as calcium absorption in the duodenum and proximal intestine is bypassed (13). Vitamin D, which is needed to facilitate calcium absorption, is fat soluble and poorly absorbed after BPD. One study demonstrated very low serum vitamin D levels, reduced calcium, and elevated parathyroid hormone levels consistent with secondary hyperparathyroidism in patients. This triad of abnormalities may explain the slowly progressive bone loss seen with BPD (11). A small number of BPD patients experience protein calorie malnutrition, a problem infrequently seen with the more common malabsorptive procedures, such as the RNYGP (42). The BPDDS is not considered a first-line bariatric procedure, yet the risks associated with the greater anatomic complexity and its greater rate of complications warrant its use in those patients who require greater weight loss because of an extremely high BMI (35).

3.9.5 Jejunoileal Bypass

The jejunoileal bypass, an early bariatric operation, was exclusively a malabsorptive procedure because the stomach was not modified to limit food intake. An anastomosis of proximal jejunum to the terminal ileum was created, causing significant weight loss via malabsorption in the extended loop excluded from the food stream (39). The jejunoileal bypass is no longer performed due to the resulting serious complications, including hepatic failure, cirrhosis, oxalate kidney stones, bypass enteritis, protein malnutrition, metabolic bone disease, hypocalcemia, and vitamin B_{12} and vitamin D deficiency. Recipients of the jejunoileal bypass should be screened for liver and renal dysfunction and whenever possible should undergo conversion to a more suitable anatomic bypass (35).

3.10 CONCLUSION

The potential consequences of untreated obesity are staggering: coronary heart disease; hyperlipidemia; hypertension; Type 2 diabetes mellitus; steatohepatitis and cirrhosis; cancers of the breast, colon, and uterus; infertility; amenorrhea; wound infection; arthritis; back pain; cholelithiasis; hypoventilation syndrome; sleep apnea; and asthma. Safe and effective weight loss therapy is needed, and the number of severely obese patients is increasing at an alarming rate. Other described therapies such as calorie restriction, exercise, pharmaceuticals, and behavior modification have failed to control this condition completely. The most effective treatment option available at the present time for significant obesity is surgical intervention. The surgical approach is not a cure and a commitment to follow-up is necessary for each patient, including nutritional care, group support networks, routine lab work, and screening for potential short-term and long-term complications.

REFERENCES

1. Allen, JW, Coleman, MG, & Fielding, GA. (2001) Lessons learned from laparoscopic gastric banding for morbid obesity. *Am. J. Surg. 182:* 10–14.
2. Alpert, MA, Terry, BE, & Kelly, DL. (1985) Effect of weight loss on cardiac chamber size, wall thickness and left ventricular function in morbid obesity. *Am. J. Cardiol. 55:* 783–786.
3. Ardern, DW, Atkinson, DR, & Fenton, AJ. (2002) Peri-operative use of estrogen containing medications and deep vein thrombosis: A national survey. *New Zealand Med. J. 115:* U26.
4. Balsiger, BM, Murr, MM, Pogio, JL, & Sarr, MG. (2000) Surgery for weight control in patients with morbid obesity. *Med. Clin. N. Am. 84:* 477–489.
5. Baltasar, A, Bou, R, Bengochea, M, Arlandis, F, Escriva, C, Miro, J, Martinez, R, & Perez, N. (2001) Duodenal switch: An effective therapy for morbid obesity-intermediate results. *Obes. Surg. 11:* 54–58.
6. Batterham, RL, Cohen, MA**,** Ellis, SM, Le Roux, CW, Withers, DJ, Frost, GS, Ghatei, MA, & Bloom, SR. (2003) Inhibition of food intake in obese subjects by peptide YY 3-36. *N. Eng. J. Med. 349:* 941–949.
7. Bo, O, & Modalsli, O. (1983) Gastric banding, a surgical method of treating morbid obesity: Preliminary report. *Int. J. Obes. 7:* 493–499.
8. Brolin, RE. (1998) Are vitamin B_{12} and folate deficiency clinically important after Roux-en-Y gastric bypass? *J. Gastro. Surg. 2:* 436–442.
9. Brolin, RE. (2001) Gastric bypass. *Surg. Clin. N. Am. 11:* 1077–1095.
10. Brolin, RE, Kenler, HA, Gorman, JH, & Cody, RP. (1992) Long-limb gastric bypass in the superobese. A prospective randomized study. *Ann. Surg. 215:* 387–395.
11. Chapin, BL, LeMer, HJ, Knodel, DH, & Carter PL. (1996) Secondary hyperparathyroidism following biliopancreatic diversion. *Arch. Surg. 131:* 1048–1052.
12. Charuzi, I, Lavie, P, Peiser, J, & Peled, R. (1992) Bariatric surgery in morbidly obese sleep patients: Short- and long-term follow-up. *Am. J. Clin. Nutr. 55:* 594S–596S.
13. Compston, JE, Vedi, S, Gianetta, E, Watson, G, Civalleri, D, & Scopinaro, N. (1984) Bone histomorphometry and vitamin D status after biliopancreatic bypass for obesity. *Gastroenterol. 87:* 350–356.
14. Cowan, GSM Jr., & Buffington, CK. (1998) Significant changes in blood pressure, glucose, and lipids with gastric bypass surgery. *W. J. Surg. 22:* 987–992.
15. Cutler, JA. (1991) Randomized clinical trials of weight reduction in nonhypertensive persons. *Ann. Epidemiol. 1:* 363–370.
16. DeMaria, EJ, Sugerman, HJ, Meador, JG, Doty, JM, Kellum, JM, Wolfe, L, Szucs, RA, & Turner, MA. (2001) High failure rate after laparoscopic adjustable silicone gastric banding for treatment of morbid obesity. *Ann. Surg. 6:* 809–818.
17. Geloneze, B. (2003) Ghrelin: A gut brain hormone: Effect of gastric bypass surgery. *Obes. Surg.* 13: 17–22.
18. Gollobin, C. (2002) Bariatric beriberi. *Obes. Surg. 12:* 309–311.
19. Gomez, CA. (1979) Gastroplasty in morbid obesity. *Surg. Clin. North Am. 59:* 1113–1120.
20. Greenstein, RJ, Rabner, G, & Taler, Y. (1994) Bariatric surgery vs. conventional dieting in the morbidly obese. *Obes. Surg. 4:* 16–23.
21. Hess, D, & Hess, DW. (1998) Biliopancreatic diversion with a duodenal switch. *Obes. Surg. 8:* 267–282.

22. Howard, L, Malone, M, Michalek, A, Carter, J, Alger, S, & Van Woert, J. (1995) Gastric bypass and vertical banded gastroplasty: A prospective randomized comparison and 5 year follow-up. *Obes. Surg. 5:* 55–60.
23. Jones, KB Jr. (2000) Experience with the Roux–en–Y gastric bypass, and commentary on current trends. *Obes. Surg. 10:* 183–185.
24. Kuzmak, L. (1992) Stoma adjustable silicone gastric banding. *Prob. Gen. Surg. 9:* 298–317.
25. Livingston, EH. (2002) Obesity and its surgical management (review). *Am. J. Surg. 184:* 103–113.
26. Long, SD, O'Brien, K, MacDonald, KG, Leggett–Frazier, N, Swanson, MS, Pories, WJ, & Caro, JF. (1994) Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes. *Diab. Care 17:* 373–375.
27. MacDonald, KG Jr., Long, SD, Swanson, MS, Brown, BM, Morris, P, Dohm, GL, & Pories, WJ. (1997) The Gastric bypass operation reduces the progression and mortality of non-insulin dependent diabetes mellitus. *J. Gastro. Surg. 1:* 213–220.
28. MacLean, LD, Rhode, BM, Sampalis, J, & Forse, RA. (1993) Results of the surgical treatment of obesity. *Am. J. Surg. 165:* 155–162.
29. Marceau, P, Hould FS, Simard, S, Lebel, S, Bourque RA, Potvin, M, & Biron, S. (1998) Biliopancreatic diversion with duodenal switch. *World J. Surg. 9:* 947–954.
30. Mason, EE. (1982) Vertical banded gastroplasty for obesity. *Arch. Surg. 117:* 701–706.
31. Mason, EE, & Renquist, KE. (2002) Gallbladder management in obesity surgery. *Obes. Surg. 12:* 222–229.
32. Mason, EE, & Ito, C. (1969) Gastric bypass. *Ann. Surg. 170:* 329–339.
33. Meryn, S, Stein, D, & Straus, EW. (1986) Pancreatic polypeptide, pancreatic glucagon and enteroglucagon in morbid obesity and following gastric bypass operation. *Int. J. Obes. 10:* 37–42.
34. Mokdad, AH, Serdula, MK, Dietz, WH, Bohman, BA, Marks, JS, & Koplan, JP. (1999) The spread of the obesity epidemic in the United States, 1991–1998. *J. Am. Med. Assoc.* 1519–1522.
35. Mun, EC, Blackburn, GL, & Matthews, JB. (2001) Current status of medical and surgical therapy for obesity. *Gastroenterology 120:* 669–681.
36. Murr, MM, Siadati, MR, & Sarr, MG. (1995) Results of bariatric surgery for morbid obesity in patients older than 50 years. *Obes. Surg. 5:* 399–402.
37. Nguyen, NT, Goldman, C, Rosenquist, CJ, Arango, A, Cole, CJ, Lee, SJ, & Wolfe, BM. (2001) Laparoscopic versus open gastric bypass: A randomized study of outcomes, quality of life, and costs. *Ann. Surg. 234:* 279–291.
38. Nightengale, ML, Sarr, MG, Kelly, KA, Jensen, MD, Zinmeister, AR, & Palumbo, PJ. (1991) Prospective evaluation of vertical banded gastroplasty as the primary operation for morbid obesity. *Mayo Clin. Proc. 5:* 55–60.
39. NIH conference, Consensus Development Conference Panel. (1991) Gastrointestinal surgery for severe obesity. *Ann. Int. Med. 115:* 956–961.
40. NIH consensus development conference statement. (1992) Gastrointestinal surgery for severe obesity. *Am. J. Clin. Nutr. 55:* 615S–619S.
41. NIH Technology Assessment Conference Panel. (1992) Methods for voluntary weight loss and control. *Ann. Int. Med. 116:* 942–949.
42. Noya, G, Cossu, ML, Coppola, M, Tonolo, G, Angius, MF, Fais, E, & Ruggiu, M. (1998) Biliopancreatic diversion for treatment of morbid obesity: Experience in 50 cases. *Obes. Surg. 8:* 61–66.

43. Oakes, J, Hahn, PM, Lillicrap, D, & Reid, RL. (2002) A survey of recommendations by gynecologists in Canada regarding oral contraceptive use in the perioperative period. *Am. J. Ob. Gyn. 187:* 1539–1543.
44. O'Brien, PE, Brown, WA, Smith, A, McMurrick, PJ, & Stephens, M (1999) Prospective study of a laparoscopically placed, adjustable gastric band in the treatment of morbid obesity. *Br. J. Surg. 85:* 113–118.
45. Pace, WG, Martin, EW Jr., Tetirick, T, Fabri, PJ, & Carey, LC. (1979) Gastric partitioning for morbid obesity. *Ann. Surg. 190:* 392–400.
46. Papakonstantinou, A, Alfaras, P, Komessidou, V, & Hadjiyannakis, E. (1998) Gastrointestinal complications after vertical banded gastroplasty. *Obes. Surg. 8:* 215–217.
47. Payne, JH, & DeWind, LT. (1969) Surgical treatment of obesity. *Am. J. Surg. 118:* 141–147.
48. Pories, WJ, Swanson, MS, MacDonald, KG, Long, SB, Morris, PG, Brown, BM, Barakat, HA, deRamon, RA, Israel, G, Dolezal, JM, et al. (1995) Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes. *Ann. Surg.* 222: 339–352.
49. Schauer, PR, Ikramuddin, S, Gourash, W, Ramanathan, R, & Luketich, J. (2000) Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann. Surg. 232:* 515–529.
50. Schirmer, B, Erenglu, C, & Miller, A. (2002) Flexible endoscopy in the management of patients undergoing Roux-en-Y gastric bypass. *Obes. Surg. 12:* 634–638.
51. Scopinaro, N, Gianetta, E, Civalleri, D, Bonalumi, U, & Bachi, V. (1979) Biliopancreatic bypass for obesity. II. Initial experience in man. *Br. J. Surg. 66:* 619–625.
52. Scopinaro, N, Gianetta, E, Adami, GF, Friedman, D, Traverso, E, Marinari, GM, Cuneo, S, Vitale, B, Ballari, F, Colombini, M, Baschieri, G, & Bachi, V. (1996) Biliopancreatic diversion for obesity at eighteen years. *Surgery 119:* 261–268.
53. Steinbrook, R. (2004) Surgery for severe obesity. *N. Eng. J. Med. 350* (11): 1075–1079.
54. Stocker, DJ. (2003) Management of the bariatric surgery patient. *Endocrinol. Metab. Clin. N. Am. 32:* 437–457.
55. Sugerman, HJ, Kellum, JM Jr., DeMaria, EJ, & Reines, HD. (1996) Conversion of failed or complicated vertical banded gastroplasty to gastric bypass in morbid obesity. *Am. J. Surg. 171:* 263–269.
56. Sugerman, HJ, Brewer, WH, Shiffman, ML, Brolin, RE, Fobi, MA, Linner, JH, MacDonald, KG, MacGregor, AM, Martin, LF, Oram-Smith, JC, et al. (1995) A multicenter, placebo-controlled, randomized, double-blind, prospective trial of prophylactic ursodiol for the prevention of gallstone formation following gastric bypass-induced rapid weight loss. *Am. J. Surg. 169:* 91–96.
57. Sugerman, HJ, Starkey, JV, & Birkenhauer, R. (1987) A randomized prospective trial of gastric bypass versus vertical banded gastroplasty for morbid obesity and their effects on sweets versus non-sweets eaters. *Ann. Surg. 205:* 613–624.
58. Sugerman, HJ, Fairman, RP, Sood, RK, Engle, K, Wolfe, L, & Kellum, JM. (1992) Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am. J. Clin. Nutr. 55:* 597S–601S.
59. Sugerman, HJ. (1997) Gastric surgery for morbid obesity. In: MJ Zinner, Ed., *Maingot's abdominal operations*. Stamford, CT: Appleton & Lange, pp. 1057–1077.
60. Wadden, TA, Sarwer, DB, Womble, LG, Foster, GD, McGuckin, BG, & Schimmel, A. (2001) Psychological aspects of obesity and obesity surgery. *Surg. Clin. N. Am. 81:* 1001–1024.

61. Waitman, JA, & Aronne, LJ. (2002) Obesity surgery: Pros and cons. *J. Endocrinol. Invest. 25* (10): 925–928.
62. Weiss, HG, Nehoda, H, Labeck, B, Peer-Kuhberger, MD, Klingler, P, Gadenstatter, M, Aigner, F, & Wetscher, GJ. (2000) Treatment of morbid obesity with laparoscopic adjustable gastric banding affects esophageal motility. *Am. J. Surg. 180:* 479–482.
63. Westling, A, & Gustavson, S. (2001). Laparoscopic vs. open Rouxen-en-Y gastric bypass: A prospective, randomized trial. *Obes. Surg. 11* (3): 284–292.
64. Wu, EC, & Barba, CA. (2000). Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. *Obes. Surg. 10:* 7–13.

4 Nutritional Management of the Elderly

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CONTENTS

4.1 INTRODUCTION

We live in an aging society. One in every five U.S. citizens will be over the age of 65 by the year 2030. Moreover, the over-85 age group is increasing more rapidly than any other age group. Life expectancy has increased dramatically since the turn of the 20th century, from 47 years in 1900 to 77 years in the year 2000. There has also been a shift in the leading causes of death, from infectious disease, which has decreased as a result of the advent of antibiotic therapy, to chronic debilitating diseases such as heart diseases, stroke, diabetes, and cancer.

Conditions resulting from chronic disease are often preventable. Because chronic diseases affect quality of life, health care costs, and medication management and care giving (52), care for the elderly necessarily goes considerably beyond dealing with death. To improve the health of the elderly requires focusing on prevention and treatment of these chronic diseases, including the promotion of a lifestyle that emphasizes proper diet, exercise, and the absence of tobacco use. The emphasis in *Healthy People 2010* and the agenda for productive and successful aging is to increase life expectancy while also improving the quality of life (33,54).

Nutritional concerns in the aged include macro- and micronutrient deficiency, malnutrition, and frailty, which has been coined "the sarcopenia of aging." But equal concern is with excess malnutrition and obesity and its effects on disability, functional status, and the progression of chronic diseases.

4.2 PHYSIOLOGIC CHANGES WITH AGING AND ITS EFFECTS ON NUTRITION

All humans are subject to the physiologic changes that occur with aging. However, the rate at which these changes occur varies dramatically and is clearly affected by lifestyle, genetics, and life events (11). Aging is generally associated with reduction in muscle mass and total body protein; an increase in total body fat, with a redistribution of fat stores toward the visceral sites; a decrease in total body water; and a loss of bone density. Not all age-associated physiologic changes, however, are due to age alone. For example, very few of the changes in insulin sensitivity and glucose tolerance are caused by advancing age; they are more a function of genetics, sedentary lifestyle, and body composition (16).

As we age, energy intake decreases and there is a shift in the types of foods chosen. This is, in part, due to the decrease in muscle mass and the resulting decrease in metabolic rate. It also involves changes in taste, smell, thirst, and hunger — changes that moreover may lead to a reduced enjoyment of food. Difficulties with dentition may interfere with intake; financial constraints, as well as social issues, such as living alone, also have an impact on food purchases. Other factors responsible for declining dietary intakes in the elderly include hormonal changes, such as a decrease in testosterone levels leading to an increase in leptin levels. This in turn leads to a reduction in food intake. The changes in leptin levels are accompanied by an increase in cholecytokinin, a satiety hormone, and by decreases in neuropeptide Y (42). Chronic inflammation associated with illness, such as heart disease, arthritis, and diabetes, also leads to an elaboration of cytokines that over the long term may result in anorexia and malnutrition. The restrictive therapeutic diets prescribed in the treatment of many chronic diseases, along with the sharp decline in physical activity, also contribute to poor food intake in the elderly (55).

4.3 MODIFIED FOOD GUIDE FOR THE ELDERLY

As individuals age, their declining energy needs make it advisable to choose foods that are nutrient dense and to avoid “empty” calories. Among people over the age of 70 years surveyed in NHANES III, about 40% consumed less than two-thirds of the recommended intake energy (NHANES III 1988–1994). Comparison of the average food group intakes of older men and women with those of younger men and women show that older individuals eat fewer servings of most food groups except fruit. More older men than older women meet the food guide pyramid recommendations. Interestingly, older women have a higher prevalence of obesity than older men. However, using a benchmark of servings per 1000 calories, intake of the four food groups, although higher for older men and women than for their younger counterparts, was still much less than recommended (28).

To assist older adults to visualize and choose foods properly, nutritionists at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University created a Modified Food Pyramid for 70+ Adults (see Figure 4.1; 48). This food pyramid was developed to generate discussion regarding the unique needs of the elderly; it is not an official USDA teaching tool (28). The modified food pyramid for

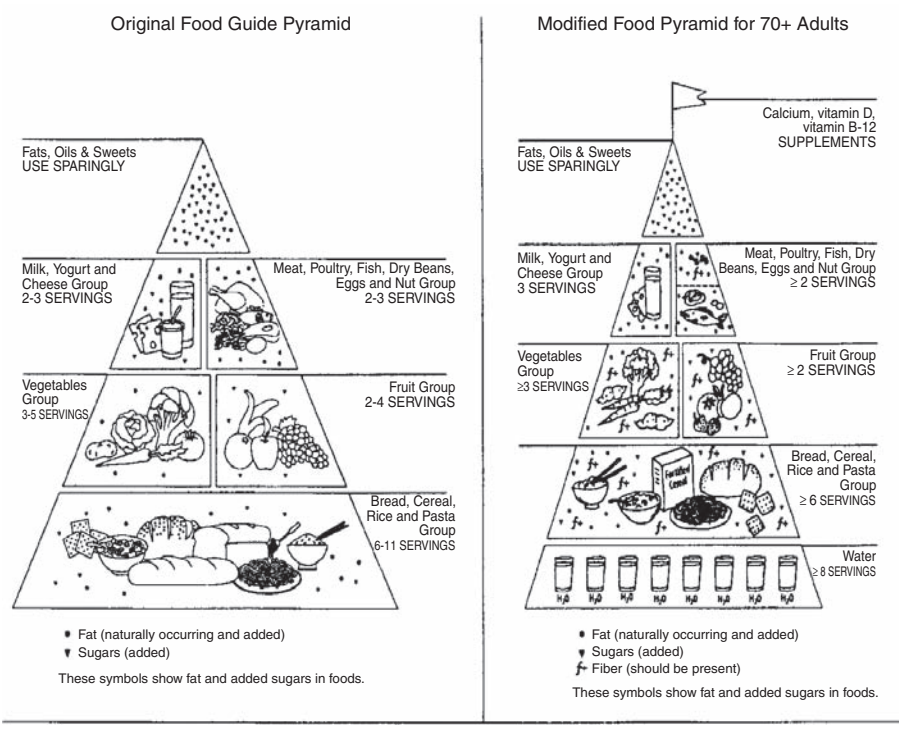

FIGURE 4.1 The modified food guide for the elderly has a narrow base (to reflect a decrease in energy needs), while emphasizing nutrient-dense foods, fiber, and water. In addition, nutrient-specific supplements may be appropriate for many older people. (Adapted from Russell RM, Rasmussen H, & Lichtenstein AH. *J. Nutr. 129:* 751–753, 1999. With permission.)

the elderly has a narrower base to reflect the decreased energy needs in the 70+ age group, but it continues to emphasize nutrient-rich foods, fiber, and water. The bottom of the pyramid is devoted to water intake, as thirst sensations are often impaired in the elderly and dehydration is not uncommon. Fiber icons ("f+") are also added throughout the pyramid to emphasize the importance of choosing fiber-rich foods.

The modified food pyramid also calls attention to the possible need for supplementation of specific nutrients, specifically vitamin B_{12}, vitamin D, and calcium (48). As a result of the prevalence of atrophic gastritis in the elderly, vitamin B_{12} in the food is not released to bind with the intrinsic factor. The elderly therefore do not absorb vitamin B_{12} readily. Meeting the increased needs of calcium and vitamin D can also be difficult. Many elderly do not consume the three servings of calcium-rich dairy foods that are needed. They may also have difficulty with lactose and therefore fail to absorb enough calcium. In addition, many elderly do not get the sun exposure required for endogenous synthesis of vitamin D, particularly in the winter months. This makes supplementation necessary.

In a University of Arizona study, standardized food frequency questionnaires were used to evaluate the dietary intakes of free-living adults aged 51 to 85 years. The intakes were then compared to the original food pyramid and the dietary

reference intakes (DRIs). More than 60% of this population did not meet the average requirements for vitamins D, E, folate, and calcium, even though their total caloric and protein intake was higher than recommended (20).

If the dietary pattern suggested by the modified food pyramid is followed, individuals with daily energy intakes of 1200 to 1600 kcal are more likely to consume 100% of the recommended dietary allowances (RDAs) for protein and essential micronutrients (48). This may suffice for individuals consuming this level of calories. Data from NHANES III suggest, however, that by age 80, 1 in 10 men consumes less than 890 kcal/d, whereas 1 in 10 women consumes less than 750 kcal/d. This makes meeting nutrient adequacy very difficult. Overt nutrient deficiencies in the elderly are uncommon, but subclinical deficiencies may be more common and can adversely affect health and functional status (7). With the development of the DRIs in 1997 and 1998, the requirements of many micronutrients are now set for individuals over 70 years of age. The 1989 RDAs did not differentiate between individuals over 50 and those over 70. Current recommendations for vitamins B_6 and B_{12} may still be too low. Also, the role of folate, its relationship to homocysteine metabolism, and its possible role in minimizing the incidence of heart disease may alter the DRI for people over 70. Table 4.1 summarizes some of the age-related changes in body composition and function that may influence nutrient requirements (7).

4.4 NUTRITION ASSESSMENT AND SCREENING IN THE ELDERLY

Most nutrition assessments rely on anthropometric, biochemical, immunological, and, more recently, subjective data such as functional status and health self-perception. Specific screening and assessment tools have been developed for the elderly through the Nutrition Screening Initiative (NSI; 44). The NSI was developed by a group of geriatric nutrition experts from the American Dietetic Association, American Academy of Family Physicians, and the National Council on Aging. It is intended to assist various clinical and program sites in identifying older individuals with nutritional problems and to assign scores that correspond to the degree of nutritional risk. There are three key components to the NSI: a screening checklist titled "Determine Your Nutritional Health," and Level I and II screens.

The mini-nutrition assessment (MNA) was developed to complement the NSI by providing a more in-depth assessment tool that is both reliable and simple to use in the elderly population (27). It includes anthropometric data such as height, weight, and weight loss; a dietary assessment; and general geriatric and self-assessment questions. These validated screening tools are used to identify individuals who require a full nutrition assessment.

A comprehensive nutrition assessment should include data on height, weight, body mass index (BMI), skinfold thickness, and body composition assessments such as mid-arm muscle circumference. Unfortunately there are no standards for many of these measurements in the elderly. With aging, 1 to 2.5 cm of height is lost per decade after maturity. As a result, weight for height assessments are difficult to interpret. Body weight also changes with advancing age, increasing into middle age,

TABLE 4.1
Examples of Age-Related Changes in Body Composition and Physiologic Function That Influence Nutrient Requirements

Change in Body Composition or Physiologic Function	Impact on Nutrient Requirement
Sarcopenia	Decreased need for calories
Osteopenia	Increased need for calcium, vitamin D
Decreased immune function	Increased need for vitamin B_6, vitamin E, zinc
Increased gastric pH acid	Increased need for vitamin B_{12}, folic acid, calcium, iron, zinc
Decreased skin capacity for vitamin D synthesis	Increased need for vitamin D
Increased wintertime parathyroid hormone production	Increased need for vitamin D
Decreased calcium bioavailability	Increased need for vitamin D, calcium
Decreased hepatic uptake of retinal	Decreased need for vitamin A
Decreased efficiency in metabolic utilization of pyridoxal	Increased need for vitamin B_6
Increased oxidative stress status	Increased need for beta carotene, vitamin C, vitamin E
Increased levels of homocysteine	Increased need for folate, vitamin B_6, vitamin B_{12}

Source: Adapted from Blumberg J. *J. Am. Coll. Nutr. 16* (6): 517–523, 1997. With permission.

stabilizing for 15 to 20 years, and then decreasing (36). Values of BMI at both extremes, i.e., <18 kg/m^2 and >30 kg/m^2, are associated with poor health outcomes (22). If an older person is only a little heavier than average, serious illness may actually be overcome more easily. However, obesity in the elderly, as in younger populations, is associated with significant morbidity.

Bioelectrical impedance measurement (BIA), which measures total body water and its distribution in the body, as well as the proportion of fat to lean tissue fat-free mass (FFM), can be used to determine body composition in the elderly. However, BIA equations must be population-specific and chosen with care; even equations developed specifically in one group of elderly individuals may under- or overestimate FFM in other elderly with different body weights and heights (14,25,29,46).

Biochemical measures, such as albumin, prealbumin, and transferrin levels, are commonly used to assess visceral protein status, yet all have limitations as nutrition assessment parameters. Serum albumin, although affected by many clinical conditions, is the most reliable prognostic indicator for rehospitalizations, extended length of stay, and other complications in the elderly (17).

A thorough nutrition assessment should also include an evaluation of the multiple medications many elderly take, many of which have drug–nutrient interactions or debilitating side effects. A recently published survey (56) assessed the nonvitamin, nonmineral dietary supplement intake of the elderly. In the cohort of subjects surveyed as part of the New Mexico Aging Process Study, supplement use increased from 14 to 46% over a 6-year period, with women having a slightly higher usage

TABLE 4.2
Age-Associated Nutritional Changes That May Affect Quality of Life

Change	Possible Consequences
Changes in body composition	Decreased muscle mass, strength and ability to perform ADL; increased fat tissue, obesity, risk of degenerative disease
Functional changes	
Diminished thirst and decreased body H_2O	Increased susceptibility to dehydration
Age-related changes in nutrient needs	Deficient (B_{12}) toxicity (vitamin A)
Changes in taste, vision, smell	Decreased enjoyment of food
Broken bones, edentulous	Limited food choices due to food consistency
Increased disease incidence	Changes in requirements, dietary restrictions
Increased use of prescription drugs	Drug–nutrient interactions, appetite changes
Social changes; loss of family, friends	Depression, decreased intake; loneliness, isolation
Decreased income	Increased food insecurity, insufficient access to food, and undernutrition

Source: Adapted from Amarantos E, Martinez A, Dwyer J. *J. Geron. Ser. A 56A:* 54–64, 2001. With permission.

of supplements such as ginkgo biloba, lecithin, black cohosh, and so forth. Often, patients will not report supplement intake to their physicians, thinking it is not important. Many supplements have, however, specific and significant interactions with commonly prescribed medications. A complete nutrition assessment should also include a review of an elderly individual's oral health and dentition, as many individuals have ill-fitting dentures, which may affect the ability to chew food. Moreover, nutrient deficiencies often have oral manifestations (see Chapter 10).

A nutrition assessment should also include an evaluation of the socioeconomic status of the individual as it affects the ability to pay for food and social support systems. It also reflects the functional status of the individual, that is, how well a person carries out the activities of daily living (i.e., feeding, cooking, and doing household tasks), how well the person cares for himself or herself, and how well he or she can walk or climb stairs.

An area of assessment that has received attention more recently is how nutritional status affects the health-related quality of life (HRQOL). Traditionally, assessment parameters focused on outcomes such as morbidity and mortality. Often these are less meaningful to the elderly than symptomatic improvement that leads to a greater degree of HRQOL (1). Good nutrition promotes HRQOL by promoting health, because it prevents dietary deficiency. Eating is a sensory pleasure and, when in company, contributes to a person's psychological well-being. Table 4.2 lists age-associated nutritional changes that may affect the HRQOL. Even though standard nutrition assessment measures may not have age-adjusted standards for the elderly, they still provide useful information that can help prevent or correct nutrition-related problems.

Practical recommendations for evaluating elderly patients who present to their primary care provider would include a "nutrition focused" physical exam: a simple assessment of height, weight, and BMI, as well as the presence or absence of muscle wasting and edema, and an evaluation of skin turgor, hair, oral mucosa, and dentition. The physician should ask the patient simple, direct questions regarding dietary intake, recent weight change, significant changes in bowel habits, the patient's living situation, who shops for food, who cooks, and so forth. It would also be useful for the physician to have the patient fill out the nutrition screen form in the office. Referrals can be made to dietitians or social workers for more in-depth nutrition and psychosocial assessments if the physician feels this is necessary. Simply suggesting and prescribing food supplements or coordinating food delivery programs, such as Meals on Wheels, may make significant improvements in the older person's nutrition health.

4.5 OBESITY AND THE ELDERLY

Obesity has become a major problem in the United States for persons of all ages, including those of advanced maturity (50 to 65 years). This is because of changes in body composition brought about by a sedentary lifestyle and poor food choices. Between the years of 1991 and 1998, the incidence of obesity in adults 60 to 69 years old increased by 44.9%. In individuals over 70 years, it increased by 28.6% (41). Obesity in the elderly causes increased disability and adversely affects quality of life. Obese persons exhibit signs of disability up to 10 years earlier than controls (18). Obesity is also associated with an increased incidence of hypertension, hyperlipidemia, and diabetes mellitus. These conditions in turn increase the incidence of cardiovascular disease, the primary cause of death in the elderly. As discussed above, BMI, the standard anthropometric index that defines obesity, is also a useful parameter for the elderly. However, because of changes in height and body composition, the standards for defining obesity in the elderly on the basis of the BMI need reevaluation (31). Controversy exists over whether the relationship between obesity and increased mortality that exists in the younger population persists as we age. Excess body weight may in fact be protective in the elderly, especially in the oldest old (4,12).

One of the largest studies of aging, the Longitudinal Study of Aging, started with an in-home survey in 1984. Follow-up surveys were performed in 1986, 1988, and 1990. The relationship between mortality and obesity was analyzed retrospectively, using the initial 1984 data from this study and controlling for many risk factors, but not for cigarette smoking. Obesity was found to be protective, compared with thin or normal weight individuals; this was confirmed by sensitivity analysis (26).

The Framingham Heart Study, which excluded former and current smokers, found increased mortality after age 65 in the obese, before and after adjustment for medical comorbidities (30). Calle et al. (8) have reported data from the American Cancer Society's Cancer Prevention Study II that suggest a U-shaped relationship between BMI and mortality for all ages. Obesity was most strongly associated with death in those individuals who had never smoked and had no history of disease. In

a group of 1448 subjects with a mean age of 79 years who underwent cardiac surgery, subjects with a lower BMI were shown to have a higher risk of complications and death from cardiovascular surgery than subjects with a higher BMI. Moreover, an increased BMI does not increase the risk of complications from cardiovascular surgery; it does, however, increase the risk of wound infections (37). However, it has also been demonstrated that in a cohort of 845 elderly subjects of low socioeconomic status, a BMI above 30 kg/m^2 was associated with higher mineral density of the femoral neck (3). The risk of osteoporosis among men and women with a BMI greater than 30 was approximately one-third of that of individuals with a normal BMI.

The BMI cut-off for obesity and overweight in the elderly remains controversial. Notwithstanding the protective effect of BMI on mortality, obesity has many adverse effects on function in old age. Overweight and obesity also increase health care costs. A recently published longitudinal study that evaluated the relationship of baseline BMI during middle age with Medicare expenditures during older age found that as BMI increased, cumulative charges to Medicare increased significantly (13).

In summary, the expert subcommittee on nutrition for the World Health Organization, in setting standards for the use and interpretation of anthropometry in the elderly, suggests that overweight individuals with BMI values between 25 kg/m^2 and 30 kg/m^2 should be considered at risk only while under 70 years of age (51). Overweight individuals over the age of 70, even without chronic disease, should maintain their current weight (51).

4.6 AGING AND IMMUNE FUNCTION

Immune function declines as we age. This process is called immunosenescence. It leads to an increased risk of infection, specifically upper respiratory infections, pneumonias, and influenza. The number of immune cells does not seem to decrease with age. Many of these cells, however, undergo functional alterations (24). The decline in immune function in the elderly is also associated with an impaired antibody response to vaccination and is often coupled with a poor nutritional state, which itself also causes impaired immune function.

Studies have investigated the effects of nutrient supplementation on immune function in the elderly, but the results have been mixed. In a recent trial (34), 65 individuals over the age of 65 were recruited from assisted and independent-living facilities in Florida. Subjects were randomized in a prospective parallel, double-blind design to receive for 183 days either 8 oz of a nutritional supplement that contained antioxidants, zinc, selenium, fermentable oligosaccharides, and structured lipids, or an isocaloric isonitrogenous control formula. The subjects receiving the experimental formula had fewer days of respiratory infections and exhibited greater lymphocyte proliferation and a more pronounced antibody response to influenza vaccination. This is one of the first studies to show a clinically meaningful outcome to a simple nutritional intervention in an elderly population.

Similarly, Meydani et al. (39), studying nursing home residents in the Boston area, found a statistically significant protective effect of a daily dose of 200 IU vitamin E on the incidence of upper respiratory infections. Although these findings need to

be extended, they demonstrate how simple, inexpensive nutritional supplements can have a significant impact on disease outcome and therefore on health in the elderly. See Chapter 9, "Malnutrition and the Immune System."

4.7 UNDERNUTRITION AND THE ROLE OF NUTRITIONAL SUPPLEMENTS IN THE ELDERLY

A low BMI and undernutrition are more prevalent in the aged than obesity, with 30 to 40% of men and women over the age of 75 at least 10% below ideal body weight. Significant protein calorie malnutrition is evident in 5 to 12% of community-dwelling older persons, whereas in hospitalized and long-term care settings, this figure increases, ranging from 23 to 85% (53). Over 40% of current hospital admissions involve elderly people, whose periods of illness and hospitalization tend to be longer than those of younger adults. As already discussed, the causes of weight loss and poor nutrition are multifactorial: chronic disease, socioeconomic impediments, poor oral health, depression, and dementia, as well as the normal functional changes associated with aging.

Nutritional status will inevitably worsen in the course of hospitalization or institutionalization, efforts to supplement nutrition intake notwithstanding. The risk of complications and death increases in direct proportion to the severity of the nutritional deficits (49). Within 1 year of discharge from a geriatric rehabilitation unit, the risk of mortality is a direct function of protein-energy undernutrition. Serum albumin and body weight, when expressed as percent of ideal at discharge, were each strong independent predictors of mortality (50).

Recognizing malnutrition, even with the help of the Nutrition Screening Initiative, is still a major problem in hospitals. Patients often are allowed to subsist on very low energy intakes for prolonged periods of time, and when the need for nutrition support is recognized, it may be too late. Numerous trials have evaluated the utility of nutritional supplementation in the elderly at risk for malnutrition. The Cochrane Metabolic and Endocrine Disorders Group (40) reviewed all randomized controlled trials of oral protein and energy supplementation in older people through March 2001. Thirty-one trials with 2464 participants are included in the analysis, but many trials were of poor quality. Supplementation appears to produce a small but consistent weight gain, to result in a shorter hospital stay, and to have had a significant and beneficial effect on mortality. The review indicated the need for further large-scale, multicenter trials to substantiate the benefits of supplementation (40). The effects of nutritional supplements on functional status and quality of life are more difficult to define and measure. In most cases, the study period is too short to show an effect.

Calcium and vitamin D supplements have been administered to older individuals in an attempt to prevent hip fractures. In 1980, 72,337 postmenopausal women from The Nurses' Health Study (19) were assessed at baseline, with follow-up assessments in 1984, 1986, 1990, and 1994. Adequate vitamin D intake had the strongest association with reduced hip fractures. Neither milk nor calcium reduced the risk of fractures. However, falls were found to have decreased 20% in women (mean age 60 years) whose diets had been supplemented with vitamin D (5). Another Cochrane

Database Review (2), evaluating the effects of nutritional supplementation for hip fracture after care, analyzed 15 randomized trials involving 943 elderly subjects (older than 65 years) who had sustained a hip fracture. Such individuals are often malnourished, and their nutritional status tends to worsen in the course of their hospital stay and during rehabilitation. Supplementation with oral protein and calories was found to have the greatest effect in reducing the length of stay in rehabilitation units. In no case was there an effect on mortality (2). However, because the trials included in this analysis were poor from a methodological viewpoint, the results should be interpreted with caution.

Supplements have been investigated to determine whether they can mitigate the functional changes that occur in the elderly with time. Debilitation and muscle atrophy used to be considered unavoidable, but adequate nutrition, social safety nets, and exercise can retard or reverse many of these functional changes. In addition to caloric and protein supplementation, specific micronutrient supplements may help improve physical function as a person ages. It has been suggested that the age-related decline in muscle function may result from oxidative damage caused by free radicals. In the Invecchiare in Chianti Study (10), the effect of a daily intake of antioxidants was evaluated, and plasma antioxidant levels were related to skeletal muscle strength and physical performance in a population of 986 Italians over 65 years of age. Vitamin C, vitamin E, β-carotene, and retinal intakes were estimated from questionnaires, whereas plasma α and γ tocopherol concentrations were measured. Plasma antioxidant concentrations were found to correlate positively with physical strength and performance. Moreover, high dietary antioxidant intakes, specifically of vitamin C, were associated with greater strength. It is known that exercise stimulates antioxidant activity and that antioxidants may be necessary for healthy muscle function, especially during the recovery phase (38). The goal of preventing and treating muscle atrophy and the resultant debilitation in the elderly is an exciting area of research that integrates nutrition, exercise physiology, and pharmaceutics in an effort to improve the quality of life of older persons.

4.8 SARCOPENIA AND THE ELDERLY

The physical frailty and muscle loss associated with aging (the sarcopenia of aging) is an important research issue in geriatric medicine that directly impacts health and well-being. Frailty and muscle loss are the major cause of nursing home institutionalization and hospital admission and, in 2000, were responsible for health care costs of approximately $18.5 billion (32). The prevalence of clinically significant sarcopenia has been estimated to range from 8.8% in young women to 17.5% in old men (43).

The New Mexico Aging Process Study (23) has attempted to quantify the relationship of sarcopenia to falls, functional impairment, and disability by utilizing Dexascan to assess body composition. Four hundred subjects were classified as sarcopenic-lean, sarcopenic-obese, or obese. Interestingly, functional impairment, disabilities, and falls were highest in the obese-sarcopenic group or, as Morley terms them, “fat-frail.” This group also exhibited a greater prevalence of Type 2 diabetes and gallbladder disease (23).

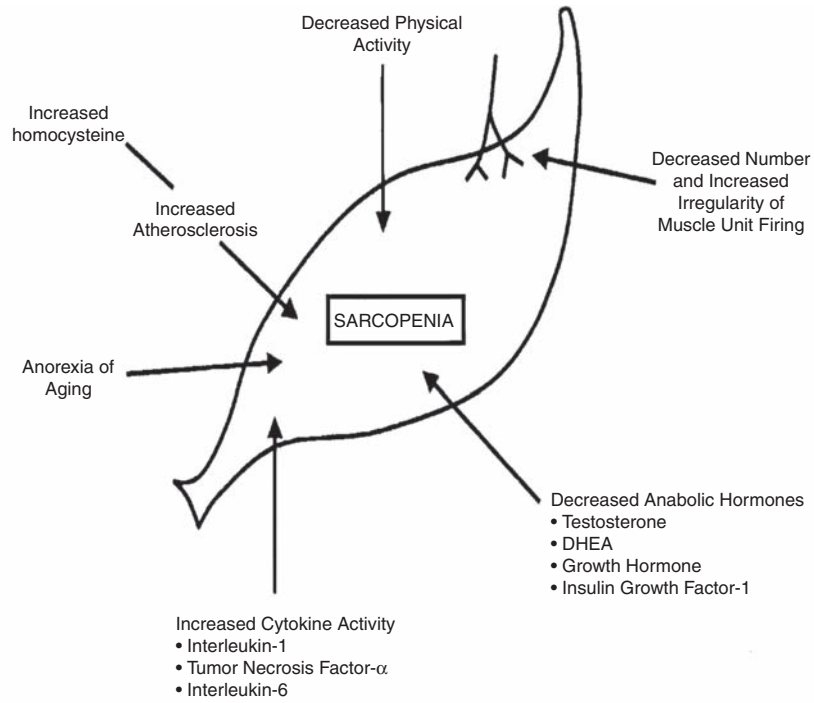

FIGURE 4.2 The multifactor origin of sarcopenia. (Adapted from Morley JE, Baumgartner RN, Roubenoff R, Mayer J, & Nair KS. *J. Lab. Clin. Med. 137:* 231–243, 2001. With permission.)

The decrease in muscle mass is paralleled by a decrease in muscle efficiency, in protein synthesis, and in type IIa muscle fibers (fast-twitch; 43). Muscle coordination is also decreased because of diminished function of the motor units innervating the muscle. Endocrinological changes that take place with aging may also contribute to sarcopenia. These include a decrease in growth hormone and testosterone, and an increase in cortisol and various cytokines, such as TNF-α, IL-1β, and IL-6. These cytokines are elaborated during critical illness and are associated with muscle wasting and increased mortality. This is true not only in hospitalized persons, but also in community-dwelling older adults (47). Other potential etiologies of the sarcopenia of aging that are currently being investigated include the possibility of reactive oxygen species causing muscle damage (21) and the role of apoptosis-activating caspases that promote muscle cell death (35). See Figure 4.2. Nevertheless, the most important etiologic factors of sarcopenia are a decline in regular physical activity and poor nutrition. These can be readily corrected through proper and timely intervention, with resistance exercise a particularly useful approach.

Resistance training is accompanied by increased fiber size, an alteration in fiber type, and an increase in protein synthesis. Significant increases in strength and muscle mass can be achieved in short-term training studies (10 to 12 weeks), even for the frail elderly (>90 years old; 15). This suggests that exercise therapy should be a part of any public health effort to improve the overall health of the aged and

to prevent sarcopenia. The optimal exercise modality and its duration and intensity are yet to be determined in the elderly.

Much is being done for the treatment and prevention of sarcopenia; it is not an inevitable consequence of aging. Investigators are utilizing anabolic hormones such as testosterone and growth hormone; exercise, specifically resistance exercise, is remarkably successful in preventing and reversing muscle atrophy; and nutrition intervention, both macro- and micronutrient supplementation, may be another appropriate treatment option. It is known that testosterone levels decrease with aging and are associated with decreased muscle mass, and studies have investigated the effects of testosterone replacement in older men with low or normal testosterone levels. Testosterone replacement will increase fat-free mass and decrease fat mass, and it appears that the effects are most pronounced in men whose baseline testosterone levels were lowest. Most studies in this area did not see an improvement or, more commonly, did not measure physical function or other health-related outcomes (6).

Exercise is the only therapy available to date that can partly reverse the age-related decline in muscle strength and muscle mass. Future research may look to combine exercise and anabolic hormones for optimal effects.

The anorexia associated with aging is also considered a causative factor of sarcopenia. Recent evidence suggests that the RDA for protein, at 0.8 g/kg, is too low for older individuals to maintain skeletal muscle, as evidenced by mid-thigh muscle area (9). This would indicate that protein supplements may be beneficial. The use of creatine in athletes has been studied extensively. One study suggests that in older persons muscle strength is increased with a combination of creatine and exercise (45). As already discussed, antioxidant supplements in the elderly may maintain skeletal muscle function. Pharmaceutical agents that reverse anorexia, such as megestrol acetate and cannabis derivatives, have had mixed results in the elderly.

To help people maintain function in old age, it is necessary that researchers identify factors that improve the quality of life as we age, maximize the nutritional status of the elderly, provide early identification of individuals at nutritional risk from undernutrition and obesity, define the optimal protein and micronutrient requirements, and work to prevent the age-related ravages of skeletal muscle loss and debilitation. These are also exciting areas for future nutritional research.

REFERENCES

1. Amarantos E, Martinez A, & Dwyer J. (2001). Nutrition and quality of life in older adults. *J. Geron. Ser. A 56A:* 54–64.
2. Avenell A, & Handoll HH (2000). Nutritional supplementation for hip fracture aftercare in the elderly. *Cochrane Database Syst. Rev. 2:* CD001880.
3. Barrera G, Bunout D, Gattas V, De la Maza MP, Leiva L, & Hirsch S (2004). A high body mass index protects against femoral neck osteoporosis in healthy elderly subjects. *Nutrition 20:* 769–771.
4. Bender R, Jockel KH, Trautner C, Spraul M, & Berger M (1999). Effect of age on excess mortality in obesity. *JAMA 281:* 1498–1504.

5. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, & Wong JB (2004). Effect of vitamin D on falls: A meta-analysis. *JAMA 291:* 1999–2006.
6. Bhasin S (2003). Testosterone supplementation for aging-associated sarcopenia. *J. Gerontol. 58A:* 1002–1008.
7. Blumberg J (1997). Nutritional needs of seniors. *J. Am. Coll. Nutr. 16* (6): 517–523.
8. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, & Heath CW (1999). Body-mass index and mortality in a prospective cohort of U.S. adults. *N. Engl. J. Med. 341:* 1097–1105.
9. Campbell WW, Trappe TA, Wolfe RR, & Evans WJ (2001). The recommended dietary allowances for protein may not be adequate for older people to maintain skeletal muscle. *J. Gerontol. 56A:* M373–M380.
10. Cesari M, Pahor M, Bartali B, Cheribini A, Penninx BWJH, Williams GR, Atkinson H, Martin A, Guralnik JM, & Ferrucci L (2004). Antioxidants and physical performance in elderly persons: The Invecchiare in Chianti (InCHIANTI) Study. *Am. J. Clin. Nutr. 79:* 289–294.
11. Chernoff R (2003). Normal aging, nutrition assessment and clinical practice. *NCP 18:* 12–20.
12. Cornoni-Huntley JC, Harris TB, Everett DF, et al. (1991). An overview of body weight of older persons, including the impact on mortality: The National Health and Nutrition Examination Survey I–Epidemiologic follow-up study. *J. Clin. Epidemiol. 44:* 743–753.
13. Daviglus ML, Liu K, Yan LL, Pirzada A, Manheim, L, Manning W, Garside DB, Wang R, Dyer AR, Greenland P, & Stamler J (2004). Relation of body mass index in young adulthood and middle age to medicare expenditures in older age. *JAMA 292:* 2743–2749.
14. Dey DK, & Bosaeus I (2003). Comparison of bioelectric impedence prediction equations for fat-free mass in a population based sample of 75 y olds: The NORA study. *Nutrition 19:* 858–864.
15. Doherty TJ (2003). Invited review: Aging and sarcopenia. *J. Appl. Physiol. 95:* 1717–1727.
16. Drewnowski A, & Evans WJ (2001). Nutrition, physical activity, and quality of life in older adults: Summary. *J. Geron. Ser. A 56A:* 89–94.
17. Ferguson RP, O'Conner P, Crabtree B, et al. (1993). Serum albumin and prealbumin as predictors of clinical outcomes of hospitalized elderly nursing home residents. *J. Am. Geriatr. Soc. 41:* 545–549.
18. Ferraro KF, Su YP, Gretebeck RJ, Black DR, & Badylak SF (2002). Body mass index and disability in adulthood: A 20-year panel study. *Am. J. Public Health 92:* 834–840.
19. Feskanich D, Willet WC, & Colditz GA (2003). Calcium, vitamin D, milk consumption, and hip fracture: A prospective study among postmenopausal women. *Am. J. Clin. Nutr. 77:* 504–511.
20. Foote JA, Giulano AR, & Harris RB (2000). *J. Am. Coll. Nutr. 19* (5): 628–640.
21. Fulle S, Protasi F, DiTano G, Pietrangelo T, Beltramin A, Boncompagni S, Vecchiet L, & Fano G (2004). The contribution of reactive oxygen species to sarcopenia and muscle ageing. *Exper. Gerontol. 39:* 17–24.
22. Galanos AN, Pieper CF, Kussin PS, Winchell MT, Fulkerson WJ, Harrell FE, Teno JM, Layde P, Conners AF, Phillips RS, & Wenger NS (1997). Relationship of body mass index to subsequent mortality among seriously ill hospitalized patients. *Crit. Care Med. 25* (12): 1962–1968.
23. Garry PJ, Owen GM, & Eldridge TO, Eds. (1997). *The New Mexico Aging Process Study.* Albuquerque: University of New Mexico.

24. Gavazzi G, & Krause KH (2002). Ageing and infection. *Lancet Infect. Dis. 2:* 659–666.
25. Genton LC, Karsegard VL, Kyle UG et al. (2001). Comparison of four bioelectrical impedence analysis formulas in health elderly adults. *Gerontology 47:* 315–323.
26. Grabowski DC, & Ellis JE (2001). High body mass index does not predict mortality in older people: Analysis of the longitudinal study of aging. *J. Am. Geriatr. Soc. 49:* 968–979.
27. Guigoz Y, Vellas B, & Garry PJ (1996). Assessing the nutritional status of the elderly: The mini-Nutrition Assessment as part of the geriatric evaluation. *Nutr. Rev. 54:* S59–S65.
28. Guthrie JF, & Lin BH (2002). Older Americans need to make every calorie count. *Food Rev. 25:* 8–13.
29. Haapala I, Hirvonen A, Niskanen L, et al. (2002). Anthropometry, bioelectrical impedence and dual-energy X-ray absorptiometry in the assessment of body composition in elderly Finnish women. *Clin. Physiol. Funct. Imaging 22:* 383–391.
30. Harris TB, Cook F, Garrison R, Higgins M, Kannel W, & Goldman L (1988). Body mass index and mortality among non-smoking older persons: The Framingham Heart Study. *JAMA 259:* 1520–1524.
31. Inelman EM, Sergi G, Coin A, Miotto F, Peruzza S, & Enzi G (2003). Can obesity be a risk factor in the elderly? *Obesity Rev. 4:* 147–155.
32. Janssen I, Shepard DS, Katzmarzyk PT, & Roubenoff R (2004). The healthcare costs of sarcopenia in the United States. *J. Am. Geriatr. Soc. 52:* 80–85.
33. Kerschner ET, & Pegues JM (1998). Productive aging: A quality of life agenda. *J. Am. Diet. Assoc. 98:* 1445–1448.
34. Langkamp-Henken B, Bender BS, Gardner EM, Herrlinger-Garcia KA, Kelley MJ, Murasko DM, Schaller JP, Stechmiller JK, Thomas DJ, and Wood SM (2004). Nutritional formula enhanced immune function and reduced days of symptoms of upper respiratory tract infection in seniors. *J. Am. Geriatr. Soc. 52:* 3–12.
35. Leeuwenburgh C (2003). Role of apoptosis in sarcopenia. *J. Gerontol. 58A:* 999–1001.
36. Martin AD, Carter JEL, Hendy KC, & Malina RM. (1988). Segment lengths. In: TG Lohman, AF Roche, R Martorell, Eds. *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Publishers, pp. 9–26.
37. Maurer MS, Luchsinger JA, Wellner R, Kukuy E, & Edwards NM (2002). The effect of body mass index on complications from cardiac surgery in the oldest old. *J. Am. Geriatr. Soc. 50:* 988–994.
38. Maxwell SRJ, Jakeman P, Thomason H, Leguen C, and Thorpe GH (1993). Changes in plasma antioxidant status during eccentric exercise and the effect of vitamin supplementation. *Free Radical Res. Commun. 19:* 191–202.
39. Meydani SN, Leka LS, Fine BC, Dalla GE, Keusch GT, Singh MF, & Hamer DH (2004). Vitamin E and respiratory tract infections in elderly nursing home residents. *JAMA 292:* 828–836.
40. Milne AC, Potter J, Avenell A (2004). Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst. Rev. 4:* 1–131.
41. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, & Koplan JP (1999). The spread of the obesity epidemic in the United States, 1991–1998. *JAMA 282:* 1519–1522.
42. Morley JE (2001). Decreased food intake with aging. *J. Geron. Ser. A 56A:* 81–88.
43. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, & Nair KS (2001). Sarcopenia. *J. Lab. Clin. Med. 137:* 231–243.

44. *Nutrition Interventions Manual for Professionals Caring for Older Adults* (1992). Washington DC: Nutrition Screening Initiative.
45. Rawson ES, Wehnert ML, & Clarkson PM (1999). Effects of 30 days of creatine ingestion in older men. *Eur. J. Appl. Physiol. 80:* 139–144.
46. Roubenoff R, Baumgartner RN, Harris TB, et al. (1997). Application of bioelectrical impedence analysis to elderly population. *J. Gerontol. 52A:* M129–136.
47. Roubenoff R, Parise H, Payette HA, Abad LW, D'Agostino R, Jacques PF, Wilson PWF, Dinarello CA, & Harris TB (2003). Cytokines, insulin-like growth factor 1, sarcopenia and mortality in very old community-dwelling men and women: The Framingham Heart Study. *Am. J. Med. 115:* 429–435.
48. Russell RM, Rasmussen H, & Lichtenstein AH (1999). Modified food guide pyramid for people over seventy years of age. *J. Nutr. 129:* 751–753.
49. Sullivan DH, & Walls RC (1995). The risk of life-threatening complications in a select population of geriatric patients: The impact of nutritional status. *J. Am. Coll. Nutr. 14:* 29–36.
50. Sullivan DH, Sun S, & Walls RC (1999). Protein-energy undernutrition among elderly hospitalized patients. *JAMA 281:* 2013–2019.
51. The Expert Subcommittee on the Use and Interpretation of Anthropometry in the Elderly (1998). Uses and interpretation of anthropometry in the elderly for the assessment of physical status report to the Nutrition Unit of the World Health Organization. *J. Nutr. Health Aging 2:* 5–17.
52. The State of Aging and Health in America 2004: A report from the Merck Institute of Aging and Health, the Centers for Disease Control, and the Gerontological Society of America. www.cdc.gov/aging; www.miahonline.org.
53. Thomas D (2002). Undernutrition in the elderly. *Clin. Geriatr. Med. 18:* 13–14.
54. U.S. Department of Health and Human Services (1998). *Healthy People 2010 Objectives: Draft for Public Comment*. Washington, DC: U.S. Government Printing Office.
55. Westerterp KR, & Meijer EP (2001). Physical activity and parameters of aging: A physiological perspective. *J. Geron. Ser. A 56A:* 7–12.
56. Wold RS, Lopez ST, Yau CL, Butler LM, Parreo-Tubbeh SL, Waters DL, Garry PJ, & Baumgartner RN (2005). Increasing trends in elderly persons' use of nonvitamin, nonmineral dietary supplements and concurrent use of medications. *JADA* 54–62.

5 Food Allergy

Abba I. Terr

CONTENTS

5.1 INTRODUCTION

Food, necessary for human nutrition, is also a potential source of disease, including allergy. Food allergy is not uncommon and can range in severity from a simple annoyance to a rapidly fatal anaphylactic reaction. A correct diagnosis of allergy and identification of the specific food to which a person is allergic are essential if future reactions are to be avoided.

The term *adverse reactions* describes all conditions that may occur when a particular food is eaten. Food allergy is only one of many possible adverse reactions and refers to a disease in which a food component is antigenic. The antigen, usually

TABLE 5.1
Foods with Natural Chemicals That May Simulate Allergy

Food	Chemical	Effect
Some cheese	Histamine	Flushing and itch
	Tyramine	Headache
	Phenylethylamine	CNS stimulation
Chocolate	Phenylethylamine	CNS stimulation
	Theobromine	CNS stimulation
Red wine	Histamine	Flushing and itch
	Phenylethylamine	CNS stimulation
Spinach	Histamine	Flushing and itch
Eggplant	Histamine	Flushing and itch
Coffee	Caffeine	CNS stimulation
Cola	Caffeine	CNS stimulation
Banana	Serotonin	CNS stimulation
Avocado	Serotonin	CNS stimulation
Tomato	Serotonin	CNS stimulation

Note: CNS = central nervous system.

a protein that induces an allergic response, is called an allergen. However, not all immune responses result in allergy.

Allergy refers to diseases in which the immune response to an environmental antigen (e.g., a food) induces inflammation that is detrimental to the patient. This is in contrast to immunity, a situation in which the immune response is protective against an infectious microorganism or toxic chemical.

Food intolerance is the term used by allergists for an adverse reaction that is not allergic. Nonallergic reactions to foods are frequently mistaken for allergy. The condition may be pathologic, or it may be subjective only, and the mechanism may be known or unknown. For example, certain foods contain chemicals that have pharmacologic properties, such as caffeine in coffee that causes stimulation or histamine-like compounds in wines that cause flushing and headache. Some individuals are susceptible to these effects, while others are not. Those who are susceptible may incorrectly perceive their "sensitivity" as an allergy (see Table 5.1). *Toxicity* is the direct effect of a naturally occurring chemical in the food, such as mushroom poisoning, or a bacterial toxin from a contaminant, such as *Staphylococcus* or *E. coli*.

5.2 THE NORMAL IMMUNE RESPONSE

The immune response is a stepwise process involving cells that ultimately generate both antibodies and sensitized lymphocytes that recognize a specific antigen.

Antibodies are referred to chemically as immunoglobulins and are found in the blood as well as in tissues of the body. There are five classes of immunoglobulin

TABLE 5.2
Cross-Reactivity of Foods and Other Allergens

Food	Other Allergens
Melon	Ragweed pollen
Banana	Ragweed pollen
	Latex
Apple	Birch pollen
Pear	Birch pollen
Potato	Birch pollen
Hazelnut	Birch pollen
Carrot	Birch pollen
Celery	Birch pollen
	Mugwort pollen
	Grass pollen
Kiwi	Birch pollen
	Latex
Chestnut	Latex
Avocado	Latex

molecules, which differ in their chemical structure and are known as isotypes. They are called IgG, IgA, IgM, IgD, and IgE. These differ in some properties, but all react with the specific antigen that was responsible for their production. The effect of antibodies on the system is referred to as humoral immunity.

Antibodies of the IgG isotype are the most abundant in the serum and are responsible for long-lasting immunity. IgM antibodies are produced early during the immune response and are transient. IgA antibodies are generated by the mucosal immune system, including the gastrointestinal tract. IgE antibodies are responsible for the common forms of allergic diseases.

Cell-mediated immunity does not involve antibodies. It refers to specifically sensitized lymphocytes that are the product of antigenic stimulation and in turn react with the specific antigen. When the antigen induces inflammation, it is called cell-mediated hypersensitivity, and the antigen is referred to as an allergen.

Specificity and cross-reactivity are important concepts in immunity and in allergic disease. Specificity refers to the ability of the immune system to recognize very small differences in the chemical structure of different protein molecules. Cross-reactivity occurs when two or more different allergens contain the same molecular group and therefore are recognized by the same antibody. There are numerous examples of cross-reactivity among food allergens. There are also cross-reactions between allergens in foods and other environmental substances, such as pollens and natural rubber latex (see Table 5.2).

The gastrointestinal tract has a unique immune system of its own, called the gastrointestinal associated lymphoid tissue (GALT). Anatomically, GALT encompasses lymphoid tissue and cells throughout the gastrointestinal tract; in terms of volume, it is larger than the systemic immune system.

Mucosal immunity differs from systemic immunity in a number of ways. A unique property of GALT is production of a specialized form of immunity, known as secretory IgA antibodies (sIgA). These antibodies form molecular complexes with their corresponding food antigens (Ag), thereby retarding absorption of the intact food antigen. This in turn lengthens the time during which the complex undergoes normal digestion by proteolytic enzymes. Nevertheless, intact food protein antigens, including those that may be allergenic, are absorbed and enter the systemic circulation. This gives rise to low levels of IgG, IgA, and IgM antibodies in the circulation, as well as cell-mediated immunity. Low antibody levels in response to foods are a normal occurrence and have no detrimental or pathologic significance.

Immunological tolerance is a condition in which the immune system does not respond to an antigen. This provides protection from harmful effects that would otherwise result from reactions to self-antigens. Disruption of the normal state of immunologic self-tolerance leads to autoimmune diseases, as exemplified by systemic *lupus erythematosus*.

Oral tolerance refers to a situation when the oral administration of an antigen fails to induce a systemic immune response or when the response is diminished. A high dose of the antigen given orally prevents the subsequent immune response to the administered antigen. The effect is specific for that antigen only and does not constitute a generalized immune suppression. Although oral tolerance can be demonstrated experimentally, its significance as a normal physiologic process is not fully understood. However, since the normal process of eating foods involves exposing the immune system to large quantities of potential food antigens, oral immunologic tolerance may be necessary for normal nutrition because it protects foods from immunologic attack.

5.3 THE ALLERGIC RESPONSE

Allergy is a two-step process. In the first step, called sensitization, the immune system recognizes a foreign protein (e.g., in a food) as an antigen, thereby generating an immune response. The immune response results in specific antibodies and/or specifically sensitized T lymphocytes. Once a state of sensitivity occurs, subsequent exposure to the antigen results in an allergic state, often referred to as the elicitation phase because it elicits the pathology of the disease.

There are a number of allergic diseases, reflecting the complexity of the immune response. They are typically classified by the Gell and Coombs system, which is based on the particular immune pathway involved in the disease (see Table 5.3).

Type I reactions are mediated by IgE antibodies, which react with the allergen on tissue mast cells or circulating basophils. These cells then release certain chemical mediators, such as histamine, resulting in local or systemic pathologic effects. The effects on blood vessels lead to vasodilation and, if extreme, to hypotension and shock. Cutaneous and mucosal effects produce pruritus and flushing, usually accompanied by urticaria and/or angioedema because of increased vascular permeability. Airborne allergens cause conjunctival and eyelid itching, rhinitis, and bronchospasm. Orally ingested allergens cause itching and swelling of the lips, tongue, and palate;

TABLE 5.3
Gell and Coombs Classification of Allergic Diseases, Including Mechanisms and Testing Methods

Class	Mechanism	Typical Diseases	Skin Tests	*In Vitro* Tests
I	IgE antibody–mediated	Atopy, anaphylaxis	Immediate wheal/flare	RAST or ELISA
II	IgG (or IgM) antibody–mediated cytolytic	Drug-related hemolytic anemia	N/A	N/A for food allergy
III	IgG (or IgM) antibody–mediated inflammatory	Serum sickness	Intradermal arthus	Precipitin assay
IV	T cell–mediated	Allergic contact dermatitis	1. Patch test 2. Intradermal DTH	*In vitro* lymphocyte transformation test

Note: N/A = not applicable; DTH = delayed-type hypersensitivity (48 h); RAST = radioallergosorbent test; ELISA = enzyme-linked immunosorbent assay.

laryngeal edema; and gastrointestinal smooth muscle spasm resulting in vomiting, diarrhea, and abdominal pain. All of these effects do not necessarily occur with each allergen exposure. If the exposure occurs by injection or oral ingestion, multiple organs may be involved; this is referred to as systemic anaphylaxis.

Type II reactions are mediated by IgG or IgM antibodies, which form a complex with the antigen. If the antigen is a component of a cell, such as a virus or a transfused red blood cell, the antigen complex activates the complement system. This results in cytotoxicity. If the infection is by a virus, cell disruption (lysis) is desirable because it prevents replication of the virus. It is undesirable, however, in the case of a mismatched blood transfusion. Type II allergic reactions are typically caused by drugs that bind to a patient's blood cells, which are then inadvertently destroyed by lysis. This mechanism also may occur in very rare instances of milk-induced thrombocytopenia (10).

Type III reactions also involve IgG or IgM antibodies and complement, but in this instance the reactions lead to tissue or organ inflammation. This response may be the basis for celiac disease, dermatitis herpetiformis, pulmonary hemosiderosis, and some cases of arthritis and intestinal blood loss, all of which have on occasion been attributed to a food allergen. To date, however, there is little evidence to support this hypothesis.

Type IV reactions are cell-mediated forms of hypersensitivity that do not involve antibodies. They constitute the mechanism of allergic contact dermatitis.

5.4 ALLERGIC DISEASES

Atopy (atopic allergy) refers to a condition affecting about one-third of the population in whom there is a genetic tendency to produce IgE antibodies in response to certain

protein allergens commonly found in the environment. These include pollens of trees, grasses, and weeds; mold spores; the house dust mite; and emanations from animals, such as cats, dogs, and horses. They also include, but to a lesser extent, some of the natural proteins in foods. The atopic diseases — allergic rhinitis, bronchial asthma, and atopic dermatitis — can coexist in the same patient. Because genetic factors predispose to atopy, the condition is often familial. In patients without the genetic predisposition to atopy, the same natural exposure to allergens in pollens, molds, dust, or foods does not induce the formation of specific IgE antibodies and will not lead to atopic disease.

Many atopic persons have IgE antibodies to food allergens, yet exhibit no clinical signs of allergic disease. The reasons for this phenomenon are unknown, but it is essential to recognize that this "sensitization without elicitation (overt disease)" is very common.

Anaphylaxis is a systemic allergic disease that is also caused by IgE antibodies, but it is outside the scope of atopic allergy. It is a medical emergency that leads to the rapid appearance of urticaria, angioedema, bronchospasm, shock, and other systemic effects. It may be fatal. The allergens most often responsible for anaphylaxis are organic chemicals, proteins, and nonproteins, especially drugs, foods, and venom from Hymenoptera stinging insects. Exposure is therefore the result of injection or ingestion. In a highly sensitive patient, inhalation or contact of the allergen with a mucous membrane or the skin may on rare occasions be enough to trigger anaphylaxis. Urticaria/angioedema is a localized form of anaphylaxis that involves the vasculature of the skin or mucous membranes and is caused by allergens similar to those that elicit anaphylaxis. Anaphylaxis and urticaria/angioedema can affect atopic or nonatopic persons and do not appear to be genetically determined.

Serum sickness is an acute disease characterized by skin rash, joint inflammation, and fever. It is an allergic reaction to drugs; it has never been clearly associated with foods. It is caused by IgG or IgM antibodies, which activate the complement system of blood plasma. Once activated, the complement system generates a systemic inflammation that is transient and resolves when the patient discontinues using the drug that caused the disease.

Allergic contact dermatitis is a superficial inflammatory disease of the skin causing redness, swelling, papules, and vesicles. It affects the skin directly in contact with the allergen. It is caused by cell-mediated hypersensitivity and does not involve antibodies (4). The disease is mediated by the effector T lymphocyte, which specifically recognizes the contact allergen. The most common allergen is pentadecylcatechol, a chemical in poison ivy, poison oak, and poison sumac. (These are the common names of the plants and of the diseases. The diseases are in fact allergic, not poisonous [toxic] conditions.) Allergic contact dermatitis is also frequently caused by allergens in jewelry, perfumes, cosmetics, rubber products, and some topical medications. Other items that may contact the skin induce the disease less commonly. The disease can also be an occupational hazard.

Allergic contact dermatitis is also the result of an uncommon food allergy (8), with the skin erupting at sites where the food has come in contact with the skin. In infants it is primarily the skin around the mouth that is affected. In food handlers, it affects the hands and constitutes an occupational disease. Allergic contact derma-

titis is called delayed hypersensitivity, because it requires many hours, typically 12 h to several days, after skin contact with the food before the reaction begins. The delayed latency period makes diagnosing the condition challenging. On the other hand, IgE-mediated allergic diseases, both atopy and anaphylaxis, are often referred to as immediate hypersensitivity, because onset following exposure typically occurs within minutes of contact.

5.5 PREVALENCE OF FOOD ALLERGY

Food allergy is much less common than perceived by the general public (2). According to surveys some 20% of the population believes that they are allergic to foods. However, in the vast majority of cases, the subjective self-diagnosis cannot be confirmed. A definitive diagnosis is made by allergy specialists, who rely on a searching history and examination, appropriate testing for allergy, and confirmation by double-blind placebo-controlled food challenges. This is the "gold standard" for diagnosis and reveals that only 1 to 2% of adults have bona fide food allergy (28). Furthermore, the prevalence of food allergy differs among different population groups. It depends on age (most common prior to age 2), atopy (more common, especially in patients with atopic dermatitis), diet (availability of particular foods depending on geography and cultural practices), breastfeeding, and the presence of other diseases. Anaphylaxis, the most serious form of food allergy, occurs in 0.004% (1 in 250,000) of the U.S. population.

5.6 NATURAL HISTORY OF FOOD ALLERGY

Reliable information about the prognosis of food allergy is minimal. In infants and children, allergy to foods frequently remits after several years, with the notable exception of anaphylaxis, especially to nuts and peanuts. More than 80% of infants who exhibit an allergy to milk, egg, wheat, or soy, as demonstrated by a double-blind, placebo-controlled food trial, had lost their allergy when rechallenged by age 3 (30). Most adult-onset food allergy reactions are also transient, although they may persist for years before remitting. Children with documented food allergy should be monitored annually by serial skin testing. They should scrupulously avoid the allergenic food as long as the test is positive. Only when the test reverts to negative should a clinical loss of hypersensitivity be considered. To verify the loss of allergy, a small test dose of the food should be administered in a medical facility where appropriate treatment is immediately available, should a reaction occur.

5.7 FOOD ALLERGENS

Any food is potentially allergenic, but some foods cause allergic reactions more commonly than others. In almost all cases, the allergen is a protein, usually about 10,000 to 60,000 Da (10 to 60 kDa) in molecular weight. Each foodstuff typically contains a number of different proteins, some of which constitute potential allergens, which vary from patient to patient. The protein allergens in foods, like the inhalant

TABLE 5.4
Nomenclature of Selected Purified Food Allergens

Food	Allergen	Nomenclature
Cow milk	Alpha-lactablumin	Bos d 4
	Beta-lactoglobulin	Bos d 5
	Albumin	Bos d 5
Soy	Hydrophobic seed protein	Gly m 1
	Profilin	Gly m 2
Chicken egg	Ovomucoid	Gal d 1
	Ovalbumin	Gal d 2
	Lysozyme	Gal d 4
Shrimp	Tropomycin	Met e 1
Peanut	Vicilin	Ara h 1
	Conglutin	Ara h 2
Lobster	Tropomycin	Pan s 1
Cod	Parvalbumin-beta	Gad c 1
Rice	Trypsin inhibitor	Ory s 1

allergens such as pollens, often contain a small amount of carbohydrate and are therefore called glycoproteins. Nevertheless, the allergenicity is in the protein portion of the molecule. The common allergens are often called major, while those found infrequently are referred to as minor. An increasing number of food allergens have been purified and identified (see Table 5.4).

Cow's milk contains more than 20 different proteins, many of which have been identified as allergens (5). They are present in both the casein and whey fractions. Pasteurization does not significantly denature the allergens. Most patients with cow's milk allergy tolerate beef without reactions. On the other hand, there is a high degree of cross-reactivity between cow's milk and goat and sheep milk, so these may not be suitable substitutes in patients with allergy to cow's milk (19).

Chicken egg allergy is almost always an allergy to the egg white and not the yolk. Egg white contains 23 different glycoproteins. Four of these are major allergens, of which ovomucoid is the most frequent (16). Although most patients allergic to chicken egg can tolerate chicken meat and skin, a few with exquisite anaphylactic sensitivity may react to the meat also. Cross-reactions with egg allergens from other birds, such as duck, turkey, and goose, are common.

Legumes are the most common allergy-causing foods in the United States. Peanut allergy is a particularly prominent cause of food-induced anaphylaxis and therefore the subject of considerable research interest. At least 16 allergenic proteins have been identified to date, with three of them major peanut allergens. The allergenicity due to peanut proteins is not found in peanut oil, but it remains in virtually all processed peanut products, such as flour.

Soybean allergy, especially in children and infants, must be taken into account in infants fed on a soy-based formula because of their allergy or intolerance to cow's

milk. Soy is extensively used in many food preparations because of its high protein content and low cost. Several allergenic soy proteins have been identified. The allergen is not found in pure soybean oil, but some allergens may be present in commercial sources of the oil, in lecithin preparations, and in margarines. There is potential allergic cross-reaction among legumes when tested in the laboratory, but other legumes, such as beans, peas, and licorice, are far less likely to cause clinically evident allergic reactions. Most peanut-sensitive patients can tolerate other legumes (6).

Tree nuts cause allergy, especially in adults. These include brazil nuts, cashews, filberts (hazelnut), hickory nuts, pecans, pine nuts, pistachios, and walnuts. Cross-reactions among these are common but not always present. No known allergenic cross-reactivity exists between these tree nuts and any legumes, including peanut.

Fish is the most common food to cause allergy in adults (1). There are hundreds of edible species of fish. Allergenic cross-reactivity among fish is extensive.

Crustaceans and mollusks are also important, although the majority of allergy-like reactions, especially urticaria and angioedema, are not immunologic. Allergenic cross-reactivity occurs among different crustaceans and among different mollusks, but not between them.

Cereal grains, including wheat, barley, rye, oats, rice, corn, sorghum, and millet, are a more important cause of allergy in children than in adults. The grains account for 70% of the world protein consumption. The allergens vary by disease, e.g., globulin and glutenin cause IgE oral allergy, and albumin is the allergen in baker's asthma. Gliadin is the protein that causes celiac disease. Allergenic cross-reactivity among grains is common. Occupational food allergy is usually manifested as asthma, rhinitis, and/or dermatitis and is caused by inhalation of airborne flour dust. In baker's asthma, skin tests of cereal grains are positive in more than half of the cases, whereas clinical disease occurs in only 20% (34). Most patients with baker's asthma have no allergic reaction to the ingestion of the same food causing the asthmatic reaction.

5.8 CLINICAL MANIFESTATIONS OF FOOD ALLERGY

5.8.1 IgE-Mediated Allergic Diseases

IgE antibodies cause the large majority of well-documented food allergies. The specific IgE antibody to the food is identified by the radioallergosorbent skin test (RAST). The reaction begins promptly after ingestion of the food, and there is objective evidence of allergic inflammation.

Anaphylaxis is the most serious form of allergy because of the potential for a rapid fatal outcome. Food allergy is a frequent cause of anaphylaxis, particularly in children (27). There are about 100 fatalities per year in the United States from food-induced anaphylaxis (26) and an estimated 1000 nonfatal but life-threatening reactions (6). As a general rule, the more quickly the reaction begins after the food is eaten, the more severe the reaction will become. The amount of allergen causing anaphylaxis can be exceedingly small. The likelihood of a fatal outcome is increased in a patient with asthma, even if the asthma is not active at the time. Although anaphylaxis and the atopic diseases (allergic rhinitis, asthma, and atopic dermatitis) are both caused by IgE antibodies, atopy is not a precondition for anaphylaxis. Most

patients with anaphylaxis to a food, however, are atopic. The disease affects females twice as often as males. In some infants, the reaction occurs on the first feeding of the food, in which case it is probable that sensitization occurred from exposure to the allergen through breastfeeding.

The anaphylactic reaction consists of pruritus, urticaria, angioedema, contact urticaria, erythema, laryngeal edema, rhinitis, conjunctivitis, bronchospasm, hypotension or shock, nausea, vomiting, abdominal cramps, diarrhea, and uterine or bladder cramps. Not all of these symptoms occur in every case, but at least two organ systems are involved. If treatment is administered immediately, the reaction subsides promptly, with little or no residual abnormalities after several hours. The allergist evaluating a patient for food anaphylaxis generally does so after the incident and therefore must rely on the patient's history. The most common foods to cause anaphylaxis are wheat, shellfish, fruit, milk, celery, and fish. Although peanut and egg white are reported less frequently, they are especially important because minute amounts may be present in some food preparations unbeknownst to the patient. The allergen is likely to be hidden when it is contained in a pastry, salad, sandwich, hors d'oeuvre, or candy. Testing to confirm the specific food sensitivity is done by either the skin test method or by RAST, which detects the specific IgE antibody in the patient's serum. Either test is usually highly reliable to determine specific sensitivity. Confirmation by double-blind, placebo-controlled food challenge is not recommended because of the potential danger.

Some patients with exquisite sensitivity to a food — especially fish, mollusks, crustaceans, eggs, and peanut — may experience an allergic reaction to inhaling fumes of the food (11). The reaction may consist of allergic rhinitis, conjunctivitis, laryngeal edema, bronchospasm, vomiting, and even, on rare occasions, anaphylactic shock. The foods most commonly reported are fish (especially mollusks and crustaceans), eggs, and peanut.

Food-dependent, exercise-induced anaphylaxis is an IgE-mediated food reaction that occurs when a patient exercises within 2 to 3 h after or before eating a meal containing the food allergen (17). In some cases, urticaria or anaphylaxis without other systemic effects may occur. Foods that are especially likely to be implicated in this rare disease are celery, shrimp, oyster, chicken, peach, and wheat. The patient may eat the food with impunity if there is no accompanying physical exercise, or if exercise in the absence of eating the food during this time interval fails to induce anaphylaxis.

By definition, anaphylaxis is a systemic disease. However, the term gastrointestinal anaphylaxis is used to describe a reaction that begins within minutes (or up to 2 h) after ingestion of a food. It results in symptoms of nausea, abdominal pain, cramps, vomiting, and sometimes diarrhea, but without any other symptoms or signs of systemic anaphylaxis. In children with this condition who ingest the food frequently, it may cause poor appetite and abdominal pain.

Allergic eosinophilic gastroenteritis is an uncommon condition in some atopic patients who are allergic to both inhalant and food allergens. In adults, the ingestion of the food allergen causes postprandial nausea and vomiting, abdominal pain, diarrhea, and occasionally steatorrhea and weight loss (22). Complications include hypoalbuminemia and iron deficiency anemia. In some infants, it causes protein-

losing enteropathy with failure to thrive (23). There is eosinophilia in the blood, intestinal secretions, and ascites fluid, and eosinophilic infiltration throughout the gastrointestinal tract. Many children and adolescents with this disease do not have specific IgE antibody to foods. These patients may respond to a nonprotein diet or to systemic corticosteroid therapy if the specific causative food is not identified and eliminated. Some patients have evidence of autoimmunity of the gastrointestinal tract and of other organs. Occasionally this occurs in common variable immunodeficiency or IgA deficiency.

Cutaneous reactions are common. Immediate reactions caused by IgE antibodies produce acute urticaria, angioedema, or both. These occur especially from the ingestion of fish, shellfish, tree nuts, and peanuts in adults, and from eggs, milk, peanuts, and tree nuts in children. The reaction subsides promptly and does not occur unless the food is eaten again. Contact urticaria results when areas of skin come in contact with raw meats, fish, fruits, and occasionally other foods. Chronic urticaria/angioedema is a condition of frequently recurring hives or swelling that persists for weeks or months and is rarely if ever caused by foods. In fact it is almost always idiopathic because a search for any causative allergen or underlying condition is usually negative.

Atopic dermatitis is a manifestation of atopy. Patients with this disease may also have asthma or allergic rhinitis in addition to the skin disease. It is a chronic pruritic skin inflammatory disease often in a symmetric distribution. Allergy testing will frequently, but not always, show evidence of IgE sensitivities to foods as well as to inhalant allergens, especially to the house dust mite. The role of food allergy in causing or exacerbating the skin eruption is controversial. However, one-third of children with severe atopic dermatitis given double-blind, placebo-controlled food challenge with foods to which they tested positive had immediate pruritic skin eruptions (8). In some cases, elimination of those foods resulted in improvement. Foods that gave a negative skin test resulted in a negative challenge. Gastrointestinal and respiratory symptoms accompanied some of the challenges. Ninety percent of these food challenge reactions were to egg, milk, peanut, soy, and wheat. Based on these and other findings, it is likely that some children with atopic dermatitis, perhaps as many as one-third, have demonstrable food allergy (8).

The oral allergy syndrome is a localized immediate “contact” allergic reaction of the oropharynx. The symptoms are pruritus and angioedema of the lips, tongue, palate, and throat, beginning about 5 min after the food enters the mouth and resolves promptly thereafter. It typically results from eating uncooked fruits and vegetables, and it affects patients with allergy to those food allergens that cross-react with certain plant pollens. These patients typically have symptomatic allergic rhinoconjunctivitis (“hay fever”) to the cross-reacting pollen (3).

5.8.2 Non–IgE-Mediated Allergic Diseases

Heiner’s Syndrome is a rare disease of infants in whom ingestion of milk results in recurrent pulmonary infiltrates, anemia, and, in some cases, pulmonary hemosiderosis. The cause is frequent milk aspiration producing high concentrations of IgG antibodies to milk. These antibodies then trigger a Type III immune complex allergic

reaction in the lung (15). The diagnosis can be confirmed by the presence of precipitating antibodies to milk.

5.9 NONALLERGIC IMMUNOLOGIC DISEASES ASSOCIATED WITH FOOD INTOLERANCE

The gastrointestinal tract is a site of intense immunologic activity because of exposure to potential antigens from harmless bacteria and foods, yet without causing inflammation. In fact, the mucosal immune system downregulates (inhibits) responses to these antigens, without preventing the system from suitably responding to microbial pathogens. A breakdown in this immune regulation causes certain diseases of the gastrointestinal tract. Some of these conditions are associated with specific foods, while others are not.

Gluten-sensitive enteropathy (GSE; celiac sprue or nontropical sprue) is genetically determined. It is an inflammatory disease of the small intestine that causes villous atrophy and malabsorption (35) due to the inability to induce oral tolerance to cereal grain storage proteins, especially the gliadin (29) fraction of gluten in wheat, barley, and rye. GSE may be associated with a vesicular skin disease, dermatitis herpetiformis (GSE-DH), which consists of a pruritic papulovesicular symmetric rash (14). In celiac sprue, the pathology of the GI tract is similar to that in celiac disease, and the intestinal tract responds similarly to a gluten-free diet.

Lifelong dietary elimination of gliadin-containing foods, even in patients with mild disease, prevents permanent villous atrophy and complications, which include intestinal carcinoma and lymphoma. Nutritional supplements and certain anti-inflammatory drugs may be required as well.

There is also a complex spectrum of diseases in which food hypersensitivity occurs because of exposure to food substances prior to the development of oral tolerance. Like GSE, these cause intestinal villous atrophy leading to malabsorption, but without the genetically determined sensitivity to gliadin.

The most frequent of these conditions is a hypersensitivity to cow's milk or other proteins when exposure to the food protein occurs prior to the normal development of oral tolerance to that protein. The disease therefore affects young children, but the condition is transient.

Enterocolitis syndrome is a disease of infants under 3 months of age, who have protracted vomiting and diarrhea. These result in dehydration, acidosis, and methemoglobinemia (24). It is believed to be caused by allergy to cow's milk and to soy, the predominant foods eaten at that age. Deliberate diagnostic challenge with the suspected food causes diarrhea and vomiting in 1 to 3 h. Symptoms resolve in 72 h when the food is eliminated from the diet. Occasionally other foods may cause a similar disease in older children; rarely, seafoods may do so in adults. The stools contain blood, eosinophils, and neutrophils. Jejunal biopsy reveals flattened villi, edema, lymphocytes, eosinophils, and mast cells. It is not an IgE-mediated allergic disease, and the immunopathogenesis is uncertain at this time.

Eosinophilic colitis occurs during the first few months of life in infants who are fed cow's milk and/or soy, but it may occur also in breast-fed infants (20). There is

no apparent gastrointestinal discomfort in the infant, but there is gross or occult blood in the stools. Microscopic pathology includes eosinophilia in the epithelium and lamina propria, and edema and neutrophils in the distal colon. Elimination of the responsible food results in clearing in 72 h.

Enteropathy is also a disease of early infancy. There is diarrhea with or without vomiting, failure to thrive, and malabsorption. Cow's milk is the usual cause, but soy, egg, wheat, rice, chicken, or fish may be responsible (18). Biopsy of the intestinal tract shows patchy villous atrophy, mild lymphocytic infiltration, and edema.

5.10 NONIMMUNOLOGIC REACTIONS TO FOODS

Gustatory rhinorrhea refers to a condition of excessive and annoying nasal secretions that some persons experience after eating certain foods, especially spicy ones, or even after eating any meal. The condition is caused by stimulation of muscarinic parasympathetic nerves.

Lactose intolerance is caused by a deficiency of lactase in the gastrointestinal mucosa. This results in lactose fermentation in the bowel, causing gas and bloating. Primary lactase deficiency may be found in 80% of North American Blacks, Arabs, and Asians, but in only 10% of Northern European Caucasians. Secondary lactase deficiency occurs transiently for about 2 weeks after an acute gastrointestinal infection. A more permanent secondary deficiency may complicate a variety of chronic gastrointestinal diseases.

5.11 FOOD ADDITIVES

Thousands of chemicals are routinely added to foods to preserve the food, inhibit microbial growth, add color, enhance taste, prolong shelf life, and change its physical properties and appearance. They are not necessarily listed as ingredients in the final product. Several of these are potential causes of disease, but not of allergy (31).

The frequency of reactions to food additives is difficult to estimate because of different criteria used for diagnosis, but most studies report that it affects between 0.01% and 0.20% in the general population (9), although the rate is probably higher (1 to 2%) in children (13). The true prevalence as determined by blinded placebo-controlled challenges would probably be considerably lower.

Sulfites are used to inhibit certain enzymes that cause browning of fresh fruits and vegetables. Many asthmatic patients experience an acute asthma exacerbation from inhalation of sulfur and various sulfur compounds (31), and a small percentage of them react similarly to ingestion of sulfite-containing foods and beverages (12; see Table 5.5). In some cases the reaction is severe, even fatal. The mechanism is not thought to have an allergic cause.

Monosodium glutamate (MSG) produces in some susceptible people a complex of symptoms including headache, burning, and sweating. This is popularly referred to as the Chinese restaurant syndrome, since MSG is frequently used as a taste enhancer in some Chinese food. Reproducing these effects in susceptible individuals by using a double-blind, controlled protocol has proved to be very difficult.

TABLE 5.5
Some Foods Containing Sulfites Likely to Exacerbate Asthma

High Content	Medium Content
Wine	Wine vinegar
Most dried fruits	Dried potatoes
Some fruit juices	Some commercial gravies
Molasses	Some commercial sauces
Sauerkraut juice	Fruit toppings
	Maraschino cherries
	Pectin
	Sauerkraut
	Fresh shrimp
	Pickled foods
	Cocktail onions
	Relishes

On the basis of anecdotal reports and uncontrolled studies, tartrazine, the yellow food dye, is thought to cause chronic urticaria. No properly controlled experimental study has yet confirmed that this chemical causes urticaria or angioedema (32).

5.12 DIAGNOSIS OF FOOD ALLERGY

A thorough history and complete physical examination are necessary to establish the nature, extent, and duration of symptoms and their association with the ingestion of a suspected food before any form of testing is undertaken. The history should include the timing of acute reaction following the ingestion of the food, the quantity of food required to trigger a suspected reaction, and consistency of the reactions over time. Hidden ingredients in foods must also be considered. A personal and family history of atopic or other disease patterns may be important, as is a thorough review of other diseases past and present. A complete physical examination is critical to detect objective signs of allergic inflammation and to search for other possible diseases. In some cases the diagnosis may be obvious, as in a patient with several anaphylactic reactions to peanut, but frequently a differential diagnosis is necessary. Specific testing is then appropriate to confirm the correct or most likely diagnosis.

Diet–symptom diaries provide a more accurate documentation if the history is not adequate. Diaries are especially useful in disproving a patient's false assumption that a particular food has caused reactions. It is best to review the diary with the patient. Such diaries are especially helpful for those with intermittent urticaria/angioedema.

Diagnostic elimination diets have long been used by allergists. They are generally based on the results of skin testing or foods suspected on the basis of the history. Records, to be accurate, must be complete and must include the time when an item

of food is eaten, as well as all symptoms or reactions. They also must include other events, such as medications that may be alternative causes for the patient's symptoms. The diet must be monitored with a written diet–symptom record. The purpose of the elimination diet is to elucidate symptoms and objective physical or laboratory findings. If the suspected diet component is eliminated, an open challenge is performed by reincluding the suspect food. A positive response then establishes the cause but not the mechanism. A reaction in an open challenge could result from allergy, toxicity, or an enzyme deficiency, or it may even be due to a psychological response. If ongoing chronic symptoms fail to improve in 2 weeks, the diet should be abandoned. If symptoms improve or clear completely, the foods that had been eliminated are added back one at a time, and all changes should be entered in the food diary. If a particular food causes a reaction consistent with the previous symptoms, it is again eliminated and subsequently reintroduced. In general, three successive positive provocative unblinded tests can be considered significant, although the mechanism must then be determined.

Tests for a specific immune response must be appropriate to the suspected allergic reaction (see Table 5.1). An allergy test is not a test of allergic disease. It is the procedure used to show that a person has the specific antibodies or T cell sensitivities being tested. Sensitization is necessary — but is not by itself sufficient — to diagnose an allergic disease. Many people react positively to tests that show specific IgE antibodies to one or more food allergens, yet they do not experience a reaction when they eat the food. This means that they are sensitized but not allergic to that food. Other factors that are unknown cause expression of the allergy when that food is eaten. The distinction between sensitization (a positive test without disease) and allergy (a positive test and disease) is important so as to prevent unnecessary food avoidance. If the suspected cause is mediated by IgE antibodies, either the immediate wheal/erythema skin test or the *in vitro* serum assay for specific IgE antibodies to foods is appropriate. The skin test is more sensitive, but reading and interpreting the result are subjective and require training and experience. Immediate skin testing to food allergens should be done exclusively by the prick testing method using commercially available allergen extracts (33). Testing with a sample of fresh food can be done as long as the test result is compared with that obtained in normal nonallergic control subjects. A false negative result can occur from an inactive extract. The positive predictive value of prick skin test for disease is 50%, and the negative predictive value is 95%. Skin testing is most useful for suspected food allergy causing anaphylaxis. Most commercial medical laboratories offer a panel of food RAST.

The predictive value of patch testing to foods is currently unknown. Nevertheless, the test should be highly useful in allergic contact dermatitis because it simulates the disease "in miniature" (33).

Endoscopy of the stomach or small bowel with or without biopsy during oral challenge with a food allergen to observe for objective changes may be required in some patients with suspected food-induced gastroenteropathy.

The double-blind placebo-controlled food challenge is the gold standard for proof of a specific food-induced disease, but a positive result does not provide the mechanism of the reaction. It is usually appropriate to perform the oral food chal-

lenge unblinded or single-blinded first; if it is negative, it is unnecessary to proceed further. The test has been especially valuable for analyzing food-related symptoms without objective evidence of a physical reaction.

The procedure for double-blind placebo-controlled food challenge is demanding (7,21). The suspect food is eliminated from the diet for 7 to 13 d or longer to make the patient asymptomatic. The challenges are administered while the patient is fasting and free of antihistamines or any other drug that might inhibit or mask the reaction. The first challenge requires a dose that is unlikely to cause a reaction. Subsequent challenge doses are doubled and administered every 15 to 60 min until 10 g of the test food is tolerated. At that intake level, the test is considered negative. Food extracts and placebo controls are given in random order. The food challenges are administered as lyophilized extracts packed into capsules or dissolved in liquid. Because false negative reactions occur, a negative result should be repeated with an open challenge. Following the session, the patient should be observed for up to 2 h if an IgE reaction is suspected, up to 4 to 8 h for milk enterocolitis, and up to 24 to 48 h for eosinophilic enterocolitis and the like. Wherever appropriate and possible, an objective measure of disease should be included, such as pulmonary function testing, nasal smear for eosinophils, or histamine or tryptase content of plasma or urine.

5.13 TREATMENT

The only sure treatment of food allergy is elimination of the food from the diet. Where a suspected food allergen can be identified by skin test or RAST, elimination from the diet results in disease resolution. In most cases, the allergy is limited to one food, one class of food, or a small number of different foods. Therefore, nutritional deficiency is not likely to complicate avoidance therapy. Some infants and a few adults, however, have multiple food allergies. In those cases, a diet must be devised that will ensure proper nutrition.

In some cases it is possible to eliminate the allergen only partially, provided the diet is accompanied by appropriate drug therapy. Drugs that may offer protection for IgE-mediated disease include antihistamines, mast cell stabilizers (cromolyn, ketotifen), and corticosteroids. The efficacy of leukotriene inhibitors alone or in combination with other drugs has yet to be demonstrated. Immediate injection of epinephrine is used in cases of anaphylaxis. Patients with anaphylactic sensitivity, therefore, should carry a supply of epinephrine on them at all times.

IgE-mediated food allergy should not be treated immunologically, although this could theoretically eliminate or reduce allergic sensitivity to foods. Immunotherapy has long been known to be effective and safe for patients who have allergic rhinitis caused by inhalant allergens and for those with anaphylaxis to venom from the stings of Hymenoptera insects. Currently there is uncertainty about its effectiveness in allergic asthma from inhalant allergens.

Clinical trials using extracts of foods in patients with food-induced anaphylaxis to date have been frustrated by excessive numbers of serious and even fatal systemic reactions. Clinical studies of food immunotherapy are continuing, however, and this

approach may eventually prove to be useful. If it does, it is likely to require some type of modification of the allergen to avoid reactions from the treatment itself.

5.14 UNPROVEN "FOOD ALLERGY" CONDITIONS

Behavioral changes in children and adults have sometimes been attributed to the ingestion of certain foods and food additives. Sugar, dietary salicylates, aspartame and certain other chemicals, food preservatives, and food coloring agents have achieved notoriety as the culprits in such conditions as attention deficit hyperactivity disorder (ADHD), but there is no scientific proof for this theory. Properly controlled food challenge and elimination protocols have failed to substantiate claims that these dietary chemicals influence behavior.

Migraine or other types of headache, epilepsy, arthritis, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), infantile colic, and sudden infant death syndrome each have advocates of food allergy as cause. Yet there is no clinical or scientific basis for such an association.

5.15 CONTROVERSIAL PRACTICES

Unproven theories, diagnostic methods, and treatments are commonly recommended for food allergy. Pseudomedical practices are called "alternative" or "complementary," but they cannot substitute for or add to those based on scientific evidence. Acupuncture, homeopathy, herbalism, and unsubstantiated nutritional advice form a large and pervasive industry. Evidence-based medicine can be practiced with compassion without resorting to these modalities.

5.15.1 Controversial Theories

"Allergic toxemia" (allergic tension–fatigue syndrome) applies to persons with fatigue and other subjective symptoms postulated to be caused by multiple food allergies. The recommended treatment is elimination of milk, wheat, chocolate, corn, and sometimes other foods from the diet. There is no mechanism for ascribing fatigue per se to food allergy or toxicity, and there is no evidence that the diet is effective. The patient with fatigue should be evaluated for physical disease or a psychopathological condition.

"Delayed food allergy," supposedly caused by IgG antibodies to foods, has been studied but not confirmed. The concept has been used to explain subjective symptoms that are most likely of psychiatric origin. Such patients may be preoccupied with complicated elimination diets for many months or years with little or no relief.

5.15.2 Inappropriate Diagnostic Procedures

The cytotoxic test examines white blood cells from a patient's blood sample for changes when the blood is exposed to a food extract on a microscope slide. This procedure is uncontrolled, and investigation has shown there is no correlation with clinical food allergy or intolerance.

Testing for specific IgG antibodies to foods by the radioallergosorbent (IgG RAST) procedure can detect small quantities of these antibodies in serum samples of both allergic and nonallergic patients. The test is not diagnostic for food allergy.

A test for detecting food-immune complexes in the serum has been recommended as a diagnostic test for food allergy. While such complexes can indeed be detected, especially after eating a meal, there is no evidence that the test is useful for food allergy diagnosis.

The pulse test monitors for an increase in the pulse rate of greater than 10 beats/min after eating a food. This has been claimed to indicate allergy to that food. There is neither rationale nor empirical evidence to support such a test.

Provocation–neutralization testing is performed by injecting a food (or other) allergen extract while recording subjective sensations, which are then interpreted as allergy to the food. Additional test doses are then given until the patient reports no symptoms, at which time the "reaction" is said to be neutralized. There is no scientific basis for this procedure, and controlled studies show that it is useless. The procedure is sometimes performed sublingually.

Applied kinesiology is a bizarre procedure that supposedly results in the loss of muscle strength while the patient is exposed to a food whose extract is placed on the person's body. There is no physiologic theory to support such a "test," and there have been no clinical trials to support its use.

Electrodermal testing for allergy diagnosis is another bizarre procedure, using a machine to measure the electrical resistance of the skin when a food extract is placed in the machine's electrical circuit. This procedure and its theory are untested and scientifically implausible.

5.15.3 Unproven Therapies

The proponents of the provocation–neutralization procedure recommend sublingual or subcutaneous administration of allergen extracts to "neutralize" symptoms caused by foods (or other allergens). There is no substantiation for this claim and no rational immunologic explanation.

Elimination diets based on the unproven diagnostic methods described above can never be recommended. The practitioners of these unproven tests often diagnose multiple food allergies. To avoid highly restrictive diets, they often prescribe a so-called rotary diversified diet. This consists of a diet plan in which individual foods are eaten in a rotary schedule so that the same food is not consumed more frequently than about once every 4 d. It has been claimed that the risk of developing a food allergy is positively correlated with the frequency of consumption of that food. However, there is no evidence for that statement.

Treating allergic diseases with dietary supplements, such as multiple vitamins, minerals, and amino acids, is not logical, because allergy is not caused by a deficiency of any of these items. There is no evidence that this practice is effective.

Enzyme-potentiated desensitization consists of injecting an extract of a food (or other allergen) with the enzyme beta-glucuronidase. Various treatment protocols have been recommended, but there are no reliable studies to support the use of this procedure.

5.16 SUMMARY

Foods that are required for nutrition may occasionally be responsible for disease, including allergic reactions. Food allergy can vary from a mild annoyance to severe and life-threatening anaphylactic shock. The usual diagnostic methods for detecting food allergies include a medical and environmental history, physical examination, skin testing, the radioallergosorbent test, and, if necessary, a diagnostic elimination diet. Well-documented cases of food allergy are mostly attributable to IgE antibodies. Rare cases of delayed-onset pulmonary disease in infants and small children believed to be caused by IgG antibodies have been reported.

Management of food allergy can be accomplished only when it is based on an accurate diagnosis; generally it requires a specific elimination diet tailored to the patient. In the case of food anaphylaxis, avoidance of the allergenic food must be complete.

Those who are involved with the care of food-allergic patients must be aware of the pitfalls of unproven and unscientific theories and methods of diagnosis and treatment.

REFERENCES

1. Aas, K. (1966). Studies of hypersensitivity to fish: A clinical study. *Int. Arch. Allergy Appl. Immunol. 29,* 346–363.
2. Altman, DR, & Cerement, LT. (1996). Public perceptions of food allergy. *J. Allergy Clin. Immunol. 97,* 1247–1251.
3. Anderson, LB, Dreyfuss, EM, Logan, J, Johnstone, D. E., & Glaser, J. (1970). Melon and banana sensitivity coincident with ragweed pollinosis. *J. Allergy 45,* 310–319.
4. Beltrani, V. S., & Beltrani, V. P. (1997). Contact dermatitis: A review. *Ann. Allergy 78,* 160–195.
5. Bleumink, E., & Young, E. (1968). Identification of the atopic allergens in cow's milk. *Int. Arch. Allergy Appl. Immunol. 34,* 521–543.
6. Bock, S. A., & Atkins, F. M. (1989). The natural history of peanut allergy. *J. Allergy Clin. Immunol. 83,* 900–904.
7. Bock, S. A., Sampson, H. A., Atkins, F. M., Zeiger, R. S., Lehrer, S., Sachs, M., Bush, R. K., & Metcalfe, D. D. (1988). Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J. Allergy Clin. Immunol. 82,* 986–997.
8. Burks. J. W. (1954). Classic aspects of onion and garlic dermatitis in housewives. *Ann. Allergy 12,* 592–595.
9. Bush, R. K., & Taylor, S. L. (1989). Adverse reactions to food and drug additives. In *Allergy: Principles and Practice,* 5th ed. (E. Middleton, Jr., C. E. Reed, E. F. Ellis, N. F. Atkinson, Jr., J. W. Yunginger, and W. W. Busse, Eds.), Chap. 83. St. Louis: Mosby, pp. 1183–1198.
10. Caffrey, E. A., Sladen, G. E., Isaacs, P. E. T, & Clark, K. G. A. (1981). Thrombocytopenia caused by cow's milk. *Lancet 2,* 226–240.
11. Crespo, J. F., Pascual, C., Dominguez, C., Ojeda, I., Munoz, F. M., & Esteban, M. M. (1995). Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. *Allergy 50,* 257–261.

12. Delohery, J., Simmul, R., Castle, W. D., & Allen, D. H. (1984). The relationship of inhaled sulfur dioxide reactivity to ingested metabisulfite sensitivity in patients with asthma. *Am. Rev. Resp. Dis. 130,* 1027–1032.
13. Fuglsang, G., Madsen, C., & Saval, P. (1993). Prevalence of intolerance to food additives among Danish schoolchildren. *Pediatr. Allergy Immunol. 4,* 123–129.
14. Hall, R. P. (1987). The pathogenesis of dermatitis herpetiformis: Recent advances. *J. Am. Acad. Dermatol. 16,* 1129–1144.
15. Heiner, D. C., & Sears, J. W. (1960). Chronic respiratory disease associated with multiple circulating precipitins to cow's milk. *Am. J. Dis. Child. 100,* 500–502.
16. Hoffman, D. R. (1983). Immunochemical identification of the allergens in egg white. *J. Allergy Clin. Immunol. 71,* 481–486.
17. Horan, R., & Sheffer, A. (1991). Food-dependent, exercise-induced anaphylaxis. *Immunol. Allergy Clin. N. Am. 11,* 757–766.
18. Kuitunen, P., Visakorpi, J. K., Savilahti, E., & Pelkonen, P. (1975). Malabsorption syndrome with cow's milk intolerance: Clinical findings and course in 54 cases. *Arch. Dis. Child. 50,* 351–356.
19. Langland. T. (1983). A clinical and immunological study of hen's egg white. VI. Occurrence of proteins cross-reacting with allergens in hen's egg white as studied in egg white from turkey, duck, goose, seagull, and in hen's egg yolk, and hen and chicken sera and flesh. *Allergy 38,* 399–412.
20. Machida, H. M., Catto Smith, A. G., Gall, D. G., Trevenen, C., & Scott, R. B. (1994). Allergic colitis of infancy: Clinical and pathologic aspects. *J. Pediatr. Gastroenterol. 19,* 22–26.
21. Metcalfe, D., & Sampson, H. (1990). Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J. Allergy Clin. Immunol. 86,* 421–442.
22. Min, K., & Metcalfe, D. (1991). Eosinophilic gastroenteritis. *Immunol. Allergy Clin. N. Am. 11,* 799–813.
23. Moon, A., & Kleinman, R. (1995). Allergic gastroenteropathy in children. *Ann. Allergy Asthma Immunol. 74,* 5–12.
24. Powell, G. K. (1978). Milk- and soy-induced enterocolitis of infancy. *J. Pediatr. 93,* 553–560.
25. Reese, G. & Lehrer, S. B. (1999). Food Allergens, in *Food Hypersensitivity and Adverse Reactions: A Practical Guide for Diagnosis and Management* (M. Frieri and B. Kettelhut, Eds.), Chap. 4. New York: Marcel Dekker, pp. 69–79.
26. Sampson, H. A. (1999). Food allergy, Part 1: Immunopathogenesis and clinical disorders. *J. Allergy Clin. Immunol. 103,* 717–728.
27. Sampson, H. A. (2003). Food allergy. *J. Allergy Clin. Immunol. 111,* S547.
28. Scott, H., Fausa, O., Ek, J., & Brandtzaeg, P. (1984). Immune response patter in celiac disease: Serum antibodies to dietary antigens measured by an enzyme-linked immunosorbent assay. *Clin. Exp. Immunol. 57,* 25–32.
29. Sicherer, S. H. (2002). *Lancet 360,* 710–710.
30. Simon, R. A. (1996). Adverse reactions to food and drug additives. *Immunol. Allergy Clin. North Am. 16,* 137–176.
31. Stevenson, D. D., Simon, R. A., Lumry, W. R., & Mathison, D. A. (1986). Adverse reactions to tartrazine. *J. Allergy Clin. Immunol. 78,* 182–191.
32. Terr, A. I. (1997). Mechanisms of hypersensitivity. In *Human Immunology,* 9th ed. (D. P. Stites, A. I. Terr, & T. G. Parslow, Eds.), Chap. 26. Stamford, CT: Appleton & Lange, pp. 376–388.

33. Thiel, H., & Ulmer, W. (1980). Baker's asthma: Development and possibility for treatment. *Chest 78,* 400–405.
34. Trier, J. S. (1991). Celiac sprue. *N. Engl. J. Med. 325,* 1709–1719.
35. Yunginger, J. W., Sweeney, K. G., Stumer, W. Q., Giannandrea, L. A., Teigland, J. D., Bray, M., Benson, P. A., York, J.-A., Biedrzycki, L., & Squillace, D. L. (1988). Fatal food-induced anaphylaxis. *JAMA 260,* 1450–1452.

6 Nutritional Considerations in the Management of Pregnancy and Lactation

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CONTENTS

6.1 INTRODUCTION

Nutrition prior to pregnancy, during pregnancy, and in the postpartum lactation period can play an important role in a woman's health and that of her infant. Overall, pregravid maternal health has become increasingly recognized as a positive predictor of healthy maternal and neonatal outcomes. Preconceptional health promotion recognizes that traditional prenatal care often begins too late to impact the most important period of time in the pregnancy, organogenesis. Maximizing the health of a woman during fetal organogenesis, the critical time from days 17 to 56 of gestation, is a most significant factor in preventing major birth defects (40,49). Nutritious eating habits and a healthy, active lifestyle are key components that are important for maintenance of an appropriate weight, body mass index (BMI), and level of physical fitness. These factors reduce the risk of pregnancy complications, birth defects, and poor fetal growth, and ultimately optimize the health of both mother and infant. A health care provider should review these concepts at each encounter or well-woman examination with women of childbearing age. Nutrition during pregnancy is of essential importance in supporting and contributing to the growth of the fetus. While energy needs are increased, optimal nutrition requires the selection of nutrient-dense foods to ensure adequate intake of nutrients without excess calories. For many women, this requires a change in their routine eating and drinking habits. Overall, many physiologic changes occur in the woman with respect to nutrient metabolism to support pregnancy growth without significantly changing dietary needs.

Nutrition during pregnancy influences and prepares the woman's body for the demands of lactation. Breastfeeding substantially increases the mother's requirements for many nutrients and calories. The magnitude of the increase is affected by the extent and duration of breastfeeding. Lactating women should be encouraged to continue to eat a healthy diet and obtain nutrients from foods, supplementing if necessary.

An increasing number of women with chronic illnesses and diseases become pregnant each year. While specific information should be sought regarding the mother's particular condition, the general nutrition principles discussed in this chapter will benefit most conditions. This chapter reviews the nutritional considerations important for the continuum of prepregnancy, pregnancy, and lactational periods of a woman's life. It stresses the importance of maximizing all aspects of a woman's health prior to conception.

6.2 NUTRITIONAL RECOMMENDATIONS FOR ALL WOMEN OF CHILDBEARING AGE

Optimization of health outcomes of women and their infants starts with adoption of healthy lifestyle habits prior to pregnancy. It is unfortunate, however, that few women seek health and nutrition advice prior to conception. In addition, nearly 60% of all pregnancies in the United States, and 81% of teen pregnancies, are unintended, and the women thereby miss the opportunity to optimize maternal nutrition prior to conception (36).

The importance of early prenatal care is recognized by the majority of women. In 2002, 84% of women began prenatal care in their first trimester (2). However, because the first prenatal visit typically takes place after one or two absent menstrual cycles, an early opportunity to provide advance nutritional counseling that benefits the period of fetal organogenesis is again missed. For genuine impact, nutritional guidance should be given to women in advance so that they can practice it at the time of conception. Because more than 70% of women 18 to 39 years of age seek preventive health services each year (75), each health care visit constitutes an opportunity for health care providers to disseminate preconceptional health care and nutrition advice. Two proven examples of the success of nutritional preconceptional maternal care include prevention of birth defects in infants of diabetic mothers with better periconceptional glycemic control (38) and prevention of neural tube defects (NTDs) through routine supplementation of folic acid prior to conception (14,48,51).

6.2.1 General Nutritional Requirements

Nutritional requirements of women generally differ from those of men in that women need lower energy intake and less protein, fat, and carbohydrates. On the other hand, women's calcium and iron needs are higher. In the early 1990s, the U.S. Food and Nutrition Board defined the dietary reference intakes (DRIs) (33). Two of the DRIs used frequently in discussing healthy diets include recommended dietary allowances (RDAs) and adequate intakes (AIs). RDAs describe the average daily nutrient intake that meets the nutritional needs of nearly all (97 to 98%) of healthy individuals within a given age and gender group (53). AIs are an estimated adequate intake value based on the estimated amount consumed by a healthy population. An AI is used when an RDA cannot be determined. Table 6.1 gives daily DRIs or AIs for prepregnant, pregnant, and lactating women.

Good nutrition, derived from essential vitamins and minerals in a diverse, well-balanced diet, is associated with a decreased risk of poor pregnancy outcomes. Good nutrition should therefore be a goal for all women, whether or not they plan to become pregnant. Table 6.2 lists nutrient-rich food sources.

6.2.2 Calories and Body Mass Index

Required energy intakes are lower in women compared to men. Active teenage and adult women require 2000 to 2200 kcal/d. Sedentary women have lower requirements, at 1600 kcal/d. Calculation of BMI is based on a measure of weight for height, and it correlates with body fat. (See Table 6.3 for formulas used in calculating

TABLE 6.1
Daily Dietary Reference Intakes or Adequate Intakes for Prepregnant, Pregnant, and Lactating Women

	All Females			Pregnant Females			Lactating Females		
Age	**<18**	**19–30**	**31–50**	**<18**	**19–30**	**31–50**	**<18**	**19–30**	**31–50**
Calories	2200	2200	2200	2500	2500	2500	2700	2700	2700
Carbohydrate (g)	130	130	130	175	175	175	210	210	210
Protein (g)	46	46	46	71	71	71	71	71	71
Fiber (g)[a]	26	25	25	28	28	28	29	29	29
Vitamin A (μg)	700	700	700	750	770	770	1200	1300	1300
Vitamin C (mg)	65	75	75	80	85	85	115	120	120
Vitamin D (μg)[a]	5	5	5	5	5	5	5	5	5
Vitamin E (mg)	15	15	15	15	15	15	19	19	19
Vitamin K (μg)[a]	75	90	90	75	90	90	75	90	90
Thiamine (B_1; mg)	1.0	1.1	1.1	1.4	1.4	1.4	1.4	1.4	1.4
Riboflavin (B_2; mg)	1.0	1.1	1.1	1.4	1.4	1.4	1.6	1.6	1.6
Niacin (mg)	14	14	14	18	18	18	17	17	17
Folate (μg)	400	400	400	600	600	600	500	500	500
Vitamin B_6 (μg)	1.2	1.3	1.3	1.9	1.9	1.9	2	2	2
Vitamin B_{12} (μg)	2.4	2.4	2.4	2.6	2.6	2.6	2.8	2.8	2.8
Sodium (g)[a]	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Potassium (g)[a]	4.7	4.7	4.7	4.7	4.7	4.7	5.1	5.1	5.1
Chloride (g)[a]	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Calcium (mg)	1300	1000	1000	1300	1000	1000	1300	1000	1000
Phosphorus (mg)	1250	700	700	1250	700	700	1250	700	700
Magnesium (mg)	360	310	320	400	350	360	360	310	320
Fluoride (mg)[a]	3	3	3	3	3	3	3	3	3
Iron (mg)	15	18	18	27	27	27	10	9	9
Zinc (mg)	9	8	8	13	11	11	14	12	12
Iodine (μg)	150	150	150	220	220	220	290	290	290
Selenium (μg)	55	55	55	60	60	60	70	70	70
Chromium (μg)[a]	24	25	25	29	30	30	44	45	45
Copper (μg)	890	900	900	1000	1000	1000	1300	1300	1300
Manganese (mg)[a]	1.6	1.8	1.8	2.0	2.0	2.0	2.6	2.6	2.6
Molybdenum (μg)	43	45	45	50	50	50	50	50	50

Note: Values represent Recommended Daily Allowances (RDAs) unless otherwise noted.

[a] Adequate intake (AI).

Sources: From Institute of Medicine, Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate (2004); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997). With permission. These reports may be accessed via http://www.nap.edu.

TABLE 6.2
Nutrient-Rich Food Sources

Nutrient	Food Sources
Calcium	Dairy products, fish with edible bones, tofu processed with calcium sulfate, foods made with milk, bok choy, broccoli, collards, kale, mustard, turnip greens
Folate	Dark leafy green vegetables, avocados, citrus fruits, eggs, peas, corn, dried beans, liver, lean beef, green beans, whole grains, fortified cereals and breads
Magnesium	Nuts, seeds, legumes, green vegetables, whole grains, scallops, oysters
Vitamin B_6	Bananas, prunes, watermelon, potatoes, sweet potatoes, spinach, some legumes, nuts, meat, fish, fortified cereals
Zinc	Yogurt, eggs, seeds, legumes, whole grains, meat, poultry, seafood

TABLE 6.3
Body Mass Index Calculation

Metric Calculation

$$\text{BMI} = \frac{\text{Weight (in Kilograms)}}{(\text{Height (in Meters)}) \times (\text{Height (in Meters)})}$$

English Calculation

$$\text{BMI} = \frac{\text{Weight (in Pounds)}}{(\text{Height (in Inches)}) \times (\text{Height (in Inches)})} \times 703$$

the BMI.) The BMI can assist with prepregnancy nutrition and activity counseling. A balance between energy intake and energy expenditure is essential for maintenance of a healthy weight. Moderate daily physical activity of at least 30-minute duration should be encouraged.

Women with a BMI that is either high or low may have issues that complicate pregnancy, fetal growth, or delivery of an infant. Women who maintain a low body weight or BMI, or who have a history of eating disorders, often take longer to conceive. Being underweight or exercising vigorously can increase the risk of anovulatory menstrual cycles, subfertility, and intrauterine growth restriction in pregnancy (69). Obesity, on the other hand, is a significant and growing problem in the United States. Perhaps as many as one-third of U.S. women have a BMI above the normal range. Maternal overweight is associated with a higher risk of a delivery by cesarean section and a higher incidence of anesthetic and postoperative complications. Low Apgar scores, macrosomia, and NTDs are more frequent in infants of obese mothers than in infants of normal-weight mothers (23,64). Infants born to obese women are also at risk of future obesity (23,74). Both obesity and inadequate weight gain during pregnancy have negative effects on initiation and continuation of breastfeeding (42).

6.2.3 Folic Acid

Multiple studies have demonstrated that periconceptional folic acid supplementation, i.e., supplementation prior to conception and during the first trimester, significantly

reduces the occurrence of NTDs in high-risk patients and low-risk primigravidas (14,46,48,51,73). The current recommendation of 400 μg/d of folic acid prior to conception decreases the incidence of NTDs by 50 to 70% (8). These lesions, which include spina bifida aperta, spina bifida cystica or myelomeningocele, anencephaly, and rachischisis, constitute a spectrum of one of the most common congenital malformations in the United States.

Folic acid is a synthetic precursor of naturally occurring folate. Folate is found in foods such as leafy green vegetables, legumes, citrus fruits, and melons. However, naturally occurring folate is less bioavailable than is folic acid and may have to be taken in quantities greater than the daily recommended dose of 400 μg (28,72). In addition, several studies reveal that the majority of women do not meet the RDA of folate from food (28,72). For example, in the study by Werler et al. (72), women consumed an average of 250 μg/d of folate from naturally occurring foods. Even if the potential increase in folic acid consumption from fortified food was added, using the 1998 USDA requirement of cereal grain fortification with folic acid (140 μg/g of wheat, corn, and rice flours; corn grits and meals; farina; rice; and macaroni and noodle products) (20), the intake would still be suboptimal at 380 μg/d of folate or folic acid (72). Moreover, because folate is less bioavailable, a larger intake is needed to provide the same protective benefit. Many foods are naturally rich in folate; see Table 6.2. Folate is water soluble and is easily destroyed by cooking. Raw fruits and vegetables are best, but cooking by microwave or steaming helps to preserve the folate content.

More than half of all pregnancies are unplanned (36,49). Therefore, the Center for Disease Control (CDC) recommends that *all* women of childbearing age receive a daily supplement of 400 to 600 μg folic acid to reduce the risk of NTDs (8). This recommendation and reasoning should be discussed at all routine wellness visits for women. Supplementation can be achieved with an over-the-counter women's daily multivitamin. Folic acid supplementation should begin at least 1 month prior to conception to ensure adequate levels at the time of neural tube closure (11). Some experts recommend routine doses of 600 to 800 μg folic acid daily to maximize the protective effect.

Many women are at an increased risk of having an infant with an NTD because of their own past medical history or family history. See Table 6.4 for a list of additional supplementation advised for women with histories indicating an elevated risk of NTDs. Women with Type 1 diabetes mellitus or a seizure disorder who are on antiepileptic drugs, or who have conditions that require folic acid antagonist medications should take an increased amount of folic acid daily. Women with a previously affected child or a personal or family history of NTD should take 4 to 5 mg/d of folic acid (43).

Folic acid supplementation may also reduce the risks of preterm delivery, low birth weight, and fetal growth retardation (8,61), as well as reduce the risks of major congenital malformations such as heart defects (12,14,61,63), urinary tract abnormalities (12), oral facial clefts (13,27,62,70), limb defects (63), and pyloric stenosis (26). Future research may uncover additional fetal developmental deformations whose incidence may also be reduced by folic acid supplementation.

TABLE 6.4
Folate Supplementation for Women of Childbearing Age

Maternal History	Folic Acid Supplement
Healthy	0.4 mg
Insulin-dependent diabetes Type 1	1 mg
On folic acid antagonists (aminopterin, methotrexate)	1 mg
Seizure disorder on medications (valproate or carbamazepine)	0.4–5 mg
Previous child with NTD	4 mg
Personal history of NTD	4 mg
1st, 2nd, or 3rd degree relative with NTD	4 mg

Note: NTD = neural tube defect.

Source: From Locksmith, G.J., & Duff, P. *Obstet. Gynecol. 91:* 1027–1034, 1998.

6.2.4 Calcium

Calcium is an important nutrient that should be discussed at all routine wellness visits for women. Data from the USDA suggest that the average daily calcium intake by women aged 20 to 29 years is 778 mg and by women 30 to 50 years is 719 mg, amounts far short of the recommended 1000 mg/day for women over the age of 18. Dairy products, green leafy vegetables, fish with bones, tofu, and many other foods (see Table 6.2) are good calcium sources in the diet. Calcium fortification of many common foods is increasing. A woman's daily calcium intake should be estimated and, if necessary, supplemented so that intake will approach the 1000 mg/d recommendation. Women under 25 years of age, who have not yet attained peak bone mass, should be counseled about the benefits of calcium and weight-bearing activities in maximizing bone density.

6.2.5 Iron

Iron deficiency is the most common nutritional deficiency in the world (44), with an estimated 90% of women not consuming adequate amounts. Anemia is a very frequent maternal complication during pregnancy, affecting about half of all U.S. gestations. During their reproductive years, women are at an increased risk of iron deficiency and iron deficiency anemia due to menstruation blood loss. Menstrual losses can account for a loss of 20 to 40 mg/month of iron. Even though the body recycles iron well, additional iron needs to be provided via the diet or by supplementation.

Iron deficiency anemia is the most commonly known sequel of iron deficiency. However, even early iron deficiency that has not yet led to anemia can cause a variety of problems because of the role played by iron in many proteins, enzymes, and cofactors. Symptoms and signs can include fatigue, irritability, exercise or work intolerance, and impaired motor and mental functioning. Iron deficiency (without anemia) in adolescent females has been associated with decreased learning ability and memory (5). Women with dietary restrictions such as vegetarianism are at par-

TABLE 6.5
Food Sources Rich in Iron

- Fortified cereals
- Brown rice
- Enriched and whole-grain breads
- Liver and lean meats
- Shellfish
- Dark leafy green vegetables
- Cooked dry beans, peas, lentils
- Apricots
- Prunes

ticular risk of iron deficiency. The RDA for iron in women ages 11 to 50 is 15 mg/d. Iron-rich foods are listed in Table 6.5. Routine iron supplementation can be provided with a once-daily over-the-counter women's multivitamin-mineral supplement.

6.3 NUTRITIONAL RECOMMENDATIONS FOR PREGNANCY

Pregnancy is a time when maternal anatomy and physiology change significantly to provide support for the developing fetus. From cell division to expansion of body fluids and organ size, all of these processes require more energy, vitamins, and water than in the nonpregnant woman. This section reviews information regarding caloric, weight gain, protein, vitamin, and mineral requirements, as well as nutritional safety. In general, U.S. women who are pregnant are unlikely to be deficient in nutrients other than folic acid and iron. The current recommended DRIs are listed in Table 6.1.

6.3.1 Calories

To meet the increased nutrient needs of pregnancy, the healthy woman will increase her energy intake by increasing her food and supplement intake. See Table 6.6 for recommended daily food servings for pregnant and lactating women. In addition to the pregravid baseline energy needs, energy requirements are greatest between 10 weeks and 30 weeks of gestation, when a substantial proportion of maternal fat is deposited for third-trimester fetal growth and to support lactation (65). The estimated additional energy need approximates 300 kcal/d for a woman of average activity level (39). The additional calories are needed to support placental and fetal growth and to enhance maternal energy stores. To avoid excessive weight gain, the additional calories should be thoughtfully met with balanced additions to the diet.

6.3.2 Weight Gain

Prenatal care visits with a health care provider help ensure a healthy pregnancy outcome for mother and baby. Monitoring weight gain at these visits provides an

TABLE 6.6
Recommended Daily Food Servings for Pregnant and Lactating Women

Foods	Daily Servings
Fruits	2–4
Vegetables	3–5
Whole grains, enriched breads, cereals	6–11
Dairy products	3–4
Meat, fish, poultry, eggs, nuts, beans, peas	3–4
Fats and sweets	Eat sparingly
Alcohol	Avoid

Sources: From *Healthy Eating During Pregnancy,* International Food Information Council Foundation (January 2003). Adapted from *Eating for Two,* March of Dimes (2002), and the *Dietary Guidelines for Americans,* Fifth Edition, U.S. Department of Agriculture and the U.S. Department of Health and Human Services (2004).

opportunity to evaluate eating habits and routines. A woman within normal range for BMI will conceive more easily and is likely to have fewer pregnancy and delivery complications than a woman with an abnormal BMI. Obese women have higher rates of hypertension and gestational diabetes, and their deliveries are more likely to require induction or a cesarean section. In addition, obese women have more infants born with NTDs (64) and have more problems initiating lactation after delivery (29,42).

Guidelines for weight gain based on prepregnancy age, weight, height, BMI, and activity level were published by the Institute of Medicine (IOM) in 1990 (see Table 6.7). This information was compiled with the goal of delivering a healthy 3- to 4-kg infant, by balancing optimal fetal growth with a minimum of labor and delivery risks and of postpartum weight retention. These recommendations were reevaluated in 1997 by the Department of Health and Human Services Maternal and Child Health Bureau. Its review concluded that a formal revision of these guidelines was not yet warranted. The work group made the following recommendations, however:

1. The rate of weight gain as well as total weight gain should be assessed during all three trimesters of pregnancy (see Table 6.8 for recommended weight gain by trimester).
2. Healthy eating habits should be promoted, and specific strategies should be provided to help women stay within the weight gain range.

TABLE 6.7
Recommended Maternal Weight Gain/Rate of Gain During Pregnancy

Prepregnancy State (BMI)	Body Mass Index (BMI)	Gain (kg)	Gain (lb)	Rate of Gain Trimester 2 and 3 per Month	
				kg	lb
Underweight (<19.8)	<19.8	12.5–18	28–40	2.3	5
Normal (19.8–26)	19.8–25	11.5–16	25–35	1.8	4
Overweight (26–29)	26–29	7–11.5	15–25	1.2	2.6
Obese (>29)	>29	>7	>15	0.9	2
Twin	Any BMI	16–20	35–45		
Triplet	Any BMI	23	50		

Sources: From *Healthy Eating During Pregnancy,* International Food Information Council Foundation (January 2003), Food and Nutrition Board, Institute of Medicine; *Nutrition During Pregnancy,* Washington, DC: National Academy Press (1990).

TABLE 6.8
Recommended Weight Gain by Pregnancy Trimester

Trimester	Weight Gain
1	2–4 lb total
2	1/2–1 lb/week
3	1.2 lb/week

Source: From *Nutrition During Pregnancy,* Food and Nutrition Board, Institute of Medicine, Washington, DC: National Academy Press (1990).

3. Adolescents less than 2 years postmenarche and African American women should be advised to stay within the IOM-recommended BMI-specific weight range, discouraging weight gain at the upper end of the range or restricting weight gain altogether (68).

In a recent systematic review of fetal and maternal outcome studies, pregnancy weight gain within the IOM's recommended ranges was shown to lead to the best outcome for both mothers and infants. Regrettably, it was also determined that weight gain in most pregnant women was not within the IOM's recommendations (1).

In general, the lower the prepregnancy BMI, the greater the weight gain to be encouraged so as to build maternal fat stores for pregnancy and lactation. The reason is that women with a low BMI are more likely to have infants with lower birth weights. Smaller weight gains are recommended for women with elevated BMIs to minimize further deposition of adipose tissue, while still providing for an optimal fetal environment.

The pattern of weight gain during pregnancy is also proving to be of importance. Several studies suggest that there are crucial periods in pregnancy when weight gain

has the greatest effect on infant birth weight. The pattern of weight gain has implications for the mother as well. In one small study, mothers who gained excessively in the first 20 weeks of pregnancy had higher postpartum weight retention, irrespective of their BMIs (50). Weight gain during the first 3 months should be only 2 to 4 lb. In the second and third trimesters, a weight gain of 1/2 to 1 lb/week is normal due to the rapid growth of the fetus during that time. Low gestational weight gain is associated with many fetal problems, including intrauterine growth restriction, low birth weight, and increased risks of perinatal morbidity and mortality. High gestational weight gain is associated with fetal macrosomia, the need for a cesarean section due to cephalopelvic disproportion, and postpartum weight retention (1).

6.3.3 Folic Acid

Folic acid supplementation decreases the risk of NTDs and possibly of other congenital anomalies. Ideally, supplementation with folic acid should begin in the preconceptual period, as the neural tube closes between 17 d and 26 d after conception. The routine recommended daily dose of folic acid supplementation is 400 μg/d, to start at least 4 weeks prior to conception (see Table 6.4). Higher doses of folic acid are sometimes recommended. Women known to be at increased risk of having an infant with NTDs should take up to 4 to 5 mg/d of folic acid. Supplementation with folic acid should continue at least through the first trimester of pregnancy.

6.3.4 Calcium

Pregnancy and lactation are periods of high calcium need. The mother's body, by increasing bone calcium turnover and increasing calcium absorption from the gastrointestinal tract, can adapt to meet maternal and fetal needs without requiring an increase in calcium intake (43,55). Maternal bone mineral turnover increases throughout pregnancy, thereby facilitating increased calcium transfer across the placenta with increasing gestational age, particularly in the third trimester. There is no evidence to suggest that these changes reflect insufficient calcium intake or can be prevented with an increase in dietary calcium (56). No additional calcium supplementation is required, provided the woman is consuming the recommended 1000 mg/d. Some studies suggest, however, that only 6% of women of childbearing age report consuming the recommended daily amount of calcium from the food they eat and other sources. Women who do not eat dairy products or who have other dietary restrictions will have difficulty reaching this recommendation without supplementation. Calcium-rich foods are listed in Table 6.2.

The role that calcium may play with respect to prevention and treatment of gestational hypertension, preeclampsia, and eclampsia is currently unclear (59). While some studies suggest a benefit, others have not shown that calcium supplementation minimizes the incidence of these conditions. A possible explanation is that calcium supplementation benefits only women whose diets are low in calcium. Presently evidence does not support routine calcium supplementation of all pregnant women. However, additional dietary calcium may benefit pregnant teens, women with low calcium intake, and those at high risk of pregnancy-induced hypertension.

6.3.5 Iron

During pregnancy, iron requirements are significantly elevated. However, iron intake and stores are inadequate in a large number of women, even in developed countries. Many women enter into pregnancy with a low iron endowment due to poor dietary intake, closely spaced pregnancies, or menstrual losses. Because maternal blood volume increases as much as 35 to 40% in pregnancy, the typical diet cannot meet iron needs, and routine iron supplementation is recommended. Iron intake during pregnancy should be 30 mg/d (36a) and should start in the first trimester.

A well-balanced diet that contains meat, fish, or poultry, which contain heme iron, can provide 12 to 14 mg/d of iron. Non-heme iron, found in whole grains and produce, is another source. Non-heme iron is more readily absorbed in the presence of vitamin C, but its absorption may be decreased by other food components such as calcium in dairy products, oxalic acid in spinach, phosphates in milk and egg whites, phytates in beans and other vegetables, and tannins in tea. Iron-rich foods are listed in Table 6.5. Iron supplements are best absorbed and tolerated when taken with meals. In the face of documented maternal anemia (hemoglobin <11.0), the intake should be 60 to 120 mg/d of elemental iron.

Response to supplementation, with an increase in hemoglobin and reticulocyte count, can be documented within 1 to 2 weeks of starting iron-replacement therapy. Even in the absence of anemia, routine iron supplementation for all women should begin by week 12 of gestation.

6.4 DIETARY ENVIRONMENTAL HAZARDS

6.4.1 Fish and Mercury Contamination

Environmental contamination of fish with methylmercury is one of the main concerns with seafood intake during pregnancy. While virtually all fish contain some trace amounts of methylmercury, long-living predatory fish such as shark, swordfish, tilefish, and king mackerel contain the most. These fish should be avoided in pregnancy (21). Tuna does not contain as much mercury as the predatory fish, but on average it has more than cod, haddock, and salmon. Tuna intake should be limited to no more than two tuna steaks or four medium-sized cans of tuna per week. Other fish should be limited to an average of 12 oz/week of cooked fish (about two meals) to minimize the influence the mercury could have on the developing nervous system of the fetus. Local advisory boards should be consulted about the safety of fish caught locally in rivers and streams. Find up-to-date information on-line at http://www.foodsafety.gov.

6.4.2 Harmful Bacteria

6.4.2.1 Salmonella

Avoidance of uncooked or undercooked eggs and raw meat, poultry, fish, and shellfish is recommended during pregnancy due to the potential for illness secondary to

bacterial contamination with Salmonella. Thoroughly cooking and appropriate handling of these foods should eliminate any cause for concern.

6.4.2.2 Listeria

Pregnant women are advised against eating pate and soft or mold-ripened cheeses such as Brie, Camembert, and blue cheeses due to the risk of Listeria. Thorough cooking of these cheeses should kill Listeria, so eating them after cooking should be safe. Hard cheeses, such as cheddar, and processed cheeses are considered safe.

6.4.3 Other Dietary Hazards

6.4.3.1 Alcohol

The teratogenic effects of alcohol on the developing fetus have been recognized for centuries. Maternal alcohol abuse has been associated with an increased risk of spontaneous abortions, increased infant mortality, and intrauterine growth restriction. Birth defects are very common in infants born to women who are heavy drinkers (defined as five to six drinks per day), with minor or major congenital malformations occurring at about three times the rate of infants born to women who abstain from alcohol.

A spectrum of findings has been documented in infants born to women who drink alcohol, from fetal alcohol effects (FAEs) to the more commonly known fetal alcohol syndrome (FAS). FAS was first described in 1973 as a constellation of abnormalities common to offspring of chronic alcoholic women (10). FAS is at the more severe end of the spectrum, with problems in the infant such as intrauterine and postnatal growth retardation, cranio-facial dysmorphology, and central nervous system effects. The estimated U.S. incidence of FAS is 2.8 to 4.8 per 1000 live births.

FAE describes less severe alcohol-related effects associated with wide patterns of drinking (9). Findings include lower birth weights and impaired brain growth, as well as changes in child behaviors such as a higher level of activity, greater difficulty in following instructions, temper tantrums, and eating problems (9,19). Slower cognitive processing and mental developmental delays are reported among infants exposed to 0.5 oz/d of alcohol (37).

The most deleterious effects of alcohol occur during the first trimester of pregnancy, the period of organogenesis, when structural and functional abnormalities occur. Exposure to alcohol later in pregnancy contributes to growth restriction. Abstinence from alcoholic beverages is recommended during the preconceptional period, as well as during pregnancy, as no safe level of alcohol intake has been established.

6.4.3.2 Caffeine

The effect of caffeine on pregnancy has been well studied over the past two decades. Despite early suggestions that caffeine was related to an increased rate of miscarriage, birth defects, and low birth weight, recent studies have not shown moderate caffeine intake to be a problem. The Food and Drug Administration (FDA) has evaluated the

evidence and recommends that consumption of moderate amounts of caffeine is acceptable. But, as with other dietary habits, pregnant women should consume caffeine in moderation <300 mg per day, i.e., the equivalent of 1–2 cups of coffee (32).

6.4.3.3 Herbs

The use of complementary and alternative medicine, an umbrella term used to describe a number of therapies that fall outside conventional allopathic medicine, has increased dramatically in the United States. Herbal medicine can be defined as the use of plants and plant remedies in the treatment and prevention of disease. Many Americans believe that herbal supplements, other than standard vitamins and minerals, are generally good for their health and are safe because they are found in nature. Current U.S. law defines herbal products as dietary supplements, and, therefore, they are not subject to FDA regulation. Manufacturers of herbal products are not required to document safety or effectiveness. In addition, no quality standards have been established, and individual products may vary or be contaminated. Few studies have been conducted that have tested the use of herbal preparations in pregnant women. Pregnancy-related symptoms should be discussed with the woman's physician. Neither she nor her physician should assume that it is safe to take an herbal remedy. Because the use of alternative therapies has become increasingly popular, it is important for health care providers to initiate conversations with patients about their use of herbal remedies.

6.4.3.4 Low-Calorie Sweeteners

There are multiple low-calorie sweeteners on the market, such as aspartame, saccharin, acesulfame K, sucralose, and neotame. The FDA has approved all of these for use in pregnant women, and studies have shown no reproductive risk to offspring (34). As with all dietary recommendations, use in moderation is prudent.

6.4.3.5 Peanuts

Peanuts and peanut butter are excellent sources of folate and protein and are still considered to be safe for women without personal or family histories of peanut allergy. There is scant literature to suggest allergic sensitization of infants by women who consume peanut products while pregnant (22).

6.5 NUTRITIONAL CONSIDERATIONS IN THE MANAGEMENT OF LACTATION

Human milk is the gold standard of infant nutrition. In order to produce a premium-quality product such as breast milk, it is often assumed that the diet consumed by a breastfeeding mother has to be of high quality and nutritional value. Famine, war, and natural disasters have shown that even when nutritional staples are sparse, breastfeeding mothers continue to provide excellent nutrition for their infants, often at the expense of depleting their own stores (3,16). Nevertheless, promotion of optimal

TABLE 6.9
Supplementation Recommendations for Women with Restricted Eating Patterns

Condition	Description	Supplement Recommended
Caloric restriction	<1800 kcal/d	Multivitamin/mineral supplement
Complete vegetarianism	Avoidance of all animal products including meat, fish, dairy, eggs	Increase B_{12}-containing foods B_{12} supplement (2.6 μg/d)
Dairy avoidance	Avoidance of milk, cheese, or calcium-rich foods	Increase calcium-rich foods Supplement elemental calcium
Vitamin D avoidance Limited sun exposure	Dark-skinned individuals Sunlight restrictive clothing or headcoverings	Vitamin D (10 μg/d maternal supplement) Infant supplementation with vitamin D (200 IU/d)

maternal nutrition and energy intake should continue to be the goal in the transition from pregnancy to the postpartum period. Energy and nutrients are needed to promote lactation, as well as to provide for the continued health and healing of the mother.

Pregnancy is often an impetus for health behavior change. Many women report making healthier lifestyle and dietary decisions during pregnancy than they would otherwise (4). Women often choose to breastfeed because of the numerous health benefits for the infant. The decision to breastfeed may contribute to maintaining a healthier maternal lifestyle. It is a prime opportunity for health care personnel to recognize and encourage the continuation of positive behavior changes.

Lactation is an energy-expensive process, estimated at 750 kcal/d. Breast milk production directly affects short- and long-term maternal nutritional status and body composition. Lactating women have increased demands for energy and nutrients above both the prepregnancy and pregnancy requirements. The metabolic adjustments that redirect nutrient utilization from maternal needs to milk synthesis and secretion involve nearly every maternal organ system. In general, the amounts of nutrients the mother secretes into milk are directly related to the extent and duration of lactation. Fortunately, lactating women who meet the RDA for energy are likely to meet the RDA for all nutrients except calcium and zinc (see Table 6.1). If nutrient intake is lower than the total demand for both maternal maintenance needs and milk production, the mother's body will mobilize available nutrients from body tissues during lactation. At intakes less than 2700 kcal/d, nutrient density may be low for calcium, magnesium, zinc, vitamin B_6, and folate (35). Specific recommendations for women with restricted eating patterns are noted in Table 6.9.

6.5.1 Nutritional Requirements

To establish nutritional requirements for the lactating mother, it is necessary to take into consideration the preexisting health status of the woman and the volume and composition of her breast milk. Women often express concern about the quality of their breast milk because they do not eat a well-balanced diet. Studies of breastfeed-

ing women in the United States have demonstrated that, overall, the women were well nourished. However, there have been only a limited number of studies, and their subjects were not of diverse socioeconomic backgrounds. As the number of women who choose to breastfeed their infants rises, studies may reveal more nutritional inadequacies. If one assumes that lactating and nonlactating women have similar diets, it is likely the intake of calcium, folate, vitamin B_6, magnesium, and zinc in both groups are insufficient. These nutrients are found in a wide variety of foods eaten by most women daily (see Table 6.2).

Women are often concerned that their volume of milk is directly related to their own food intake. Milk production, however, most closely correlates with the frequency of feeding and the amount of milk that is regularly removed from the breast by the nursing infant or breast pump (54). Women are also concerned that certain foods will be transferred to the infant via breast milk and will cause adverse reactions. There is no evidence that any particular foods should be limited in the maternal diet. Observation of the infant and recall of maternal dietary intake may be necessary if concerns regarding the infant arise.

Human milk is a unique dynamic fluid, made to order as the infant grows. For example, the milk for the premature infant on day 3 is higher in total calories, lipid, protein, sodium, and chloride and lower in lactose than milk for a term infant of the same age. However, even with the adaptive changes in composition, human milk alone cannot sustain the very small premature infant. The composition of human milk nevertheless is remarkably constant as far as fat, protein, vitamins, minerals, and trace elements are concerned. Nursing mothers should be encouraged to eat a well-balanced diet, keeping in mind the DRIs and Nutritional Requirements for Americans with a few additions (see Table 6.1 and Table 6.6). Continuation during lactation of prenatal vitamins or a multivitamin supplement is recommended.

6.5.2 Calories

Lactation is supported in part by mobilization of maternal tissue stores accumulated prior to and during the pregnancy. The additional energy comes from maternal dietary intake. In general, caloric intake should be at least 1800 kcal/d. A few sources recommend as much as 2700 kcal/day (24,35). Well-nourished women are able to mobilize some energy from tissue stores; however, an addition of 400 to 500 kcal/d to the average woman's prepregnant diet is recommended. If women can eat a variety of foods to meet their hunger and drink to their thirst, counting calories is not necessary (41). Recommended daily food servings are listed in Table 6.6.

6.5.3 Fluids

There is also an increased need for free water during lactation. Women should drink enough fluids to prevent thirst. Excess fluid consumption has been associated with decreased milk production in some women (18). New mothers should adopt the practice of having something to drink each time they nurse their infant. Contrary to some cultural beliefs, a woman does not need to drink milk to make abundant breast milk. In fact, some infants whose mothers drink an excessive or even a routine

amount of cow's milk may develop milk protein intolerance. Cow's milk protein can pass through the breast milk to the infant, causing symptoms such as intestinal gas, fussiness, and occasionally occult or visible blood in the stool. Cutting back or eliminating dairy products from the maternal diet may be necessary. Intake of beverages containing caffeine should be in moderation.

6.5.4 Maternal Nutrition and Milk Supply

Concern over insufficient milk volume, real or perceived, is the most common reason women cite for discontinuing breastfeeding. Very few women cannot lactate due to anatomic or hormonal abnormalities. Therefore, lactogenesis progresses normally in the majority of mothers, and it is secondary lactational management problems that interfere with milk supply. The majority of women can provide an abundant supply of breast milk if breastfeeding practices are optimal. While good maternal nutrition and rest are important, milk removal from the breast is absolutely essential to maintain lactation. Early, frequent, and thorough milk removal from the breasts ensures a growing and stable breast milk supply.

To achieve this, breastfeeding should begin within 1 h of delivery. Mothers should strive for 8 to 12 feedings at the breast daily. In the event the infant is premature or ill and unable to breastfeed, the mother should begin to express milk from the breasts. This can be done by hand or with a variety of manual or electric breast pumps. Initially, milk expression should occur at least every 3 h. Once maternal supply is abundant, one study suggests that pumping at least 5 times per day for a total of more than 100 min is necessary to maintain significant milk production (30). It is essential that hospital policies support these practices.

The most common cause of insufficient breast milk is mismanagement. Management problems include inadequate opportunities to breastfeed, such as maternal–infant separation, fatigue, inadequate breastfeeding sessions due to insufficient latch, inappropriate supplementation with formula, or a sleepy infant. Recognition of the milk removal/production principle helps staff and families realize the importance of milk removal for maintaining adequate yield. Families should be educated on breastfeeding well in advance of arrival of the infant.

When there is a concern about milk supply, the assistance of a lactation consultant is invaluable. Problems can often be remedied by observing feeding practices, by reassuring the mother, and by increasing milk removal by the nursing infant or by a breast pump. In some situations, galactagogues such as metoclopromide may provide assistance in increasing milk supply.

6.5.5 Weight Loss During Lactation

Most women who gain the recommended amount of weight during pregnancy can return to prepregnancy weight by 6 months after delivery (60). While studies are conflicting and the differences in weight loss are marginal, breastfeeding women appear to lose slightly more weight postpartum than do women who choose not to breastfeed. Maternal weight loss is greater in the first 12 months postpartum in breastfeeding mothers and most marked in the second 6 months (15). Calorie restric-

TABLE 6.10
Mothers at High Risk for Nutritional Deficiencies During Lactation

- Teen mothers
- Mothers of multiples
- Past or present history of dietary restriction
- Maternal weight less than 85% of recommended
- Suboptimal weight gain during pregnancy
- Economic deprivation
- Rapid weight loss while breastfeeding
- Pregnant while breastfeeding

Source: Adapted from American Dietetic Association (1996).

tion does not adversely affect milk production as long as caloric intake for the mother is in excess of 1500 kcal/d (7,58,67).

Many women wish to diet and focus on weight loss with or without exercise while breastfeeding. Several studies of short and long duration with diet and activity modification indicate that weight loss has no adverse effects on the mother, infant, or lactation (6,18,45,47). In most cases, a weight loss of 1 to 1.5 lb/week can be sustained during lactation without effect on breast milk supply or fat content. Regular exercise is beneficial for the mother, and moderate physical activity has not been shown to affect lactation. With vigorous activity, lactic acid in the breast milk increases rapidly, and infants may refuse to nurse. This can be remedied by breastfeeding prior to vigorous exercise and just after recovery from the exercise (17).

Mothers should be encouraged to lower intake of calories from fat and to increase physical activity, rather than choosing fad-diet regimens. The use of low-carbohydrate diets during lactation has not been studied. Theoretical concerns with respect to elevated plasma lipids, prolonged ketosis, reduced milk supply, and dietary deficiencies in micronutrients and fiber seem to make a low-carbohydrate intake undesirable.

Specific nutritional high-risk situations are noted in Table 6.10. Women who are underweight prior to pregnancy or who have low weight gain during pregnancy should increase their energy intake by 650 kcal/d for the first 6 months of lactation. Supplementation recommendations for women with restricted eating patterns are noted in Table 6.9.

6.5.6 Calcium

Lactation involves the continued mobilization of calcium from the maternal skeleton. Approximately 200 mg/d of calcium is secreted in breast milk. Significant, yet reversible changes in the maternal skeleton occur in the first 3 to 6 months of lactation and are then reversed during later lactation and within 3 months postweaning (56). According to Prentice, “On the strength of current evidence it appears that pregnancy and lactation are associated with physiological adaptive changes in mineral metabolism

that are independent of maternal mineral supply within the range of normal dietary intakes. These processes provide the minerals necessary for fetal growth and breast milk production without requiring an increase in maternal dietary intake or compromising maternal bone health in the long term" (57). The CDC calcium recommendation is therefore not increased during lactation but remains at 1200 mg/d (55).

Achieving this level of calcium intake may be difficult for women who have dietary limitations. Calcium supplementation may be particularly important to breastfeeding mothers under the age of 25 whose own bone mass is still increasing. Vitamin D supplementation should be considered for those at risk for vitamin D deficiency. Rebuilding and maintaining maternal calcium stores, especially in light of future pregnancies and increased calcium demand, is important to protect against the risk of osteoporosis in the future.

6.5.7 Iron

The recommended amount of iron intake during lactation is the same as before pregnancy, i.e., 15 mg/d. Maternal history of anemia or excessive blood loss at delivery would increase the need for maternal supplementation with iron. Approximately 14% of maternal iron stores are lost through breast milk in the course of 6 months of breastfeeding. This represents half of what would be lost via menses. Supplementation may be needed if the mother is still breastfeeding when menstruation resumes.

6.5.8 Other Nutritional Considerations

6.5.8.1 Alcohol

Excessive alcohol consumption during lactation should be avoided as significant amounts of alcohol are secreted into breast milk. If the amount and duration of alcohol consumption are limited, the effects on the infant are not considered to be harmful. Excess alcohol consumption may lead to decreased milk production and perhaps decreased intake due to alteration of milk taste. The immediate effects of excessive alcohol transfer on the infant may include drowsiness, irritability, or weak suck. Prolonged exposure could harm development and decrease linear growth (25). The occasional alcoholic beverage when consumed with food is generally compatible with breastfeeding. One ounce of alcohol (the amount in one serving of beer or wine or one mixed drink) is metabolized in the adult in 3 h. Mothers can generally return to breastfeeding when they are no longer feeling the effects of the alcohol. Chronic or excessive alcohol users should not breastfeed their infants.

6.5.8.2 Caffeine

Maternal consumption of caffeine in moderation during lactation is thought to be safe. Some mothers report a change in infant sleep or behavior patterns when caffeine is in their diet. However, the amount of caffeine that passes into breast milk is minimal, with a relative infant dose of less than 6% of the maternal dose (25). Caffeine rapidly enters breast milk, and the decay of caffeine in milk is similar to

plasma (66). Peak levels of caffeine are noted 60 to 120 min after ingestion. The half-life in adults is 4.9 h; the half-life in neonates is as high as 97.5 h (25). There is some evidence that chronic intake of caffeinated coffee may reduce the iron content of breast milk (52). It is recommended that breastfeeding women limit consumption of caffeine to the equivalent of 1 to 3 cups of coffee per day.

6.5.8.3 Peanuts

Peanuts and peanut butter are a readily available, convenient source of protein for breastfeeding mothers. Allergic sensitization to peanuts, however, is becoming increasingly common. Several studies have documented a relationship between peanut consumption by pregnant and breastfeeding mothers and the increased likelihood of allergic sensitization to peanuts by their child (31,71). Exposure to food allergens in breast milk originating from the maternal diet is thought to be responsible for occult sensitization. Families with a history of atopy and siblings with peanut allergy are at highest risk (31). Currently, there is no recommendation regarding peanut product avoidance during pregnancy and lactation. However, it may be prudent that mothers with personal or family history of peanut sensitivity or atopy refrain from including peanut products in their diets (22).

REFERENCES

1. Abrams, B, Altman, S L, & Pickett, K E (2000) Pregnancy weight gain: Still controversial. *Am. J. Clin. Nutr. 71:* 1233S–1241S.
2. Arias, E, MacDorman, M F, Strobino, D M, & Guyer, B (2003) Annual summary of vital statistics. *Pediatrics 112:* 1215–1230.
3. Bates, C J, & Prentice, A (1994) Breast milk as a source of vitamins, essential minerals and trace elements. *Pharmacology and Therapeutics* 62: 193–220.
4. Bronner, Y L, & Auerbach, K G. (2005) Maternal nutrition during lactation. In: *Breastfeeding and human lactation,* 3rd ed., J Riordan, Ed. Sudbury: Jones and Barlett, pp. 437–457.
5. Bruner, A, Joffe, A, Duggan, A K, Casella, J F, & Brandt, J (1996) Randomised study of cognitive effects of iron supplementation in non-anemic iron deficient adolescent girls. *Lancet 348:* 992–996.
6. Butte, N F (2000) Dieting and exercise in overweight, lactating women. *NEJM 342:* 502.
7. Butte, N F, Garza, C, Stuff, J E, Smith, E O, & Nichols, B L (1984) Effect of maternal diet and body composition on lactational performance. *Am. J. Clin. Nutr. 39:* 296–306.
8. Centers for Disease Control and Prevention. (1992) Recommendations for use of folic acid to reduce the numbers of spina bifida cases and other neural tube defects.
9. Chiriboga, C A (2003) Fetal alcohol and drug effects. *Neurologist 9:* 267–279.
10. Clarren, S K, & Smith, D W (1978) The fetal alcohol syndrome. *NEJM 298:* 1063–1067.
11. Czeizel, A E (1995) Nutritional supplementation and prevention of congenital abnormalities. *Curr. Opin. Obstet. Gynecol. 7:* 88–94.
12. Czeizel, A E (1996) Reduction of urinary tract and cardiovascular defects by preconceptional multivitamin supplementation. *Am. J. Med. Genet. 62:* 179–183.

13. Czeizel, A E (2000) Primary prevention of neural-tube defects and some other major congenital abnormalities: Recommendations for the appropriate use of folic acid during pregnancy. *Paediatric Drugs 2:* 437–449.
14. Czeizel, A E, & Dudas, I (1993) Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *NEJM 327:* 1832–1835.
15. Dewey, K G (1993) Maternal weight-loss patterns during prolonged lactation. *Am. J. Clin. Nutr. 58:* 162–166.
16. Dewey, K G (1997) Energy and protein requirements during lactation. *Annu. Rev. Nutr. 17:* 19–36.
17. Dewey, K G, & Lovelady, C A (1993) Exercise and breastfeeding: A different experience. *Pediatrics 91:* 514–515.
18. Dusdieker, L B, Hemingway, D L, and Stumbo, P J (1994) Is milk production impaired by dieting during lactation? *Am. J. Clin. Nutr. 59:* 833–840.
19. Faden, V B, & Graubard, B I (2000) Maternal substance use during pregnancy and developmental outcome at age three. *J. Subst. Abuse 12:* 329–340.
20. Food and Drug Administration. Department of Health and Human Services. (1996) Amendment of standards of identity for enriched grain products to require addition of folic acid. *Federal Register: 61.*
21. Food and Drug Administration. Environmental Protection Agency. Department of Health and Human Services. (2004) What you need to know about mercury in fish and shellfish. Advice for women who might become pregnant, women who are pregnant, nursing mothers, young children. http://vm.cfsan.fda.gov/~dms/admehg3.html.
22. Frank, L, Marian, A, Visser, M, Weinberg, E, & Potter, P C (1999) Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children. *Pediatric Allergy & Immunology 10:* 27–32.
23. Galtier-Dereure, F, Boegner, C, & Bringer, J (2000) Obesity and pregnancy: Complications and cost. *Am. J. Clin. Nutr. 71:* 1242S–1248S.
24. Gunderson, E P (2003) Nutrition during pregnancy for the physically active woman. *Clinical Obstetrics and Gynecology 46:* 390–402.
25. Hale, T (2004) *Medications and mothers' milk: A manual of lactational pharmacology.* Amarillo, TX: Pharmasoft Publishing.
26. Hall, J, & Solehdin, F (1998) Folic acid for the prevention of congenital anomalies. *Eur. J. Pediatr. 157:* 445–450.
27. Hayes, C, Werler, M M, Willett, W C, & Mitchell, A A (1996) Case-control study of periconceptional folic acid supplementation and oral clefts. *Am. J. Epidemiol. 143:* 1229–1234.
28. Hendricks, K (1998) Diet, activity, and other health-related behaviors in college-age women. *Nutrition Reviews 56:* 65–75.
29. Hilson, J A, Rasmussen, K M, & Kjolhede, C L (1997) Maternal obesity and breastfeeding success in a rural population of white women. *Am. J. Clin. Nutr. 66:* 1371–1378.
30. Hopkinson, J M, Schanler, R J, & Garza, C (1988) Milk production by mothers of premature infants. *Pediatrics 81:* 815–820.
31. Hourihane, J O, Dean, T P, & Warner, J O (1996) Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: Results of a questionnaire survey, skin prick testing, and food challenges. *BMJ 313:* 518–521.
32. International Food Information Council Foundation (2002) Caffeine and women's health. http://www.ific.org/publications/brochures/caffwomenbroch.cfm.

33. International Food Information Council Foundation (2002) Dietary reference intakes: An update. http://www.ific.org/publications/other/driupdateom.cfm.
34. International Food Information Council Foundation (2004) Sugars & low-calorie sweeteners. http://www.ific.org/nutrition/sugars/index.cfm.
35. Institute of Medicine. Subcommittee on nutrition during lactation. (1991) *Nutrition during lactation*. M Hamosh, Ed. Washington, DC: National Academy Press.
36. Institute of Medicine. Committee on unintended pregnancies (1995) Best intentions: Unintended pregnancy and the well-being of children and families. S S Brown and L Eisenberg, Eds. Washington, DC: National Academy Press.
36a. Institute of Medicine. Food and Nutrition Board (1993) *Iron deficiency amenia: Recommended guidelines for the prevention, detection, and management among U.S. children and women of childbearing age*. R Earl and C E Woteki, Eds. Washington, DC: National Academy Press.
37. Jacobson, J L, Jacobson, S W, & Sokol, R J (1993) Teratogenic effects of alcohol on infant development. *Alcohol Clin. Exp. Res. 17:* 174–183w.
38. Kendrick, J M (2004) Preconception care of women with diabetes. *J. Perinatal Neonatal Nursing 18:* 14–27.
39. King, J C (2000) Physiology of pregnancy and nutrient metabolism. *Am. J. Clin. Nutr. 71:* 1218S–1225S.
40. Korenbrot, C C, Steinberg, A, Bender, C, & Newberry, S (2002) Preconception care: A systematic review. *Maternal and Child Health Journal 6:* 75–88.
41. Labbok, M H (2001) Effects of breastfeeding on the mother. *Pediatric Clinics of North America 48:* 143–158.
42. Li, R, Jewell, S, & Grummer-Strawn, L (2003) Maternal obesity and breast-feeding practices. *Am. J. Clin. Nutr. 77:* 931–936.
43. Locksmith, G J, & Duff, P (1998) Preventing neural tube defects: The importance of periconeptional folic acid supplements. *Obstet. Gynecol. 91:* 1027–1034.
44. Looker, A, Dallman, P, Carroll, M, Gunter, E, & Johnson, C (1997) Prevalence of iron deficiency in the United States. *JAMA 277:* 973–976.
45. Lovelady, C A, Garner, K E, Moreno, K L, & Williams, J P (2000) The effect of weight loss in overweight, lactating women on the growth of their infants. *NEJM 342:* 449.
46. Lumley, J, Watson, L, Watson, M, & Bower, C (2005) Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database of Systematic Reviews*. 2. Amendments of 4/29/01 and 5/31/01.
47. McCrory, M A, Nommsen-Rivers, L A, Mole, P A, Lonnerdal, B, & Dewey, K G (1999) Randomized trial of the short-term effects of dieting compared with dieting plus aerobic exercise on lactation performance. *Am. J. Clin. Nutr. 69:* 959–967.
48. Milunsky, A, Jick, H, Jick, S S, Bruell, C L, MacLaughlin, D S, Rothman, K J, & Willett, W (1989) Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *JAMA 262:* 2847–2852.
49. Moos, M K (2004) Preconceptional health promotion: Progress in changing a prevention paradigm. *J. Perinatal Neonatal Nursing 18:* 2–13.
50. Mucscati, S, Gray-Donald, K, & Koski, K (1996) Timing of weight gain during pregnancy: Promoting fetal growth and minimizing maternal weight retention. *Int. J. Obes. 20:* 526–532.
51. Mulinare, J, Cordero, J F, Erickson, J D, & Berry, R J (1988) Periconceptional use of multivitamins and the occurrence of neural tube defects. *JAMA 260:* 3141–3145.

52. Nehlig, A, & Debry, G (1994) Consequences on the newborn of chronic maternal consumption of coffee during gestation and lactation: A review. *J. Am. Coll. Nutr. 13:* 6–21.
53. National Research Council (1989) Recommended dietary allowances. Washington, DC: National Academy Press, Food and Nutrition Board.
54. Peaker, M, & Wilde, C J (1987) Milk secretion: Autocrine control. *News on Physiological Sciences 2:* 124–126.
55. Prentice, A (2000) Calcium in pregnancy and lactation. *Annu. Rev. Nutr. 20:* 249–272.
56. Prentice, A (2000) Maternal calcium metabolism and bone mineral status. *Am. J. Clin. Nutr. 71:* 1312S–1316S.
57. Prentice, A (2003) Micronutrients and the bone mineral content of the mother, fetus and newborn. *J. Nutr.* 133: 1693S–1699S.
58. Prentice, A M, Paul, A A, Prentice, A, Black, A E, Cole, T J, & Whitehead, R G (1986) Cross-cultural differences in lactational performance. In: *Maternal and environmental factors,* M Hamosh and A Goldman, Eds. New York: Plenum Press, pp. 13–44.
59. Ritchie, L D, & King, J C (2000) Dietary calcium and pregnancy-induced hypertension: Is there a relation? *Am. J. Clin. Nutr. 71:* 1371S–1374S.
60. Schauberger, C W, Rooney, B L, & Brimer, L M (1992) Factors that influence weight loss in the puerperium. *Obstet. Gynecol. 79:* 424–429.
61. Scholl, T O, & Johnson, C (2000) Folic acid: Influence on the outcome of pregnancy. *Am. J. Clin. Nutr. 71:* 1295S–1303S.
62. Shaw, G M, Lammer, E J, Wasserman, C R, O'Malley, C D, & Tolarova, M M (1995) Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet 346:* 393–396.
63. Shaw, G M, O'Malley, C D, Wasserman, C R, Tolarova, M M, & Lammer, E J (1995) Maternal periconceptional use of multiviatmins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. *Am. J. Med. Genet. 59:* 536–545.
64. Shaw, G M, Velie, E M, & Schaffer, D (1996) Risk of neural tube defect–affected pregnancies among obese women. *JAMA 275:* 1093–1096.
65. Sohlstrom, A, & Forsum, E (1995) Changes in adipose tissue volume and distribution during reproduction in Swedish women as assessed by magnetic resonance imaging. *Am. J. Clin. Nutr. 61:* 287–295.
66. Stavchansky, S, Combs, A, Sagraves, R, Delgado, M, & Joshi, A (1988) Pharmacokinetics of caffeine in breastmilk and plasma after single oral administration of caffeine to lactating mothers. *Biopharm. Drug Dispos. 9:* 285–299.
67. Strode, M A, Dewey, K G, & Lonnerdal, B (1986) Effects of short-term caloric restriction on lactational performance of well-nourished women. *Acta Paediatr. Scand. 75:* 222.
68. Suitor, C W, Paine, L, Prendergast, E A, Sofka, D, Schall, J, & Stubbs-Wynn, P E (1997) Maternal weight gain: A report of an expert work group. U.S. Department of Health and Human Services. Public Health Service. Health Resources and Services Administration.
69. Taylor, A (2003) ABC of subfertility: Extent of the problem. *BMJ 327:* 434–436.
70. Tolarova, M M, & Harris, J (1995) Reduced recurrence of orofacial clefts after periconceptional supplementation with high-dose folic acid and multivitamins. *Teratology 51:* 71–78.
71. Vadas, P, Wai, Y, Burks, W, & Perelman, B (2001) Detection of peanut allergens in breast milk of lactating women. *JAMA 285:* 1746–1748.

72. Werler, M M, Louik, C, & Mitchell, A A (1999) Achieving a public health recommendation for preventing neural tube defects with folic acid. *Am. J. Public Health 89:* 1637–1640.
73. Werler, M M, Shapiro, S, & Mitchell, A A (1993) Periconceptional folic acid exposure and risk of occurrent neural tube defects. *JAMA 269:* 1257–1261.
74. Whitaker, R (2004) Predicting preschooler obesity at birth: The role of maternal obesity in early pregnancy. *Pediatrics 114:* e29–36.
75. Wyn, R, Brown, E R, & Yu, H (1996) Women's use of preventive health services. In: Women's health: The commonwealth fund survey. M M Falik and K S Collins, Eds. Baltimore, MD: Johns Hopkins University Press, pp. 49–75.

7 Facilitating Patient Behavior Change in Clinical Nutritional Management

Richard K. Fleming, Carol Curtin, and Linda Bandini

CONTENTS

7.1 INTRODUCTION

Effective nutritional management is of critical importance in the treatment of patients with chronic conditions and diseases (5,6). However, for a great many patients, starting and sustaining new nutritional regimens at home and work requires a significant change in behavior, for which they need support. Patients must be able to accept clinician-recommended behavior change, understand what needs to be done differently, establish these changes in their daily lives, receive feedback on progress, and sustain the changes over time. Psychologists have long been concerned with the

challenges associated with initiating and sustaining behavior change and have been active in developing and testing approaches for increasing patient adherence to medical regimens (7,8). This chapter discusses behavioral challenges facing patients, as well as the role of clinicians, in clinical nutritional management; summarizes relevant psychological theory that emphasizes applied behavior analysis and social cognitive theory approaches; provides a selective review of research on simple and comprehensive behavioral interventions used to promote nutritional adherence; presents a practical, evidence-based model for promoting patient adherence; and identifies important areas for future research and practice.

It is beyond the scope of this chapter to address the unique nutritional management challenges associated with each disorder or disease covered in this volume. Accordingly, two illustrative areas will be addressed: obesity and cystic fibrosis. We believe that both the nutritional management challenges and the intervention approaches addressed by the body of research in these areas provide the foundation for how behavioral intervention may be applied more generally to other conditions.

7.2 BEHAVIORAL CHALLENGES: PATIENT ADHERENCE AND THE ROLE OF CLINICIANS IN NUTRITIONAL MANAGEMENT

Patience adherence to clinician-prescribed treatment regimens is a significant problem in the management of many chronic conditions and diseases (7,8). In this volume, Peebles and Hammer (28) describe the complex familial and psychosocial factors involved in the treatment of childhood obesity. Obesity presents a constellation of medical risks. Unchecked in childhood and adolescence, it can lead to Type 2 diabetes, heart disease, and other chronic conditions later in life. Obesity is also socially stigmatizing. Patients' (even children's) patterns of overeating often are entrenched firmly and resistant to change. Adding to the problem is the fact that the social environment perpetuates sedentary behavior and consumption of large portions and energy-dense foods.

Increasingly, clinicians and associates need to alert families to the potential for overweight and obesity in their children (e.g., through assessing body mass index on a routine basis) and to assist them in becoming better educated about sound nutritional practices. They will also need to be prepared to provide or refer families to skills-training programs that result in effective parental modeling and reinforcement at home. These skills are needed to promote the lifestyle changes in child eating and physical activity that are needed to combat the problem in the long term. Chapter 2 in this volume addresses adult obesity (36), an area in which the need for behavioral management is comparable, but where the opportunity to use cognitive behavioral intervention to improve patient self-control and self-management is greater.

Cystic fibrosis is a genetic disease that affects primarily the respiratory and pancreatic systems, resulting in recurrent pulmonary infections, pancreatic insufficiency, and fat malabsorption (41). Approximately 30,000 persons in the United States (1 in 2500 births) currently are affected (4). Treatment requires strict adherence to a complex daily nutritional regimen to ensure adequate caloric intake, along with

chest physiotherapy and vigorous exercise to remove sputum. Despite the serious consequences associated with not following this regimen, nonadherence has been estimated to be 50% in pediatric populations (22), a problem shared with treatment regimens for other conditions that are similarly complex and intensive (19). Interventions must address parent education, parenting skills, the child's level of emotional maturity and understanding, and the clarity and specificity of physician–family communication. Cystic fibrosis is just one case in which the immediacy of consequences associated with adherence and nonadherence affects behavior. For example, the relatively immediate relief of symptoms after taking antibiotics may reinforce adherence to that behavior. By contrast, outcomes that are more delayed, subtle, or incremental, e.g., maintenance of health status associated with taking prescribed vitamins on a daily basis, may not be sufficient to reinforce and maintain that behavior (4).

It is important to note that variables that influence nutritional adherence in these and other areas extend well beyond the patient's personal motivation or "will power" to change. For example, obesity is greatly influenced by the "pull" of environment, which more than ever encourages the consumption of convenient energy-dense foods, large portions, and sedentary behavior. The most recent expert recommendations for curbing this epidemic call for the development of health-promoting school policies and cultural norms, safe community environments, and programs that facilitate physical activity (25). Also called for are government legislative and regulatory policies that support the choice of healthy foods, as well as family education and training with respect to those choices. In other words, there is a public health need to change the environment so as to minimize obesity. Until these policies are adopted, patients suffering from obesity and other conditions must learn to succeed in their current environment, largely by changing their behavior. Encouragement and compassion will be needed from clinicians and associates.

Research suggests that physicians' attitudes about patients with obesity may contribute to a lack of intervention. In a survey of 620 primary care physicians, it was found that more than half viewed their obese patients as "awkward, unattractive, and noncompliant" (16). The physicians often perceived obesity as a personal psychological problem and had little sensitivity to the powerful influence of environment. Moreover, less than half of the physicians felt competent in prescribing weight loss programs; only 14% felt they had met with success in helping obese patients to lose weight. In short, a more informed, compassionate, and stepwise approach seems needed to assist patients in their battle with obesity.

What is the role of the clinician and associates in the treatment of nutritional management problems? Office-based advice, brief counseling, instructions, and the use of protocols for patient monitoring represent the first line of intervention to promote adherence. Formal educational programs may also be indicated, particularly when complex nutritional decisions will be required of the patient or family. However, in the many cases in which the patient's current lifestyle and motivation must be changed substantially, a comprehensive behavioral intervention program will be needed. Yet clinicians typically do not have training in behavioral approaches. Comprehensive behavioral programs are difficult if not impossible to implement in most office practices, due in part to the need for an intensive, team-based approach

(38). An approach for providing simple to comprehensive behavioral interventions will be described later.

Specific procedures used in behavioral intervention depend on the nature and treatment requirements associated with the medical condition, patient characteristics (age, cognitive/developmental level, motivation, expectations, self-confidence), the patient's social and environmental context, and more. However, behavioral approaches derive from a powerful psychological model of human learning that encompasses individual assessment, education (knowledge), training (skills), and follow-through. The model, described next, is sufficiently general to apply to a range of conditions.

7.3 PSYCHOLOGICAL THEORY: APPLIED BEHAVIOR ANALYSIS, SOCIAL COGNITIVE THEORY, AND THE TRANSTHEORETICAL MODEL

Psychological factors affecting nutritional adherence include patients' working knowledge of their condition, the rationale for change, their expectations and confidence that they will succeed, the nature and strength of their current behavioral patterns, and the nature and influence of their social and physical environment. Each of these factors must be addressed in some manner for the patient to have the best chance of success. The areas of behavioral and cognitive–behavioral psychology, referred to more specifically as applied behavior analysis (ABA) and social cognitive theory (SCT), respectively, have produced a better understanding of external environmental influences on personal health–related behavior and a host of clinically effective approaches for promoting individual behavior change.

7.3.1 Applied Behavior Analysis

Applied behavior analysis, often referred to as "behavior modification" (but ABA encompasses a more complete and nuanced approach to assessment and intervention), is an assessment and treatment approach that is restricted to the consideration of objectively verifiable events. Stated differently, ABA is characterized by the following features:

- An emphasis on observable and measurable behavior (what people publicly say or do)
- Analysis of social and physical events that reliably precede and trigger relevant behaviors, referred to as antecedents, and events that follow and positively reinforce or punish behaviors, known as consequences
- Treatments that involve the systematic presentation of antecedents and consequences, with the dual purpose of inducing and reinforcing desired behaviors
- Regular recording and data-based monitoring of behavior for ongoing evaluation and feedback
- A self-correcting process of revision and continued monitoring

ABA derives from B. F. Skinner's early research at Harvard University, which changed psychologists' understanding of how behavior "operates" (hence the term operant psychology) in the individual's environmental context and how the consequences of behavior in that context can dramatically impact future occurrence and form. Beginning in the late 1960s, researchers began to apply Skinner's operant principles, particularly positive reinforcement, to the treatment of important human problems. ABA research and practice continue, holding a small but important if not reemergent niche in psychology. Complete coverage of ABA is beyond the scope of this chapter; the reader is referred to time-honored texts by Sulzer-Azaroff and Mayer (39) and Cooper, Heron, and Heward (9).

The three-term contingency (also referred to as A-B-C, in which A = antecedent, B = behavior, and C = consequence) is at the conceptual heart of ABA. It refers to the process by which desired behavior change comes to be established firmly in its environmental context. Consider an example: The parents of an overweight child plan to positively reinforce (C) their son's healthy eating behavior (B), leading ultimately to improved weight control. The parents have been taught that they need to pay close attention to some specific antecedents (A) to encourage healthy eating. They have shopped with their child (a distal antecedent, or setting event) and stocked the refrigerator and cupboards with healthy foods, eliminating most of the unhealthy choices. Next, they involve the child in meal preparation, including the identification and selection of foods for the meal. They comment, "What a healthy meal this will be! Hey, after dinner, let's celebrate by playing a game … your choice."

The parents' actions and words, as well as the food itself, serve as more proximal antecedents to desired behavior of healthy eating, which takes place during the meal. This meal-preparation–eating-reinforcement scenario is illustrative of the contingencies that are planned and implemented systematically in family-based ABA interventions. Of utmost importance is that such experiences occur frequently and with procedural consistency. When they do, the experience of reinforcement for healthy eating strengthens the function of the antecedents: planning meals, shopping, preparing meals, the sight of healthy foods, cooking, and the parents' encouraging words. Once the relationship between antecedents, behavior, and reinforcement is strengthened through repetition, the antecedents begin to exert independent positive influence over the child's behavior, a principle referred to as stimulus control. The development of such environmental influence greatly enhances the likelihood that favorable behavior change will occur and be maintained.

The three-term contingency can also be applied to the way clinicians prepare patients to follow their nutritional regimens. For example, clinician advice and instructions (A) given in the office are apt to be followed by some initial changes in patient behavior (B). The patient's initial efforts provide an opportunity to reinforce and thus strengthen adherence. As advised by the clinician, the patient would record his or her daily adherence on a monitoring chart and then be asked to report the results, in response to a phone call from the office at the end of the first week and at a follow-up appointment in 2 weeks. The patient's reporting provides the opportunity for positive reinforcement by the clinician in the form of praise and approving feedback (C). Completing this A-B-C cycle will strengthen both patient

behavior (through positive reinforcement) and the influence of brief antecedents (because follow-through will result in reinforcement). For patients who are highly motivated and well organized, antecedents alone may provide the impetus for behavior change, with sufficient reinforcement coming in the form of self-satisfaction. However, research on training for behavioral adherence has demonstrated repeatedly that without external reinforcement for behavior change, antecedents alone tend to be ineffective (7,8,14).

It is common but unfortunate for clinicians to rely solely on antecedents in the form of office-based advice, brief counseling, and instructions, with the expectation that patients will act on what they are told. While antecedents may increase patients' knowledge about the reasons for adhering to treatment and may provide their initial motivation, they do not address the most critical behavioral aspects for long-term follow-through: development of skills to plan and implement changes in behavior, and positive reinforcement for those efforts. For example, research on diabetes prevention has shown that intensive lifestyle intervention is more effective than standard nutrition education for preventing new cases of diabetes in high-risk, overweight individuals with impaired glucose tolerance (40). This and other studies, reviewed later, suggest that instructions and nutrition education programs are necessary but far from sufficient to ensure nutritional adherence by patients.

ABA research has shown that for individuals to succeed at changing long-term behavior, they need to practice and learn new skills, and have their behavior and key outcomes monitored (including self-monitoring). In addition, they must receive credible feedback and contingent reinforcement, and must be encouraged to set incremental goals. Who will provide follow-up monitoring, feedback, and assistance with goal setting to patients? Physicians may need to hire auxiliary personnel or limit the size of their practice to assist patients. Hopefully, future research will show that follow-up services are cost effective and will be reimbursed.

7.3.2 Social Cognitive Theory

Albert Bandura (1) expanded upon ABA's three-term contingency and its reliance on observable events to develop and test a model (originally social learning theory) that included cognitive mediators of action. Cognitive mediators were viewed as private, or covert, behaviors that intervene between environmental antecedents and behavior. Of particular importance were the ways in which people interpreted, perceived, assessed, and planned their behavior in response to distinct personal or social situations. Researchers' increased emphasis on cognition, which paralleled the cognitive revolution in psychology, has evolved and has come to be known as social cognitive theory. In their review of health behavior change approaches, Baranowski et al. (2) review SCT in detail and describe important cognitive mediators. Of greatest importance are individuals' expectancy outcomes, considered a motivational variable, and perceived self-efficacy, a resource variable.

Outcome expectancy refers to the way in which people weigh the advantages and disadvantages of behavior change prior to committing to action. For example,

the advantages of eating healthier and increasing physical activity may include improved health, vitality, and appearance, along with a decreased risk of serious health problems. Disadvantages may include the emotional and appetitive discomfort of abstaining from certain foods, the experience of discomfort while exercising, and the impatience associated with such a long-term commitment.

If behavior change is viewed as desirable, self-efficacy comes into play. It refers to perceived confidence in the ability to succeed at a task, such as following a specific nutritional regimen. Self-efficacy derives from successful, reinforced experience and has been correlated with treatment outcomes in recent research (2). There are two practical implications: prior experience and resulting self-efficacy may predispose a patient to greater success at behavior change, and interventions should promote early reinforcement and success. How is this accomplished? By goal setting, supported by reinforcement for goal accomplishment. Goal setting refers to developing challenging but achievable short-term goals, and a motivational strategy to help build success. Research on goal setting has shown it to be an important component in adult behavioral treatment in obesity (34).

7.3.3 The Transtheoretical Model

The transtheoretical model (TTM) of behavior change (33) asserts that change is a temporal process in which individuals adopt or discontinue behaviors as a function of four factors:

- The extent to which they are prepared to alter their behavior at a given point of time (stages of change)
- An assessment of the advantages and disadvantages of maintaining their current behavior (outcome expectancies)
- Their confidence in their ability to undertake and succeed at change (self-efficacy)
- The actual processes involved in implementing change

The TTM approach posits five stages of change. In the precontemplation stage, the individual has no plans to change or has not even considered that change is warranted. In the contemplation stage, the person recognizes that change may be advantageous, considers taking it within the next 6 months, but may remain ambivalent. An individual in the preparation stage plans to make a change within the next month and may have begun to take preliminary steps, such as purchasing exercise equipment or low-fat snacks. During the action stage, the individual is engaged in the process of change but has been doing so for less than 6 months. Considerable energy and commitment is expended, and external rewards, such as social recognition, or material rewards usually are required to sustain momentum. In the maintenance phase, the individual has sustained behavioral change for more than 6 months, with new behaviors becoming more habitual and requiring less personal energy. Rewards may become internalized, for example, a sense of personal accomplishment and satisfaction. The challenge during maintenance is to sustain change and address

factors that may lead to relapse. This may be accomplished through the use of cognitive behavioral methods.

At present, TTM offers a useful approach to viewing the process of behavior change as a complex and highly individual experience that occurs over time. However, scientific evidence that supports the reliability and predictive validity of TTM is lacking (24,30).

7.4 REVIEW OF RESEARCH ON BEHAVIORAL INTERVENTIONS TO PROMOTE PATIENT ADHERENCE

Research on behavioral intervention has investigated various programmatic combinations of ABA and SCT procedures, also referred to as treatment "components." Multicomponent programs have proved to be more effective than simpler antecedent-based procedures (advice, brief counseling, and educational sessions). Common among comprehensive programs is the recognition that participants in behavior-change programs must be:

- As ready for and committed to change as is possible
- Educated as to the reasons and behaviors associated with the regimen they are about to undertake
- Trained to mastery in the host of skills necessary to succeed
- Engaged in structured and supportive follow-through procedures

Comprehensive behavioral programs are time and resource intensive, which may require that the treating physician refer the patient to a specialized program. Accordingly, it is reasonable first to ask how effective less-intensive antecedent procedures have been in promoting patient adherence.

7.4.1 Antecedent Interventions: Advice, Counseling, and Education

Kreuter et al. (21) questioned the assumption stated in the Healthy People 2000 (10) national disease prevention objectives and the Preventive Task Force practice guidelines (32) that "patients who receive physician advice are often more likely to successfully enact behavioral changes" (p. 426). Four hundred and ninety-six (496) adult patients who earlier had received illustrated educational materials completed baseline and follow-up questionnaires on their cigarette smoking, physical activity, and dietary fat consumption. They were also asked whether subsequently they had received advice from their physician about lifestyle behavior. Forty-four percent reported that their physician had indeed advised them to change at least one of the three health behaviors, allowing the creation of two groups (advice vs. no advice).

There was no between-group difference in patients' recall of having received educational materials. There were no statistical differences between the proportion

of patients who reported reading or keeping the materials. Smokers who had received physician advice were 37% more likely to have quit smoking for at least 24 h, but they were no more likely than those who had not received advice to have quit for at least seven consecutive days. There were no differences between patients who had and had not received advice with respect to lowering dietary fat and reducing fat intake from meat sources and fried foods. Patients who had received physician advice had reduced their fat intake from dairy sources slightly more than those who had not. Thus, while physician advice may serve as a catalyst for patient behavior change, a more coordinated system of individualized information, resources, and services, including monitoring and reinforcement, seems needed to promote adherence.

In another study on physician advice, the duration of advice was found to be a strong predictor of patient recall (15). Visit context also proved important. Recall was somewhat more likely when advice was given during well care rather than general illness visits. However, there was a twofold increase when advice was given during a visit by a patient with a health behavior–relevant diagnosis. This indicates that physicians may be able to identify and capitalize on "teachable moments" with their patients. Unfortunately, the study did not discuss the deep chasm between recall of advice and actual behavior change. In a related study, obese and overweight patients in primary care reported that what they most wanted from their physician was dietary advice in the form of help with setting realistic weight goals and recommendations for appropriate exercise (29). The authors discussed the need for increased advice and encouragement for patients with weight problems, but they barely mentioned the relationship between advice and behavior change.

Stark (37) asked whether nutrition counseling could be made more behavioral in the treatment of childhood cystic fibrosis, where weight gain and the expectoration of sputum through chest physiotherapy and exercise are the goal. The author's comprehensive treatment approach, Behavioral Intervention for Change Around Growth and Energy, or Be In CHARGE, combines nutrition education (systematic counseling) and behavioral intervention. That combination has been found to be almost twice as effective as nutrition counseling alone. Stark recommends that nutrition counseling should be made more behavioral by including patient or parental self-monitoring, feedback, and goal setting, and by tailoring interventions to the individual. Given the complexity and frequency of cystic fibrosis treatment, the most intensive form of behavioral intervention is likely to be needed. This would include removing antecedent stimuli that are known to sidetrack treatment, establishing new antecedents that promote adherence (stimulus control), setting achievable goals, providing frequent positive reinforcement and feedback, and developing written agreements (behavioral "contracts") between parent and child that establish how reinforcement is provided when goals are met.

As mentioned, studies on diabetes prevention have shown that intensive lifestyle intervention (ILI) is more effective than standard nutrition education (SNE) in preventing new cases of diabetes in high-risk overweight individuals with impaired glucose tolerance (40). The Diabetes Prevention Program (DPP), a 27-center randomized control trial in the United States, was designed to determine whether ILI would delay the onset of diabetes in overweight individuals with impaired glucose

tolerance (11). ILI was compared to a group receiving SNE and another group receiving the drug metformin and standard lifestyle therapy. The ILI group received behavioral intervention and lifestyle coaching. Group members had frequent contact with their health professional, their programs were individualized, and they had access to a network for resources and support. Goals were set for both weight loss and physical activity. Subjects in the SNE group were presented with written information and had an annual 20- to 30-min meeting that focused on healthy eating and appropriate physical activity. The ILI group showed significantly greater weight loss and a lower incidence of Type 2 diabetes than the other two groups.

Wolf et al. (43) conducted a randomized controlled study to compare the case management approach led by a registered dietitian with "usual care" in patients with obesity and Type 2 diabetes. The patients in the case management group had individual visits with a dietitian, attended six small group meetings, and received monthly phone calls over a 1-year period. Patients in the usual care group were provided antecedents in the form of educational materials and were free to participate in other programs (but not the case management program). Results indicate that the case management approach was associated with greater weight loss than the usual care approach. This suggests that this moderate-cost program (approximately $350/person) is effective in improving the health of persons with Type 2 diabetes.

Mayer-Davis et al. (26) conducted a randomized control trial in individuals with diabetes who live in two medically underserved rural communities in South Carolina. One group received an ILI, modified from the DPP study discussed above. A second group received a reimbursed lifestyle intervention (a condensed version of the ILI program). A third group received an individual session (nutrition education, advice, counseling) with a nutritionist at the start of the 12-month study period. Weight loss after 12 months was significant only in the ILI group.

The American Diabetes Association, the American Society for Clinical Nutrition, and the North American Association for the Study of Obesity have recently published a set of recommended strategies for achieving and maintaining a healthy body weight through lifestyle intervention. In this collective statement, the groups acknowledge the difficulty patients face in attempting long-term health-related behavior change (eating and activity) and state, "the role of the clinician is to encourage, monitor and support the patient during this process." They suggest an approach in which the clinician first identifies problem behaviors and then, with the patient, agrees on achievable target goals (goal setting). Next, office-based strategies are identified to encourage behavior change. They include self-monitoring, stimulus control, and problem solving. Even though frequent contact between the health provider and the patient (as often as once weekly or once every 2 weeks) leads to a better outcome, the relatively limited time a physician could make available suggests that other health professionals in the office (nurses, assistants) may need to be employed to provide more frequent contact. Referrals could also be made to a registered dietitian or other team members (20).

This brief review of the effectiveness of antecedents vs. more comprehensive approaches indicates the need for behavioral intervention that targets encouragement, monitoring, and reinforcement of behavior change in patients. The recom-

mendations described here are likely to apply also to other illnesses that require behavior modification.

What comprises a comprehensive, intensive lifestyle behavioral intervention program? The following section addresses this question by reviewing research in two well-developed and challenging areas of behavior change, childhood obesity and cystic fibrosis.

7.4.2 Comprehensive Behavioral Intervention Programs

The research literature on ABA and SCT is particularly well developed in the area of childhood obesity. A brief review will illustrate how clinicians might capitalize on family involvement and what effective behavioral programs should entail. Peebles and Hammer (28) emphasize the need for family involvement in the behavioral treatment of childhood obesity. Citing Barlow and Dietz (3), they recommend "an assessment of patient and family readiness to engage in treatment" and "the appropriate teaching of parenting skills and family support" as "a foundation of any weight maintenance or weight loss program for children." In a review of behavior intervention research in childhood obesity, Robinson (35) summarized the following steps for parents: provide healthful food choices, develop children's abilities to make healthful decisions, encourage and support physical activity, limit television and other screen time to less than 2 h/d, serve as positive role models for eating and activity, and discuss children's health status with the family's health care provider. Current evidence-based recommendations in childhood obesity stress the need for intensive behavioral intervention, which will begin in the clinician's office but needs to extend beyond the office through targeted referral.

Family-based weight reduction (FBWR) programs that combine nutrition and physical activity education with ABA strategies have been shown to be effective with overweight children (27,12,13). McLean et al. (27) reviewed 16 randomized controlled trials of FBWR interventions that included at least 1-year follow-up. Beneficial effects were seen when a comprehensive set of behavior change methods was used and when parents and children participated together in learning and applying ABA and SCT methods. Epstein et al. (12) conducted a 10-year follow-up study with 76 of their prior research participants (families of overweight or obese children) and found that parent participation, including parent goals for dietary improvements, was an important psychosocial mechanism in effective behavior change.

Does behavioral intervention work equally well for all patients? This question is important for other areas of nutritional adherence in which patients face difficult challenges. Epstein and colleagues' research (12,13) in obesity has been primarily with children with moderate obesity. Levine et al. (23) conducted a systematic replication of Epstein's program, this time targeting children with severe obesity. The authors also sought to determine whether children's participation would affect indices of psychological health, including depression, anxiety, and eating attitudes. Twenty-four families completed an initial assessment and participated in the intensive 10- to 12-session program, which addressed the goals of increasing healthy eating and physical activity, while decreasing unhealthy eating and sedentary behaviors. Epstein's Stoplight program was used to specify healthy vs. unhealthy food

types and to define portion sizes in a manner that could be monitored with ease. Calorie goals were set between 1200 kcal/d and 1500 kcal/d, depending on the child's initial body weight.

Results indicated that one-third of participants dropped out, citing logistical difficulties and schedule conflicts; children lost an average of 5.5 lb during the 10- to 12-week intervention phase, with parallel decreases noted in body mass index (BMI) and percent overweight; weight losses were not maintained at follow-up, 4 to 13 months postintervention; and children gained an average of 19 lb between the end of the intervention and the 13-month follow-up, but they also grew an average of 1.6 in. The children reported significant improvement in psychosocial measures over the course of the intervention, particularly in self-reported mood (symptoms of depression and anxiety), which were maintained at follow-up, despite weight re-gain. In addition, the authors reported that, although the number of participants was small, significantly more African American than White families dropped out. They also noted that attendance at early sessions may predict completion of the full intervention program. This suggests that motivational contingencies may be needed to reinforce early attendance. In short, the study highlights how a specific clinical subpopulation may respond differently to comprehensive educational and behavioral interventions, and that research with different populations or subpopulations is needed.

Cystic fibrosis is another area in which behavioral interventions have been investigated extensively. A recent systematic review concluded that ABA methods can be used effectively to increase adherence to diet and chest physiotherapy treatments, but that little research has been conducted on adherence to exercise regimens (4). Exercise adherence, particularly when the regimen is tedious and time consuming, presents an understandable challenge, but research to date suggests that individualized selection of enjoyable activities, frequent supervision, and parent management of the ABA program have been effective (31).

A recent article in *The New Yorker* provides an interesting anecdote illustrating how an astute physician might successfully assess and modify the adherence behavior of older children with cystic fibrosis through brief office-based intervention (17). Dr. Warren Warwick, a noted pediatrician specializing in cystic fibrosis, was conducting a routine 3-month check-up with a 17-year-old female patient. He noticed a slight dip in the patient's latest lung-function measurement and asked her to explain how that might have occurred. Some confrontational but respectful probing revealed that the patient had not been taking her treatments regularly. That was due in large part to her having a new boyfriend and a new job, which made taking treatments less practical and publicly more visible and stigmatizing. Dr. Warwick took a moment with his patient to sketch out the cumulative effects of decreased lung functioning in patients with cystic fibrosis, recognizing that, to his patient, there were no immediate adverse effects of missing a treatment. After more conversation, Dr. Warwick had sufficient information to propose some practical but firm behavioral contingencies: his patient would employ her friend to hold her to her daily breathing treatments, she would keep her medications with her and take them on her own at school (rebelliously defying the school nurse!), and, immediately, she would start extra therapy at the hospital to regain lost ground. In short, effective behavioral interven-

tion is borne of a clinician's sincere and probing interest in the factors affecting a patient's adherence, and of recognition that such factors are both powerful and modifiable. In some cases the solution may be relatively simple, as in this anecdote; in others it will be more involved.

7.5 A PRACTICAL MODEL FOR PROMOTING PATIENT ADHERENCE

Table 7.1 offers an evidence-based model for clinicians who seek to provide optimal office- and referral-based interventions. The left-hand column describes office-based procedures that should be used when initiating any nutritional regimen with a patient. The emphasis is on clear and empathic communication, as the physician explains the medical rationale and specific behavioral requirements of the regimen. The physician should interview the patient in order to identify and overcome challenges that the patient will face in following the regimen at home. The patient should be asked to describe the regimen and its implementation. With complex regimens, the patient should be asked to practice (role-play) with auxiliary personnel. The patient should be provided a monitoring form and instructed to record daily adherence to the regimen and to write down questions for the physician. Finally, weekly follow-up calls are scheduled: the physician or an auxiliary staff member calls the patient to review the monitoring forms and answer questions. The next office visit is scheduled for 2 weeks to 1 month hence. During the follow-up visit, the physician determines the need for additional education or comprehensive behavioral intervention, based on the patient's level of adherence. Educational and behavioral programs may be offered through the office or by referral to high-quality providers.

Additional education is required for patients who need assistance in making complex decisions to carry out their regimen, e.g., meal and physical activity planning. The components of high-quality education programs are outlined in the top half of the center column of Table 7.1. If the patient struggles to adhere to the regimen due to ineffective self-management skills or poor motivation, training in behavior management skills is warranted. Components of effective behavioral interventions are listed in the bottom half of the center column. Education and training may be provided in the office, if staffed to do so, or through referral. The right-hand column lists essential follow-up steps that must be taken by the physician and auxiliary personnel to reinforce patient adherence positively. Coordination between the referral agency (if one is used) and the office is essential.

7.6 CONCLUSIONS AND FUTURE RESEARCH

In summary, the use of comprehensive behavioral interventions to improve patient adherence to nutritional regimens has received significant attention in recent years. Controlled research has shown that behavioral interventions are generally effective but labor intensive and require a high level of well-defined and coordinated effort. It is important to note that antecedent-based interventions in the form of advice, brief counseling, instructions, and education alone are insufficient to produce behav-

TABLE 7.1
A Practical Model for Promoting Patient Adherence

Advice, Counseling, and Instruction Conducted by Treating Physician	Patient Education and Training Conducted by Office Personnel or Referral Agency Staff	Follow-Up Assessment and Feedback Conducted by Physician or Auxiliary Personnel, Coordinated with Referral Agency Staff
Prepare for and meet with patient or family, with time for questions.	**Education** (knowledge base)	Brief, scheduled follow-up sessions
Explain patient's condition in simple terms, with handouts.	Group or individual format	Weekly at first, then bi-weekly and monthly
Present a clear rationale for strict adherence to the nutritional regimen.	One or more 1-h sessions	Office visit, phone, email options
Describe the regimen and provide written instructions for posting at home.	Handouts:	Patient or family member:
Present and explain monitoring protocol and form(s).	Objectives	Describes progress, problems
Interview the patient to identify likely barriers to adherence. Determine solutions.	Rationale (why)	Presents monitoring data
Ask for and answer the patient's questions.	Instructions	Physician or personnel:
Probe the patient's understanding of what has been presented. Role-play if necessary.	Take-home forms	Offers feedback and praises progress
Refer patients with complex conditions to programs that provide formal education and training in behavioral intervention (middle column).	Instructor presents content	Assists in problem solving as appropriate
Have the patient commit to a scheduled phone call from the office to review monitored adherence and schedule the next office follow-up meeting.	Simple, clear, visual, engaging	Sets short-term goals with patient
	Question and answer	Schedules next contact
	Summary	Reviews actions patient will take
	Resources on Internet	
	Training (skill base)	
	Interwoven with **education**	
	Covers skills for:	
	Following regimen	
	Implementing behavior change[a]	
	Presenter demonstrations	
	Patient role-play, practice	
	Guidance as needed	
	Feedback	
	Repeated practice	
	Summary, final questions, scheduling	

Monitoring
Patient and office personnel track behavior change for follow-up review, problem analysis, and feedback.

[a] Monitoring, goal setting, stimulus control, feedback, reinforcement.

ioral change in a great many patients, particularly when the nutritional regimen is complex or represents a drastic shift from the patient's entrenched habits. However, this is not to downplay the role of an astute clinician who may be able to counsel, instruct, and motivate patients to action, particularly in the case of older children and adults. Clinicians may not be able to provide complete behavioral intervention services from their office-based practices, but to optimize patient adherence they can follow a model (see Table 7.1) in which they provide high-quality advice, counseling, and instructions when nutritional regimens are initiated; arrange for patient monitoring (supply forms and instructions) and office-initiated follow-up that includes positive reinforcement for incremental adherence; and refer patients to more comprehensive programs when they are observed to struggle with adherence, despite initial office-based efforts.

In future research, attention must be given to ways in which the cost of delivering comprehensive behavioral interventions can be reduced without reducing clinical effectiveness. In one study, group behavioral intervention was found to be as effective as a combination of group and individual interventions, and thus more cost effective (18). Also, pending more investigation, it may prove unnecessary to include all procedural components that have been used in the research on behavioral intervention to date. Component analysis research has been scant, but it would help to determine the necessary make-up and cost effectiveness of interventions. Ultimately the results would guide clinicians in determining how best to allocate their time and when referral to a comprehensive program is needed.

Recent research on the use of the Internet may also provide a cost-effective means of providing behavioral intervention (42). In a study with overweight adolescent African American girls, an Internet-based family behavioral intervention was more effective than a formal nutrition and physical activity education curriculum, also delivered on-line, in reducing adiposity. Although the Internet-based behavioral intervention was not as effective as similarly configured *in vivo* behavioral interventions reported in prior research, this study establishes the potential for the Internet to be used as a cost-effective adjunct to *in vivo* interventions, including office-based efforts.

REFERENCES

1. Bandura, A. *Social Foundations of Thought and Action: A Social Cognitive Theory.* Englewood Cliffs, NJ: Prentice Hall, 1986.
2. Baranowski, T, Cullen, KW, Nicklas, T, Thompson, D, & Baranowski, J. Are current health behavioral change models helpful in guiding prevention of weight gain efforts? *Obes. Res. 11:* 23S–43S, 2003.
3. Barlow, S, & Dietz, WH. Obesity evaluation and treatment: Expert committee recommendations. *Pediatrics 102:* e29, 1998.
4. Bernard, RS, & Cohen, LL. Increasing adherence to cystic fibrosis treatment: A systematic review of behavioral techniques. *Ped. Pulmon. 37:* 8–16, 2004.
5. Bronner, F (Ed.). *Nutrition and Clinical Management of Chronic Conditions and Diseases*. Boca Raton: CRC Press, 2005.

6. Bronner, F (Ed.). *Nutritional Aspects and Clinical Management of Chronic Disorders and Diseases*. Boca Raton: CRC Press, 2003.
7. Brownell, KD, & Cohen, LR. Adherence to dietary regimens. 1: An overview of research. *Behav. Med. 20:* 149–154, 1995.
8. Brownell, KD, & Cohen, LR. Adherence to dietary regimens. 2: Components of effective interventions. *Behav. Med. 20:* 155–165, 1995.
9. Cooper, JO, Heron, TE, & Heward, WL. *Applied Behavior Analysis*. New York: Macmillan, 1987.
10. Department of Health and Human Services. *Healthy People 2000: National Health Promotion and Disease Prevention Objectives*. Washington, DC: Dept. of Health and Human Services, 1991. DHHS publication PHS 91-50212.
11. Diabetes Prevention Program (DPP): Description of lifestyle intervention. *Diabetes Care 25:* 2165–2172, 2002.
12. Epstein, LH, Valoski, A, Wing, RR, & McCurley, J. Ten-year follow-up of behavioral, family-based treatment for obese children. *JAMA 264:* 2519–2523, 1990.
13. Epstein, LH. Family-based behavioral intervention for obese children. *Int. J. Obes. Relat. Metab. Dis. 20:* S14–21, 1996.
14. Fleming, RK. An integrated behavioral approach to transfer of interpersonal leadership skills. *J. Management Educ. 16:* 341–353, 1992.
15. Flocke, SA, & Stange, KC. Direct observation and patient recall of health behavior advice. *Prev. Med. 38:* 343–349, 2004.
16. Foster, GD, Wadden, TA, Makris, AP, Davidson, D, Sanderson, RS, Allison, DB, & Kessler, A. Primary care physicians' attitudes about obesity and its treatment. *Obes. Res. 11:* 1168–1177, 2003.
17. Gawande, A. The bell curve: What happens when patients find out how good their doctors really are? *The New Yorker,* Dec. 6, 2004.
18. Goldfield, GS, Epstein, LH, Kilanowski, CK, Pauch, RA, & Kogut-Bossler, B. Cost-effectiveness of group and mixed family-based treatment for childhood obesity. *Int. J. Obes. Relat. Metab. Disord. 25:* 1843–1849, 2001.
19. Hudson, J, Fielding, D, Jones, S, & McKendrick, T. Adherence to medical regime and related factors in youngsters on dialysis. *Br. J. Clin. Psychol. 26:* 61–62, 1987.
20. Klein, S, Sheard, NF, Pi-Sunyer, X, Daly, A, Rosett, JW, Kulkarni, K, & Clark, NG. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: Rationale and strategies. *Diabetes Care 27:* 2067–2070, 2004.
21. Kreuter, MW, Chheda, SG, & Bull, FC. How does physician advice influence patient behavior? Evidence for a priming effect. *Arch. Fam. Med. 9:* 426–433, 2000.
22. La Greca, A, & Schuman, WB. Adherence to prescribed medical regimens. In MC Roberts (Ed.), *Handbook of Pediatric Psychology* (2nd ed.). New York: Guilford Press, pp. 55–83, 1995.
23. Levine, MD, Ringham, RM, Kalarchian, MA, Wisniewski, L, & Marcus, MD. Is family-based behavioral weight control appropriate for severe pediatric obesity? *Int. J. Eat. Disord. 30:* 318–328, 2001.
24. Littell, JH, & Girvin, H. Stages of change: A critique. *Behav. Mod. 26:* 223–273, 2002
25. Lobstein, T, Baur, L, & Uauy, R. Obesity in children and young people: A crisis in public health. *Obes. Rev. 5:* 4–104, 2004.
26. Mayer-Davis, EJ, D'Antonio, AM, Smith, SM, Kirkner, G, Martin, SL, Parra-Medina, D, & Schultz, R. Pounds off with empowerment (POWER): A clinical trial of weight management strategies for black and white adults with diabetes who live in medically underserved rural communities. *AJPH 94:* 1736–1742, 2004.

27. McLean, N, Griffin, S, Toney, K, & Hardeman, W. Family involvement in weight control, weight management and weight-loss interventions: A systematic review of randomized trials. *Int. J. Obes. Relat. Metab. Dis. 27:* 987–1005, 2003.
28. Peebles, R, & Hammer, LD. Childhood obesity. In F Bronner (Ed.), *Nutrition and Clinical Management of Chronic Conditions and Diseases*. Boca Raton: CRC Press, 2005.
29. Potter, MB, Vu, JD, & Croughan-Minihane, M. Weight management: What patients want from their primary care physicians. *J. Fam. Pract. 50:* 513–518, 2001.
30. Povey, R, Conner, M, Sparks, P, James, R, & Shepherd, R. A critical examination of the application of the Transtheoretical Model's stages of change to dietary behaviours. *Health Ed. Res.: Theory Prac. 14:* 641–651, 1999.
31. Prasad, SA, & Cerny, FJ. Factors that influence adherence to exercise and their effectiveness: Application to cystic fibrosis. *Pediatr. Pulmonol. 34:* 66–72, 2002.
32. Preventive Task Force. *Guide to Clinical Preventive Services* (2nd ed.). Baltimore, MD: Williams & Wilkins, 1996.
33. Prochaska, JO, Johnson, SS, & Lee, P. The transtheoretical model of behavior change. In: E Schron, J Ockene, S Schumaker, & WM Exum (Eds), *The Handbook of Behavioral Change* (2nd ed.). New York: Springer, pp. 159–84, 1998.
34. Robinson, TN. Behavioural treatment of childhood and adolescent obesity. *Int. J. Obes. Relat. Metab. Disord. 23:* S52–57, 1999.
35. Robinson, TN. *The IOM Report on Preventing Childhood Obesity: Health in Balance*. North American Association for the Study of Obesity Annual Scientific Meeting, Las Vegas, NV, 2005.
36. Sharma, NS, Calleo-Cross, A, & Aronne, LJ. Adult obesity, with special reference to bariatric surgery. In F Bronner (Ed.), *Nutrition and Clinical Management of Chronic Conditions and Diseases*. Boca Raton: CRC Press, 2005.
37. Stark, LJ. Can nutrition counseling be more behavioral? Lessons learned from dietary management of cystic fibrosis. *Proc. Nutr. Soc. 62:* 793–799, 2003.
38. Stettler, N. The global epidemic of childhood obesity: Is there a role for the paediatrician? *Obes. Rev. 5:* 91–92, 2004.
39. Sulzer-Azaroff, B, & Mayer, GR. *Behavior Analysis for Lasting Change*. Forth Worth, TX: Harcourt Brace College Publishers, 1991.
40. Tuomilehto, J, Lindstrom, J, Eriksson, JG, Valle, TT, Hamalainen, H, Ilane-Parikka, P, Keinanen-Kiukaanniemi, S, Laakso, M, Louheranta, A, Rastas, M, Salminen, V, & Uusitupa, M. Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New Engl. J. Med. 344:* 1342–1350, 2001.
41. Valentine, CJ, Griffin, IJ, & Abrams, SA. Nutritional support in children. In F Bronner (Ed.). *Nutritional Aspects and Clinical Management of Chronic Disorders and Diseases*. Boca Raton: CRC Press, 2003.
42. White, MA, Martin, PD, Newton, RL, Walden, HM, York-Crowe, EE, Gordon, ST, Ryan, DH, & Williamson, DA. Mediators of weight loss in a family-based intervention presented over the Internet. *Obes. Res. 12:* 1050–1059, 2004.
43. Wolf, AM, Conaway, MR, Crowther, JQ, Hazen, KY, Nadler, JL, Oneida, B, & Bovbjerg, VE. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving control with activity and nutrition (ICAN) study. *Diabet. Care 27:* 1570–1576, 2004.

8 Genetic Diseases and Errors of Metabolism

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CONTENTS

8.1 INTRODUCTION

The concept "inborn error of metabolism" was introduced by Garrod to describe a block in a metabolic process, causing diseases that follow a familial pattern (17). Identification of intermediary metabolites from inborn errors of metabolism resulted in the discovery of enzyme defects leading to the presence in the body of metabolites not normally detected. A high level of such a metabolite indicates a block in the natural flow of metabolic processes, resulting in a disease — an inborn error of metabolism. Modulation of intermediary metabolites is a method of treatment for some inborn errors of metabolism.

For example, in phenylketonuria (PKU), the treatment involves dietary modulation of phenylalanine. The treatment of inborn errors of metabolism must begin early in life, before irreversible damage occurs. In 1963, Guthrie and Susi published a bacterial inhibition assay for detecting PKU in the newborn; this assay has become the universal basis for screening for this disease (21). Since then, screening of the newborn has been expanded to indentify many more inborn errors of metabolism by using the novel technology of gas chromatography and tandem mass spectroscopy

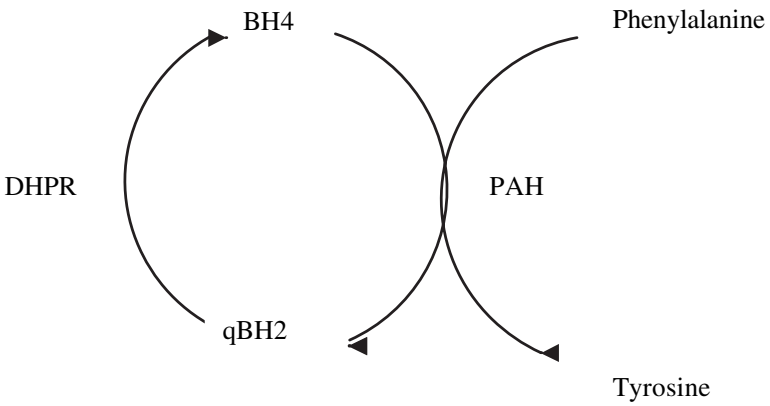

FIGURE 8.1 The first step in the catabolism of phenyalanine is its hydroxylation to tyrosine. This requires the enzyme phenylalanine hydroxylase (PAH) and the cofactor tetrahydrobiopterin (BH_4). When tyrosine is formed, BH_4 is oxidized to quinonoid dihydropteridine (qBH_2), which is reduced by the enzyme dihydropteridine reductase (DHPR), and PAH is activated again.

(GC/MS/MS; 12). Treatment strategies vary with each disease and include restriction of substrate, vitamin or cofactor supplementation, supplementation of a deficient product, or conjugation of a toxic metabolite. This chapter reviews examples of treatment strategies in various inborn errors of metabolism, with emphasis on PKU as the classic example of a genetic disease treated by dietary restriction of the substrate, phenylalanine.

8.2 PHENYLKETONURIA

Phenylketonuria is an autosomal recessive error of phenylalanine metabolism that occurs in about 1 in 10,000 to 15,000 births in the United States (51). The disease is found in all ethnic groups, but it is more common in persons of Northern European background. Folling, in 1934, first described siblings with mental retardation associated with phenylketones in their urine, hence the name phenylketonuria (16). In 1947, Jervis identified the defective enzyme as phenylalanine hydroxylase (PAH), which hydroxylates phenylalanine to tyrosine (Figure 8.1; 26). In 1953, Bickel et al. (7) documented that restricting the substrate, phenylalanine, in patients with PKU prevented the severe manifestations of the disease. The successful treatment led to mandatory newborn screening programs in the United States.

The clinical features of untreated PKU include developmental delay and mental retardation. Patients often have seizures, microcephaly, eczema, and pigment dilution, and they emit a peculiar odor. As patients get older, hyperkinesis becomes a feature of the untreated patient (51).

The biochemical findings in patients with untreated PKU include elevated phenylalanine in the blood, urine, and spinal fluid. The normal concentration of blood phenylalanine is 60 to 180 μmol/l (1 to 2 mg/dl). Patients with untreated PKU have blood phenylalanine concentrations that often exceed 1200 μmol/l (20

mg/dl). When an infant is found to have an elevated blood level of phenylalanine, this must be confirmed by quantifying the infant's levels of amino acids in the blood. To confirm a PKU diagnosis, the infant's blood level of phenylalanine should be elevated, and its tyrosine blood concentration should be normal. Phenylalanine hydroxylase requires the cofactor tetrahydrobiopterin (BH_4) to convert phenylalanine to tyrosine (Figure 8.1). The cofactor BH_4 is also involved in the hydroxylation of tyrosine to dopamine and in the hydroxylation of tryptophan to 5-hydroxytryptophan in the pathway of serotonin. Infants with deficiency of the cofactor (BH_4) will have elevated blood phenylalanine concentrations; however, the treatment for BH_4 cofactor problems is completely different from that for treatment for PKU (37). Infants with elevated blood phenylalanine concentrations must be evaluated for BH_4 problems.

Phenylketonuria has a wide clinical spectrum. More than 400 mutations have been identified on the PAH gene that lead to a range of clinical severity of PKU (52). The most common, severe mutation among European individuals is substitution of tryptophan for arginine in position 408 (R408W) of PAH. Y414C is an example of a mutation associated with a milder form of PKU.

The blood phenylalanine concentration is the result of the type of formula fed to the infant and of the length of time that has elapsed before the diagnosis. Phenylalanine concentrations in the range of 120 to 360 μmol/l, while the infant is on a normal diet, indicate benign hyperphenylalaninemia, a condition that occurs in about 10% of PKU patients. These do not require diet therapy, but their blood phenylalanine concentrations need to be monitored. Blood phenylalanine concentrations greater than 360 μmol/l require dietary phenylalanine restriction (51).

Dietary management involves restriction of dietary phenylalanine, an essential amino acid that cannot be produced in the body. Some phenylalanine must be provided for normal growth and tissue maintenance. Tyrosine, the hydroxylation product of phenylalanine, becomes an essential amino acid for a patient with PKU. Special medical foods that contain no phenylalanine and adequate amounts of tyrosine are available. Most are fortified with vitamins and minerals and some are quite energy rich.

The special medical food provides 80 to 90% of the dietary protein. Initially the infant is started at about 45 mg/kg phenylalanine, along with adequate protein and energy intake. Breast milk or commercial formula is used to provide essential phenylalanine, and intake is adjusted to maintain the blood phenylalanine concentration in the range 120 to 360 μmol/l. Appropriate weight gain is the best indicator of dietary adequacy. As infants get older, phenylalanine provided in the breast milk or commercial formula is replaced with phenylalanine from solid foods. Measured amounts of fruits, vegetables, and starchy foods are given along with the medical food. High-protein foods such as meat, eggs, milk, and cheese are not introduced, as their phenylalanine content is very high. The National Collaborative Study for PKU found that low blood phenylalanine concentrations are correlated with good dietary control and lead to good outcome in children with PKU (3,25,41). Reports show that PKU patients tend to have neurological deterioration after discontinuing diet therapy, and a lifelong diet low in phenylalanine is now advocated (15,23,57).

TABLE 8.1
Guidelines for Treatment of PKU Based on the National Institutes of Health Consensus Development Conference Statement

- Confirm diagnosis and start dietary treatment no later than 10 days of age
- Blood phenylalanine goals:
  - 120 to 360 μmol/l (2 to 6 mg/dl) from birth through 12 years
  - 120 to 900 μmol/l (2 to 15 mg/dl) after 13 years (120 to 600 μmol/l strongly encouraged)
- Monitoring blood phenylalanine levels:
  - Birth to 1 year, once per week
  - 1 through 12 years, twice per month
  - After 13 years, once per month
- Lifelong treatment for all patients

8.2.1 NIH Treatment Guidelines

To formulate guidelines for metabolic clinic physicians and dietitians, the National Institutes of Health held a Consensus Development Conference, "Phenylketonuria: Screening and Management," on October 16–18, 2000. The conference resulted in a statement that gives guidelines to the metabolic clinics regarding the screening and management of PKU (48). The NIH Consensus recommended that clinics in the United States follow the guidelines of maintaining blood phenylalanine concentrations in the range 120 to 360 μmol/l (2 to 6 mg/dl) until patients with PKU are 13 years of age. After that age, the recommendation is 120 to 900 μmol/l (2 to 15 mg/dl), while a narrower range of 120 to 600 μmol/l (2 to 10 mg/dl) is strongly encouraged. Monitoring needs to be individualized during the initial phase of treatment. Once the blood phenylalanine concentration is in the desired range, the NIH Consensus guidelines recommend that blood be monitored once per week for the first year of life, twice monthly from 1 year until 13 years of age, and once per month thereafter. Table 8.1 summarizes treatment guidelines based on the NIH Consensus Development Conference Statement.

The NIH Consensus Guidelines also recommend that a phenylalanine-restricted diet must be started as early in the newborn period as possible (age <10 d) in order to prevent the mental retardation associated with PKU. Dietary phenylalanine restriction is used for any infant with persistent blood phenylalanine concentrations above 600 μmol/l (10 mg/dl). The dietary regime includes reduction of dietary phenylalanine to a level that will promote normal growth and development without allowing the blood phenylalanine to become too high. Tyrosine becomes an essential amino acid and needs to be provided in increased amounts.

A low-phenylalanine diet should be followed throughout life as loss of intelligence quotient, decline in school performance, increased behavior problems, and white matter abnormalities have been reported in patients who discontinued the diet (48).

8.2.2 Tetrahydrobiopterin-Responsive PAH Deficiency

Kure et al. (31) were the first to report on four patients with PAH deficiency whose blood phenylalanine levels went down after oral intake of the cofactor BH_4. Since then, there have appeared many reports of patients with PAH deficiency who responded to BH_4 (4,10,24,34,35,38,40,47,53,54,55,58, 59,62). In these cases the metabolism of the cofactor was normal. However, the addition of a large dose of BH_4 normalized the blood phenylalanine concentration. In one U.S. study, as many as 50 to 60% of patients with PKU responded to a single load of BH_4 (40). The number of patients who respond to BH_4 and the impact of BH_4 supplementation on the treatment of PKU remain unknown and require further study. Neither pharmacokinetics of BH_4 nor the K_m mutation of PAH fully explain all the cases that respond to BH_4 (9,14,38). Conceivably BH_4 acts as a chemical chaperone that extends the half-life and the residual activity of PAH. Patients with mutations of PAH, with the enzyme retaining residual activity, can benefit from BH_4 supplementation. It is recommended to genotype patients with PKU (48), inasmuch as the PKU data bank has information on the residual activity and phenotype associated with such mutations (8).

8.3 MATERNAL PKU

Women with PKU who are not on a low-phenylalanine diet and have elevated blood phenylalanine concentrations are at risk to have babies that are small for gestational age and have mental retardation, microcephaly, and congenital heart disease (33). The effect of high blood phenylalanine in the pregnant woman leads to the "maternal PKU syndrome." The infants have facial dysmorphology similar to that of infants born with fetal alcohol syndrome.

In 1984, a study was initiated to find out whether a diet restricted in phenylalanine during pregnancy would reduce the morbidity associated with maternal PKU (29,30,39,49). Relationships between the maternal genotype, phenotype, and cognitive outcome have been reported (20,22). Factors that affect offspring size include the maternal blood level of phenylalanine, dietary protein intake, dietary intake of energy, and maternal weight gain (42). Adequate intake of vitamin B_{12} is required to prevent congenital heart disease in mothers with the PKU syndrome (43). Blood phenylalanine concentrations should be reduced to <6 mg/dl prior to conception and maintained in the range 2 to 6 mg/dl throughout the pregnancy. Blood phenylalanine should be determined at least weekly. During pregnancy the overall nutritional status, with emphasis on protein, calories, and vitamins such as folate and vitamin B_{12}, needs to be addressed and social support encouraged. Adequate intake of these nutrients may help prevent congenital heart disease and microcephaly in children born to PKU mothers (42,44).

8.4 GALACTOSEMIA

Galactosemia is an inherited autosomal recessive disease caused by deficient activity of the enzymes galactokinase, epimerase, and galactose-1-phosphate uridyltrans-

ferase (GALT; 6). Most states screen for GALT deficiency but do not screen for the other disease-related steps involved in galactose metabolism, i.e., kinase or epimerase deficiency, as these diseases are less severe for the affected individual. Patients with GALT deficiency present with failure to thrive after ingestion of a lactose-containing formula. Frequently, newborns have vomiting or diarrhea. Liver dysfunction is manifested by jaundice and a higher than normal plasma concentration of conjugated bilirubin. Cataracts are visible by ophthalmoscopic examination. Untreated babies tend to die from *E. coli* sepsis early in life.

Restriction of lactose intake leads to dramatic improvement. However, improvement is not always complete. Some patients may have residual neurological abnormalities or speech problems, and females often have ovarian dysfunction (27,50,60). It is not known whether the residual effects are caused by ingestion of small amounts of dietary galactose.

Most patients with galactosemia are treated with a powdered soy formula that contains small amounts of galactose. Casein hydrolysates, added to liquid soy formulas, increase the galactose content of the diet. "Lactose free" formulas contain even higher amounts of galactose. As the patient gets older and eats a greater variety of foods, the sources of galactose become more numerous. Many foods contain free galactose, whereas others contain bound galactose that is released upon digestion. Meats contain bound galactose in the form of glycoproteins and glycolipids. The galactose content of many foods is now known, thus making it possible to limit the galactose content of the diet (1,18). Recently, new elemental formulas have become available that contain no galactose. The elemental formulas and knowledge of the galactose content of foods make for a better treatment response. Whether strict avoidance of dietary galactose will reduce the side effects associated with treated galactosemia is not known.

The gene for GALT has been cloned, and mutations have been described (6). Of particular interest is a "classic" mutation where arginine replaces glutamine in amino acid position 188 of the enzyme molecule, Q188R. This is the most common and most severe mutation in GALT. Patients with the mild Duarte Variant often have serine 135 substituted for leucine in the polypeptide chain (S135L). This allele is common among African American patients. Patients with the Duarte Variant may need galactose restriction only in the first year of life.

How to follow treatment of galactosemia is not clear. In many centers, galactose-1-phosphate in RBC is used as a measure of dietary compliance. Recent reports suggest that galactitol also needs to be monitored (5).

8.5 BIOTINIDASE

Biotinidase deficiency, an autosomal recessive disease, is an example of an inborn error of metabolism that is treated by supplementation of the cofactor for carboxylases, biotin (64). Biotinidase cleaves biotin from holocarboxylases during metabolic degradation. The liberated biotin is then reutilized.

In patients with biotinidase deficiency, not enough biotin is present for reuse by the three mitochondrial biotin-dependent carboxylases: propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and pyruvate carboxylase. Untreated patients

present with hypotonia, seizures, skin rash, and alopecia (19,28,32,46,61). The urine contains metabolites, such as 3-hydroxyisovalerate, 3-methylcrotonylglycine, methylcitrate, 3-methylcrotonate, and 3-hydroxypropionate. The treatment involves supplementation with 10 mg biotin taken once daily.

Screening of the newborn identifies infants with the disease. The gene has been cloned, and mutations have been analyzed. Some patients have partial defects with considerable residual enzyme activity; this results in mild disease and excellent prognosis. All forms of biotinidase deficiency respond promptly to biotin supplementation.

8.6 ISOVALERIC ACIDEMIA

The binding of toxic substances produced by a metabolic block is yet another mode of therapy for some inborn errors of metabolism. Isovaleric acidemia is caused by deficiency of the enzyme isovaleryl-Co-A dehydrogenase, which is in the pathway of leucine catabolism (56). The abnormal accumulation of isovalerylglycine in urine and isovalerylcarnitine in serum is diagnostic. Most patients develop vomiting, acidosis, lethargy, and coma in the newborn period; however, some patients exhibit these symptoms only with underlying illness. Isovaleric acid in urine and sweat gives a peculiar odor of "sweaty feet syndrome" during a period of crisis.

Isovaleric acidemia responds well to treatment with protein restriction and supplementation with glycine (250 mg/kg), which binds to isovaleric acid and is excreted as isovalerylglycine. Carnitine also binds to isovaleric acid, and carnitine supplementation may be added to the treatment regime.

The disease is autosomal recessive, and mutation analysis can be done (63). The prognosis is good, provided treatment starts early in life and compliance is maintained.

8.7 MAPLE SYRUP URINE DISEASE

The decarboxylation of the branched chain amino acids, leucine, isoleucine, and valine, requires a multiunit enzyme system, i.e., the branched chain ketoacid dehydrogenase (13). Deficiency of any of the subunits of this enzyme leads to maple syrup urine disease (MSUD). The worldwide incidence of the disease is approximately 1:200,000. However, in the Mennonite community in Pennsylvania the incidence is 1:176. Among Mennonites, the component E1α of the branched chain ketoacid dehydrogenase is deficient, caused by substituting for tyrosine by asparagine at amino acid 393 (Y393N). The high frequency of this mutation among Mennonites is due to the "founder" effect. It is possible to detect the mutation before birth in informative families and to start treatment at birth (36,45).

Maple syrup urine disease is subdivided into three forms: classic, intermittent, and mild; the classic is the most severe form. Some forms may be thiamin responsive. In the classic form, diagnosis may be made because the urine smells of maple syrup. These infants appear normal at birth but, during the first week of life, develop vomiting, lethargy, ketosis, and coma. The diagnosis is established by a high plasma

TABLE 8.2
The Urea Cycle Enzymes

Enzyme	Substrates	Product
N-acetylglutamate synthase	Glutamic acid + acetylCoA	N-acetylglutamate (NAGS)
Carbamylphosphate synthase	$CO_2 + NH_3 + ATP + NAGS$	Carbamylphosphate
Ornithine transcarbamylase	Ornithine + carbamylphosphate	Citrulline
Arginine succinate synthase	Citrulline + aspartate	Argininosuccinic acid
Argininosuccinase	Argininosuccinic acid	Arginine + fumeric acid
Arginase	Arginine	Urea + ornithine

Note: Eliminate ammonia, produce arginine and ornithine to keep the cycle going.

level of leucine, isoleucine, valine, and allo-isoleucine, and by increased excretion of the keto-acids of the branched chain amino acids. The treatment of MSUD involves dietary restriction of the branched chain amino acids, while preventing deficiency of any branched chain amino acids. If isoleucine is restricted too severely, adverse results will ensue. For treatment protocols, see Acosta and Yannicelli (2).

Patients with the intermittent form of MSUD develop ataxia following intercurrent infections. The mild form is due to an increase in residual activity of the dehydrogenase complex. In cases of mild forms of MSUD, thiamin administration may increase the enzyme half-life. This in turn leads to dramatic clinical and biochemical improvement. When thiamin is administered initially, it may take 2 to 3 weeks of treatment before a favorable response is observed.

All forms of MSUD are autosomal recessive, and the deficiency of the different subunits of the enzyme may account for the wide spectrum of clinical and biochemical variability.

8.8 UREA CYCLE DEFECTS

The urea cycle enzymes have two roles: to prevent the accumulation of ammonia and to synthesize arginine. Urea cycle defects are classified as inborn errors of metabolism that lead to hyperammonemia and arginine deficiency (11). Table 8.2 lists the enzymes in the urea cycle. Treatment includes protein restriction and the use of an alternate pathway for the synthesis and excretion of waste nitrogen. If there is a urea cycle defect, nitrogen accumulates as glutamate, alanine, or ammonia, with ammonia the most toxic.

The signs and symptoms of the disease depend on the plasma concentration of ammonia. As ammonia starts to rise there is lethargy, vomiting, and refusal to eat. As the ammonia increases, the lethargy becomes more pronounced and is accompanied by hyperventilation and grunting respirations. This stage is followed by seizures, coma, respiratory arrest, increased intracranial pressure, and dilated pupils. In the severe forms, infants become comatose within 2 to 4 d of life. In the acute treatment phase, peritoneal or hemodialysis is used to remove ammonia. Precursor compounds are given to promote conjugation of nitrogen and lead to nitrogen

excretion through an alternative pathway. Examples are sodium benzoate, which binds glycine and is then excreted as hippuric acid, and sodium phenylacetate, which binds with glutamate to increase excretion as sodium phenylacetylglutamate. When oral intake becomes possible, sodium phenylbutyrate is given to increase nitrogen excretion. Because of defects in the urea cycle, dietary nitrogen intake has to be limited. If infants are treated after a serious episode in the newborn period, the prognosis is guarded (11).

Most enzymatic defects in the urea cycle are autosomal recessive, except for ornithine transcarbamylase, which is sex linked. DNA-based diagnosis has allowed for direct mutation analysis and has improved diagnosis. The outcome is better when siblings are treated immediately after birth (11).

8.9 SUMMARY

The availability of gas chromatography and tandem mass spectroscopy (GC/MS/MS), now utilized by most states in the United States, makes it possible to identify more inborn errors of metabolism in the newborn. In the past, programs typically screened newborns for two to four diseases, yet today most state programs can screen for at least 10 diseases. Treatment for many of these includes a change in dietary intake, with varying success. Commercially prepared medical foods are available to treat many of these diseases. In most cases, treatment or special medical foods need to be adhered to throughout life to prevent acute metabolic crises or undesirable developmental changes in later life.

REFERENCES

1. Acosta, P.B., & Gross, K.C. (1995). Hidden sources of galactose in the environment. *Eur. J. Pediatr. 154,* 587–592.
2. Acosta, P.B., & Yannicelli, S. (2001). Maple Syrup Urine Disease (MSUD). In *The Ross Metabolic Formula System Nutrition Support Protocols,* Ross Products Division, Colombus, OH, 74–102.
3. Azen, C., Koch, R., Friedman, E.G., Berlow, S., Coldwell, J., Krause, W., Matalon, R., McCabe, E., O'Flynn, M., Peterson, R., Rouse, B., Scott, C.R., Sigman, B., Valle, D., & Warner, R. (1991). Intellectual development in 12-year-old children treated for phenylketonuria. *Am. J. Dis. Child., 145,* 35–39.
4. Bernegger, C., & Blau, N. (2002). High frequency of tetrahydrobiopterin-responsiveness among hyperphenylalaninemia: A study of 1,919 patients observed from 1988 to 2002. *Mol. Genet. Metab., 77,* 304–313.
5. Berry, G.T., Reynolds, R.A., Yager, C.T., & Segal, S. (2004). Extended [^{13}C] galactose oxidation studies in patients with galactosemia. *Mol. Genet. Metab., 82,* 130–136.
6. Beutler, E. (1997). Disorders of galactose metabolism. In *The Molecular and Genetic Basis of Neurological Disease*. R.N. Rosenberg, S.B. Prusiner, S. Di Mauro, R.L. Barchi, Eds. Butterworth-Heinemann, Boston, 1099–1108.
7. Bickel, H., Gerrard, A.J., & Hickman, E.M. (1953). Influence of phenylalanine intake on phenylketonuria. *Lancet, 2,* 812.
8. Blau, N. http://www.bh4.org.

9. Blau, N., Fiege, B., Ballhausen, D., Schircks, B., Kierat, L., Leimbacher, W., & Thony, B. (2003). Pharmacokinetic of orally administered tetrahydrobiopterin and its stability in plasma. *J. Inherit. Metab. Dis., 26,* S23.
10. Blau, N., & Trefz, F. (2002). Tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency: Possible regulation of gene expression in a patient with the homozygous L48S mutation. *Mol. Genet. Metab., 75,* 186–187.
11. Brusilow, S.W., & Horwich, A.L. (2001). Urea cycle enzymes. In *The Metabolic and Molecular Bases of Inherited Disease*. C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, Eds. McGraw-Hill, New York, 1909–1964.
12. Chace, D.H., & Naylor E.W. (1999). Expansion of newborn screening programs using automated tandem mass spectrometry. *MRDD Research Review, 5,* 150–154.
13. Chuang, D.T., Shih, V.E. (2001). Maple syrup urine disease (branched-chain ketoaciduria). In *The Metabolic and Molecular Bases of Inherited Disease*. C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, Eds. McGraw-Hill, New York, 1971–2006.
14. Dhondt, J.L., Ogier, H., Benoist, J.F., Belhesme, C., & Giraud, M. (2003). The interpretation of tetrahydrobiopterin loading test in hyperphenylalaninemia. *J. Inherit. Metab. Dis. 26,* S18.
15. Fisch, R. Chang, P., Weisberg, S., Guldberg, P., Guttler, F., & Tsai, M.Y. (1995). Phenylketonuric patients decades after diet. *J. Inherit. Metab. Dis., 18,* 347–353.
16. Folling, A. (1934). Uber ausscheidung von pheylbrenztraubensaure in den harn als stoffwechselanomalie in verbindung mit imbesillitat. *Z. Physiol. Chem., 227,* 169–176.
17. Garrod, A.E. (1908). The Croonian lectures on inborn errors of metabolism. *Lancet, 2,* 73.
18. Gross, K.C., & Acosta, P.B. (1991). Fruits and vegetables are a source of galactose: Implications in planning the diets of patients with galactosemia. *J. Inher. Metab. Dis., 14,* 253–258.
19. Grunewald, S., Champion, M.P., Leonard, J.V., Schaper, J., & Morris, M. (2004). Biotinidase deficiency: A treatable leukoencephalopathy. *Neuropediatrics 35,* 211–216.
20. Guldberg, P., Levy, H.L., Hanley, W., Koch, R., Matalon, R., Rouse, B., Trefz, F., de la Cruz, F., Henriksen, K., & Guttler, F. (1996). Phenylalanine hydroxylase gene mutations in the United States: Report from the Maternal PKU Collaborative Study. *Am. J. Hum. Genet., 59,* 84–94.
21. Guthrie, R., & Susi, A. (1963). A simple phenylalanine method for determining phenylketonuria in large populations of newborn infants. *Pediatrics, 32,* 338–343.
22. Guttler, F., Azen, C., Guldberg, P., Romstad, A., Hanley, W.B., Levy, H.L., Matalon, R., Rouse, B.M., Trefz, F., de la Cruz, F., & Koch, R. (1999). Relationship among genotype, biochemical phenotype, and cognitive performance in females with phenylalanine hydroxylase deficiency: Report from the Maternal Phenylketonuria Collaborative Study. *Pediatrics, 104,* 258–262.
23. Hanley, W., Feigenbaum, A., Clarke, J.T.R., Schoonheyt, W., & Austin, V. (1993). Vitamin B12 deficiency in adolescents and young adults with phenylketonuria. *Lancet, 342,* 997.
24. Hennermann, J.B., Vetter, B., Kulozik, A.E., & Monch, E. (2002). Partial and total tetrahydrobiopterin-responsiveness in classical and mild phenylketonuria (PKU). *J. Inher. Metab. Dis.,* 25, S21.
25. Holtzman, N.A., Kronmal, R.A., van Doorninck, W., Azen, C., & Koch, R. (1986). Effect of a great loss of dietary control on intellectual performance and behavior of children with phenylketonuria. *N. Engl. J. Med., 314,* 593–598.

26. Jervis, G. (1953). Phenylpyruvic oligophrenia deficiency of phenylalanine oxidizing system. *Proc. Soc. Exp. Biol. Med., 82,* 514–515.
27. Kaufman, F.R., Kogut, M.D., Donnell, G.N., Goebelsmann, U., March, C., & Koch, R. (1981). Hypergonadotrophic hypogonadism in female patients with galactosemia. *N. Engl. J. Med., 304,* 994–998.
28. Kimura, M., Fukui, T., Tagami, Y., Fujiwaki, T., Yokoyama, M., Ishioka, C., Kumasaka, K., Terada, N., & Yamaguchi, S. (2003). Normalization of low biotinidase activity in a child with biotin deficiency after biotin supplementation. *J. Inher. Metab. Dis., 26,* 715–719.
29. Koch, R., Hanley, W., Levy, H., Matalon, R., Rouse, B., Trefz, F., Guttler, F., Azen, C., Friedman, E., Platt, L., de la & Cruz, F. (2000). Maternal phenylketonuria: An international study. *Mole. Gene. Metab., 71,* 233–239.
30. Koch, R., Friedman, F., Azen, C., Hanley, W., Levy, H., Matalon, R., Rouse, B., Trefz, F., Waisbren, S., Michals-Matalon, K., Acosta, P., Guttler, F., Ullrich, K., Platt, L., & de la Cruz, F. (1999). The International Collaborative Study of Maternal Phenylketonuria. Status report 1998. *MRDD Research Reviews, 5,* 117–121.
31. Kure, S., Hou, D.C., Ohura, T., Iwamoto, H., Suzuki, S., Sugiyama, N., Sakamoto, O., Jujii, Y.K., Matsubara, S.Y., & Narisawa, K. (1999). Tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency: A novel clinical entity. *J. Pediat., 135,* 375–378.
32. Laszlo, A., Schuler, E.A., Sallay, E., Endreffy, E., Somogyi, C., Varkonyi, A., Havass, Z., Jansen, K.P., & Wolf, B. (2003). Neonatal screening for biotinidase deficiency in Hungary: Clinical, biochemical and molecular studies. *J. Inher. Metab. Dis., 26,* 693–698.
33. Lenke, R.L., Levy H.L. (1980). Maternal phenylketonuria and hyperphenylalaninemia: An international survey of the outcome of untreated and treated pregnancies. *N. Engl. J. Med., 303,* 1202–1208.
34. Leuzzi, V., Carducci, Ca., Carducci, Cl., Artiola C., & Antonozzi, I. (2003). Intra- and inter-individual variations of blood Phe under 6-R-BH_4 loading in phenylalanine hydroxylase (PAH) deficiency. *J. Inherit. Metab. Dis., 26,* S21.
35. Lindner, M., Haas, D., Mayatepek, E., Zschocke, J., & Burgard, P. (2001). Tetrahydrobiopterin responsiveness in phenylketonuria differs between patients with the same genotype. *Mol. Genet. Metab., 73,* 104–106.
36. Love-Gregory, L.D., Dyer, J.A., Grasela, J., Hillman, R.E., & Phillips, C.L. (2001). Carrier detection and rapid newborn diagnostic test for the common Y393N maple syrup urine disease allele by PCR-RFLP: Culturally permissible testing in the Mennonite community. *J. Inher. Metab. Dis., 24,* 393–403.
37. Matalon, R., Michals, K., Blau, N., & Rouse, B. (1989). Hyperphenylalaninemia due to inherited deficiencies of tetrahydrobiopterin. In *Advances in Pediatrics* L.A. Barness, D.C. DeVivo, G. Morrow, et al., Eds. Year Book Medical Publishers. Chicago, pp. 67–82.
38. Matalon, R., Koch, R. Michals-Matalon, K., Moseley, K. & Stevens, R. (2002). Tetrahydrobiopterin-responsive phenylalanine hydroxylase mutations. *J. Inher. Metab. Dis., 25,* 23S.
39. Matalon, R., Michals-Matalon, K., Azen, C., Koch, R., Rouse, B., Hanley, W., Levy, H., Trefz, F., & de la Cruz, F. (1998). Maternal PKU: Microcephaly at birth and 2 years of age. *J. Inherit. Metab. Dis., 21,* S17.
40. Matalon, R., Koch, R., Michals-Matalon, K., Moseley, K., Surendran, S., Tyring, S., Erlandsen, H., Gamez, A., Stevens, R., Romstad, A., Moller, L.B., & Guttler, F. (2004). Biopterin responsive phenylalanine hydroxylase deficiency. *Genet. Med., 6,* 27–32.

41. Michals, K., Azen, C., Koch, R., Acosta, P., & Matalon, R. (1988). Blood phenylalanine levels and intelligence of ten-year-old children with phenylketonuria in the National Collaborative Study. *J. Am. Diet. Assoc., 88,* 1226–1229.
42. Michals-Matalon, K., Acosta P., & Azen, C. (2003). The role of nutrition in pregnancy with phenylketonuria and birth defects. *Pediatrics, 112,* 1534–1536.
43. Michals-Matalon, K., Matalon, R., Acosta, P., & Azen, C. (1999). Congenital heart disease in maternal phenylketonuria: Effects of blood phenylalanine and nutrient intake. *MRDD Research Reviews, 5,* 122–124.
44. Michals-Matalon, K., Platt, L.D., Acosta, P., Azen, C., & Walla, C.A. (2002). Nutrient intake and congenital heart disease in maternal phenylketonuria. *Am. J. Obstet. Gynecol., 187,* 441–444.
45. Morton, H.D., Strauss, K.A., Robinson, D.L., Puffenberger, E.G., & Kelley, R. (2002). Diagnosis and treatment of maple syrup disease: A study of 36 patients. *Pediatrics, 109,* 999–1008.
46. Moslinger, D., Muhl, A., Suormala, T., Baumgartner, R., Stockler-& Ipsiroglu, S. (2003). Molecular characterization and neuropsychological outcome of 21 patients with profound biotinidase deficiency detected by newborn screening and family studies. *Eur. J. Pediatr., 162,* S46–S49.
47. Muntau, A.C., Roschinger, W., Habich, M., Demmelmeir, P., Hoffmann, B., Sommerhoff, C.P., & Roscher, A.A. (2002). Tetrahydrobiopterin as an alternative treatment for mild phenylketonuria. *N. Engl. J. Med., 347,* 2122–2132.
48. National Institutes of Health Consensus Development Panel. (2001). National Institutes of Health Consensus Development Conference Statement. Phenylketonuria: Screening and management. *Pediatrics, 108,* 972–982.
49. Rouse, B., Azen, C., Koch, R., Matalon, R., Hanley, W., de la Cruz, F., Trefz, F., Friedman, E., & Shifrin, H. (1997). Maternal Phenylketonuria Collaborative Study (MPKUCS) offspring: Facial anomalies, malformations and early neurological sequelae. *Am. J. Med. Genet., 69,* 89–95.
50. Schweitzer, S., Shin, Y., Jakobs, C., & Biodehl, L. (1993). Long-term outcome in 134 patients with galactosemia. *Eur. J. Pediatr., 152,* 36–43.
51. Scriver, C.R., & Kaufman, S. (2001). Hyperphenylalaninemias: Phenylalanine hydroxylase deficiency. In *The Metabolic and Molecular Bases of Inherited Disease,* C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, Eds. McGraw-Hill, New York, 1667–1724.
52. Scriver, C.R., Waters, P.J., Sarkissian, C., Ryan, S., Prevost, L., Cote, D., Novak-Teebi, S., & Nowacki, P.M. (2000). PAHdb: A locus-specific knowledgebase. *Hum. Mutat. 15,* 99–104.
53. Shintaku, H., Kure, S., Ohura, T., Okano, Y., Ohwada, M., Sugiyama, N., Sakura, N., Yoshida, I., Yoshino, S., Matsubara, Y., Suzuki, K., Aoki, K., & Kitagawa, T. (2003). Diagnosis and long-term treatment of tetrahydro-biopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. *J. Inherit. Metab. Dis., 26,* 22.
54. Spaapen, L.J.M., Bakker, J.A., Velter, C., Loots, W., Rubio, M.E., Forget, P.P., Duran, M., Dorland, L., Poll-The, B.T., Ploos van Amstel, H.K., Bekhof, J., & Blau, N. (2000). Tetrahydrobiopterin-responsive hyperphenylalaninemia (HPA) in Dutch neonates. *J. Inher. Metab. Dis., 23S,* 45.
55. Steinfeld, R., Kohlschutter, A., Zschocke, J., Lindner, M., Ullrich, K., & Lukacs, Z. (2002). Tetrahydrobiopterin monotherapy for phenylketonuria patients with common mild mutations. *Eur. J. Pediatr., 161,* 403–405.

56. Sweetman, L., & Williams, J. (2001). Branched chain organic acidemias. In *The Metabolic and Molecular Bases of Inherited Disease,* C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, Eds. McGraw-Hill, New York, 2125–2164.
57. Thompson, A.J., Smith, I.L., Brenton, D., Youl, B.D., Rylance, G., Davidson, D.C., Kendall, B., & Lees, A.J. (1990). Neurological deterioration in young adults with phenylketonuria. *Lancet, 336,* 602–605.
58. Trefz, F., Blau, N., Aulehla-Scholz, C., Korall, H., & Frauendienst-Egger, G. (2000). Treatment of mild phenylketonuria (PKU) by tetrahydrobiopterin (BH4). *J. Inher. Metab. Dis., 23S,* 47.
59. Trefz, F., Aulela-Scholz, C., & Blau, N. (2001). Successful treatment of phenylketonuria with tetrahydrobiopterin. *Eur. J. Pediatr., 160,* 315.
60. Waggoner, D.D., Buist, N.R.M., & Donnell, G.N. (1991). Long term prognosis in galactosemia: Results of a survey of 350 cases. *J. Inher. Metab. Dis., 13,* 802–818.
61. Weber, P., Scholl, S., & Baumgartner, E.R. (2004). Outcome in patients with profound biotinidase deficiency: Relevance of newborn screening. *Dev. Med. Child. Neuro., 46,* 481–484.
62. Weglage, J., Grenzebach, M., Teeffelen-Heithoff, T., Marquardt, R., Feldmann, J., Denecke, D., Godde, D., & Koch, H.G. (2002). Tetrahydrobiopterin responsiveness in a large series of phenylketonuria patients. *J. Inherit. Metab. Dis., 25,* 321–322.
63. Willard, J.M., Reinard, T., Mohsen, A.-W., & Vockley, J. (2001). Cloning of genomic and cDNA for mouse isovaleryl-CoA dehydrogenase (IVD) and evolutionary comparison to other known IVDs. *Gene, 270,* 253–257.
64. Wolf, B. (2001). Disorders of biotin metabolism. In *The Metabolic and Molecular Bases of Inherited Disease,* C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle, Eds. McGraw-Hill, New York, 3935–3962.

9 Malnutrition and the Immune System

R.K. Chandra

CONTENTS

9.1 INTRODUCTION

For millennia, society has recognized the critical importance of dietary intake and health. This includes protection from infection as depicted in the Four Horsemen of the Apocalypse. Malnutrition aggravates the risk of infection, and this has been documented in numerous epidemiological studies in the past 50 years. Besides poor sanitation, contaminated food and water, overcrowding, lack of knowledge of health and nutrition, and inadequate immunization, impaired immune response is a key pathogenetic factor in the malnutrition–infection interaction. This applies both to what may be called resurgent diseases, such as influenza, measles, tuberculosis, diarrhea, and respiratory infections, and to newly emergent diseases, such as HIV (human immunodeficiency virus) infection, Legionnaire's disease, Ebola, and SARS (severe acute respiratory syndrome). It is to be emphasized that both nutrient deficiencies and excesses impair the function of the immune system and make the host vulnerable to infectious disease and other disorders (2–4). Growing data indicate that changes in nutritional immune status may have a causal role in many chronic diseases, including cancer, inflammatory bowel disease, autoimmune disorders,

allergy, and others. This selective review highlights the well-known findings and provides a few practical recommendations.

Early epidemiologic studies in Asia, Africa, and South America established the relationship between overt protein–energy malnutrition (PEM) and increased incidence and severity of common respiratory and gastrointestinal infections resulting in higher mortality among young children (12). For example, in children with PEM, the incidence of diarrhea is increased by at least 40% and the duration of each episode is two to three times longer than in well-nourished controls. Similar findings have been reported for lower respiratory tract infections, both bacterial and viral.

9.2 THE IMMUNE SYSTEM

Host resistance depends on a number of factors. The immune system forms the central pillar of this defense and can be likened to an umbrella (see Figure 9.1). Traditionally the immune system is divided into two tiers, nonspecific and specific. Nonspecific or innate immunity consists of physical barriers such as skin and mucous membranes, cilia, mucus, phagocytes, complement system, lysozymes, natural killer (NK) cells, and others. Specific or adaptive immunity is of two types: antibodies of five different immunoglobulin isotypes (IgG, IgA, IgM, IgD, and IgE) and cell-mediated immunity, which depends primarily on T-lymphocytes and their activation products (such as interferon, interleukins, and tumor necrosis factors). The nonspecific and specific factors of immunity are not entirely independent and interact with each other.

The immune responses can be influenced by several factors, including genetic endowment, diet and nutritional status (*vide infra*), nutrient supplements, physical exercise, emotional stress, temperature of the body and of the environment, and chronic diseases, including infections. For example, modest physical exercise enhances several immune responses, but prolonged intense vigorous exercise, such as marathon racing, impairs immunity and often results in a bout of acute respiratory infection. Stress such as that preceding a university examination reduces the function of NK cells and phagocytes and may result in common infections.

9.3 PROTEIN–ENERGY MALNUTRITION AND DEFICIENCIES OF INDIVIDUAL NUTRIENTS

The effect of nutritional deficiencies on immunity has been the subject of many books and review articles. Briefly, protein–energy malnutrition results in a reduction in cell-mediated immunity, fewer T-lymphocytes (especially CD4+ helper cells), phagocyte dysfunction such as chemotactic migration and microbicidal capacity, reduced levels of complement proteins C3 and factor B, and decreased production of interferon-gamma and interleukin-2 (see Figure 9.2). Similar findings have been noted in deficiency of individual nutrients such as zinc, iron, selenium, vitamin A, vitamin B_6, folic acid, and vitamin E. For example, zinc deficiency results in impaired delayed hypersensitivity reactions, decreased migration of microphages, and reduced cytokine production. In addition, reduced activity of serum thymulin, a nine–amino

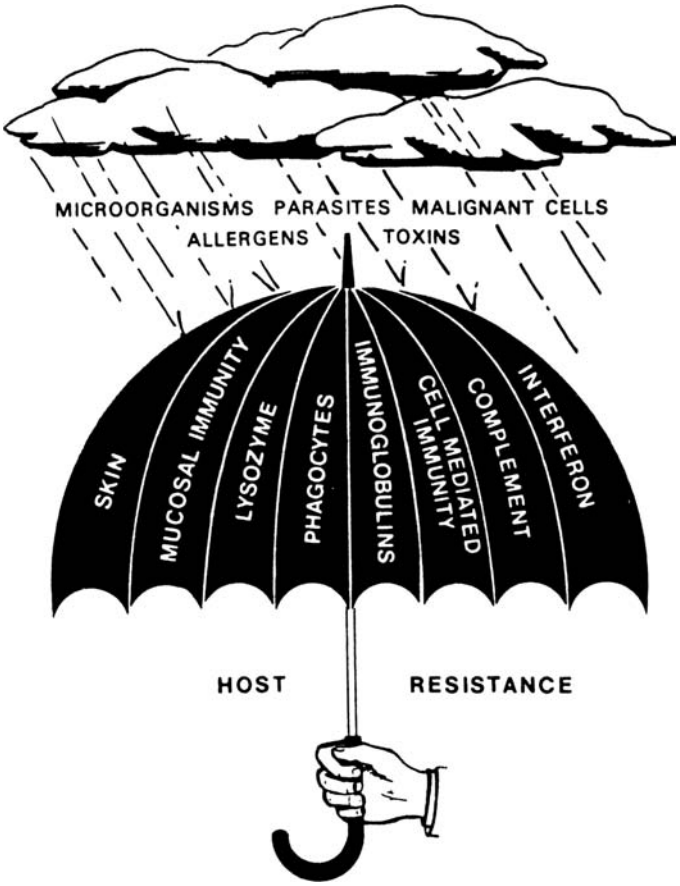

FIGURE 9.1 A simple view of host defenses as a protective umbrella, consisting of skin and mucous membranes, complement system, interferon, lysozymes, phagocytes, immunoglobulins, and cell-mediated immunity.

acid polypeptide secreted by thymic epithelial cells, is a sensitive nutrient-specific measure of zinc deficiency. Iron deficiency decreases the ability of phagocytes to kill ingested bacteria and fungi; it also reduces NK cell activity. The data have been replicated in all age groups and in laboratory animals.

The importance of nutrition for immunity has been demonstrated for all age groups, but three periods of life need particular emphasis.

9.4 LOW BIRTH WEIGHT INFANTS

In different parts of the world, the incidence of low birth weight, defined as weight less than 2.5 kg for babies born after 37 weeks, varies from 7 to 41% (13). In addition to other physiologic handicaps, these infants are prone to infection. This may well be due to impaired immune responses. In many infants, these problems with immu-

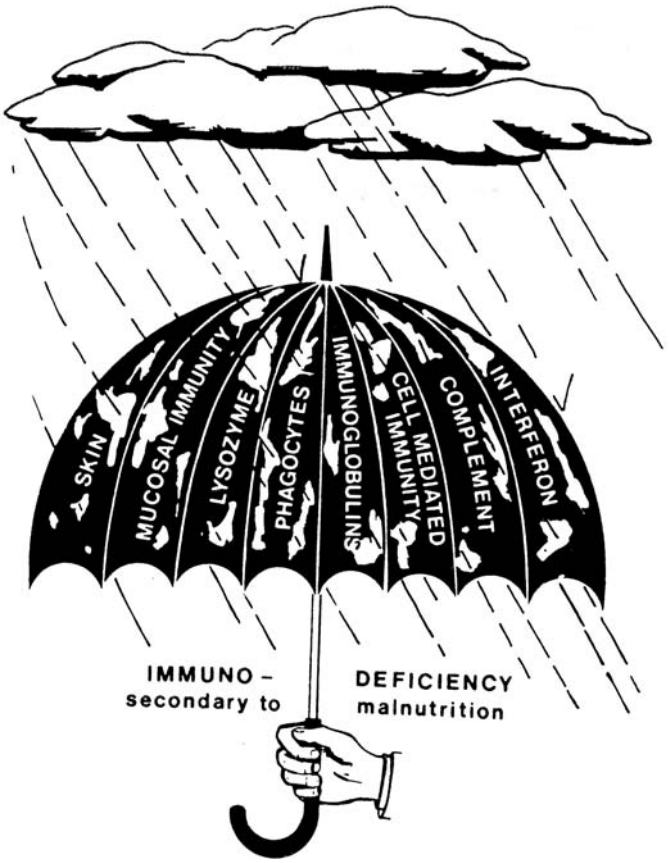

FIGURE 9.2 Host defenses are breached in malnutrition, resulting in infections.

nity may last for several years, as has also been documented in animal models of intrauterine malnutrition. The provision of extra amounts of zinc and/or iron improves immune responses, but the best result is observed when all essential vitamins and trace elements are given as a supplement for the first 6 to 12 months of life. Such an intervention results in enhanced immune responses and reduced morbidity (5). In animal models of intrauterine malnutrition, the effect on immune responses is observed for at least three generations.

9.5 ADOLESCENTS

Another vulnerable population group is adolescents. In many countries, the prevalence of eating disorders such as anorexia nervosa and bulimia has reached epidemic proportions. In individuals with these disorders, evidence of nutritional deficiencies and of impaired immunity parallels what has been observed in young children with protein-energy malnutrition (10). Iron deficiency is rampant among teenagers and affects several physiological systems, including immunity, cognition, gastrointestinal

TABLE 9.1
Immunological Data in Elderly Subjects Given a Placebo or a Micronutrient Supplement

Variable	Placebo	Supplement
T cells %:		
CD3+	52.8	66.1
CD4+	42.1	48.9
NK cells %	9.3	12.7
NK cell activity	27	41
IL-2 (units/ml)	3.6	12.8
Antibody response to influenza virus vaccine	2.1[a]	3.2[a]

Note: Data are given for observations made after 12 months of use of placebo or supplement. Data are shown as means. All values between the two groups are statistically significantly different. NK = natural killer.

[a] Log reciprocal.

Source: From Chandra RK. *Lancet 340:* 1124–1127 (1992). With permission.

function, scholastic performance, and temperature homeostasis (14). Once again, the provision of a suitable supplement containing optimum amounts of trace elements and vitamins is associated with heightened immune responses and reduced occurrence of infection. Improved cognitive function is an added benefit.

9.6 ELDERLY

Renewed interest in the health of the elderly is due principally to two reasons. First, the proportion and absolute number of older persons is increasing in every country. In India and China, a 1% increase in this age group means an increase of 10 million individuals. Second, older persons are ill more often, and their illnesses last longer. For example, pneumonia is usually an easily treatable illness in the young, requiring about a week of antibiotic therapy. In seniors, pneumonia requires more aggressive and longer therapy and can be fatal. It has now been shown that aging is associated with a variety of immunologic deficiencies (1). The response to common vaccines is diminished in the elderly, thereby decreasing the protective efficacy of immunization, a factor of immense public health importance.

Many studies have looked at individual nutrients in the elderly, but this is unlikely to be the logical approach, because deficiencies are often multiple. Based on surveys of the prevalence and severity of nutritional deficiencies and on dose–response curves to discover the optimum amount of each vitamin and trace element, supplements have been devised and tested in randomized controlled trials (6; see Table 9.1). It has been shown that the provision of a supplement containing modest amounts of all essential micronutrients is associated with enhanced immune responses and reduced occurrence of respiratory and other infections. Given the high cost of health

care in most countries, this is a highly cost-effective preventive strategy. At the same time, recent data suggest that megadoses of nutrients carry significant side effects and are detrimental for the immune system, resulting in more frequent and more severe infection. In addition to benefits for the immune system, the provision of micronutrient supplements is advantageous for cognitive functions and for prevention of osteoporosis and macular degeneration.

9.7 OTHER DISORDERS

Besides these age groups, the role of nutrition in maintenance and enhancement of immunity has been examined in a number of disease states (9), including HIV infection, cancer, diabetes, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, eating disorders, and chronic infection. Recent work in populations with high prevalence of HIV has shown that the provision of good diet and of nutritional supplements improves the quality of life, decreases infections, and increases the length of survival. Also, such interventions reduce the mother-to-infant transmission of the viral infection. In inflammatory bowel disorders, nutritional supports increase general well-being and reduce the need for or dose of corticosteroid therapy. In tuberculosis, the provision of an appropriate micronutrient supplement accelerates the conversion of sputum that is positive for acid-fast *Mycobacterium tuberculosis* organisms to a sputum-negative status (7). This is of enormous public health significance and would reduce the cost of national programs for control of tuberculosis.

9.8 OBESITY AND EXCESS INTAKE OF NUTRIENTS

Obesity may also be considered a form of "malnutrition," and, as in protein–energy malnutrition, it is accompanied by a number of changes in immune responses (8,11). These include reduced lymphocyte stimulation response and phagocyte dysfunction. The incidence of upper and lower respiratory infections is increased. In addition to obesity, an excess intake of several nutrients, including zinc, iron, vitamin A, and vitamin E, is associated with reduced immune responses and increased morbidity due to infection, fractures, and bleeding. Thus, moderation should be the key recommendation in nutritional advice.

There is recent evidence to suggest that obese individuals have higher levels of many markers of inflammation, including C-reactive protein and interleukin-6 (8). This could be one of the mechanisms for the development of atherosclerosis in high-risk individuals.

9.9 PRACTICAL ADVICE

9.9.1 Children

From infants to adolescents, children are picky eaters, and their nutritional intake is less than optimum in the majority of individuals. Occasionally this may result in overt clinical deficiencies, such as iron-deficiency anemia among teenage girls. In

the majority, however, such dietary practices lead to subclinical deficiencies. Of course, the first step must be to take a detailed history of dietary intake and any associated factors that affect food intake, absorption, and needs, e.g., smoking or use of contraceptive pills. This should then lead to practical advice about optimum food intake. Adolescents should be given a wide variety of choices in each major food group.

It is often observed that subclinical deficiencies of vitamins and trace elements exist in the majority of children. For this reason, it is prudent to advise a suitable multivitamin supplement to be administered daily. This will ensure prevention and correction of subclinical deficiencies and result in better immunity, fewer infections, improved cognition, and higher bone mineral density.

9.9.2 Senior Citizens

Many factors increase the risk of nutrient deficiencies in those over 60 years of age, including loss of spouse, physical and psychological isolation, physical disability such as arthritis, malabsorption, diseases such as diabetes and cancer, multiple medications, and alcohol abuse. Common deficiencies involve folic acid and vitamins B_6, B_{12}, C, D, and E. These deficiencies are often subclinical. It is neither practical nor economic to test every person's blood to identify those who have nutritional problems. At the same time, the administration of modest amounts of vitamins and trace elements is without side effects and can be recommended for everyone above the age of 60. There is much evidence to suggest that this will result in better immunity, fewer infections, reduced occurrence of hospitalization, better physical capacity, less risk of cataract and macular degeneration, and more positive health in general. The preparation chosen should preferably be based on dose–response curves for each of its ingredients and should in any case be backed by credible objective research.

9.10 CONCLUSION

Nutrition is undeniably a critical determinant of immunity and good health. In addition to a balanced diet, many age groups require and would benefit from the regular use of a micronutrient supplement that would enhance immunity and reduce infection, thereby decreasing suffering and improving survival. These groups include small-for-gestation low birth weight infants, school-age children, adolescents, and the elderly.

REFERENCES

1. Adolfsson O, & Meydani SN. Nutrition and the aging immune response. In: Rosenberg IH, Sastre A, eds. *Nutrition and Aging*. Basel, Karger, 2002: 207–222.
2. Calder PC, Field CJ, & Gill HS, eds. *Nutrition and Immune Function*. New York, Cabi Publishing, 2002.
3. Chandra RK. McCollum Award Lecture. Nutrition and immunity: Lessons from the past and new insights into the future. *Am. J. Clin. Nutr. 53:* 1087–1101, 1991.

4. Chandra RK, ed. *Nutrition and Immunology in the 21st Century.* Toronto, TSAR Health, 2004.
5. Chandra RK. Interactions between early nutrition and the immune system. In Bock GR, Whelan J, eds. *The Childhood Environment and Adult Disease*. Ciba Foundation Symposia 156, 1991: 72–92.
6. Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. *Lancet 340:* 1124–1127, 1992.
7. Chandra RK. Nutrient supplementation as adjunct therapy in pulmonary tuberculosis. *Int. J. Vitam. Nutr. Res. 74:* 144–146, 2004.
8. Chandra RK. Obesity, immunity and health. In Caroli M, Chandra RK, Ferlaut M-L, eds. *Childhood Obesity: Recent Knowledge and Future Directions*. 2004. In press.
9. Labadarios D, & Pichard C, eds. *Clinical Nutrition: Early Intervention*. Basel, Karger, 2002.
10. Marcos A, Montero A, Lopez-Varela S, Gomez-Martinez S, et al. Anthropometric measurements and immune responses in elite gymnasts and in patients with anorexia nervosa. *Nutr. Res. 18:* 247–257, 1998.
11. Samartin S, & Chandra RK. Obesity, overnutrition and the immune system. *Nutr. Res. 21:* 243–262, 2001.
12. Scrimshaw NS, Taylor CE, & Gordon JE. *Interactions of Nutrition and Infection*. Geneva, World Health Organization, 1968.
13. Suskind RM, & Tontisirin K, eds. *Nutrition, Immunity and Infection in Infants and Children*. Philadelphia, Lippincott, 2001.
14. Vyas D, & Chandra RK. Functional implications of iron deficiency. In: Stekel A, ed. *Iron Nutrition in Infancy and Childhood*. New York, Raven Press, 1984, 45–59.

10 Nutritional and Dietary Considerations in Management of Chronic Oral Diseases

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CONTENTS

10.1 INTRODUCTION

Dental caries and periodontal diseases are, by far, the most common oral diseases worldwide and may well be the most common chronic diseases of mankind. Diverse lesions of the oral mucosa are also widespread. Caries and periodontal disease have been extensively investigated and are now recognized as constituting chronic infections. Data to indicate nutritional determinants of susceptibility and progression are sparse for periodontal diseases; however, with respect to dental caries, there are extensive data to indicate potent dietary, albeit not overall nutritional, influences on it. Mucosal lesions are often associated with nutritional deficiency states.

Partial or total loss of teeth (edentulous status) often is the outcome of dental caries and periodontal disease and may have significant nutritional impact. Nonetheless, people can live without teeth and not profoundly suffer physically; yet, the quality of life and nutrient intake may be significantly affected by tooth loss. In some societies, the disfigurement that results from major tooth loss has an effect on social acceptance or standing.

This chapter deals with nutritional and dietary considerations as they affect oral mucosal disease, gingival/periodontal disease, and dental caries. In addition, the chapter explores consequences to nutrition of partial or total tooth loss and use of artificial dentures. Issues related to the management of these diseases are briefly considered, but a detailed discussion of treatment strategies is beyond the scope of this chapter. Gaps in knowledge that may inhibit enlightened management of patients with nutritional problems are pointed out as either fertile or problematic areas for research.

10.2 ORAL MUCOSAL DISEASE

Images of oral mucosal abnormalities, especially those of the tongue, that have been attributed to nutritional deficiency states appear in many textbooks of oral pathology, medicine, and diagnosis (9,90). These abnormalities, especially those described as "bald" tongues with atrophy of filiform papillae or as beefy-red, fissured, or pale tongues, have been attributed to deficiencies of various vitamins (B_1, B_2, B_6, niacin) or to anemia due to deficiency of vitamin B_{12} or iron.

It is evident from the literature, whether based on studies of isolated patients or of endemic areas of malnutrition, that micronutrient deficiencies are associated with mucosal and tongue manifestations (30). Generalizations from isolated cases and attribution of causes are, however, hazardous and may divert attention from other more common disease states, at least in the developed world. Extensive search of the literature reveals there are only very limited data available from controlled studies on mucosal disease causation. The same applies to the effects of nutritional deficiency on pathogenesis of oral diseases in impoverished people in the developed or undeveloped worlds. No interventional studies appear to have been reported.

Unquestionably, many normal people have fissured tongues, and many, if not most, chronically xerostomic (dry mouth) patients have fissured, bald, or red tongues that reflect a combination of diminished salivary flow rate, altered salivary defense molecule abundances or composition, and associated changes of oral flora. Oral floral shifts in dry mouth patients commonly favor mucosal surface ascendancy of *Candida* species, usually *C. albicans*, which appears to be a low-level indigenous microorganism of the human mouth, especially in males (16,45,116). Thus, oral atrophic or erythematous candidiasis can be considered an opportunistic infection in the setting of xerostomia. In fact, entities termed chronic atrophic candidiasis and chronic erythematous candidiasis are now recognized as common in patients with Sjögren's syndrome (45,51,91,107,108). In many cases, these atrophic and erythematous changes remit with anti-*Candida* topical therapy (20) or, in the case of chronic anticholinergic medication use, with their discontinuation (21). Clinicians should not assume that oral candidiasis is manifested by thrush (pseudomembranous can-

didiasis) in such patients; thrush is more usually observed in patients who are immunosuppressed or using broad spectrum antibiotics chronically (9,90).

It is thus important to regard most abnormalities of the oral and especially tongue mucosa as nonspecific, unless there is compelling reason to allow attribution to specific disease. Management with vitamin therapy, cholinomimetic agents, lubricants, or antifungal agents should be based on diagnostic data with therapy contingent upon diagnosis. It should be recognized that many millions of Americans chronically use a variety of agents that are either anticholinergic-by-intent (e.g., antispasmodic) or anticholinergic-by-side-effect (e.g., many antidepressant, antipsychotic, antihistaminic, and some antihypertensive drugs). Furthermore, the number of Americans with Sjögren's syndrome ranges from 1.5 to 2.5 million in a population of roughly 280 million. About 9 out of 10 Sjögren's sufferers are women of peri- to postmenopausal age. If one assumes that half the population is female, and that half of them are peri- or postmenopausal, 3 to 4% of peri- and postmenopausal women seen by physicians and dentists are likely to have Sjögren's syndrome, with its characteristic progressive xerostomia and resultant mucosal changes. The number of individuals who take medications with anticholinergic effect is even more impressive (71,88). Because these conditions are much more common in the developed countries than frank deficiency diseases, they are a far more likely cause of oral mucosal abnormalities than an underlying nutritional deficiency.

Caution must be voiced regarding individuals with cancer or disease states that affect ingestion, absorption, or energy metabolism or that result from unmet functional dependencies of the elderly or disabled. Because oral diseases per se are seldom seen as posing survival risks, they are seldom the focus of attention among care givers to dependents or nursing home residents, yet they can have significant impact on health and the quality of life (82,104,126,130).

Common diseases of the oral mucosa, often incorrectly attributed to having arisen from nutritional deficiency states, include aphthous ulcers (canker sores), benign migratory glossitis (geographic tongue), erythema migrans, both reticular and erosive forms of lichen planus, pemphigus, and mucous membrane pemphigoid. There are no strong data that associate nutrient deficiency states with either their induction or modification (83).

10.3 PERIODONTAL DISEASES

Most people in the developed world may not appear to be nutritionally deficient, but they frequently have gingivitis/periodontitis. Before considering how nutritional status can affect periodontal health, it is necessary to briefly review these diseases of the gums (gingivae). Many diseases affect the gingivae and the tooth-supporting deeper tissues of the jaws (collectively called the periodontium), but by far the most common are termed gingivitis (gingival inflammation) and chronic periodontitis, to which gingivitis frequently but not invariably evolves. Periodontitis is an inflammatory state that leads to progressive migration of the attachment of the gingivae along the roots of the teeth, resulting in destruction of the ligament that connects the teeth to the alveolar (tooth socket) bone, resorption of that bone, and eventual loosening and exfoliation of the teeth. Relatively infrequent acute gingivitis/periodontitis enti-

ties will not be discussed here. Common gingivitis and periodontitis are chronic conditions that undergo periods of remission and exacerbation (102), a situation that complicates their study. Between 10 years and some 60 years may elapse between inception of gingivitis and exfoliation of teeth due to periodontitis. Often individual teeth rather than the entire dentition are affected. With time, partial loss of the dentition may evolve into a state of total edentulism.

The chronicity of these infectious, inflammatory diseases, especially in the setting of multiple potent confounding variables, may, however, obscure real nutritional influences. The potency of the covariates — most notably, effectiveness of patient oral hygiene to remove dental plaque; professional tooth surface debridement of dental plaque and calculus (19); smoking (48,87); and diabetes (32,54,97,105) — superimposed on the oscillatory (102) progression of these diseases, discourages investigation from a nutritional standpoint. Moreover, a nutritional signal may be obscured by the background noise of the infection, the host's immune response to it, and the potent covariants.

Malnutrition has been suggested as a risk factor in acutely exacerbating the gingivitis/periodontitis that has been described as necrotizing ulcerative gingivitis (trench mouth; 33).

Probably the best-known nutritional association with gingivitis and, specifically, its sometimes acute inflammation and bleeding is the severe vitamin C deficiency of early seafarers. The deficiency was ameliorated, historically, by citrus fruit ingestion, with the consequent, now-quaint description of British sailors as "limeys" (52). Vitamin C deficiency was later shown not to be causative of gingivitis/periodontitis but rather to be superimposed on its bacteriological/host response bases. Vitamin C treatment of either laboratory animals or humans with gingivitis/periodontitis had no clear beneficial effects (64), and epidemiological studies indicate there is only a weak association between the two conditions (57). Thus neither case-control nor interventional studies support the notion that gingivitis is a direct result of vitamin C deficiency.

Even though no convincing dietary or nutritional conditions are known to be associated with various periodontitis states (5), it may be premature to exclude these entirely. Both gingivitis and periodontitis reflect host responses to colonization by certain bacteria found in the dental plaque biofilm, especially that located between the teeth and the gingivae, an area referred to as the gingival crevice and, when deeper, the periodontal pocket. Frequent mechanical and chemotherapeutic removal of this plaque mitigates the inflammation and disease progression. If, however, certain floral components become established in this space, the risk for gingivitis/periodontitis increases, as does the aggressiveness of effects that lead to accelerated alveolar bone loss (101). The efficacy of antimicrobial interventions against periodontitis is clear (1,49,85), but it is diminished in smokers (48,87) and in uncontrolled diabetics (54,97), although some uncertainty remains with regard to diabetics (105). This indicates not only the complexity of requirements for effective therapy, but also possible nutritional effects. Because the inflammatory and bone reabsorptive effects of gingivitis/periodontitis result from the bacterial composition of the plaque biofilm and the immune responses of the host, one cannot exclude

possible nutritional effects on the B- and T-cell immune systems and on nonspecific innate host-protective mechanisms, all of which modulate disease expression.

It must be noted that most studies of gingivitis/periodontitis have been done in nominally healthy individuals. We are aware of no systematic longitudinal or interventional studies in nutritional-deficiency or nutritional-excess states that assess either the risk for these infections or the progression of these common diseases. There are, nonetheless, reports that associate obesity with periodontitis in relatively young individuals (2,93), but these effects could be manifestations of covariates, such as SES, oral hygiene practices, and diabetes.

In considering the relationship between nutrition and oral diseases, one must not omit considering the elderly or infirm, whose abilities to obtain proper nutrients while free-living are highly variable. The situation of residents of nursing homes or of institutions for the disabled in this respect is equally uncertain. Commonly, the very poor health status of many elderly includes severe gingivitis and periodontitis (92). The extent to which these are conditioned by nutrition or have resulted from the kind or number of microbial cells of the dental plaque biofilm, from compromises of the host immunity, from inattention to or inability to carry out proper oral hygiene, from smoking behavior, and so forth are difficult to determine and largely unstudied. There is also evidence that the host flora undergoes change when individuals are placed in institutions such as nursing homes or hospitals. The nosocomial effects of changes on the oral flora are now gaining attention (94).

10.4 DENTAL CARIES (TOOTH DECAY)

10.4.1 Changing Prevalence and Populations Affected

Dental caries was formerly thought to be a disease primarily of childhood and adolescence, because most of its lesions (cavities) developed within about 3 years of the eruption of a tooth (17). It is now recognized that this extremely common infectious disease is chronic in nature and continues throughout life (40,84). Several factors have contributed to this change in prevalence. These include protection of the dental enamel of young people due to water fluoridation or topical fluoride treatment (42), with resultant dentition survival into adulthood and beyond (75,110); increased longevity of the population, with more teeth at risk for caries attack (84,137); increased exposure of root surfaces due to chronic periodontitis, with resultant supragingival plaque colonization; increased number of dental fillings, the margins of which are at high risk for secondary caries (43); and increased use of medications with anticholinergic and, thus, salivation-inhibiting effects (71). In addition, dietary and nutritional effects that occur in the older years may assume significance that only recently has attracted attention (40,98).

Low birth weight children (often the offspring of malnourished mothers) have been thought to have more severe caries, but this is not supported by the relevant literature (14). Investigations of comparable communities with greatly different caries experience have not supported a role of trace elements (11), other than for the well-known potent caries-inhibiting effects of fluoride (42,138).

The progressive shift from sucrose to corn-derived sweetener use, especially in soft drinks, substantially began in the United States in the mid-1970s (13,111). This practice may have played a significant role in decreasing carious lesion prevalence in youth and adolescence, thus also increasing availability of teeth to risk for caries in the senior years. But this possibly beneficial impact may be difficult to quantify due to the confounding concomitant increase of consumption of soft drinks (58). The possibility of relatively less cariogenic effects of this alternative soft drink sweetener, by comparison with sucrose, is supported by the observation that decay of the smooth surfaces of the teeth is more prevalent in the United Kingdom, where soft drinks are made primarily with sucrose, than in the United States, where they are made predominantly with high-fructose corn sweetener, despite the higher consumption of soft drinks in the United States than in the United Kingdom (13). Data from experimental animals support this view (114). The human data are further confounded by the potent effects of fluoride, used widely since the 1970s in our society, mostly in the form of dentifrices and fluoridated water.

The prevalance of carious lesions no longer follows a normal distribution in those developed countries where relevant data are available. Rather, the distribution is skewed — a small percentage of people have most of the lesions (129,131). The cost of dental services for repair of carious lesions and the expenses of the cascade of restorative, endodontic, prosthetic, and oral surgical services consequent to caries (29) are, by contrast, mostly borne by those who have dental insurance or who are relatively affluent (28,80). Children from economically disadvantaged families have not enjoyed the same benefits of reduction in caries as those from higher-income families (126), yet they bear the burden of a disparate share of this disease, a phenomenon seen also in other countries (67). The disadvantaged adult population, of course, also has the least ability to pay for repair of the effects of this disease (126). Dental caries is especially prevalent in the elderly and the disabled (40,77,86,132,140), a topic that appears to be underinvestigated in nationwide studies.

10.4.2 Infectious Nature, Causative Bacteria, and Interactions with Diet

Dental caries is an infectious disease. Its expression is potently conditioned by diet. Germ-free animals do not develop caries, no matter what their diet or genetic background. Rodents and humans previously thought to be genetically resistant or "immune" to dental caries develop the disease when infected by cariogenic bacteria, provided the host consumes a diet that is high in carbohydrates fermentable by the infectious bacteria, largely *Streptococcus mutans*. This is especially so when that diet contains sucrose frequently and for the long term (76,117,118). These seminal points require elaboration. The interdependence of factors contributory to this disease, working in concert over time, is represented by the series of diagrams shown in Figure 10.1.

10.4.3 Evidence on the Infectious Nature of Caries

Caries was discovered to be a transmissible disease in a remarkable series of experiments done by Paul H. Keyes and Robert J. Fitzgerald in hamsters and rats

in the late 1950s and 1960s (for review, see 117). In brief, the development of lesions of the disease was shown to be dependent on colonization of teeth by certain streptococci, now termed the mutans group of streptococci, if accompanied by consumption of a diet high in simple carbohydrates. The ability of mutans streptococci to colonize the teeth and the severity and tooth surface distribution of lesions that affect not only the fissures of the teeth but their smooth surfaces were augmented by supply of a sucrose-rich diet in animals inoculated by these streptococci (35,39,44,69,114,128). Studies in rodents led to analogous results in studies of nonhuman primates (10) and in hundreds of human studies (for review, see 122). The name *Streptococcus mutans* had first been proposed in 1924 for unusual streptococci that were found in human carious lesions in England (18). These bacteria were discovered anew in hamsters and rats some 35 years later by Keyes and Fitzgerald. They were eventually recognized to colonize the teeth of humans in a remarkably localized fashion, and their colonization sites were those where lesions subsequently developed. Colonization of sites was remarkably constant over time. Sites that were not colonized remained free of lesions in the same mouths where lesions developed elsewhere (4,27,56).

Taxonomists now recognize several species of mutans streptococci (22). Humans commonly harbor only two of them (*S. mutans* and *S. sobrinus*). These bacteria, when isolated in the pure state and inoculated into experimental animals previously free of them, induce caries, if the animals are on a caries-supportive diet, that is, one rich in sucrose. If rodents, primates, or people consume sucrose frequently, these bacteria become more abundant in the dental plaque biofilm found above the gum line (supragingival plaque; 3,25,36,70,95,109,114). They adhere to and accumulate on the teeth under the selective ecological pressure of sucrose but are dislodged into saliva as a result of chewing and other ordinary oral functions. Mutans streptococci make up at most 1% of the total cultivable flora of 10^8 to 10^9 colony-forming units/ml of saliva. Mothers who have relatively high levels of mutans streptococci in the saliva during chewing (typically 10^5 to 10^7 colony-forming units/ml) have children whose teeth become colonized and develop carious lesions early in life (66,103). That these bacteria are transmitted vertically, mostly from mother to child, is confirmed by the identical bacteriocin patterns, genotypes, and ribotypes of the mutans streptococci in mothers and their children (6,7,31,72,89). Fathers much less frequently appear to be the donors of the infection (122). It is not clear whether this mother vs. father distinction results from cultural feeding and nurturing patterns or other biological factors.

The incidence of carious lesions is positively correlated with the level of colonization of the dentition by mutans streptococci and the number of sites on the dentition that are colonized (24,41). In an interesting study of naval recruits previously referred to as "caries resistant," "caries immune," or "genetically resistant," about 60% of a cohort who had been free of carious lesions up to about 19 years of age in fact developed carious lesions during about 1 year in "boot camp." This was associated with a change in diet and the emergence of detectable colonization of the teeth by mutans streptococci at lesion sites (63). New acquisition of these bacteria could not be excluded. This was reminiscent of the reports of hamster, rat, and desert rodent strains previously thought to be genetically resistant to caries, but

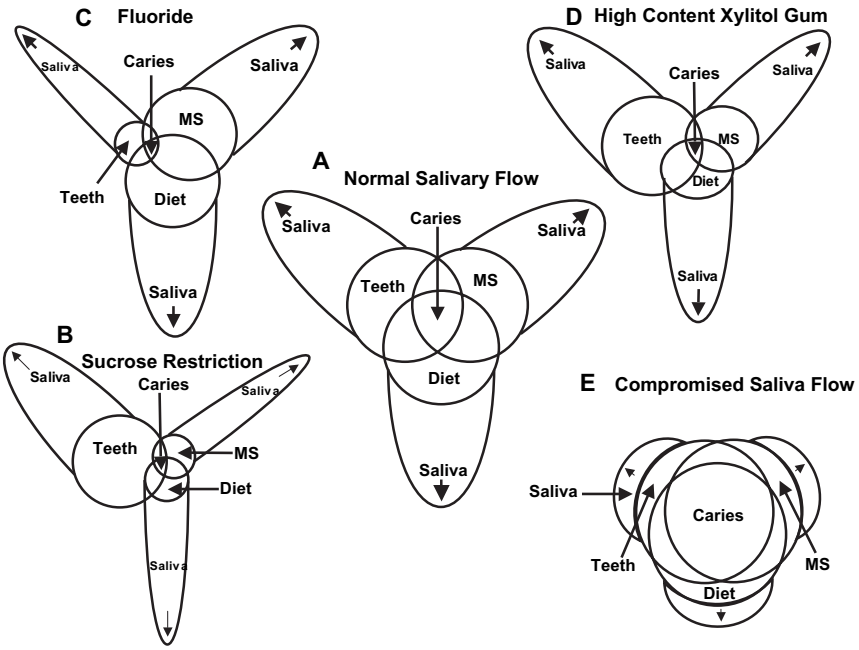

FIGURE 10.1

which turned out merely not to be infected by mutans streptococci (74,117). In those studies, multiple generations of hamsters vertically transmitted this disease, but transmission was blocked by antibiotic treatment of either disease-affected animals or their unaffected cage-mates. Although generations of hamsters developed severe lesions if infected by mutans streptococci while eating a sucrose-rich diet, the lesions failed to develop in subsequent generations if weanlings ate a diet free of sucrose, even if rich in glucose or starch. However, the lesions developed again when weanlings of the next generations were switched back to the sucrose-rich diet. Disease expression (lesion development), thus, appeared to require both infection and appropriate diet, working in concert (see Figure 10.1). These observations did not support the role of genetics of the host. Rather, they gave rise to the concept of an infectious process that is profoundly influenced by diet in its pathogenesis and lesion manifestation. In effect, caries is an opportunistic infection.

Two rare human genetic diseases are instructive. In hereditary fructose intolerance (HFI), the disaccharide sucrose and its component fructose are assiduously avoided due to risk of fatty liver degeneration that results from a defect of liver fructose-6-phosphate aldolase. HFI patients eat glucose and starch, however. Intestinal sucrase deficiency (SD) patients cannot cleave sucrose in the small intestine to its absorbable components, glucose and fructose, and consequently develop osmotic diarrhea and flatulence. They assiduously avoid sucrose but eat glucose, fructose, and starch without ill effect. Both HFI and SD patients have vanishingly low levels of tooth colonization by mutans streptococci and have virtually no carious lesions (53,127).

In an exhaustive review of the literature on all of the microorganisms implicated in human primary dental caries, almost no other oral bacteria were seen to have convincing associations with induction of the disease (122). An exception is the case of unspeciated lactobacilli. Lactobacilli characteristically and preferentially colonize the tongue epithelium, after streptococci colonize the mouth. The lactobacilli colonize tooth surfaces poorly. However, they appear to colonize already-established

FIGURE 10.1 (See figure, facing page.) The interactions of susceptible teeth, cariogenic bacteria, and cariogenic diet necessary for expression of dental caries, and the influence of saliva. This group of Venn diagrams depicts the interactive elements in dental caries and the effects of caries-mitigating and caries-exacerbating influences. The elements — susceptible teeth, cariogenic diet, and cariogenic plaque flora rich in mutans streptococci (MS) — are shown as interacting spheres. Saliva, pictured as ellipsoids influencing those elements, functions to dissociate them. The magnitude of salivary action to dissociate these spheres is illustrated by the lengths of the ellipsoids, pulling the interactive elements apart. The central figure (*A*) indicates that in the presence of normal salivary flow and composition, carious lesions occur in susceptible teeth that are colonized by a cariogenic bacterial flora, the most important element of which is the mutans streptococci, when the teeth are exposed frequently to a cariogenic diet over time. The component of the diet critical for cariogenicity is sucrose, though other fermentable sugars are involved as substrate for the flora. Saliva, by diverse mechanisms, clears food and MS from the surfaces of the teeth, buffers acid produced by the cariogenic flora adherent to the teeth, and supplies salivary calcium, phosphate, fluoride, and proteins, at a pH above that existing in the depth of the plaque biofilm. They jointly inhibit demineralization of the tooth surface and, especially, restore and maintain those surfaces in a process termed remineralization. (*B*) Through sucrose restriction the most potent dietary supporter of caries is reduced, not only by removal of that key substrate for acid production by MS, but also by removal of the ecological selection pressure that fosters MS colonization of the teeth and MS ascendancy in the plaque biofilm. Thus, the effects of restriction on the MS are direct. (*C*) Through augmented exposure to fluoride, the solubility of tooth mineral is decreased and remineralization of the teeth by saliva is promoted. Although fluoride inhibits glycolysis by MS, the duration of MS exposure to fluoride in its usual delivery systems (water, toothpaste, gels) at metabolically inhibitory concentrations is brief and generally not thought to be biologically significant. (*D*) Through frequent exposure to xylitol, there is substitution of the highly caries-supportive between-meal snack food component (sucrose) by a nonfermentable confection. This appears to decrease colonization levels of MS on the teeth as well as to inhibit transmission of MS from mother to child. Previously hypothesized direct alteration of salivary secretion or direct xylitol effect on teeth does not presently appear supported by controlled studies. Rather, remineralization of the teeth in xylitol users appears mediated indirectly by deletion of a cariogenic component of snack foods and by xylitol's effects on acid production by MS. These reduce the acidogenic challenge to the teeth, enabling the balance of calcium and phosphate exchanges between the tooth surface and the saliva to shift in favor of remineralization. The causes of xylitol's inhibition of MS transmission from mothers to their children are complex and remain unsettled. (*E*) Compromise of salivary flow, and perhaps qualitative as well as quantitative compositional changes, as occur with anticholinergic medications, Sjögren's syndrome, and radiation damage to salivary glands, diminish the saliva-mediated dissociation of the three interactive spheres of caries, leading to greatly increased lesion development risk, albeit by mechanisms that affect the elements of the disease by different mechanisms. (Modified from J.M. Tanzer, *Risk Assessment in Dentistry,* 1990, and J.M. Tanzer, *Int. Dent. J. 45:* 65–76, 1995.)

carious lesions, especially those found on the tooth's root surfaces, and may be associated with lesions of the dentin (122).

10.4.4 Evidence from the Literature on Dietary Correlates of Caries

Mandel (79) and Keene (61) have written particularly cogent reviews on the history of the association of caries with sugar consumption by humans. Keene's review includes some of the microbiological data that were becoming available at that time. Some aspects of these reviews are worth recalling. Skeletal remains found in Europe and Hawaii reveal root surface caries to have been an ancient disease, associated with periodontal disease-resultant exposure of the root surfaces to the oral environment. The crowns of the teeth of these skeletons, however, were remarkably free of carious lesions. With the commercial growth and widespread distribution of sucrose, beginning in the mid-19th century, lesions of the crowns of the teeth became much more prominent in dated skeletal remains, not only in Western populations but also among societies where coronal dental caries had previously been rarely observed — for example, Inuits, Eskimos, Tristan da Cunhans, and residents of the Isle of Lewis. Coronal caries spread explosively in association with this apparent dietary change. It is possible that commercial transport of sugar to and acceptance by isolated peoples not only could have brought sucrose to new populations, but also could have brought mutans streptococci–infected people into contact with uninfected ones; no data are available on this latter possibility.

Sugar deprivation, as occurred during the Nazi occupation of Western Europe and among Japanese children during World War II, was associated with sharp declines of carious lesions. These lesions returned during the postwar recovery years, corresponding with the restitution of former diets higher in sucrose. While war diets were also low in protein and fat, sugar and sugar-containing foods were in particularly short supply during World War II (112,123,124).

How diet affects caries was studied in notable controlled interventional clinical trials done after World War II. Some detailed the strong positive correlation of caries incidence in institutionalized adults in Sweden with the "stickiness" of sugary foods eaten at high frequency between meals and, by contrast, the relatively weak association of the same food quantities taken with meals (47). This potent effect of between-meal sweets, almost entirely sucrose in content, probably reflected not stickiness per se, but dwell time of the food in the mouth. A study of U.S. children with deciduous teeth documented the potent effect of decreasing frequency of between-meal snack consumption, almost entirely sucrose sweetened, on the drop in the rate of caries (134). A study that switched the entire diet of Australian adolescents from a meat/sugar-rich one to a lacto/vegetarian one was associated with profoundly decreased incidence of caries. A return to the earlier caries incidence occurred when the adolescents resumed their former diets (50). The famous Turku Sugar Studies, a single-blinded study of mainly young adults, studied fructose-for-sucrose or xylitol-for-sucrose substitutions in the entire diet, by comparison with that same diet made with its usual sucrose (96). There was decreased caries

incidence among subjects on the fructose-for-sucrose substitution and essential cessation of decay among subjects on the xylitol-for-sucrose substitutions.

Several specific food substitution studies have been done. Perhaps the most notable is that with Belizian 10- to 13-year-olds who used chewing gums containing either sucrose, sorbitol, xylitol, or mixtures of sorbitol and xylitol, or no gum, during 40 months. The study was done in a society with high background sucrose use. It revealed significant cariogenicity of sucrose in this between-meal-consumed vehicle and beneficial effects of the sucrose substitutes, especially of the nonfermentable xylitol (78), which clearly reduced caries incidence by comparison with non-gum use. This was not just a sucrose substitution effect, but also an anticaries effect. Of course, the virtually decay-free state of HFI and SD patients, who must not eat sucrose, should be recalled. Randomized interventional studies that increased sucrose consumption in humans resulted in significant caries incidence increases (36,109).

It must be remembered that in the United States, since about 1975, much of caloric dietary sweetener use has shifted from sucrose to corn-derived sweeteners, mostly glucose and high-fructose corn syrups (13,111); the greatest part of this use is in soft drinks. This time frame, 1975 to the present, is the same as that when fluoridated drinking water and fluoridated toothpastes (virtually 100% of toothpaste now sold) became prevalent. Consequently, current studies of the effects on caries prevalence as a function of the consumption of sweets show blunted correlations with decay. Most studies do not discriminate between which sweetener is being consumed or in which form, thereby possibly disguising potent variables, and recent studies in the developed world have been done in the setting of high population exposure to fluoride (for example, 15).

To some degree, this shift of caloric sweetener type was and remains a consequence of the complex factors that result in lower prices in the United States for corn-derived sweeteners as compared to sucrose, economic factors that do not apply in most of the rest of the world. Increased distribution of sucrose to the developing world, especially in the form of soft drinks, raises concern about increased caries prevalence in those countries, where soft drinks appear to be increasingly marketed and used (23,58,139). This is supported by the strong positive correlation between world sucrose consumption — estimated on the basis of sugar inventory — and worldwide incidence of caries (81). This correlation becomes weaker, however, in countries where there is widespread use of fluorides (58) and where, as in the United States, corn-derived sweeteners are replacing sucrose in the processing of soft drinks (13).

10.4.5 Relationships Between Virulence of the Mutans Streptococci and Fermentable Carbohydrates, Especially Sucrose

Streptococci are obligate carbohydrate fermentors, deriving essentially all of their energy from glycolysis. They have no intact respiratory or Krebs cycle enzyme systems. There is strong association between their metabolism of simple fermentable carbohydrates, especially sucrose, and their expression of virulence. The mutans streptococci ferment a particularly wide array of hexoses, hexose alcohols, and

disaccharides (including sucrose) found in food and are equipped with transport systems to enable this fermentation (99,100,135). They do not ferment pentoses or pentose alcohols such as xylitol (125). If the sugar supply is adequate and if the pH in the mouth is below 7, they convert hexoses and disaccharides to lactic acid (113,119). The acid then acts on the tooth surface and causes its demineralization, and, eventually, cavities form. Lactic acid dehydrogenase mutants (LDH^-), unable to make lactic from pyruvic acid, are not cariogenic, even though they convert pyruvic to acetic and formic acid end products (34,60). However, the pKs of these two acids are higher than that of lactic acid. The mutants can colonize the teeth, but they do not cause decay, apparently because demineralization of enamel requires the lowering of plaque pH to levels created by a lactic acid-rich environment.

Also, in states of exogenous carbohydrate abundance (for example, when the host is eating and there are fermentable food residues near the teeth), the mutans streptococci (except *S. sobrinus*) synthesize intracellular glycogen-like polysaccharide from common exogenous mono- or disaccharides (8). The resultant endogenous storage molecule is degraded to hexose phosphates and then to acid when the supply of exogenous fermentable carbohydrate is exhausted, such as occurs between meals or when the host sleeps. The intracellular polysaccharide's storage and catabolism thus enable long-term ATP generation, pH depression in dental plaque biofilm, and provide an apparent ecological advantage over less acid-tolerant oral bacteria that otherwise reside on the teeth. Mutants defective in synthesis of this storage polysaccharide substantially lose virulence (121).

It is the synthesis of peculiar extracellular glucose homopolymers (glucans) uniquely from sucrose, however, that substantially explains the special significance of this dietary carbohydrate to virulence of the mutans streptococci. Such polymers are constitutively produced by three cell-surface/extracellular glucosyl-transferases. Those glucans containing abundant α-1-3 linkages among their α-1-6 linkages that are produced *in situ* on the teeth apparently confer the ability to adhere to the teeth and gain great ecological advantage at that locus. Mutants defective in synthesis of these extracellular water-insoluble glucans fail to colonize smooth surfaces of teeth and fail to induce carious lesions there (37,38,73,120). Wild type mutans streptococci, once they have colonized essentially irreversibly, based on this sucrose-dependent adhesion phenomenon, can apparently support their energetic needs from either sucrose or other fermentable monosaccharides, with resultant production of lactic acid. They cannot ferment starch, and unboiled starch by itself does not appear to be cariogenic in either humans or experimental animals (115,122). Of course, there are abundant experimental animal and human data to indicate that the more frequent the sucrose presentation, the more potent the cariogenic challenge. Similar data are not available with respect to the impact per se of high-fructose corn sweetener consumed in soft drinks.

The synthesis by most mutans streptococci of water-soluble extracellular fructose polymers, also from sucrose (or raffinose), and their subsequent degradation in times of exogenous carbohydrate substrate paucity are relatively weak virulence determinants (12,136).

There has been great interest in possible immunization against caries by targeting the sucrose/glucosyl-transferase/adhesion/cell-surface-binding-site system. There

has also been great interest in competitive infection utilizing LDH^- bacteriocin-producing engineered strains of *S. mutans*. Both topics are beyond the scope of this paper, and neither strategy is available for human use today.

Several other traits of the mutans streptococci have been implicated in their virulence (73), and more are being recognized.

10.4.6 Randomized Clinical Trials to Inhibit Caries

At least 25 studies have attempted to inhibit the caries process among normal subjects by reduction of colonization levels of mutans streptococci. In some studies, subjects were stratified on the basis of bacterial levels into high-risk and low-risk categories. In other studies, the levels of infection were used to intervene again when the key bacterial titers had risen to the point that was considered to represent heightened risk. These studies, for obvious ethical and practical reasons, were often multistrategic (e.g., 46) and, thus, variably confounded, because they also provided patients what were deemed to be best probable caries-preventive strategies and treatment. Among the confounding strategies used were ones focused on mitigating the solubility of the teeth and fostering remineralizing incipient white spot carious lesions (done with topical fluoride treatments, fluoride toothpaste, and drinking water fluoride); excavation and repair of carious lesions and sealing of high-risk tooth areas (tooth pits and fissures); and intensive tooth-brushing instruction and professional tooth cleaning (to remove dental plaque). Possible anticaries benefits that would result from reducing cariogenic flora were most directly addressed by periodic topical disinfection of the teeth with antiseptics and use of sucrose substitutes in the diet. In nearly all studies, the fundamental strategy consisted of reducing the intake of fermentable carbohydrates.

The multistrategy approaches to caries inhibition studies thus set a very high threshold for detection of specific effects of dietary and antimicrobial interventions per se, and their isolated impact on caries incidence was difficult to quantify. Some studies, however, were sufficiently well controlled to make the dietary and antimicrobial effects unambiguous. These studies have been reviewed, and extensive supporting evidence tables have been published (122). Among the most striking findings were the observation that high levels of mutans streptococci in the maternal saliva of mothers were associated with the early transmission of the bacteria to their children and thus with high prevalence and incidence of carious lesions in their children (65,66). While the interventions during childhood were transient, the benefits have so far been documented for up to 7 years. An arguably unexpected result was seen in studies of mothers randomly assigned to frequently use high-content xylitol chewing gum from the approximate time of eruption of the deciduous dentition of their children. Two accepted strategies (by the Finnish public health guidelines) for reducing caries in mothers and the probability of transmission of mutans streptococci to their children — the repeated sealing of mothers' teeth with either fluoride-supplemented or chlorhexidine-supplemented varnish — served as control interventions for a randomized, blinded trial that monitored the effects on the children. The strategies were imposed until the children were 3 years old. Five years after inception of the study, the xylitol strategy had greatly reduced the probability

of transmission of mutans streptococci to the children and had dramatically reduced their caries incidence, even after the treatments of mothers had ended 2 years previously (59,103).

10.4.7 Special Patient Needs and Potential Strategies

In patients with the autoimmune disease Sjögren's syndrome, salivary secretion is compromised and involves both flow and compositional changes. They often develop oral mucositis and aggressive tooth decay (45,106,108; Figure 10.1). Salivary gland shutdown is severe and rapid in head/neck radiation patients, some chemotherapy patients, and patients who have suffered salivary gland excision or duct ligation due to malignancy. It is also widely recognized by dental, if not many medical practitioners, that patients who use antipsychotics, antidepressants that have norepinephrine reuptake inhibition properties, antispasmodics, some antihypertensives, antihistamines, and so forth have an increased risk for caries (141). These patients, in trying to keep their mouth moist, are often counseled to suck on hard candies or drink fruit juice in an effort to mitigate the xerostomia that is a great obstacle to speech, chewing, and swallowing. Such advice increases their caries risk and complicates caries management.

Another group of patients who are not often thought of as being at heightened caries risk is those who have chronic pancreatitis or gallbladder disease. They are placed on extremely low-fat diets, with simple carbohydrates, commonly sucrose syrup, becoming a major source of calories.

Virtually none of these or similar patient management problems have been the subject of interventional studies that involve dietary substitutions or replacements to mitigate caries risk, even though constructive and useful caries inhibitory strategies have been known for more than three decades to be effective for head/neck cancer patients (see 26,62). There may be reluctance to mount such studies, because of the recognition that to study untreated controls would likely be ethically problematic.

10.5 NUTRITIONAL CONSEQUENCES OF EDENTULOUS STATUS

Both dental caries and periodontal disease have a high probability of leading to the loss of teeth. Generally, this occurs by the extraction or exfoliation of single or groups of teeth. In addition to the esthetic consequences of tooth loss, chewing function is impaired (133). Today, fewer people in the United States are edentulous than in the past (84,126), but this improvement has not been shared by all segments of American society (137).

There are limited data on nutritional deficiencies that result from partial or total edentulism. It is a common experience for those sharing meals with partially or totally edentulous individuals to observe their dramatically altered food choices. More data are available on diet changes by edentate patients who wear artificial dentures. Here, food choices are associated with nutritional deficiencies, best documented for vitamins, fiber, zinc, magnesium, calcium, and macronutrients (55,68). Yet millions of people who have few or no natural teeth do not suffer from apparent

nutritional deficiencies. Education and food supplements can help in preventing deficiencies, but minimizing dental caries and periodontal disease is bound to be the surest way of preventing nutritional problems due to loss of teeth.

REFERENCES

1. Addy, M (2003). The use of antiseptics in periodontal therapy. In: *Clinical Periodontology and Implant Dentistry* (4th ed.). Lindhe, J, Karring, T & Lang, N P, eds. Oxford, U.K.: Blackwell Munksgaard, pp. 464–493.
2. Al-Zahrani, MS, Bissada, NF, & Borawskit, EA (2003). Obesity and periodontal disease in young, middle-aged, and older adults. *J. Periodontol. 74:* 610–615.
3. Aranibar Quiroz, EM, Lingström, P, & Birkhed, D (2003). Influence of short-term sucrose exposure on plaque acidogenicity and cariogenic microflora in individuals with different levels of mutans streptococci. *Caries Res. 37:* 51–57.
4. Babaahmady, KG, Challacombe, SJ, Marsh, PD, & Newman, HN (1998). Ecological study of *Streptococcus mutans*, *Streptococcus sobrinus* and *Lactobacillus* spp. at sub-sites from approximal dental plaque from children. *Caries Res. 32:* 51–58.
5. Beck, JD, & Arbes, SJ, Jr. (2002). Epidemiology of gingival and periodontal diseases. In: *Carranza's Clinical Periodontology* (9th ed.). Newman, M G, Takei, H H & Carranza, F A, eds. Philadelphia: W. B. Saunders, pp. 74–103.
6. Berkowitz, RJ, & Jones, P (1985). Mouth-to-mouth transmission of the bacterium *Streptococcus mutans* between mother and child. *Arch. Oral Biol. 30:* 377–379.
7. Berkowitz, RJ, & Jordan, HV (1975). Similarity of bacteriocins of *Streptococcus mutans* from mother and infant. *Arch. Oral Biol. 20:* 725–730.
8. Birkhed, D, & Tanzer, JM (1979). Glycogen synthesis pathway in *Streptococcus mutans* strain NCTC 10449S and its glycogen synthesis-defective mutant 805. *Arch. Oral Biol. 24:* 67–73.
9. Bork, K, Hoede, N, Korting, GW, Burgdorf, WHC, & Young, SK (1996). *Diseases of the Oral Mucosa and the Lips*. Philadelphia: W. B. Saunders, p. 377.
10. Bowen, WH (1969). The induction of rampant dental caries in monkeys (*Macaca irus*). *Caries Res. 3:* 227–237.
11. Bowen, WH, Velez, H, Aguila, M, Velasquez, H, Sierra, LI, & Gillespie, G (1977). The microbiology and biochemistry of plaque, saliva, and drinking water from two communities with contrasting levels of caries in Colombia, S.A. *J. Dent. Res. 56* Spec. No.: C32–C39.
12. Burne, RA, Rubinfeld, B, Bowen, WH, & Yasbin, RE (1986). Tight genetic linkage of a glucosyltransferase and dextranase of *Streptococcus mutans* GS–5. *J. Dent. Res. 65:* 1392–1401.
13. Burt, BA (1993). Relative consumption of sucrose and other sugars: Has it been a factor in reduced caries experience? *Caries Res. 27* Suppl. 1: 56–63.
14. Burt, BA, & Pai, S (2001). Does low birthweight increase the risk of caries? A systematic review. *J. Dent. Educ. 65:* 1024–1027.
15. Burt, BA, & Pai, S (2001). Sugar consumption and caries risk: A systematic review. *J. Dent. Educ. 65:* 1017–1023. Full report and evidence tables available online at: http://www.nidcr.nih.gov/NewsAndReports/ReportsPresentation/ConsensusDevConf/Agenda.htm.
16. Cannon, RD, & Chaffin, WL (1999). Oral colonization by *Candida albicans*. *Crit. Rev. Oral Biol. Med. 10:* 359–383.

17. Carlos, JP, & Gittelsohn, AM (1965). Longitudinal studies of the natural history of caries. II. A life-table study of caries incidence in the permanent teeth. *Arch. Oral Biol. 10:* 739–751.
18. Clark, JK (1924). On the bacterial factor in the aetiology of dental caries. *Br. J. Exp. Pathol. 5:* 141–147.
19. Lindhe, J, Karring, T & Lang, NP, eds. (2003). *Clinical Periodontology and Implant Dentistry* (4th ed.). Oxford, U.K.: Blackwell Munksgaard, p. 1044.
20. Siegel, MA, Silverman, S, Jr. & Sollecito, TP, eds. (2001). *Clinician's Guide to Treatment of Common Oral Conditions* (5th ed). Baltimore: The American Academy of Oral Medicine, p. 22.
21. Cohen-Brown, G, & Ship, JA (2004). Diagnosis and treatment of salivary gland disorders. *Quintessence Int. 35:* 108–123.
22. Coykendall, AL (1989). Classification and identification of the viridans streptococci. *Clin. Microbiol. Rev. 2:* 315–328.
23. Dawson, H (1994). Market outlook: Crunch time. *Beverage World International 12:* 16–22, 1994.
24. De Stoppelaar, JD, Van Houte, J, & Backer Dirks, O (1969). The relationship between extracellular polysaccharide-producing streptococci and smooth surface caries in 13-year-old children. *Caries Res. 3:* 190–199.
25. De Stoppelaar, JD, Van Houte, J, & Backer, DO (1970). The effect of carbohydrate restriction on the presence of *Streptococcus mutans*, *Streptococcus sanguis* and iodophilic polysaccharide-producing bacteria in human dental plaque. *Caries Res. 4:* 114–123.
26. Dreizen, S, & Brown, LR (1976). Xerostomia and dental caries. In: *Microbial Aspects of Dental Caries: Proceedings of a Workshop on Microbial Aspects of Dental Caries,* June 21–24, 1976 (Vol. 1). Stiles, HM, Loesche, WJ & O'Brien, TC, eds. Washington, DC: Information Retrieval, pp. 263–273.
27. Duchin, S, & van Houte, J (1978). Relationship of *Streptococcus mutans* and lactobacilli to incipient smooth surface dental caries in man. *Arch. Oral Biol. 23:* 779–786.
28. Edelstein, BL (2002). Disparities in oral health and access to care: Findings of national surveys. *Ambul. Pediatr. 2:* 141–147.
29. Elderton, RJ, & Davies, JA (1984). Restorative dental treatment in the General Dental Service in Scotland. *Br. Dent. J. 157:* 196–200.
30. El-Lozy, M, Herrera, MG, Latham, MC, McGandy, RB, McCann, MB, & Stare, FJ (1980). *Nutrition: A Scope Publication.* Kalamazoo, MI: Upjohn, p. 112.
31. Emanuelsson, IR, Li, Y, & Bratthall, D (1998). Genotyping shows different strains of mutans streptococci between father and child and within parental pairs in Swedish families. *Oral Microbiol. Immunol. 13:* 271–277.
32. Emrich, LJ, Shlossman, M, & Genco, RJ (1991). Periodontal disease in non-insulin-dependent diabetes mellitus. *J. Periodontol. 62:* 123–131.
33. Enwonwu, CO (1972). Epidemiological and biochemical studies of necrotizing ulcerative gingivitis and noma (cancrum oris) in Nigerian children. *Arch. Oral Biol. 17:* 1357–1371.
34. Fitzgerald, RJ, Adams, BO, Sandham, HJ, & Abhyankar, S (1989). Cariogenicity of a lactate dehydrogenase-deficient mutant of *Streptococcus mutans* serotype c in gnotobiotic rats. *Infect. Immun. 57:* 823–826.
35. Fitzgerald, RJ, & Keyes, PH (1960). Demonstration of the etiologic role of streptococci in experimental caries in the hamster. *J. Am. Dent. Assoc. 61:* 9–19.
36. Folke, LE, Gawronski, TH, Staat, RH, & Harris, RS (1972). Effect of dietary sucrose on quantity and quality of plaque. *Scand. J. Dent. Res. 80:* 529–533.

37. Freedman, ML, & Tanzer, JM (1974). Dissociation of plaque formation from glucan-induced agglutination in mutants of *Streptococcus mutans*. *Infect. Immun. 10:* 189–196.
38. Freedman, ML, & Tanzer, JM (1982). The use of mutants to study the glucan-associated pathophysiology of *Streptococcus mutans*. In: *Microbiology,* Schlessinger, D, ed. Washington, DC: American Society for Microbiology, pp. 186–190.
39. Frostell, G, Keyes, PH, & Larson, RH (1967). Effect of various sugars and sugar substitutes on dental caries in hamsters and rats. *J. Nutr. 93:* 65–76.
40. Fure, S (2004). Ten-year cross-sectional and incidence study of coronal and root caries and some related factors in elderly Swedish individuals. *Gerodontology 21:* 130–140.
41. Gibbons, RJ, Depaola, PF, Spinell, DM, & Skobe, Z (1974). Interdental localization of *Streptococcus mutans* as related to dental caries experience. *Infect. Immun. 9:* 481–488.
42. Glass, RL, ed. (1982). The first international conference on the declining prevalence of dental caries. *J. Dent. Res. 61:* 1301–1383.
43. Goldberg, J, Tanzer, J, Munster, E, Amara, J, Thal, F, & Birkhed, D (1981). Cross-sectional clinical evaluation of recurrent enamel caries, restoration of marginal integrity, and oral hygiene status. *J. Am. Dent. Assoc. 102:* 635–641.
44. Guggenheim, B, Konig, KG, Herzog, E, & Muhlemann, HR (1966). The cariogenicity of different dietary carbohydrates tested on rats in relative gnotobiosis with a *Streptococcus* producing extracellular polysaccharide. *Helv. Odontol. Acta 10:* 101–113.
45. Guggenheimer, J, & Moore, PA (2003). Xerostomia: Etiology, recognition and treatment. *J. Am. Dent. Assoc. 134:* 61–69; quiz 118–119.
46. Gunay, H, Dmoch-Bockhorn, K, Gunay, Y, & Geurtsen, W (1998). Effect on caries experience of a long-term preventive program for mothers and children starting during pregnancy. *Clin. Oral Investig. 2:* 137–142.
47. Gustafsson, BE, Quensel, CE, Lanke, LS, Lundqvist, C, Grahnen, H, Bonow, BE, & Krasse, B (1954). The Vipeholm dental caries study: The effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years. *Acta Odontol. Scand. 11:* 232–264.
48. Haffajee, AD, & Socransky, SS (2001). Relationship of cigarette smoking to the subgingival microbiota. *J. Clin. Periodontol. 28:* 377–388.
49. Haffajee, AD, Socransky, SS, & Lindhe, J (2003). The effect of therapy on the microbiota in the dentogingival region. In: *Clinical Periodontology and Implant Dentistry* (4th ed.). Lindhe, J, Karring, T & Lang, NP, eds. Oxford, U.K.: Blackwell Munksgaard, pp. 561–575.
50. Harris, R (1963). Biology of the children of Hopewood House, Bowral, Australia. 4. Observations on dental-caries experience extending over five years (1957–61). *J. Dent. Res. 42:* 1387–1399.
51. Hernandez, YL, & Daniels, TE (1989). Oral candidiasis in Sjögren's syndrome: Prevalence, clinical correlations, and treatment. *Oral Surg. Oral Med. Oral Pathol. 68:* 324–329.
52. Hodges, RE, Hood, J, Canham, JE, Sauberlich, HE, & Baker, EM (1971). Clinical manifestations of ascorbic acid deficiency in man. *Am. J. Clin. Nutr. 24:* 432–443.
53. Hoover, CI, Newbrun, E, Mettraux, G, & Graf, H (1980). Microflora and chemical composition of dental plaque from subjects with hereditary fructose intolerance. *Infect. Immun. 28:* 853–859.
54. Hugoson, A, Thorstensson, H, Falk, H, & Kuylenstierna, J (1989). Periodontal conditions in insulin-dependent diabetics. *J. Clin. Periodontol. 16:* 215–223.

55. Hung, HC, Willett, W, Ascherio, A, Rosner, BA, Rimm, E, & Joshipura, KJ (2003). Tooth loss and dietary intake. *J. Am. Dent. Assoc. 134:* 1185–1192.
56. Ikeda, T, Sandham, HJ, & Bradley, EL, Jr. (1973). Changes in *Streptococcus mutans* and lactobacilli in plaque in relation to the initiation of dental caries in Negro children. *Arch. Oral Biol. 18:* 555–566.
57. Ismail, AI, Burt, BA, & Eklund, SA (1983). Relation between ascorbic acid intake and periodontal disease in the United States. *J. Am. Dent. Assoc. 107:* 927–931.
58. Ismail, AI, Tanzer, JM, & Dingle, JL (1997). Current trends of sugar consumption in developing societies. *Community Dent. Oral Epidemiol. 25:* 438–443.
59. Isokangas, P, Soderling, E, Pienihakkinen, K, & Alanen, P (2000). Occurrence of dental decay in children after maternal consumption of xylitol chewing gum, a follow-up from 0 to 5 years of age. *J. Dent. Res. 79:* 1885–1889.
60. Johnson, CP, Gross, SM, & Hillman, JD (1980). Cariogenic potential *in vitro* in man and *in vivo* in the rat of lactate dehydrogenase mutants of *Streptococcus mutans*. *Arch. Oral Biol. 25:* 707–713.
61. Keene, HJ (1981). History of dental caries in human populations: The first million years. In: *Animal Models in Cariology* (special supplement to *Microbiology Abstracts),* Tanzer, JM, ed. Washington, DC: Information Retrieval, pp. 23–40.
62. Keene, HJ, Daly, T, Brown, LR, Dreizen, S, Drane, JB, Horton, IM, Handler, SF, & Perkins, DH (1981). Dental caries and *Streptococcus mutans* prevalence in cancer patients with irradiation-induced xerostomia: 1–13 years after radiotherapy. *Caries Res. 15:* 416–427.
63. Keene, HJ, & Shklair, IL (1974). Relationship of *Streptococcus mutans* carrier status to the development of carious lesions in initially caries free recruits. *J. Dent. Res. 53:* 1295.
64. Kinane, DF, & Lindhe, J (2003). Chronic periodontitis. In: *Clinical Periodontology and Implant Dentistry* (4th ed.). Lindhe, J, Karring, T, & Lang, NP, eds. Oxford, U.K.: Blackwell Munksgaard, pp. 209–215.
65. Köhler, B, & Andreen, I (1994). Influence of caries-preventive measures in mothers on cariogenic bacteria and caries experience in their children. *Arch. Oral Biol. 39:* 907–911.
66. Köhler, B, Andreen, I, & Jonsson, B (1984). The effect of caries-preventive measures in mothers on dental caries and the oral presence of the bacteria *Streptococcus mutans* and lactobacilli in their children. *Arch. Oral Biol. 29:* 879–883.
67. König, KG (1982). Impact of decreasing caries prevalence: Implications for dental research. The first international conference on the declining incidence of dental caries, Glass, RL, ed. *J. Dent. Res. 61:* 1378–1383.
68. Krall, E, Hayes, C, & Garcia, R (1998). How dentition status and masticatory function affect nutrient intake. *J. Am. Dent. Assoc. 129:* 1261–1269.
69. Krasse, B (1965). The effect of caries-inducing streptococci in hamsters fed diets with sucrose or glucose. *Arch. Oral Biol. 10:* 223–226.
70. Kristoffersson, K, & Birkhed, D (1987). Effects of partial sugar restriction for 6 weeks on numbers of *Streptococcus mutans* in saliva and interdental plaque in man. *Caries Res. 21:* 79–86.
71. Kruzelock, R, Lago, D, Rabatin, V, Roberts, J, & Ahern, F (1990). Prevalence of concurrent use of anticholinergic drugs in a geriatric pharmaceutical assistance program. *J. Geriatr. Drug. Ther. 5:* 41–54.
72. Kulkarni, GV, Chan, KH, & Sandham, HJ (1989). An investigation into the use of restriction endonuclease analysis for the study of transmission of mutans streptococci. *J. Dent. Res. 68:* 1155–1161.

73. Kuramitsu, HK (1993). Virulence factors of mutans streptococci: Role of molecular genetics. *Crit. Rev. Oral Biol. Med. 4:* 159–176.
74. Larson, RH, & Fitzgerald, RJ (1968). Caries development in the African white-tailed rat (*Mystromys albicaudatus*) infected with a streptococcus of human origin. *J. Dent. Res. 47:* 746–749.
75. Liss, J, Evenson, P, Loewy, S, & Ayer, WA (1982). Changes in the prevalence of dental disease. Bureau of Economic and Behavioral Research, Council on Dental Health and Health Planning. *J. Am. Dent. Assoc. 105:* 75–79.
76. Loesche, WJ (1986). Role of *Streptococcus mutans* in human dental decay. *Microbiol. Rev. 50:* 353–380.
77. Luan, W, Baelum, V, Fejerskov, O, & Chen, X (2000). Ten-year incidence of dental caries in adult and elderly Chinese. *Caries Res. 34:* 205–213.
78. Mäkinen, KK, Bennett, CA, Hujoel, PP, Isokangas, PJ, Isotupa, KP, Pape, HR, Jr., & Mäkinen, PL (1995). Xylitol chewing gums and caries rates: A 40-month cohort study. *J. Dent. Res. 74:* 1904–1913.
79. Mandel, ID (1970). Effects of dietary modifications on caries in humans. *J. Dent. Res. 49:* 1201–1211.
80. Manski, J, Edelstein, BL, & Moeller, JF (2001). The impact of insurance coverage on children's dental visits and expenditures, 1996. *J. Am. Dent. Assoc. 132:* 1137–1145.
81. Marthaler, TM (1979). Sugar and oral health: Epidemiology in humans. In: *Health and Sugar Substitutes*. ERGOB Conference on Sugar Substitutes, Guggenheim, B, ed. Basel, Switzerland: Karger, pp. 27–34.
82. Matear, DW (1999). Demonstrating the need for oral health education in geriatric institutions. *Probe 33:* 66–71.
83. Millard, HD, & Mason, DK (1998). 3rd World Workshop on Oral Medicine University of Michigan: Ann Arbor, MI, p. 388.
84. Miller, AJ, Brunelle, JA, Carlos, JP, Brown, LJ, & Löe, H (1987). Oral health of United States adults. The national survey of oral health in U.S. employed adults and seniors. National findings: 1985–1986. Bethesda, MD: U.S. Department of Health and Human Services, NIH Pub. No. 87-2868.
85. Mombelli, A (2003). The use of antibiotics in periodontal therapy. In: *Clinical Periodontology and Implant Dentistry* (4th ed.). Lindhe, J, Karring, T & Lang, NP, eds. Oxford, U.K.: Blackwell Munksgaard, pp. 494–511.
86. Morse, DE, Holm-Pedersen, P, Holm-Pedersen, J, Katz, RV, Viitanen, M, von Strauss, E, & Winblad, B (2002). Prosthetic crowns and other clinical risk indicators of caries among old-old Swedish adults: Findings from the KEOHS Project. Kungsholmen Elders Oral Health Study. *Gerodontology 19:* 73–79.
87. Novak, MJ, & Novak, KF (2002). Smoking and periodontal disease. In: *Carranza's Clinical Periodontology* (9th ed.). Newman, MG, Takei, HH & Carranza, FA, eds. Philadelphia: W.B. Saunders, pp. 245–252.
88. Porter, SR, Scully, C, & Hegarty, AM (2004). An update of the etiology and management of xerostomia. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 97:* 28–46.
89. Redmo Emanuelsson, IM, & Wang, XM (1998). Demonstration of identical strains of mutans streptococci within Chinese families by genotyping. *Eur. J. Oral Sci. 106:* 788–794.
90. Regezi, JA, & Sciubba, JJ (1989). *Oral Pathology: Clinical-Pathologic Correlations*. Philadelphia: W.B. Saunders, p. 554.
91. Rhodus, NL, Bloomquist, C, Liljemark, W, & Bereuter, J (1997). Prevalence, density, and manifestations of oral *Candida albicans* in patients with Sjögren's syndrome. *J. Otolaryngol. 26:* 300–305.

92. Ritchie, CS, Joshipura, K, Hung, HC, & Douglass, CW (2002). Nutrition as a mediator in the relation between oral and systemic disease: Associations between specific measures of adult oral health and nutrition outcomes. *Crit. Rev. Oral Biol. Med. 13:* 291–300.
93. Saito, T, Shimazaki, Y, & Sakamoto, M (1998). Obesity and periodontitis. *N. Engl. J. Med. 339:* 482–483.
94. Scannapieco, FA, Bush, RB, & Paju, S (2003). Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease: A systematic review. *Ann. Periodontol. 8:* 54–69.
95. Scheie, AA, Arneberg, P, Orstavik, D, & Afseth, J (1984). Microbial composition, pH-depressing capacity and acidogenicity of 3-week smooth surface plaque developed on sucrose-regulated diets in man. *Caries Res. 18:* 74–86.
96. Scheinin, A, & Mäkinen, KK (1975). Turku sugar studies: I–XXI. *Acta Odontalogica Scandinavia 33:* 1–351.
97. Seppälä, B, Seppälä, M, & Ainamo, J (1993). A longitudinal study on insulin-dependent diabetes mellitus and periodontal disease. *J. Clin. Periodontol. 20:* 161–165.
98. Sheiham, A, Steele, G, Marcenes, W, Lowe, C, Finch, S, Bates, CJ, Prentice, A, & Walls, AW (2001). The relationship among dental status, nutrient intake, and nutritional status in older people. *J. Dent. Res. 80:* 408–413.
99. Slee, AM, & Tanzer, JM (1982). Sucrose transport by *Streptococcus mutans:* Evidence for multiple transport systems. *Biochim. Biophys. Acta 692:* 415–424.
100. Slee, AM, & Tanzer, JM (1983). The repressible metabolism of sorbitol (D-glucitol) by intact cells of the oral plaque-forming bacterium *Streptococcus mutans*. *Arch. Oral Biol. 28:* 839–845.
101. Socransky, SS, & Haffajee, AD (2003). Microbiology of periodontal disease. In: *Clinical Periodontology and Implant Dentistry* (4th ed.). Lindhe, J, Karring, T & Lang, NP, eds. Oxford, U.K.: Blackwell Munksgaard, pp. 106–149.
102. Socransky, SS, Haffajee, AD, Goodson, JM, & Lindhe, J (1984). New concepts of destructive periodontal disease. *J. Clin. Periodontol. 11:* 21–32.
103. Söderling, E, Isokangas, P, Pienihakkinen, K, & Tenovuo, J (2000). Influence of maternal xylitol consumption on acquisition of mutans streptococci by infants. *J. Dent. Res. 79:* 882–887.
104. Solomon, CS, Shaikh, AB, & Arendorf, TM (1995). An efficacious oral health care protocol for immunocompromised patients. *Spec. Care Dentist. 15:* 228–233.
105. Soskolne, WA (1998). Epidemiological and clinical aspects of periodontal diseases in diabetics. *Ann. Periodontol. 3:* 3–12.
106. Soto-Rojas, AE, & Kraus, A (2002). The oral side of Sjögren's syndrome: Diagnosis and treatment: A review. *Arch. Med. Res. 33:* 95–106.
107. Soto-Rojas, AE, Villa, AR, Sifuentes-Osornio, J, Alarcon-Segovia, D, & Kraus, A (1998). Oral candidiasis and Sjögren's syndrome. *J. Rheumatol. 25:* 911–915.
108. Soto-Rojas, AE, Villa, AR, Sifuentes-Osornio, J, Alarcon-Segovia, D, & Kraus, A (1998). Oral manifestations in patients with Sjögren's syndrome. *J. Rheumatol. 25:* 906–910.
109. Staat, RH, Gawronski, TH, Cressey, DE, Harris, RS, & Folke, LE (1975). Effects of dietary sucrose levels on the quantity and microbial composition of human dental plaque. *J. Dent. Res. 54:* 872–880.
110. Stamm, JW, Banting, DW, & Imrey, PB (1990). Adult root caries survey of two similar communities with contrasting natural water fluoride levels. *J. Am. Dent. Assoc. 120:* 143–149.

111. *Sugar and Sweeteners Situation and Outlook Yearbook* (July 2004). Market and Trade Economics Division, Economic Research Service, U.S. Department of Agriculture, SSS-2004. Full report available online at: http://usda.mannlib.cornell.edu/reports/erssor/specialty/sss-bb/2004/sss2004.pdf.
112. Takeuchi, M (1961). Epidemiological study on dental caries in Japanese children before, during and after World War II. *Int. Dent. J. 11:* 443–457.
113. Tanzer, JM (1972). Studies on the fate of the glucosyl moiety of sucrose metabolized by *Streptococcus mutans*. Fifth International Conference on Oral Biology, Zurich. *J. Dent. Res. 51:* 415–423.
114. Tanzer, JM (1979). Essential dependence of smooth surface caries on, and augmentation of fissure caries by, sucrose and *Streptococcus mutans* infection. *Infect. Immun. 25:* 526–531.
115. Tanzer, JM (1986). Testing food cariogenicity with experimental animals. *J. Dent. Res. 65:* 1491–1497.
116. Tanzer, JM (1994). Problems associated with the dry and sore mouth of Sjögren's syndrome: Recognition and management of yeast infections. *Moisture Seekers Newsletter 12:* 1–5.
117. Tanzer, JM (1995). Dental caries is a transmissible infectious disease: The Keyes and Fitzgerald revolution. *J. Dent. Res. 74:* 1536–1542.
118. Tanzer, JM, Baranowski, LK, Rogers, JD, Haase, EM, & Scannapieco, FA (2001). Oral colonization and cariogenicity of *Streptococcus gordonii* in specific pathogen-free TAN:SPFOM(OM)BR rats consuming starch or sucrose diets. *Arch. Oral Biol. 46:* 323–333.
119. Tanzer, JM, Chassy, BM, & Krichevsky, MI (1971). Sucrose metabolism by *Streptococcus mutans*, SL-I. *Biochim. Biophys. Acta 261:* 379–387.
120. Tanzer, JM, Freedman, ML, Fitzgerald, RJ, & Larson, RH (1974). Diminished virulence of glucan synthesis-defective mutants of *Streptococcus mutans*. *Infect. Immun. 10:* 197–203.
121. Tanzer, JM, Freedman, ML, Woodiel, FN, Eifert, RL, & Rinehimer, LA (1976). Association of *Streptococcus mutans* virulence with synthesis of intracellular polysaccharides. In: *Microbial Aspects of Dental Caries: Proceedings of a Workshop on Microbial Aspects of Dental Caries, June 21–24, 1976* (Vol. 1). Stiles, HM, Loesche, WJ & O'Brien, TC, eds. Washington, DC: Information Retrieval, pp. 597–616.
122. Tanzer, JM, Livingston, J, & Thompson, AM (2001). The microbiology of primary dental caries in humans. *J. Dent. Educ. 65:* 1028–1037. Full report and evidence tables available online at: http://www.nidcr.nih.gov/NewsAndReports/ReportsPresentation/ConsensusDevConf/Agenda.htm.
123. Toverud, G (1957). The influence of war and post-war conditions on the teeth of Norwegian school children. II. Caries in the permanent teeth of children aged 7–8 and 12–13 years. *Milbank Mem. Fund Q. 35:* 127–196.
124. Toverud, G (1957). The influence of war and post-war conditions on the teeth of Norwegian school children. III. Discussion of food supply and dental condition in Norway and other European countries. *Milbank Mem. Fund Q. 35:* 373–459.
125. Trahan, L, Bareil, M, Gauthier, L, & Vadeboncoeur, C (1985). Transport and phosphorylation of xylitol by a fructose phosphotransferase system in *Streptococcus mutans*. *Caries Res. 19:* 53–63.

126. U.S. Department of Health and Human Services (2000). *Oral Health in America: A Report of the Surgeon General*. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health. Full report available online at: http://www2.nidcr.nih.gov/sgr/sgrohweb/welcome.htm.
127. Van Houte, J, & Duchin, S (1975). *Streptococcus mutans* in the mouths of children with congenital sucrase deficiency. *Arch. Oral Biol. 20:* 771–773.
128. Van Houte, J, Upeslacis, VN, Jordan, HV, Skobe, Z, & Green, DB (1976). Role of sucrose in colonization of *Streptococcus mutans* in conventional Sprague-Dawley rats. *J. Dent. Res. 55:* 202–215.
129. Vargas, CM, Crall, JJ, & Schneider, DA (1998). Sociodemographic distribution of pediatric dental caries: NHANES III, 1988–1994. *J. Am. Dent. Assoc. 129:* 1229–1238.
130. Vargas, CM, Kramarow, EA, & Yellowitz, JA (2001). *The Oral Health of Older Americans: Aging Trends, No. 3*. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention.
131. von der Fehr, FR (1982). Evidence of decreasing caries prevalence in Norway. The first international conference on the declining incidence of dental caries, Glass, RL, ed. *J. Dent. Res. 61:* 1331–1335.
132. Warren, JJ, Cowen, HJ, Watkins, CM, & Hand, JS (2000). Dental caries prevalence and dental care utilization among the very old. *J. Am. Dent. Assoc. 131:* 1571–1579.
133. Wayler, AH, Muench, ME, Kapur, KK, & Chauncey, HH (1984). Masticatory performance and food acceptability in persons with removable partial dentures, full dentures and intact natural dentition. *J. Gerontol. 39:* 284–289.
134. Weiss, RL, & Trithart, AH (1960). Between-meal eating habits and dental caries experience in preschool children. *Am. J. Public Health 50:* 1097–1104.
135. Wen, ZT, Browngardt, C, & Burne, RA (2001). Characterization of two operons that encode components of fructose-specific enzyme II of the sugar:phosphotransferase system of *Streptococcus mutans*. *FEMS Microbiol. Lett. 205:* 337–342.
136. Wexler, DL, Penders, JE, Bowen, WH, & Burne, RA (1992). Characteristics and cariogenicity of a fructanase-defective *Streptococcus mutants* strain. *Infect. Immun. 60:* 3673–3681.
137. Winn, DM, Brunelle, JA, Selwitz, RH, Kaste, LM, Oldakowski, RJ, Kingman, A, & Brown, LJ (1996). Coronal and root caries in the dentition of adults in the United States, 1988–1991. *J. Dent. Res. 75* Spec. No.: 642–651.
138. Winter, GB (1990). Epidemiology of dental caries. *Arch. Oral Biol. 35* Suppl: 1S–7S.
139. Woodward, M, & Walker, AR (1994). Sugar consumption and dental caries: Evidence from 90 countries. *Br. Dent. J. 176:* 297–302.
140. Wyatt, CC (2002). Elderly Canadians residing in long-term care hospitals: Part II. Dental caries status. *J. Can. Dent. Assoc. 68:* 359–363.
141. Zelickson, BD, & Rogers, RS, 3rd. (1986). Drug reactions involving the mouth. *Clin. Dermatol. 4:* 98–109.

11 Dermatology and Nutrition

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CONTENTS

11.1 INTRODUCTION: THE ROLE OF NUTRITION IN DERMATOLOGY

There are several well-recognized relationships between nutrition and dermatology, including dermatitis herpetiformis and gluten, acrodermatitis enteropathica and zinc, and erythropoietic porphyria and β-carotene.

Dermatitis herpetiformis (DH) is a chronic, extremely pruritic, grouped papular and vesicular skin disorder associated with a gluten-sensitive enteropathy with intestinal inflammation and villous atrophy. Gluten in the gut triggers an immune response resulting in deposits of IgA and complement at the dermal–epidermal junction. These deposits ultimately cause the pruritic rash. Relief is achieved with sulfone medications such as Dapsone, but these medications do not cure the disease. To achieve complete remission of the disorder, patients need to adhere to a strict gluten-free diet, eliminating all foods containing wheat, rye, and barley.

Acrodermatitis enteropathica (AE) is an autosomal recessive disorder of zinc absorption due to defective zinc transport. Patients with AE present in infancy after breastfeeding has ceased. Presenting signs include an erythematous eczematous rash periorally, on acral skin, and in the anogenital region. Associated symptoms include gastrointestinal disturbance, irritability, lethargy, and failure to thrive. The pathogenesis of AE relates to the immune functions of zinc. In AE, T cell number and mitogen-induced activation are decreased, delayed-type hypersensitivity is reduced, thymic hormone levels are lower, and neutrophil responses including chemotaxis and phagocytosis are reduced. Oral zinc supplementation (30 to 45 mg/d) induces complete remission of the disorder.

The porphyrias are a group of disorders caused by enzymatic defects in heme biosynthesis. Erythropoietic porphyria develops as a result of defects in ferrochelatase. Porphyrins accumulate in the skin and generate free radicals that damage the skin when patients are exposed to sunlight. Skin begins to burn, itch, develop erythema, and swell within a short time of exposure to the sun. Relief can be obtained with β-carotene, which functions by scavenging cutaneous free radicals.

The complete etiologies of more prevalent dermatoses, including acne vulgaris, acne rosacea, atopic dermatitis, and psoriasis, are unknown. Even though the specific causes of these diseases are not known, immune activation appears to play a role in their pathogenesis. The cause of the heightened immune responses is unclear, but it is most likely a combination of genetic and environmental influences. The human genome has changed relatively little in the past several thousands of years; our environment has changed significantly. Changes include urbanization, immunization programs, and the industrialization of the food supply, to name a few. It is

only recently that we have begun studying the impact of these changes on human immune defenses.

Research in the areas of nutritional biochemistry and immunology is revealing an immunological connection between two of our largest immune organs, the gut and the skin. Foreign antigen encountered in the gut, in the form of food antigen or bacterial products, can prime immune cells to produce an immune response in organs such as the skin. Understanding this link may give insight into the prevention of diseases like psoriasis and atopic dermatitis. Inflammatory responses generated in the gut activate the release of neuropeptides from peripheral nerve fibers, leading to vasodilation and flushing of the skin. Discovering the specific triggers of this mechanism may help control symptoms of acne rosacea. The health of the gut thus appears to have an impact on dermatological diseases.

The balance of nutrients that are consumed also appears to affect the skin. Due to the industrialization of food, many edibles are not consumed in their native form. To extend shelf life, fats and oils are stripped of vitamin E and essential fatty acids prior to bottling. The result is the consumption of oxidized unessential fat. Essential fatty acids and antioxidants, necessary for many cellular processes, direct immune responses through the production of specific fatty acid hormones (prostanoids) and influence oxidation-sensitive genes and enzymes. In the serum of infants who develop atopic dermatitis, the ratio of pro-inflammatory to anti-inflammatory fatty acids is high. Also, the essential long chain fatty acid, gamma-linolenic acid (GLA), may reduce the metastatic potential of cancerous cells such as melanoma by influencing the strength of basement membrane proteins.

In acne vulgaris, the age-old debate of the impact of sugar and refined foods on acne formation will be addressed with some interesting new research regarding the role of insulin and insulin-like growth factor-1. Additionally, the initiating event in acnegenesis will be scrutinized, as pro-inflammatory fatty acids like arachidonic acid (not hyperdesquamation of keratinocytes) may be at the root of acne formation.

In acne rosacea, gastrointestinal disorders associated with gut inflammation will be addressed with a review of *Helicobacter pylori,* bacterial-induced toxins, and gut-derived bradykinin (a potent vasodilator induced by gut inflammation). Nutritionals such as fiber, found to be beneficial in rosacea, will be discussed.

In atopic dermatitis, exposure to foreign antigen in the gut early in life and defects in the intestinal barrier may be the initiating events that cause children to develop this pruritic inflammatory skin disorder. Breastfeeding may be the earliest preventive measure against atopic dermatitis. Furthermore, the role played by the ratio of anti-inflammatory to pro-inflammatory essential fatty acids in the development and treatment of atopic dermatitis will be analyzed.

In psoriasis, bacteria-derived endotoxin in the gut may be a cause of the disease. Controlling toxins and oxidative stress in the gut will be reviewed as treatments for psoriasis.

In skin cancer, obesity has been associated with a higher risk of developing melanoma in men. To prevent development of melanoma and nonmelanoma skin cancer, caloric restriction, the use of antioxidants, and vitamin D have been advocated; the evidence for these approaches will be reviewed.

11.2 ACNE VULGARIS

11.2.1 Description of Acne Vulgaris

Acne vulgaris is the most common skin disorder in the United States, affecting nearly 17 million people, including 85% of individuals between the ages of 11 and 30 (95). It arises from dysfunction of pilosebaceous units. It has been shown that four events lead to the formation of acne, including:

- Increased activity of sebaceous glands
- Abnormal differentiation of the follicle with hyperdesquamation of keratinocytes
- Colonization and proliferation of *Propionibacterium acnes* with bacterial-induced enzymic cleavage of free fatty acids
- Inflammation and host reactivity

The exact etiology of acne is still being investigated, but it is well established to be multifactorial, with heredity, hormones, and environmental factors playing a role. Some medications are known to cause acneiform eruptions, including anabolic steroids, corticosteroids, halogenated products, and many others (131). Recent investigations point to inflammation being the initiating event (88).

Evidence against bacteria initiating acne lesions comes from the observation that bacteria colonize both normal follicles and acne lesions (75); likewise, the severity of acne does not correlate with the numbers of bacteria within the follicle (25). In addition, it has been shown that sebocytes in culture can independently manufacture fatty acids in the absence of bacteria (53). It is possible that bacteria perpetuate inflammation but are not required for lesion initiation.

Table 11.1 describes treatments for acne.

11.2.2 Nutritional Aspects

Proinflammatory lipids such as arachidonic acid (AA) possess properties that could initiate acne lesions. AA and products of AA metabolism, 12-hydroxyeicostetraeinoic acid (12-HETE) and leukotriene-B4 (LTB-4), as well as interleukin-1 (IL-1), are capable of disrupting the follicle wall and permitting spread of the folliculo-sebaceous contents to the dermis with subsequent infiltration of inflammatory cells. Evidence shows that these inflammatory fats may be at the root of acnegenesis (60,82,88,127,140,195).

Hyperdesquamation of keratinocytes has been thought to spawn acne lesions, with bacterial proliferation and inflammation occurring secondary to follicular plugging. However, in 2002 Jeremy and colleagues found that skin from acne patients had higher levels of inflammatory mediators, such as IL-1, and inflammatory adhesion molecules, including E-selectin and vascular adhesion molecule-1, whether or not the sample was taken from specific lesions or uninvolved skin (88). This suggests that patients with acne have, within the environment of their skin, a milieu of inflammatory factors that favors hypercornification of the epithelium. In fact, addi-

TABLE 11.1
Treatments for Acne

	Structure and Function	Comments
	Topical Agents	
1. Tretinoin	All-cis-retinoic acid; normalizes follicular keratinization	Drug of choice for comedonal acne
2. Adapalene	Napthoic acid derivative; normalizes follicular keratinization	Drug of choice for comedonal acne
3. Tazarotene	Synthetic, acetylenic retinoid; normalizes follicular keratinization; anti-inflammatory; immunomodulatory	Drug of choice for comedonal acne; erythema, pruritus, and peeling more common
4. Salicylic acid	Comedolytic activity	Used for comedonal and mild inflammatory acne when 1–3 not tolerated; can be used in combination with topical retinoids
5. Azeleic acid	Dicarboxylic acid with bactericidal activities	Used for comedonal acne when 1–3 not tolerated; can be used in combination with topical retinoids
6. Glycolic acid		Used for comedonal acne when 1–3 not tolerated, or in combination with topical retinoids
7. Benzoyl peroxide	Oxidizes bacterial proteins; bactericidal and comedolytic	Used for comedonal acne when 1–3 not tolerated; used for mildly inflammatory acne; may be used in combination with topical retinoid for better effect; when combined with topical antibiotic helps prevent resistance; may be used in combination with glycolic acid and zinc
8. Antibiotics: erythromycin, clindamycin, sodium sulfacetamide	Eliminates *P. acnes* from follicles; suppresses chemotaxis	Used for mild to moderate inflammatory acne; skin irritation is rare
	Oral Agents	
1. Antibiotics: tetracycline, doxycycline, minocycline	Antibacterial; direct anti-inflammatory properties of tetracycline	Used for inflammatory acne; tetracycline is low cost and has high efficacy; subantimicrobial doses of doxycycline (20 mg twice daily) is effective for adults with moderate acne

TABLE 11.1 (Continued)
Treatments for Acne

	Structure and Function	Comments
2. Contraceptives	Ethinyl estradiol plus progesterone (± antiandrogenic effects)	Used for hormonally induced acne; Orthotricyclen, Yasmin, Orthocept, Desogen, Orthocycline
3. Isoretinoin	13-Cis-retinoic acid; targets all four pathogenic steps	Used for severe, recurrent, or scarring acne; teratogenic
	Light Therapies	
1. Blue light	405 to 420 nm	Expensive; used with topical 20% 5-aminolevulinic acid (ALA)
2. Laser	Low irradiation energy density	Mild to moderate inflammatory acne; expensive
	Nutritional Treatments	
1. Reduce intake of refined carbohydrates, fried foods, and hydrogenated fats	Proposed mechanisms include lowering insulin-induced follicular changes and reducing saturated fat-induced adhesion molecule expression	
2. Avoid halogens		Avoid consuming chlorinated water and soft drinks that contain natural and synthetic bromides
3. Fiber	Reduces erythema in acneiform disorders; use of ground flaxseeds (containing γ-linolenic acid) increases ratio of ω-3 fatty acids and may help reduce proinflammatory milieu of skin environment	Ground flaxseeds (containing γ-linolenic acid); 1 to 2 tablespoon/d
4. Probiotics	Restore optimal intestinal flora	Important with oral antibiotics use (Natren; Metagenics Ultra Flora); 2 billion colony equivalents daily
5. Multivitamin containing vitamin A, vitamin E, and zinc	Antioxidants; reduce free radical–induced tissue damage and inflammation	Crayhon Research Body Vibrance: 1 packet/d, or Biotics Bio-Multi-Plus (available iron-free and iron- and copper-free): 3 tablets/d
6. Chromium; alpha-lipoic acid	Blood sugar stabilization	Designs for Health Chromium Synergy: 200 μg/d; Designs for Health Alpha-Lipoic Acid: 100 to 300 mg twice daily

TABLE 11.1 (Continued)
Treatments for Acne

	Structure and Function	Comments
7. Omega-3 fats; Evening Primrose Oil (EPO), GLA	Increase ratio of ω-3 fatty acids and may help reduce proinflammatory milieu of skin environment	Nordic Naturals Cod Liver Oil: 1 to 2 g daily; EPO: 100 mg daily
8. Topical tea tree oil (10%) after mild cleansing	Bactericidal agent	Test small area for contact sensitivity before use

tion of exogenous IL-1α to follicles *in vitro* induces spontaneous cornification, similar to the acne precursor lesion, the microcomedo (60).

It has been suggested that the relative deficiency of anti-inflammatory essential fatty acids such as dihomogammalinolenic acid (DGLA), an omega-6 (ω-6) fatty acid, and eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), omega-3 (ω-3) fatty acids, in the keratinocyte may lead to a disruption in the barrier function of the follicle, as these fats have been shown to maintain the integrity of basement membrane interactions (127). Inadequate cutaneous concentrations of essential fats may cause a perpetuation of inflammation (127). Linoleic acid, derived from sesame oil and a precursor to DGLA, reduces the expression of neutrophil-recruiting adhesion molecules when applied to the endothelium (140). Palmitic acid, a saturated fatty acid found in many processed foods, causes no reduction in adhesion molecule expression (140).

Another AA product, LTB-4, has been implicated in acnegenesis (195). It stimulates the recruitment of neutrophils, macrophages, and eosinophils and production of other pro-inflammatory cytokines. A small-scale study tested the effects of an anti-inflammatory agent, Zileuton, which inhibits the formation of LTB-4. After 3 months of treatment, patients had a 70% reduction in inflammatory acne lesions (195). Interestingly, isotretinoin was found in one study to inhibit LTB-4-induced neutrophil migration, which may be a mechanism of its antiacne actions (188).

In addition, LTB-4 is a ligand for the peroxisome proliferator–activator receptor (PPAR) alpha (PPARα) (39). PPARs are members of the nuclear hormone receptor superfamily that includes the retinoic acid receptors, vitamin D receptor, and thyroid hormone receptors, all of which exert effects on keratinocyte differentiation and proliferation, epidermal hydration barrier, wound healing, and sebaceous gland activity (75). Activation of PPARα was found to stimulate the accumulation of lipid in cultured sebocytes (144). When dihydrotestosterone was added to PPAR activators such as LTB-4, an additive effect in lipid droplet formation was seen (144). PPAR activation may therefore cause changes in the sebocyte distinct from androgens. Supplementation with EPA and DHA, inhibitors of LTB-4 formation, may attenuate the formation of acne via direct anti-inflammatory activities or through modulation of PPAR receptors. However, no clinical trials on EPA, DHA, and acne have been performed.

The role of sugar in acne vulgaris is the subject of an age-old debate, and many investigations about the relationship were conducted in the 1960s and 1970s. Some

intriguing new evidence about the role of sugar in acne comes from the work of Cordain et al. (35), who determined the prevalence of acne vulgaris in two nonwesternized populations: the Kitavan Islanders of Papua New Guinea and the Ache hunter-gatherers of Paraguay. Cordain and his colleagues examined 1200 Kitavan individuals — 300 of whom were aged 15 to 25 years — and found no single case of acne vulgaris. Similarly, no acne was seen in 115 Ache individuals. These investigators propose that the diets of these two populations are responsible for the absence of acne and that the vast quantities of high-glycemic foods consumed by Westerners cause acne. Cordain and colleagues recognize the impact of genetics but point out that South American Indians and Pacific Islanders, with a gene pool similar to that of the Ache and Kitavan, have acne since adopting a western lifestyle.

Hyperinsulinemia causes high levels of insulin-like growth factor-1 (IGF-1) and low levels of insulin-like growth factor binding protein 3 (IGFBP-3). IGF-1 is required for keratinocyte proliferation (145). IGFBP-3 inhibits growth by binding IGF-1. An elevated ratio of IGF-1:IGFBP-3 leads to unregulated growth and thus abnormal keratinocyte differentiation, a main feature of acne. In addition, insulin and IGF-1 both stimulate androgen synthesis and sebum production, another contributor to acne formation. Indeed, past studies have shown that proper glycemic control through the use of tolbutamide (38), a sulfonylurea that increases insulin release from pancreatic β cells, and chromium (113), a nutrient that improves the insulin sensitivity of peripheral tissues, leads to improvements in acne.

Due to the side effects of high doses of vitamin A in acne treatment, the synthetic derivative isotretinoin (13-cis-retinoic acid) replaces it with great efficacy (99). The molecular mechanisms of isotretinoin are not fully known. It appears to inhibit cell proliferation and lipid synthesis of sebaceous gland cells (194), decrease androgen receptor expression (160), and decrease 5-alpha-reductase activity (134) — all key contributors to acne formation. It is the most effective acne treatment available at this time (99). It is not without side effects, however (99), and women of childbearing age who are taking isotretinoin must adhere to a strict birth control regimen, as abnormal fetal development is reported with isotretinoin exposure.

Nontoxic levels of vitamin A, if combined with vitamin E, can be effective in the treatment of hyperkeratotic disorders (5). Vitamin E appears to regulate retinol levels, as rats fed a vitamin E–deficient diet had low blood levels of vitamin A, no matter how much vitamin A was supplemented; levels returned to normal once vitamin E was restored (4). In addition, Michaelsson and Edqvist showed that men with severe acne and low activity of glutathione peroxidase — a selenium-dependent enzyme — had improvement in their acne after supplementation with 0.2 mg of selenium and 10 mg of tocopheryl succinate twice daily for 6 to 12 weeks (117).

Vitamin B_5 (pantothenic acid) and vitamin B_6 (pyridoxine) are involved in steroid hormone synthesis and may help regulate fluctuating hormone levels during premenstrual acne flares (155). High levels of B_6 may cause acne (131).

Zinc has been shown to be an effective treatment for acne. The exact mechanism is unknown, but it may be related to the zinc-dependent oxidation of retinol to retinoic acid. Other zinc-dependent processes include synthesis of retinol-binding protein, inhibition of 5-alpha reduction of testosterone, wound healing, and immune modulation. Zinc sulfate has shown mild efficacy, but nausea, vomiting, and diarrhea limit

its utility (184). When 30 mg zinc gluconate was administered for 3 months, a reduction in acne lesions was observed (43). However, daily intake of 100 mg minocycline, a tetracycline derivative, was found to be even more effective than zinc. Topical zinc oxide combined with chloroxylenol (Nels cream), an antiseptic, proved to be as efficacious as 5% benzoyl peroxide when applied twice daily for 8 weeks (128).

Tea tree oil is an extract from the Australian tree *Melaleuca alternifolia*. It is known for its bactericidal properties. In a randomized trial, 10% tea tree oil was more effective at clearing methicillin-resistant staph aureus (MRSA) colonization from skin lesions than chlorhexidine or silver sulfadiazine (44). In a single blind trial, 5% tea tree oil gel was as effective as 5% benzoyl peroxide lotion in reducing the number of inflammatory acne lesions and comedones. Benzoyl peroxide was found to work more quickly, but tea tree oil had fewer side effects.8 Allergic contact dermatitis as a result of tea tree oil has been reported (30). This may be due to oxidized oil in shelf-aged products.

11.3 ACNE ROSACEA

11.3.1 Description of Acne Rosacea

Rosacea is an acneiform disorder and most commonly affects people in the third to sixth decades of life. The etiology is unknown, and there is no known cure. Some evidence points to infection by hair follicle mites *Demodex follicularum* and *Demodex brevis,* as patients with rosacea have greater numbers of these skin mites (142). Treatment with tetracycline has led to improvement in rosacea symptoms but to no change in the number of mites (16). The bacterium *Helicobacter pylori* (*H. pylori*) has also been implicated in the pathogenesis of the disorder (40), as have other gastrointestinal insults. Factors known to cause flares in symptoms include caffeine, alcohol, spicy foods, exposure to the warm sun or to cold, strong emotion, and stress.

Rosacea is a chronic disorder with relapsing and remitting periods. Classic signs include facial erythema on the nose, cheeks, chin, and forehead, accompanied by papules, pustules, nodules, and telangectasias. People with chronic inflammation can develop hypertrophy of the sebaceous glands in the nose (rhinophyma). The features of rosacea that distinguish it from acne vulgaris are the classically distributed erythema, telangectasias, and absence of comedones.

Patients with rosacea have a hypersensitive facial vasculature. Specific triggers cause intense flushing, with redness and heat. Extravasation of fluid and immune cells leads to edema and inflammation. The cause of blood vessel hypersensitivity is unknown.

Table 11.2 describes treatments for rosacea.

11.3.2 Nutritional Aspects

Rosacea has been associated with gastrointestinal tract disorders, including *H. pylori* infection (40), insufficient acid secretion (hypochlorhydria and achlorhydria) (146), other digestion defects, and inflammatory disorders such as ulcerative colitis (UC) (181).

TABLE 11.2
Treatments for Rosacea

	Structure and Function	Comments
	Topical Agents	
1. Antibiotics: metronidazole	Antibacterial	Maintenance therapy; indicated for generalized erythema and inflammatory lesions
2. Azelaic acid (Finacea)	Dicarboxylic acid with bactericidal activities	Maintenance therapy; indicated for generalized erythema and inflammatory lesions
3. Sulfacetamide/sulfur	Antibacterial agent that competitively antagonizes para-aminobenzoic acid/ keratolytic	Maintenance therapy; indicated for generalized erythema and inflammatory lesions
4. Tacrolimus	Suppresses cellular immunity (inhibits T lymphocyte activation), possibly by binding to an intracellular protein, FKBP-12	Alternative to topical steroids; FDA approved for children 2 years and older; does not cause skin atrophy; safe on face and neck
5. Picrolimus	Suppresses cellular immunity (inhibits T lymphocyte activation), possibly by binding to an intracellular protein, FKBP-12	Alternative to topical steroids; FDA approved for children 2 years and older; does not cause skin atrophy; safe on face and neck
	Oral Agents	
1. Antibiotics: tetracycline 250 to 1500 mg daily; doxycycline 50 to 100 mg once to twice daily; minocycline 50 to 200 mg daily; Periostat 20 mg twice daily	Antibacterial and anti-inflammatory	Indicated for nodular and ocular rosacea and persistent symptoms; duration: 4 weeks with tapering dose for 4 weeks; Periostat: a subantimicrobial dose is suggested to have greater efficacy in treating erythema
2. Clonidine	Stimulates alpha2-adrenoceptors in the brain stem, inhibiting sympathetic outflow from the central nervous system	Prevents flushing
	Light Treatments	
1. Pulse dye laser	585 nm	May help improve stubborn erythema and telangectasias
	Surgical Treatments	
1. Scalpel shaving; microdebrider	Removes excess soft tissue	Used for rhinophyma
	Nutritional Treatments	
1. Eliminate all trigger foods		These foods are generally patient-specific

TABLE 11.2 (Continued)
Treatments for Rosacea

	Structure and Function	Comments
2. Use alcohol, caffeine, and spicy foods sparingly	Vasodilating foods exacerbate flushing	
3. Probiotics	Restore optimal intestinal flora with chronic use of antibiotics	Metagenics Ultra Flora: includes fructo-oligosaccharides (fuel for lactobacillus and bifidobacteria)
4. L-glutamine	Major nutrient for enterocyte repair and healing; improves intestinal barrier function	Designs for Health/Biotics: 1 to 3 g/d
5. Digestive enzymes	Include pancreatic enzymes found to improve symptoms in rosacea	Biotics Intenzyme Forte: with each meal
6. Fiber (ground flaxseeds)	Increases membrane ratio of ω-3 fatty acids and helps bind intestinal toxins	Containing γ-linolenic acid: 1 to 2 tablespoons/d
7. Topical alpha-lipoic-acid/ CoQ10/Vitamin C	Topical antioxidants have shown to be effective in rosacea	Designs for Health Derma-Q gel cream

In a study looking at the prevalence of *H. pylori* infection, controls and individuals with rosacea had similar responses to *H. pylori* serologic testing (150); this suggests that the presence of *H. pylori* does not correlate well with rosacea. In a comparable study, no difference in *H. pylori* serologic results was obtained between controls and rosacea subjects; yet, patients with rosacea showed improvement in symptoms after anti-*H. pylori* treatment consisting of amoxicillin, metronidazole, and bismuth (168).

Serological evidence of *H. pylori* does not signify active infection. Rather, it is an indication of a history of exposure. This may be the reason for the conflicting evidence regarding the association of *H. pylori* and rosacea (136). A specific indicator of active infection is the urea breath test. In a pilot study by Diaz et al. (40), patients with advanced rosacea tested positive for *H. pylori* in both the 13C-urea breath test and by ELISA (40). People with advanced forms of rosacea, compared to those with more mild disease, may therefore have active *H. pylori* infection. Further evidence for the role of *H. pylori* in the pathogenesis of rosacea is that many empiric therapies for rosacea include anti-*H. pylori* antibiotics, such as metronidazole, clindamycin, and penicillins (136).

Early studies found that patients with rosacea had reduced baseline levels of gastric acid secretion (146). A case report by Vasquez tells of a man who ingested acidic substances like vinegar and lemon to get rid of his symptoms of cutaneous lesions (resembling rosacea) and dysuria (173). When the acids were not taken, his symptoms recurred. Subsequent gastric biopsy revealed *H. pylori* infection. Treatment of *H. pylori* resulted in permanent resolution of symptoms. Another study found that patients with rosacea had significantly less secretion of pancreatic lipase than controls (7). Rosacea patients with both digestive symptoms and skin involve-

ment who received pancreatic enzyme supplements achieved resolution of both symptoms.

There have been several case reports of patients with concomitant ulcerative colitis and rosacea (181). The two disorders may be linked through vasoactive mediators induced by gut inflammation. Inflammation could be the result of many intestinal insults including UC, tumor, food antigen, *H. pylori,* or others. *H. pylori* infection is associated with increased leukotriene C4 (LTC-4) levels (3). Inflammation in the GI tract, or any tissue, leads to activation of inflammatory mediators, including the vasodilating substance kallikrein. Kallikrein is metabolized to bradykinin, a potent vasodilating agent. Patients with rosacea exhibit kallikrein-kinin activation in their blood (93,156), and peak flushing correlates with increased bradykinin levels (59). This suggests that the flushing erythema in rosacea patients is due to the effects of high circulating levels of kallikrein-kinin produced by gut inflammation acting on facial blood vessels. Another mechanism by which bradykinin produced in the gut can lead to facial flushing is through stimulation of afferent nerve fibers. Neurokinins such as Substance P are expressed in afferent nerve fibers and enteric neurons of the gut and also in intestinal muscle, epithelium, and the vascular system. These neuropeptides are released from sensory nerve fibers during intestinal inflammation and are known to evoke flushing (73,186). Evidence for this mechanism in rosacea is the finding of abundant Substance P–secreting neurons localized around affected blood vessels in rosacea patients (93,110).

Colon cancer and rosacea were linked in a report of an 80-year-old man who had undergone an orchiectomy due to prostate cancer. The colon cancer recurred in this patient coincident with his first presentation of rosacea (110). Hormonal changes and tumor-derived vasoactive substances may have caused this patient's rosacea (110).

In another case, a patient with rosacea without gastrointestinal disturbance was given fiber in the form of wheat bran along with an activated charcoal tracer and was cleared of her rosacea symptoms (93). The investigators suggested that intestinal bacteria may be responsible for activation of kallikrein-kinin and that increasing intestinal propulsion may reduce this activation. Another mechanism is that the bacteria-induced toxins that cause intestinal inflammation became bound to the charcoal.

Some believe that patients with rosacea have a breakdown of the antioxidant defense system. A study by Oztas and colleagues (126) found that patients with mild rosacea have higher than normal superoxide dismutase activity and normal malondialdehyde levels (a marker of ROS-mediated lipid peroxidation). Patients with severe disease have lower levels of superoxide dismutase and higher levels of malondialdehyde compared to controls. This suggests that patients with severe disease do not have adequate concentrations of antioxidants to handle free radical–induced damage. Patients with mild disease, on the other hand, can adapt to increased free radical generation by upregulating the activity of superoxide dismutase.

Vitamins C, A, and B have been reported to play a role in rosacea therapy. Topical vitamin C has been shown to help reduce erythema in rosacea (29). In an observer-blinded, placebo-controlled study, 75% of participants achieved reductions in erythema by using a topical 5% vitamin C preparation (29). Low-dose oral isotretinoin (10 mg/d) and tretinoin cream (0.025%) have been shown to be beneficial

in the treatment of acne rosacea (46,167). There have been early reports of successful management of rosacea with B vitamins; however, more current reports suggest that high doses of vitamin B_2 (riboflavin), vitamin B_6 (pyridoxine), and vitamin B_{12} (cobalamin) cause facial eruptions similar to rosacea (85). No adverse findings have been reported for niacin (vitamin B_3); however, this vitamin, unless taken in the inositol hexanicotinate form, is known to cause flushing.

11.4 ATOPIC DERMATITIS

11.4.1 Description of Atopic Dermatitis

Atopic dermatitis (AD), also known as eczema, is a chronic, pruritic, inflammatory skin disorder with a tendency for excessive inflammation. It affects up to 17% of children (100) and 3% of adults (122). The initial symptom is pruritus without a rash; therefore, it is known as "the itch that rashes, not the rash that itches." The disorder typically presents in childhood, with 50% of patients developing AD in the first year of life (91).

The complete etiology of AD is not known, but it is most likely the product of a complicated interaction of susceptibility genes (18,20,34,102), defects in the skin barrier (77), environmental triggers (22,24,26,94,104,147,180,182), and heightened immunological responses (66,124,165). A decreased amount of fatty acids has been reported in the stratum corneum of AD patients (77), which would predispose them to chronic dry skin and susceptibility to invasion by environmental antigens. Environmental triggers include early exposure to food proteins, especially eggs, cow's milk, wheat, soy, and peanuts (147). Aeroallergens such as pollens (180), mold (94), dust mites (26), animal dander, and cockroach allergen (182) have also been implicated, as have bacteria such as *Staphylococcus aureus* (104) and yeasts such as *Pityrosporum ovale* (24), *Trychophyton* sp., *Candida* sp., and *Malassezia* sp. (22). There appear to be two types of AD, so-called "extrinsic" — affecting 80%, with immunoglobulin E (IgE)–mediated sensitization — and "intrinsic" — affecting 20%, without IgE-mediated sensitization (123). Defects in immune function are observed in AD. Patients have defective cell-mediated immunity, decreased regulatory T cells, elevated levels of IgE in the majority of cases, blood eosinophilia, and a predominance of Th2-type cytokines (62).

Table 11.3 describes treatments for AD.

11.4.2 Nutritional Aspects

For many children, early foreign antigen exposure in the gut appears to be an initiating event in the development of AD. Impairment of junctional closures between enterocytes has been suggested as a cause for the heightened immunological responses to food antigens in children with AD. A study by Majamaa and Isolauri found that sections of small intestine from children with AD had increased permeability to intact horseradish peroxidase, compared to those of age-matched controls (108). A higher than normal intestinal transfer of antigen may therefore be responsible for invoking immune responses to food antigens.

TABLE 11.3
Treatments for Atopic Dermatitis

	Structure and Function	Comments
	Topical Agents	
1. Corticosteroids	Anti-inflammatory, antiproliferative, immunosuppressive	Low potency (hydrocortisone) for mild AD; medium potency (triamcinolone) for more severe AD; high potency (dipropionate) for short periods with AD flares
2. Calcineurin inhibitors: tacrolimus, picrolimus	Suppresses cellular immunity (inhibits T lymphocyte activation), possibly by binding to an intracellular protein, FKBP-12	Alternative to topical steroids; FDA approved for children 2 years and older; does not cause skin atrophy; safe on face and neck; effective for eyelid AD; may cause stinging of the skin
3. Emollients: ointments (petroleum jelly, Aquaphor), creams (Eucerin, Cetaphil)	Low water content ointments and creams; protect against xerosis	Hydrating bath followed by immediate application of emollient may be more effective
	Oral Agents	
1. Antihistamines	Block histamine	Sedating antihistamines are more effective (diphenhydramine)
2. Corticosteroids	Function not known; anti-inflammatory, antiproliferative, immunosuppressive	Used for acute exacerbations
3. Cyclosporin	T-cell suppressant	Effective for severe AD; renal toxicity and hypertension limit utility; topical cyclosporin does not seem to be effective
	Light Therapies	
1. UVB	280 to 320 nm; thought to have immune modulating effects	Used for extensive disease
2. Narrow band UVB	311 to 313 nm; thought to have immune modulating effects	Used for extensive disease; equally efficacious with suberythemal doses; optimum wavelength for T-cell apoptosis; more expensive
3. PUVA	8-Methoxypsoralen is a photosensitizing drug; plus UVA at 320 to 400 nm	Used for extensive disease; increased incidence of melanoma and NMSC, as well as genital cancer in men

TABLE 11.3 (Continued)
Treatments for Atopic Dermatitis

	Structure and Function	Comments
	Nutritional Treatments	
1. Breast milk	Many mechanisms have been proposed for the ability of breast milk to reduce the incidence and severity of atopy	Atopic mothers who choose to breastfeed should try to eliminate all high-allergen foods, such as cow's milk, soy, egg, and peanuts for their newborn's first 6 months. Digestive enzymes (Biotics Intenzyme Forte) to adults and mothers with each meal
2. Hydrolyzed formula	Formulas consisting of amino acids have been shown to be less allergenic than cow's milk protein formulas and to protect against the development of AD	Mothers who opt not to breastfeed should consider using a hydrolyzed formula such as Alimentum Advance (Similac), Nutramigen with Lipil (Enfamil), or Neocate (SHS) for at least the first 6 months, or longer
3. L-glutamine	Major nutrient for enterocyte repair and healing; improves intestinal barrier function	Designs for Health/Biotics to adults, mothers, and infants older than 6 months: 1 to 3 g/d
4. Rotating schedule for food	Prevents sensitization to specific foods	Introduce foods to children individually and on a rotating schedule (do not give the same food more than once per week) and avoid high-allergen foods for first year
5. Caprylic acid	Reduces yeast colonization	Ecological Formulas Capricin (ages 6 and older): 1 to 3 capsules/d to improve skin superinfection or gut colonization
6. Probiotics	Restore optimal intestinal flora after use of antibiotics	Metagenics Ultra Flora (for adults and mothers): adult dose, 24 billion colony equivalents twice daily for 1 month; newborn dose, 3 billion colony equivalents daily for 1 month or longer for babies whose mothers were treated with penicillin for Group B Strep

TABLE 11.3 (Continued)
Treatments for Atopic Dermatitis

	Structure and Function	Comments
7. Vitamin E	Reduces erythema, lichenification, and pruritus and has been shown to induce remission in some patients with AD	400 IU/d for adults and children older than 1 year
8. Omega-3 fats	Reduce proinflammatory mediators and has been shown to improve symptoms in moderate to severe atopic dermatitis	Nordic Naturals Cod Liver Oil (for adults): 2 to 4 g/d for at least 3 months
9. Compounded extract	Reduces bacterial colonization and has anti-inflammatory properties	1 part witch hazel with 1 part glycyrrhetinic acid daily

Most studies have shown that breastfeeding has a protective effect on the development of atopic dermatitis in children (9,55). The mechanisms by which breast milk may prevent allergic diseases such as AD include the following:

- Breast milk contains factors that help the gut mature, creating an effective barrier against sensitization to extrinsic food antigens. Some of these factors include epidermal growth factor (EGF) and polyamines implicated in enterocyte proliferation and maturation (114,115).
- Exclusive breastfeeding delays the introduction of foreign antigen into the infant's intestinal tract.
- Development of gut mucosal immunity in the infant is enhanced by passive delivery of immune cells and secretory immunoglobulin A (sIGA).
- The specific type of fatty acid incorporated into breast milk appears to have an effect; atopic disease is seen more often in children whose mother's milk has lower amounts of α-linolenic acid (an ω-3 fat) (45).
- Breastfeeding mothers who adhere to elimination diets — removing potentially allergenic foods such as egg, cow's milk, and peanuts — may reduce the incidence of atopy in their children (84). A study by Vadas et al. reported that 11 of 23 women who ingested 50 g of peanuts secreted peanut protein allergens Ara h 1 and Ara h 2 into their milk within 2 to 6 h after consuming the peanuts (169).
- Breastfeeding causes the beneficial bacteria lactobacilli and bifidobacteria, known as probiotics, to colonize the neonatal intestine (68). In a double-blind, placebo-controlled, crossover study, administration of probiotics to 1- to 13-year-old children with AD for 6 weeks led to improvement in 56% of participants (143).
- Also, hydrolyzed protein formulas seem to provide some protection from allergy (63,67).

Prostanoid products derived from the metabolism of essential fatty acids impact the inflammatory response by affecting the production of specific cytokines. The ratio of pro-inflammatory ω-6 fatty acids compared to anti-inflammatory ω-3 fatty acids has been shown to be higher in children with atopic disease. Yu and Bjorksten compared the serum phospholipids of children ages 12 to 15 and found lower levels of the ω-3 fatty acid docosahexanoic acid and total long chain ω-3 fatty acids in children with eczema and asthma compared to nonatopic children (193). In addition, the concentration of ω-6 fatty acids correlated with serum IgE, a major mediator in extrinsic AD (193). Duchen et al. found that when insufficient levels of ω-3 fatty acids are found in breast milk, along with a high ω-6:ω-3 ratio in human milk and infant serum, more atopic symptoms are found in infants at 18 months of age (45). Therefore, improving the ratio of anti-inflammatory to pro-inflammatory essential fats in children (and breastfeeding mothers) could lead to a decreased incidence or severity of AD. In 1987, Bjorneboe et al. found that itch, scale, and overall severity of AD were improved when 1.8 g of EPA was administered for 12 weeks to a treatment group (n = 12) compared with a control group (n = 11) (12). More recently, Mayser et al. found that, compared to soybean oil, fish oil supplementation by lipid infusion reduced the severity of atopic lesions in patients hospitalized for moderate to severe atopic dermatitis (111).

Vitamin E was found to be effective in reducing the symptoms of eczema in an 8-month, single-blind, placebo-controlled trial by Tsoureli-Nikita et al. (166). Twenty-three persons taking vitamin E (n = 50), and one taking placebo (n = 46), showed "great improvement." Seven subjects taking vitamin E had a complete remission of their AD, compared to none in the placebo group. Subjective improvement was seen in facial erythema, lichenification, and pruritus. Serum IgE levels were reduced by 62% in the treatment group, with a 34% decrease reported in the placebo group.

The extracts of licorice *(Glycyrrhiza glabra)* have been shown to be beneficial for inflammatory disorders of the skin. The active ingredient of this root, glycyrrhetinic acid, potentiates the effects of hydrocortisone and inhibits cortisol from being catabolized to the inactive metabolite cortisone (163).

Topical witch hazel may be a beneficial adjunct to AD maintenance therapy, as it reduces bacterial colonization *in vivo* and *in vitro,* in addition to possessing anti-inflammatory, hydrating, and barrier-stabilizing effects (57).

11.5 PSORIASIS

11.5.1 Description of Psoriasis

Psoriasis is a chronic inflammatory disorder of the skin that classically presents with papules and plaques, with a characteristic silvery scale. It affects more than 4.5 million people in the United States (76). The age of presentation is biphasic with peaks near the third and sixth decades (72). The etiology of psoriasis is complex, and evidence points toward a combination of genetic, environmental, and immunologic factors. The first presentation of psoriasis may occur in childhood after an

episode of streptococcal pharyngitis. Many other factors can exacerbate psoriasis. Some include:

- Medications (lithium, β-blockers, NSAIDS, withdrawal of corticosteroids, antimalarial drugs) (1,187)
- Bacterial and viral infections
- Trauma to the skin
- Alcoholism (48)

Psoriasis was once regarded as a primary hyperproliferative disorder due to the blatant scale evident on lesions. Although keratinocytes in psoriasis have an accelerated cell cycle — 36 h compared to 311 h in normal skin — this seems to be a symptom of the underlying inflammatory process. It is not known how these immunologic mechanisms are coordinated to produce the final psoriatic lesion, but the following findings have been recognized (97):

- Increased trafficking of T cells into the dermis and epidermis in response to a specific (unknown) antigen.
- Activated T cells secreting interleukin 2 (IL-2) and interferon gamma (IFN-γ). This in turn leads to the production of tumor necrosis factor alpha (TNF-α), interleukin 8 (IL-8), and granulocyte-monocyte colony-stimulating factor (GM-CSF) by other immune cells.

Table 11.4 describes treatments for psoriasis.

11.5.2 Nutritional Aspects

Microorganisms such as *Candida albicans, Staphylococcus aureus,* and *Streptococcus,* as well as microbial factors such as endotoxin (LPS), have been implicated in the pathogenesis of psoriasis (61,153,179). Interestingly, many symptoms observed in acute psoriasis resemble acute endotoxemia, including fever, leukocytosis, enhanced capillary leak, lower levels of complement, and elevated liver function tests (61). Smilax sarsparilla, a compound that binds LPS, led to great improvements in 92 patients in a 1942 study (164). More recently, Gyurcsovics and Bertok (61) found that 78.8% of patients with psoriasis (n = 551) treated with oral bile acid supplementation, known to help solubilize LPS, became asymptomatic after 8 weeks. At a 2-year follow-up, 147 remained asymptomatic. Other factors that help the body handle gut-derived toxins include fiber and liver detoxification. Silymarin marianum, a flavonoid, enhances liver function, reduces inflammation, and may be of help in psoriasis (74).

Patients with psoriasis have greater intestinal permeability than controls, on the basis of increased urinary excretion of 51-Cr-EDTA (78). Intestinal defects increase intestinal exposure to gut-derived toxins, including LPS.

Free fatty acid levels are elevated in psoriatic plaques, with arachidonic acid metabolites predominant, including 12-HETE and LTB-4. 12-HETE, known to stimulate proliferation of the epidermis and induce skin inflammation, is overexpressed in keratinocytes of psoriatic plaques (80). In a separate study, LTB-4 but not

TABLE 11.4
Treatments for Psoriasis

	Structure and Function	Comments
	Topical Agents	
1. Emollients: petrolatum	Minimizes itching, tenderness, and flaking	Inexpensive; good adjunct treatment
2. Corticosteroids	Anti-inflammatory, antiproliferative, immunosuppressive	Mainstay of topical treatment; low potency (hydrocortisone) for face and intertriginous areas; higher potency for thick plaques and extensor surfaces; available in gels, lotions, and foams
3. Tar	May have antiproliferative effect and is photosensitizing	Available in shampoos, creams, and oils; may cause staining; inexpensive
4. Calcipotriene (Dovonex)	Vitamin D analog; affects growth and differentiation of keratinocytes	As effective as high-potency topical corticosteroids; may cause skin irritation; more expensive than topical steroids
5. Tazarotene	13-Cis-retinoic acid	Combination treatment with topical steroids minimizes skin irritation and reduces chance of skin atrophy from topical steroids
	Systemic Treatments	
1. Methotrexate	Folic acid antagonist; most likely a T-cell immune suppressor vs. antiproliferative for keratinocytes	Effective for psoriasis, psoriatic arthritis, and nail disease; oral, IM, SC dosing q wk; need to monitor for bone marrow and liver toxicity during treatment
2. Retinoids: acitretin	9-Cis-retinoic acid	Used for severe forms of psoriasis; can be used with UVB or PUVA for increased effectiveness in plaque psoriasis; rapid response achieved in pustular psoriasis; excellent monotherapy for palmoplantar disease; teratogenic
3. Cyclosporin	T-cell suppressant	Renal toxicity and hypertension limit utility
4. Efalizumab (Raptiva)	Inhibits T-cell activation and T-cell trafficking	For moderate to severe plaque psoriasis; monitor platelet count; risk for rebound with discontinuation in nonresponders

TABLE 11.4 (Continued)
Treatments for Psoriasis

	Structure and Function	Comments
5. Etanercept (Entrel)	TNF-α inhibitor	Used for psoriasis and psoriatic arthritis; caution with MS
6. Alefacept (Amerive)	Inhibits memory T cells	Used for moderate to severe chronic plaque psoriasis; monitor CD4 count weekly
	Light Treatments	
1. UVB	280 to 320 nm; thought to have immune modulating effects	Used for extensive disease; can be used in combination with topical tar; erythema-inducing doses 3/week until resolution, then maintenance visits
2. Narrow band UVB	311 to 313 nm; thought to have immune modulating effects	Equally efficacious with suberythemal doses; optimum wavelength for T-cell apoptosis; equipment is more expensive
3. PUVA	8-Methoxypsoralen is a photosensitizing drug; plus UVA at 320 to 400 nm	Increased incidence of melanoma and NMSC, as well as cutaneous genital cancer in men (if exposed)
	Nutritional Treatments	
1. L-glutamine	Major nutrient for enterocyte repair and healing; improves intestinal barrier function	Designs for Health/Biotics: 1 to 3 g/d
2. Ground flaxseeds	Increases membrane ratio of ω-3 fatty acids and helps bind intestinal toxins	Containing γ-linolenic acid: 1 to 2 tablespoons/d
3. Omega-3 fats	Reduces generation of pro-inflammatory mediators	Nordic Naturals Cod Liver Oil: 2 to 4 g/d for at least 3 months
4. Selenium	Cofactor for glutathione peroxidase; inhibits pro-inflammatory leukotrienes; aids in liver detoxification	200 μg/d
5. Capsaicin cream	Depletes Substance P from sensory fibers	Improves pain and itch
6. Aloe vera extract	Anti-inflammatory; inhibits the arachidonic acid pathway via cyclooxygenase	Apply 0.5% extract to skin after hydrating shower

12-HETE was elevated in lesions of guttate psoriasis (51). Addition of LTB-4 inhibitors improves psoriatic lesions (13). Injection of 10 μmol/l 15-hydroxyeicosatetraenoic acid (15-HETE), a product of DGLA known to inhibit the formation of LTB-4 and 12-HETE, into psoriatic plaques led to complete clearing of lesions in 4 out of 13 participants and significant improvement in seven people (52).

Fish oil supplementation, consisting of EPA and DHA, has produced differing results depending on the mode of administration. No improvement was seen with topical application (71) or oral supplementation (157). Marked improvement was seen with IV supplementation (112). Mayser et al., in a randomized double-blind study, found that patients hospitalized for chronic plaque-type psoriasis gained greater improvement with an EPA/DHA infusion of 4.2 g each vs. a conventional ω-6 preparation containing <0.1 g/100 ml of EPA and DHA. The body area covered by psoriasis was reduced, as were erythema, scaling, and infiltration. Serum levels of leukotriene B5 (LTB-5) and thromboxane A3 (TXA-3), less potent mediators, were increased in the ω-3 infused group within the first few days (112). It is likely that oral administration requires a longer treatment period than intravenous administration.

Levels of vitamin A have been shown to be low in patients with psoriasis (109). Treatment with etretinate and, more recently, with acitretin and topical tazarotene is effective because of the antiproliferative properties of these synthetic vitamin A analogs (56). Combination therapy consisting of acitretin and photochemotherapy (psoralen/UVA; PUVA) is highly effective.

Vitamin D regulates keratinocyte differentiation, and vitamin D analogs have become established drugs in the treatment of psoriasis. Calcipotriene, a vitamin D analog, is one such agent and is as effective as high-potency topical steroids. Studies comparing the effects of vitamin D analogs vs. coal tar, a mainstay treatment in psoriasis, have been encouraging (149). The efficacy of UV therapy may be partly due to an increase in vitamin D synthesis.

A cream made of vitamin B_{12} and avocado oil has been found to be as effective in the treatment of plaque-type psoriasis as the vitamin D_3 analog calcipotriol (161). The effects of the vitamin B_{12} cream were maintained over the entire 12-week period, with better tolerability, whereas the calcipotriol lost effectiveness after 4 weeks.

Selenium is a trace mineral with antioxidant and immunomodulatory properties. Patients with psoriasis typically have lowered levels of selenium (116). Selenium is necessary for the activation of glutathione peroxidase, an inhibitor of 5-lipoxygenase and therefore of pro-inflammatory leukotrienes. Excess alcohol consumption appears to be associated with low glutathione peroxidase activity and increased disease severity (148). Oral supplementation has not been shown to increase the selenium concentration in normal or lesional skin (49,69). Despite this, a statistically significant increase in the number of CD4+ T cells in the reticular dermis of psoriatic lesions was seen in patients given 400 μg/d for 6 weeks (69). The implications of this immune modulation are unknown. Topical application of selenium-containing shampoos has shown to be effective in psoriasis (17).

The active component of *Glycyrrhiza glabra* (licorice root), glycyrrhetinic acid, has been found to have effects similar to topical hydrocortisone. It also potentiates the effects of hydrocortisone by inhibiting 11-beta-hydroxysteroid dehydrogenase, the enzyme responsible for breaking down hydrocortisone (163).

Topical application of capsaicin has been shown to improve pain and itch in psoriasis (139). Capsaicin's effects are thought to be due to its ability to deplete the neuropeptide Substance P from sensory fibers in the skin (11).

A 12-month double-blind, placebo-controlled trial found that aloe vera, when applied topically three times daily, cleared psoriatic lesions in 25 of 30 patients (162). Aloe vera's effects are likely due to its ability to inhibit the arachidonic acid pathway via cyclo-oxygenase (172).

11.6 PREMALIGNANT AND MALIGNANT NONMELANOMA SKIN CANCER AND MELANOMA

11.6.1 Description of Nonmelanoma Skin Cancer and Melanoma

Actinic keratoses (AKs) are common precursor lesions to squamous cell carcinoma (SCC). In fact, the same abnormal keratinocytes are observed in AKs as in SCCs, except that the malignant cells do not breach the basement membrane (i.e., AKs are carcinomas *in situ*). The propensity to progress to SCC is around 0.085%/lesion/year (41). Hence, individuals with more lesions have a greater overall risk of SCC and require more aggressive treatment and more frequent follow-up. AKs arise as a result of cumulative sun exposure and age; people with fair skin are at greater risk than dark-skinned people. Individuals who are immunosuppressed are also at greater risk, as transplant patients are 65 times more likely to develop AKs than controls (87). AKs usually present as red macules or slight papules with overlying scale. UV radiation causes DNA damage along with mutations in the tumor suppressor gene p53 (21), thereby inhibiting its normal function of allowing for DNA repair and preventing damaged cells from entering the cell cycle. Continued exposure to UV radiation may induce the cell to proliferate clonally and generate an AK or, with greater exposure, an SCC.

Half of all cancer is skin cancer! Nonmelanoma skin cancers (NMSC) include SCC and basal cell carcinoma (BCC). The majority of NMSC are BCC (approximately 80%); the remainder are SCC (20%). There is no formal tumor registry available for SCCs or BCCs. Yet some 200,000 SCCs (and 800,000 BCCs) were diagnosed in the United States in 1999, with the incidence of NMSC projected to increase by 2 to 3%/year (119).

SCC is the second most commonly occurring skin cancer, with incidence probably underestimated. SCC is common among the Caucasian population, occurring most often in fair-skinned individuals. The most common cause of skin cancer is ultraviolet radiation (176). Chronic sun exposure tends to lead to SCC (54), whereas intermittent exposure is a risk for BCC (96). As mentioned, UV irradiation causes mutations in the p53 tumor suppressor gene and has been linked to SCC development (21). Other agents implicated in SCC development include polycyclic aromatic hydrocarbons, ionizing radiation, arsenic exposure (usually from a contaminated water supply), and photochemotherapy (PUVA) therapy for refractory dermatoses

(47,159). Clinically, SCC usually presents as a keratoic nodule. SCC can metastasize to regional nodes and other organs.

Basal cell cancer is the most common human cancer (132). It is generally a disease of Caucasian populations, with a predilection for fair-skinned, red-haired persons who freckle rather than tan (58). BCC occurs more often in adult populations than children, but 20% of BCCs occur in people younger than 50 years (103). Ultraviolet radiation may play a role, but the effect of UV radiation on SCC appears greater (177). Lesions are usually found on the scalp, neck, and face, especially the nose — areas of sun exposure — but also at the inner canthus, behind the ear, the genital area, and the breasts — areas protected from direct UV exposure. The genetics of BCC may differ from that of the SCC, because defects in p53 are not common in BCC (133). A typical BCC presents as a pearly, eroded papule or nodule, often with superficial telangectasia. Patients typically complain of a nonhealing ulcer that frequently bleeds. Basal cell tumors grow by contiguous spread and rarely metastasize.

Malignant melanoma (MM) is a malignancy of the pigment-producing cell, the melanocyte. Clinically these lesions most often present as a new or changing pigmented lesion that demonstrates asymmetry, variegated color, poorly circumscribed borders, and a changing diameter. The incidence of MM has tripled since 1980, and it is now rated as the most common cancer in women between 25 and 29 years of age and the second most common cancer (after breast cancer) for women 30 to 34 years old. Tumor thickness is the most important prognostic factor. Early diagnosis and complete excision constitute the best chance of cure. UV radiation may play a causative role, but the linkage is not as direct as in SCC and BCC. Because melanocytes are resistant to UV-induced apoptosis, they survive with UV-induced DNA mutations and clonally proliferate with the potential of evolving into a precursor of MM.

Table 11.5 describes treatments for skin cancer.

11.6.2 Nutritional Aspects

11.6.2.1 Calorie Restriction, Obesity, and Malignant Melanoma

Sir Francis Bacon observed that overindulging in food may cause many diseases such as cancer. In fact, calorie restriction is the most effective treatment for preventing cancer formation in experimental animals (79). Mice fed a calorie-restricted diet and subsequently injected with B16 melanoma tumor cells displayed tumors with slower growth. Calorie expenditure via exercise has also been shown to exert protein. A telephone survey in the state of Washington revealed that individuals exercising 5 d/week had a lower risk of developing MM, whereas men in the highest quartiles of height and body surface area had an increased risk of MM. No association was found between anthropomorphic data and MM incidence in women, however (152).

11.6.2.2 Dietary Fat and Nonmelanoma Skin Cancer

Animal studies have shown that high dietary fat intake increases the number of skin tumors that develop after exposure to UV radiation and decreases the length of time

TABLE 11.5
Nutritional Treatments for Skin Cancer

	Structure and Function	Comments
1. Maintain normal BMI	Elevated BMI is associated with increased melanoma risk.	Exercise and reduction of caloric intake are recommended.
2. Reduce refined sugars; use milk free from bovine growth hormone	Elevated insulin leads to increased IGF-1 levels; IGF-1 promotes the growth, migration, and survival of melanoma cells.	IGF-1 levels are 2 to 10 times higher in cows injected with rBGH.
3. Reduce total dietary fat intake		Reduction in total dietary fat led to a reduction in AK and NMSC in skin cancer patients after adopting a low-fat diet.
4. Reduce fried food intake	2-Amino-3,8-dimethylimidazo[4, 5-f]-quinoxaline (MeIQx) is a potent mutagen isolated from fried beef and present in various cooked foods.	MeIQx has been shown to increase the incidence of squamous cell carcinoma in experimental animals.
5. Supplement diet with fruits and vegetables	Calcium glucarate is the calcium salt of D-glucaric acid present in fruits, vegetables, and seeds.	Calcium glucarate has been shown to prevent tumor formation in mouse skin.
6. Increase intake of cold-water fish	Cold-water fish contains a high level of DHA and EPA, which have demonstrated photoprotective properties.	A 20-year study of the Inuit revealed they had low rates of both MM and NMSC.
7. Ground flaxseeds	Flaxseeds are a source of dietary fiber, ω-3 fat (as alpha-linolenic acid), and lignans. The lignans in flaxseed are metabolized in the digestive tract to enterodiol and enterolactone, which have estrogenic activity.	Flaxseeds have been shown to reduce skin tumors in mice in a dose-dependent manner.
8. Green tea	Catechins have multiple preventive effects on skin carcinogenesis.	5 cups/d.
9. Probiotics	Restore intestinal immune function and reduce diarrhea.	For patients on chemotherapy, restore optimal intestinal flora (Natren; Metagenics Ultra Flora); *Saccharomyces boulardii* (Moss Nutrition Florastor).
10. L-glutamine	Heals intestinal enterocytes.	For patients on chemotherapy.
11. Antioxidants	Demonstrate many photoprotective properties.	Designs for Health Ultimate Antiox-LS: lipid-soluble antioxidants including conjugated linoleic acid, mixed tocopherols, grapeseed extract,

Continued.

TABLE 11.5 (Continued)
Nutritional Treatments for Skin Cancer

	Structure and Function	Comments
		lutein, and lycopene; Designs for Health Three-A-Day Antioxidants: water-soluble antioxidants including vitamin C, NAC, biotin, selenium, green tea, and turmeric. 3 softgels of each daily.
12. Selenium	Patients with the lowest serum levels of selenium had the highest melanoma grade.	200 μg/d.
13. Vitamin D	Regulates apoptosis, tumor invasion, and angiogenesis, events important in carcinogenesis.	No evidence regarding supplementation; 400 to 800 IU/d.

between UV exposure and tumor appearance (14). Adopting a low-fat diet after a potentially cancer-causing dose of UV can negate the effects of a previous high-fat diet. Black found that reducing dietary fat intake by 20% led to fewer NMSC and premalignant lesions (15).

11.6.2.3 Omega-6 Fatty Acids and Nonmelanoma Skin Cancer

The exact role of arachidonic acid and other ω-6 fatty acids in tumorigenesis is not known; however, Fischer et al. (50) showed that inhibitors of cyclooxygenase and lipoxygenase inhibit tumor promotion. These authors hypothesize that tumorigenesis depends, at least in part, on products of arachidonic acid transformation, including 12-HETE, prostaglandin E2 (PGE2), and prostaglandin F2α (PGF2α) (50). Vanderveen et al. (170) found that PGE2 and PGF2α were present in greater amounts in BCCs exhibiting more aggressive growth patterns. Muller and colleagues (121) found that transgenic mice overexpressing epidermis-type 12-S-lipoxygenase had high levels of 12S-HETE and higher tumor levels compared to the wild-type.

11.6.2.4 Omega-3 Fatty Acids and Nonmelanoma Skin Cancer

The ω-3 fatty acids arise from dietary ingestion of α-linolenic acid; the more potent fatty acids, EPA and DHA, are synthesized through a series of enzymatic steps from this precursor fat. The greatest source of α-linolenic acid is flaxseeds; EPA and DHA are in highest concentration in cold-water fish. The abundance of EPA and DHA found in cold-water fish may play a protective role in skin carcinogenesis. Miller and Gaudette, in a 20-year observational study of the Inuit, a population known for its high fish consumption, reported low rates of both MM and NMSC

(118). On the basis of this and other studies, EPA and DHA show promise as cancer-protective nutrients.

Rhodes et al. investigated the mechanisms behind the photoprotective abilities of EPA and found that subjects given 4 g/d of purified EPA for 3 months had an increased sunburn threshold, reduced p-53 expression (interpreted as less oxidative damage to DNA), and fewer strand breaks in peripheral blood leukocytes (141).

11.6.2.5 Omega-6 Fatty Acids and Melanoma

Metabolites of the arachidonic acid cascade may promote carcinogenesis. Liu et al. found that the highly metastatic amelanotic melanoma cell line HM340 produced four times more 12-HETE than did cells with low metastatic potential (107). Furthermore, when cyclooxygenase and lipoxygenase inhibitors were applied to mouse melanoma tumor cells, the cells became noninvasive (138).

In contrast to metabolites of arachidonic acid, ω-6 fatty acids that are metabolized to linoleic acid appear to reduce the potential of melanoma cell lines. Smith and Salerno found that sesame oil (linoleic acid) reduced the proliferation rate of both normal and malignant melanocytes grown in culture (154). Similar fat exists in cow's milk, known as conjugated linoleic acid, and has been found to inhibit MM cell lines (129). Perkins and Duncan reported that high doses of GLA reduce the growth of the murine melanoma cell line, BL-6 (130)

When cancer cells, including MM, are cultured with GLA, the expression of E-cadherin, a cell adhesion molecule, increases; this could reduce a cell's propensity to metastasize. Neither linoleic acid nor arachidonic acid upregulates E-cadherin (89). GLA has other antimetastatic activities, including upregulating Maspin, a serine protease inhibitor and tumor suppressor gene, that decreases metastatic cell motility (89). GLA added to cell culture also upregulates the desmosomal protein Desmoglein (90).

11.6.2.6 Omega-3 Fatty Acids and Melanoma

Yan et al. (189) found that when 2.5, 5, and 10% ground flaxseed was added to a basal mouse diet, there resulted a 32, 54, and 63% decrease, respectively, in metastatic melanoma. Few studies have addressed the impact of polyunsaturated fatty acids (PUFAs) on melanoma in humans. When the diets of Australian women with melanoma were compared with those of cancer-free women in the same community, a strong inverse relationship was found between high PUFA consumption and melanoma incidence (6). In the same study, a 40% reduction of risk was observed in those eating more fish; however, this drop in risk did not reach statistical significance ($p = 0.18$).

In a Norwegian study, the dietary habits of more than 50,000 men and women were analyzed between the years of 1977 and 1983 to find risk factors for the development of melanoma. Contrary to the findings in the Australian women, use of cod liver oil supplementation and intake of PUFAs were associated with a greater risk of developing melanoma after normalization for height, body mass index, body

surface area, education, smoking, and physical activity (174). Therefore, it is uncertain whether ω-3 fats induce or reduce the incidence of melanoma.

11.6.2.7 Retinoids

Retinoids are necessary for normal cellular differentiation. They also inhibit the induction of ornithine decarboxylase, a rate-limiting enzyme in tumor cell proliferation (175). The utility of vitamin A in melanoma may relate to its ability to filter out harmful UV radiation and thereby to protect against UV-induced damage at the epidermal surface (31). Topical application of retinyl palmitate has been shown to be as effective as sun protection factor 20 (SPF20) at reducing erythema and thymine dimer formation, a marker of DNA damage, in the skin of volunteers exposed to UV radiation (31). Topical tretinoin may also be preventive in the development of melanoma by reducing mole atypia. Halpern and colleagues (65) examined five male patients with dysplastic nevi and instructed the men to apply topical tretinoin to half of their backs. Before and after photographs and histological exam of four nevi from both the treated and untreated sides were used to assess changes in mole morphology. One subject dropped out due to skin irritation. The four remaining patients showed reduced atypia of treated nevi by photography; histological evaluation of the treated sides revealed that 4 of 16 met criteria for atypia, compared with 13 of 16 on the untreated sides (65). Hence, topical tretinoin may be effective for reducing mole atypia, but treatment-induced inflammation may limit its utility. Provitamin A carotenoids, taken orally, have also been shown to protect against the development of UV-induced erythema when taken as a long-term supplement prior to UV exposure (70,158).

11.6.2.8 Vitamin D and Melanoma

1,25-Dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$), the most active form of the steroid hormone vitamin D, has been gaining much attention lately because it can modulate the activity of cancer cells, including melanoma (125). Vitamin D has antiproliferative effects on cells that express the vitamin D receptor because it inhibits entry into the G1/S cell cycle checkpoint (125). Vitamin D also has prodifferentiation properties, transforming cellular precursors to more mature phenotypes. More recently, vitamin D has been shown to regulate apoptosis, tumor invasion, and angiogenesis, events important in carcinogenesis. How vitamin D modulates apoptosis is incompletely understood, but it may have to do with the vitamin's ability to inhibit the activity of insulin-like growth factor (IGF), a strong antiapoptotic agent involved in the development of breast cancer (33). Vitamin D can also have direct antiapoptotic actions; for example, it can reduce cellular death following UV-induced injury (101). Cell culture experiments have shown that physiologic levels of vitamin D can inhibit growth of malignant cells of the lung (192). This is partly due to the ability of vitamin D to inhibit angiogenesis (10). Patients with MM have lower serum levels of $1,25(OH)_2D_3$, but the different was not statistically significant (36). Whether dietary supplementation can help prevent the development of MM has yet to be shown.

11.6.2.9 Vitamin C

Ascorbic acid (vitamin C) is a water-soluble antioxidant that works in conjunction with other antioxidants to remove free radicals from the cellular environment. Vitamin C is thought to protect the skin from UV-induced free radical damage, which leads to cancer formation. Vural et al. (178) found that plasma and red blood cell samples of patients with AKs (n = 13) and BCCs (n = 12) contained less ascorbate, as well as less vitamin E, thiol groups, ceruloplasmin, and RBC glutathione, when compared with controls (n = 16). Lin et al. found that topical application of 15% L-ascorbic acid with 1% alpha-tocopherol protected pig skin from the formation of sunburn cells, thymine dimers, and erythema. Both vitamin C and E were effective when applied alone, but a more substantial effect was seen when the two were combined (105).

11.6.2.10 Vitamin E

Vitamin E is a term for a general class of lipophilic antioxidants that consists of eight naturally occurring compounds known as tocopherols or tocotrienols. These compounds protect cells from UV-induced damage by directly reducing thymine dimer formation, a marker of DNA damage, and by preventing UV-induced immunosuppression and loss of Langerhans cells and of scavenging lipid radicals (64,98). Recent evidence has shown that vitamin E also influences tumorigenesis by modulating cellular transduction cascades (190).

Burke et al. investigated the ability of various combinations of vitamin E, with and without L-selenomethionine, to protect Skh:2 hairless mice from UV-induced skin changes and tumor formation. Topical L-selenomethionine, alone and in combination with topical vitamin E, produced the greatest reduction in skin damage resulting from blistering and pigmentation changes (27). Studies from hairless mice have also shown that oral vitamin E administered for 17 weeks reduced the incidence of papillomas with no adverse effects. In humans, tocopherol and tocopherol acetate, when applied after UVB exposure, reduced skin erythema by 27% (120). In the same study, topical glutathione and topical superoxide dismutase, applied postexposure, inhibited erythema by 53 and 41%, respectively. None of the treatments was effective when applied prior to irradiation. On the other hand, Drehe et al. found no protective effect for vitamin E, melatonin, or vitamin C, whether applied topically, alone or in combination, after UV irradiation (42). Oral administration of vitamin E was not effective in a small, double-blind, placebo-controlled study (18).

11.6.2.11 Synergy

Studies on the ability of antioxidants to protect against UV damage or tumorigenesis have led to conflicting results. Briganti and Picardo (23), in a recent review, propose four reasons why studies investigating antioxidants produce inconsistent results:

- Dietary administration of antioxidants may provide poor cutaneous bioavailability; along with this, topical application may have poor penetration, causing the quantities of antioxidants to be insufficient (23). Gut

microorganisms are known to degrade flavonoids; therefore, only a small proportion of antioxidants may reach the bloodstream (183).
- Antioxidants, under certain circumstances, may cause pro-oxidant activity. If the oxidation state is low and the generation of peroxyl radicals is slow, or if insufficient co-oxidant molecules are present, tocoperoxyl radicals may initiate an oxidation cascade with the surrounding PUFAs (19,83,171).
- Evaluating the efficacy of a single antioxidant does not account for the interplay of various antioxidants to regenerate one another, as is the case for vitamin C and ubiquinol, which together replenish vitamin E.

The beneficial effects of antioxidants to protect cells when ROS concentrations are high may be detrimental when moderate amounts of ROS are present. The oxidation state of the cell is known to influence signal transduction cascades, which may impact pathways leading to cell survival or apoptosis (23).

11.6.2.12 Selenium and Nonmelanoma Skin Cancer

The first clue to the importance of selenium in cancer came from epidemiological studies by Schrauzer et al. in the 1970s (135). These investigators reported an inverse relationship of dietary selenium intake and total age-adjusted cancer mortality. Several other studies found similar results. A prospective study by Yoshiwaza et al. found that male patients with selenium concentrations in the lowest quintile had triple the risk of developing advanced prostate cancer than men in the highest quintile (191).

Clark et al. investigated the effects of selenium supplementation on skin cancer in the Nutritional Prevention of Cancer Trial (32), in which 1312 patients with a prior history of NMSC were enrolled in a multicenter, double-blind, randomized placebo-controlled trial. Although a 37% lower cancer incidence and 50% reduction in total cancer mortality were found in the selenium-supplemented group, the incidence of NMSC was not significantly affected. Indeed, selenium supplementation may have led to an increased incidence of NMSC.

11.6.2.13 Selenium and Melanoma

The ability of selenium to prevent melanoma has not been investigated in clinical trials, but Redman et al. found that when selenomethionine was added to melanoma cell cultures, growth was inhibited (137). Deffuant found that the plasma level of selenium and the tumor stage of melanoma varied inversely in 200 patients. Moreover, the likelihood of recurrence was highest in patients with lowest plasma selenium levels (37).

11.6.2.14 Botanicals

Tea, the world's most popular beverage, has three main types: green, black, and oolong. It is derived from the leaves of the *Camellia sinensis* plant and contains abundant antioxidants known as catechins (polyphenols), which have been found to have multiple preventive effects on skin cancer, including inhibiting UVB-induced

inflammation (2), skin carcinogenesis, lipid peroxidation, and regression of present tumors (183).

Curcumin (diferuloylmethane) is a yellow compound derived from the root of the turmeric plant *Curcuma longa* Linn, known since ancient times for its medicinal properties. It has been shown to cause apoptosis in cell lines of both BCC (86) and MM (28).

Silymarin is a compound of several polyphenolic flavonoids derived from the milk thistle plant. Topical application has been shown to prevent skin cancer formation in mice (92). Additionally, silymarin seems to protect against UVB-induced skin edema, erythema, and cellular apoptosis in mice (92).

Garlic *(Allium sativum)* contains organosulfurs including water-soluble allyl amino acid derivatives and lipid-soluble allyl sulfides, flavonoids, and saponins. The ability of garlic to affect cancer formation is most likely due to its antioxidant properties. Two water-soluble allyl amino acid derivatives, S-allylcysteine and S-allylmercaptocysteine, have antioxidant activities (81).

Extracts made from the leaves of the *Ginkgo biloba* tree contain a number of flavonoids, including epicatechin, catechin, rutin, apigenin, luteolin, and quercetin, which have anti-inflammatory and antioxidant properties (151). Application of *Ginkgo biloba* extract to the skin of Sprague–Dawley rats induced superoxide dismutase and catalase activity, and protected from UVB-induced damage (106).

11.7 CONCLUSION

We are only beginning to learn how diet and supplemental nutrients affect the skin. It is likely that topical and systemic nutrients and diet modification will, in the near future, become a viable approach to the prevention and treatment of skin diseases.

REFERENCES

1. Abel EA, DiCicco LM, Orenberg EK, Fraki JE, Farber EM. Drugs in exacerbation of psoriasis. *J. Am. Acad. Dermatol.* 1986 Nov; 15(5 Pt 1): 1007–1022. Review.
2. Afaq F, Ahmad N, Mukhtar H. Suppression of UVB-induced phosphorylation of mitogen-activated protein kinases and nuclear factor kappa B by green tea polyphenol in SKH-1 hairless mice. *Oncogene*. 2003 Dec 18; 22(58): 9254–9264.
3. Ahmed A, Holton J, Vaira D, et al. Eicosanoid synthesis and H. pylori-associated gastritis: Increase in leukotriene C4 generation associated with H. Pylori colonization. *Prostaglandins* 1992; 44: 75–86.
4. Ames SR. Factors affecting absorption, transport, and storage of vitamin A. *Am. J. Clin. Nutr.* 1969 Jul; 22(7): 934–935.
5. Ayres S Jr., Mihan R. Acne vulgaris: Therapy directed at pathophysiologic defects. *Cutis* 1981 Jul; 28(1): 41–42.
6. Bain C, Green A, Siskind V, Alexander J, Harvey P. Diet and melanoma. An exploratory case-control study. *Ann. Epidemiol.* 1993 May; 3(3): 235–238.
7. Barba A, Rosa B, Angelini G, Sapuppo A, Brocco G, Scuro LA, Cavallini G. Pancreatic exocrine function in rosacea. *Dermatologica* 1982; 165(6): 601–606.
8. Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. *Med. J. Aust.* 1990 Oct 15; 153(8): 455–458.

9. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, Wahn U; MAS-study group. Breastfeeding duration is a risk factor for atopic eczema. *Clin. Exp. Allergy.* 2002 Feb; 32(2): 205–209.
10. Bernardi R, Modzelewski R, Trump D, Johnson C. Effects of 125 (OH)2D3 on normal and tumor derived murine endothelial cells. In: *Abstracts. The Eleventh Workshop on Vitamin D*. Nashville, TN: Riverside California, 2000; 92 [Abstr.].
11. Bernstein JE. Capsaicin in the treatment of dermatologic disease. *Cutis* 1987 Apr; 39(4): 352–353.
12. Bjorneboe A, Soyland E, Bjorneboe GE, Rajka G, Drevon CA. Effect of n-3 fatty acid supplement to patients with atopic dermatitis. *J. Intern. Med. Suppl.* 1989; 225(731): 233–236.
13. Black AK, Camp RD, Mallet AI, Cunningham FM, Hofbauer M, Greaves MW. Pharmacologic and clinical effects of lonapalene (RS 43179), a 5-lipoxygenase inhibitor, in psoriasis. *J. Invest. Dermatol.* 1990 Jul; 95(1): 50–54.
14. Black HS. Role of dietary factors in UV carcinogenesis. *Cancer Bulletin*. 1993; 45: 232–237.
15. Black HS. Influence of dietary factors on actinically-induced skin cancer. *Mutat. Res.* 1998 Nov 9; 422(1): 185–190. Review.
16. Bonnar E, Eustace P, Powell FC. The Demodex mite population in rosacea. *J. Am. Acad. Dermatol.* 1993 Mar; 28(3): 443–448.
17. Borglund E, Enhamre A. Treatment of psoriasis with topical selenium sulphide. *Br. J. Dermatol.* 1987 Nov; 117(5): 665–666.
18. Bowcock AM, Cookson WO. The genetics of psoriasis, psoriatic arthritis and atopic dermatitis. *Hum. Mol. Genet.* 2004 Apr 1; 13.
19. Bowry VW, Ingold KU, Stocker R. Vitamin E in human low-density lipoprotein. When and how this antioxidant becomes a pro-oxidant. *Biochem. J.* 1992 Dec 1; 288 (Pt 2): 341–344.
20. Bradley M, Soderhall C, Luthman H, Wahlgren CF, Kockum I, Nordenskjold, M. Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. *Hum. Mol. Genet.* 2002; 11, 1539–1548.
21. Brash DE, Rudolf JA, Simon JA, Lin A, McKenna GJ, Baden HP, Halperin AJ, Ponten J. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc. Natl. Acad. Sci. USA.* 1991 Nov 15; 88(22): 10124–1028.
22. Braunstein B, Deuell B, Platts-Mills TAE. Atopic dermatitis associated with dermatophyte infection and Trychophyton hypersensitivity. *Cutis* 1993; 51, 191–192.
23. Briganti S, Picardo M. Antioxidant activity, lipid peroxidation and skin diseases. What's new. *J. Eur. Acad. Dermatol. Venereol.* 2003 Nov; 17(6): 663–669. Review.
24. Broberg A, Faergemann J, Johansson S, et al. Pityrosporum ovale and atopic dermatitis in children and young adults. *Acta Derm. Venereol.* 1992; 72: 187–192.
25. Brown S, Shalita A. Acne vulgaris. *Lancet* 1998; 351: 1871–1876.
26. Brunsting LA. Atopic dermatitis of young adults. *Arch. Dermatol. Syph.* 1936; 34: 935–957.
27. Burke KE, Clive J, Combs GF Jr, Nakamura RM. Effects of topical L-selenomethionine with topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh: 2 hairless mice. *J. Am. Acad. Dermatol.* 2003 Sep; 49(3): 458–472.
28. Bush JA, Cheung KJ Jr., Li G. Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53. *Exp. Cell Res.* 2001 Dec 10; 271(2): 305–314.

29. Carlin RB, Carlin CS. Topical vitamin C preparation reduces erythema of rosacea. *Cosmetic Dermatol*. 2001 Feb: 35–38.
30. Carson CF, Riley TV. Safety, efficacy and provenance of tea tree (Melaleuca alternifolia) oil. *Contact Dermatitis*. 2001 Aug; 45(2): 65–67. Review.
31. Christophe A, Christian T, Olivier S, Pierre C, Liliane D, Jean-Hilaire S. Vitamin A exerts a photoprotective action in skin by absorbing ultraviolet B radiation. *J. Invest. Dermatol*. 121: 1163–1167.
32. Clark LC, Combs GF Jr., Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JL Jr., Park HK, Sanders BB Jr., Smith CL, Taylor JR. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 1996 Dec 25; 276(24): 1957–1963.
33. Colston K, Pirianov G, Mansi J. Non-classical actions of vitamin D3: Mechanisms and clinical aspects. In: *Vitamin D Endocrine System: Structural, Biological, Genetic and Clinical Aspects* (Norman AW, Bouillon R, Thomasset M, eds). Riverside, CA: University of California; 2000: 477–484.
34. Cookson WO, Ubhi B, Lawrence R, Abecasis GR, Walley AJ, Cox HE, Coleman R, Leaves NI, Trembath RC, Moffatt MF, et al. Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat. Genet*. 2001; 27, 372–373.
35. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton S, Brand-Miller J. Acne vulgaris: A disease of western civilization. *Arch. Dermatol*. 2002; 138: 1584–1590.
36. Cornwell ML, Comstock GW, Holick MF, Bush TL. Prediagnostic serum levels of 1,25-dihydroxyvitamin D and malignant melanoma. *Photodermatol. Photoimmunol. Photomed*. 1992; 9: 109–112.
37. Deffuant C. Serum selenium in melanoma and epidermotropic cutaneous T-cell lymphoma. *Acta Dermato. Venereol*. 1994; 74(2): 90–92.
38. Depaoli M, Martina G. The therapeutic action of tolbutamide in common acne and acne rosacea. *Panminerva Med*. 1961 Jul–Aug; 3: 365–366.
39. Devchand P, Keller H, Peters J, Vasquez M, Gonzalez FJ & Wahli W. The PPARα-leukotriene B4 pathway to inflammation control. *Nature* 1996; 384: 39–43.
40. Diaz C, O'Callaghan CJ, Khan A, Ilchyshyn A. Rosacea: A cutaneous marker of *Helicobacter pylori* infection? Results of a pilot study. *Acta Derm. Venereol*. 2003; 83(4): 282–286.
41. Dodson JM, et al. Malignant potential of actinic keratoses and the controversy over treatment: A patient-oriented perspective. *Arch. Dermatol*. 1991; 127: 1029.
42. Dreher F, Denig N, Gabard B, Schwindt DA, Maibach HI. Effect of topical antioxidants on UV-induced erythema formation when administered after exposure. *Dermatology* 1999; 198(1): 52–55.
43. Dreno B, Moyse D, Alirezai M, Amblard P, Auffret N, Beylot C, Bodokh I, Chivot M, Daniel F, Humbert P, Meynadier J, Poli F. Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. *Dermatology* 2001; 203(2): 135–140.
44. Dryden MS, Dailly S, Crouch M. A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. *J. Hosp. Infect*. 2004 Apr; 56(4): 283–286.
45. Duchen K, Casas R, Fageras-Bottcher M, Yu G, Bjorksten B. Human milk polyunsaturated long-chain fatty acids and secretory immunoglobulin A antibodies and early childhood allergy. *Pediatr. Allergy Immunol*. 2000 Feb; 11(1): 29–39.

46. Ertl GA, Levine N, Kligman AM. A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch. Dermatol.* 1994 Mar; 130(3): 319–324.
47. Everall JD, Dowd PM. Influence of environmental factors excluding ultra violet radiation on the incidence of skin cancer. *Bull. Cancer.* 1978; 65(3): 241–247.
48. Evstaf'ev VV, Levin MM. Dermatologic pathology in chronic alcoholics. *Vestn. Dermatol. Venerol.* 1989; (8): 72–74.
49. Fairris GM, Lloyd B, Hinks L, Perkins PJ, Clayton BE. The effect of supplementation with selenium and vitamin E in psoriasis. *Ann. Clin. Biochem.* 1989 Jan; 26 (Pt 1): 83–88.
50. Fischer SM, Mills GD, Slaga TJ. Inhibition of mouse skin tumor promotion by several inhibitors of arachidonic acid metabolism. *Carcinogenesis* 1982; 3(11): 1243–1245.
51. Fogh K, Herlin T, Kragballe K. Eicosanoids in acute and chronic psoriatic lesions: Leukotriene B4, but not 12-hydroxy-eicosatetraenoic acid, is present in biologically active amounts in acute guttate lesions. *J. Invest. Dermatol.* 1989 Jun; 92(6): 837–841.
52. Fogh K, Sogaard H, Herlin T, Kragballe K. Improvement of psoriasis vulgaris after intralesional injections of 15-hydroxyeicosatetraenoic acid (15-HETE). *J. Am. Acad. Dermatol.* 1988 Feb; 18(2 Pt 1): 279–285.
53. Fujie T, Shikiji T, Uchida N, Urano Y, Nagae H, Arase S. Culture of cells derived from the human sebaceous gland under serum-free conditions without a biological feeder layer or specific matrices. *Arch. Dermatol. Res.* 1996 Oct; 288(11): 703–708.
54. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer, II: Squamous cell carcinoma. *Arch. Dermatol.* 1995; 131: 164–169.
55. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: A systematic review and meta-analysis of prospective studies. *J. Am. Acad. Dermatol.* 2001 Oct; 45(4): 520–527. Review.
56. Geiger JM. Efficacy of acitretin in severe psoriasis. *Skin Therapy Lett.* 2003 Apr–May; 8(4): 1–3, 7.
57. Gloor M, Reichling J, Wasik B, Holzgang HE. Antiseptic effect of a topical dermatological formulation that contains Hamamelis distillate and urea. *Forsch Komplementarmed Klass Naturheilkd.* 2002 Jun; 9(3): 153–159.
58. Goldberg LH. Basal cell carcinoma. *Lancet* 1996; 347, 663–667.
59. Guarrera M, Parodi A, Cipriani C, Divano C, Rebora A. Flushing in rosacea: A possible mechanism. *Arch. Dermatol. Res.* 1982; 272(3–4): 311–316.
60. Guy R, Green MR, Kealey T. Modeling acne in vitro. *J. Invest. Dermatol.* 1996 Jan; 106(1): 176–182.
61. Gyurcsovics K, Bertok L. Pathophysiology of psoriasis: Coping endotoxins with bile acid therapy. *Pathophysiology* 2003 Dec; 10(1): 57–61.
62. Habif TP. *Clinical Dermatology,* 4th ed. St. Louis, MO: Mosby; 106.
63. Halken S, Hansen KS, Jacobsen HP, Estmann A, Faelling AE, Hansen LG, Kier SR, Lassen K, Lintrup M, Mortensen S, Ibsen KK, Osterballe O, Host A. Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: A prospective, randomized study. *Pediatr. Allergy Immunol.* 2000 Aug; 11(3): 149–161.
64. Halliday GM, Bestak R, Yuen KS, Cavanagh LL, Barnetson RS. UVA-induced immunosuppression. *Mutat. Res.* 1998 Nov 9; 422(1): 139–145.
65. Halpern AC, Schuchter LM, Elder DE, Guerry D 4th, Elenitsas R, Trock B, Matozzo I. Effects of topical tretinoin on dysplastic nevi. *J. Clin. Oncol.* 1994 May; 12(5): 1028–1035.

66. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J. Clin. Invest.* 1994; 94: 870–876.
67. Han YS, Park HY, Ahn KM, Lee JS, Choi HM, Lee SI. Short-term effect of partially hydrolyzed formula on the prevention of development of atopic dermatitis in infants at high risk. *J. Korean Med. Sci.* 2003 Aug; 18(4): 547–551.
68. Harmsen HJ, Wildeboer-Veloo AC, Raangs GC, et al. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. *J. Pediatr. Gastroenterol. Nutr.* 2000; 30: 61–67.
69. Harvima RJ, Jagerroos H, Kajander EO, Harvima IT, Aalto ML, Neittaanmaki H, Naukkarinen A, Kantola M, Miettinen UK, Horsmanheimo M. Screening of effects of selenomethionine-enriched yeast supplementation on various immunological and chemical parameters of skin and blood in psoriatic patients. *Acta Derm. Venereol.* 1993 Apr; 73(2): 88–91.
70. Heinrich U, Gartner C, Wiebusch M, Eichler O, Sies H, Tronnier H, Stahl W. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. *J. Nutr.* 2003 Jan; 133(1): 98–101.
71. Henneicke-von Zepelin HH, Mrowietz U, Farber L, Bruck-Borchers K, Schober C, Huber J, Lutz G, Kohnen R, Christophers E, Welzel D. Highly purified omega-3-polyunsaturated fatty acids for topical treatment of psoriasis. Results of a double-blind, placebo-controlled multicentre study. *Br. J. Dermatol.* 1993 Dec; 129(6): 713–717.
72. Henseler T, Christophers E. Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. *J. Am. Acad. Dermatol.* 01 Sept 1985; 13(3): 450–456.
73. Herbert MK, Holzer P. Neurogenic inflammation. II. Pathophysiology and clinical implications *Anasthesiol Intensivmed Notfallmed Schmerzther.* 2002 Jul; 37(7): 386–394. Review.
74. Hikino H, Kiso Y, Wagner H, Fiebig M. Antihepatotoxic actions of flavonolignans from *Silybum marianum* fruits. *Planta Med.* 1984 Jun; 50(3): 248–250.
75. Holland K, Cunliffe W, Roberts C. Acne vulgaris: An investigation into the number of anaerobic diphtheroids and members of the Micrococcaceae in normal and acne skin. *Br. J. Dermatol.* 1977 Jun; 96(6): 623–626.
76. http://www.psoriasis.org/facts.
77. Humbert P. Functional consequences of cutaneous lipid perturbation. *Pathol. Biol.* (Paris) 2003 Jul; 51(5): 271–274. Review.
78. Humbert P, Bidet A, Treffel P, Drobacheff C, Agache P. Intestinal permeability in patients with psoriasis. *J. Dermatol. Sci.* 1991 Jul; 2(4): 324–326.
79. Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: Mechanisms of action and applicability to humans. *Annu. Rev. Med.* 2003; 54: 131–152. Epub 2001 Dec 03. Review.
80. Hussain H, Shornick LP, Shannon VR, Wilson JD, Funk CD, Pentland AP, Holtzman MJ. Epidermis contains platelet-type 12-lipoxygenase that is overexpressed in germinal layer keratinocytes in psoriasis. *Am. J. Physiol.* 1994 Jan; 266(1 Pt 1): C243–253.
81. Imai J, Ide N, Nagae S, Moriguchi T, Matsuura H, Itakura Y. Antioxidant and radical scavenging effects of aged garlic extract and its constituents. *Planta Med.* 1994 Oct; 60(5): 417–420.
82. Ingham E, Eady EA, Goodwin CE, Cove JH, Cunliffe WJ. Pro-inflammatory levels of interleukin-1 alpha-like bioactivity are present in the majority of open comedones in acne vulgaris. *J. Invest. Dermatol.* 1992 Jun; 98(6): 895–901.

83. Ingold KU, Bowry VW, Stocker R, Walling C. Autoxidation of lipids and antioxidation by alpha-tocopherol and ubiquinol in homogeneous solution and in aqueous dispersions of lipids: Unrecognized consequences of lipid particle size as exemplified by oxidation of human low density lipoprotein. *Proc. Natl. Acad. Sci. USA*. 1993 Jan 1; 90(1): 45–49.
84. Isolauri E, Tahvanainen A, Peltola T, Arvola T. Breast-feeding of allergic infants. *J. Pediatr.* 1999 Jan; 134(1): 27–32.
85. Jansen T, Romiti R, Kreuter A, Altmeyer P. *Rosacea fulminans* triggered by high-dose vitamins B6 and B12. *J. Eur. Acad. Dermatol. Venereol*. 2001 Sep; 15(5): 484–485.
86. Jee SH, Shen SC, Tseng CR, Chiu HC, Kuo ML. Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells. *J. Invest. Dermatol*. 1998 Oct; 111(4): 656–661.
87. Jensen P, Moller B, Hansen S. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J. Am. Acad. Dermatol*. 2000; 42(2 Pt 1): 307.
88. Jeremy A, Holland D, Roberts S, Thompson K, Cunliffe W. Inflammatory events are involved in acne lesion initiation. *J. Invest. Dermatol*. 2003; 121(No. 1): 20–27.
89. Jiang WG, Hiscox S, Hallett MB, Horrobin DF, Mansel RE, Puntis MC. Regulation of the expression of E-cadherin on human cancer cells by gamma-linolenic acid (GLA). *Cancer Res*. 1995 Nov 1; 55(21): 5043–5048.
90. Jiang WG, Singhrao SK, Hiscox S, Hallett MB, Bryce RP, Horrobin DF, Puntis MC, Mansel RE. Regulation of desmosomal cell adhesion in human tumour cells by polyunsaturated fatty acids. *Clin. Exp. Metastasis*. 1997 Nov; 15(6): 593–602.
91. Jones SM. Triggers of atopic dermatitis. *Immunology and Allergy Clinics of North America* Feb 2002; 22(1).
92. Katiyar SK, Korman NJ, Mukhtar H, Agarwal R. Protective effects of silymarin against photocarcinogenesis in a mouse skin model. *J. Natl. Cancer Inst*. 1997 Apr 16; 89(8): 556–566.
93. Kendall SN. Remission of rosacea induced by reduction of gut transit time. *Clin. Exp. Dermatol*. 2004 May; 29(3): 297–299.
94. Kesten BM. Allergic eczema. *NY State J. Med*. 1954; 54: 2441–2450.
95. Kraning KK, Odland GF. Prevalence, morbidity and cost of dermatological diseases. *J. Invest. Dermatol*. 1979; 73(Suppl): 395–401.
96. Kricker A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? A case-control study in Western Australia. *Int. J. Cancer.* 1995 Feb 8; 60(4): 489–494.
97. Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *J. Am. Acad. Dermatol*. 2002; 46: 1–23.
98. Kuchide M, Tokuda H, Takayasu J, Enjo F, Ishikawa T, Ichiishi E, Naito Y, Yoshida N, Yoshikawa T, Nishino H. Cancer chemopreventive effects of oral feeding alpha-tocopherol on ultraviolet light B induced photocarcinogenesis of hairless mouse. *Cancer Lett*. 2003 Jul 10; 196(2): 169–177.
99. Kunynetz RA. A review of systemic retinoid therapy for acne and related conditions. *Skin Therapy Lett*. 2004 Mar; 9(3): 1–4.
100. Laughter D, Istvan JA, Tofte AJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. *J. Am. Acad. Dermatol*. 2000; 43: 649–655.
101. Lee J, Youn JI. The photoprotective effect of 1,25-dihydroxyvitamin D3 on ultraviolet light B-induced damage in keratinocyte and its mechanism of action. *J. Dermatol. Sci*. 1998; 18: 11–18.

102. Lee YA, Wahn U, Kehrt R, Tarani L, Businco L, Gustafsson D, Andersson F, Oranje AP, Wolkertstorfer A, Berg A. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat. Genet*. 2000; 26: 470–473.
103. Leman JA, McHenry PM. Basal cell carcinoma: Still an enigma. *Arch. Dermatol*. 2001 Sep; 137(9): 1239–1240.
104. Leyden JJ, Marpeles RR, Kligman AM. Staphylococcus aureus in lesions of atopic dermatitis. *Br. J. Dermatol*. 1974; 90: 525–530.
105. Lin JY, Selim MA, Shea CR, Grichnik JM, Omar MM, Monteiro-Riviere NA, Pinnell SR. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. *J. Am. Acad. Dermatol*. 2003 Jun; 48(6): 866–874.
106. Lin SY, Chang HP. Induction of superoxide dismutase and catalase activity in different rat tissues and protection from UVB irradiation after topical application of Ginkgo biloba extracts. *Methods Find. Exp. Clin. Pharmacol*. 1997 Jul–Aug; 19(6): 367–371.
107. Liu B, Marnett LJ, Chaudhary A, Ji C, Blair IA, Johnson CR, Diglio CA, Honn KV. Biosynthesis of 12(S)-hydroxyeicosatetraenoic acid by B16 amelanotic melanoma cells is a determinant of their metastatic potential. *Lab. Invest*. 1994 Mar; 70(3): 314–323.
108. Majamaa H, Isolauri E. Evaluation of the gut mucosal barrier: Evidence for increased antigen transfer in children with atopic eczema. *J. Allergy Clin. Immunol*. 1996 Apr; 97(4): 985–990.
109. Majewski S, Janik P, Langner A, Glinska-Ferenz M, Swietochowska B, Sawicki I. Decreased levels of vitamin A in serum of patients with psoriasis. *Arch. Dermatol. Res*. 1989; 280(8): 499–501.
110. Margolin L. Severe rosacea associated with colon cancer recurrence. *Int. J. Dermatol*. 2004 Mar; 43(3): 213–214.
111. Mayser P, Mayer K, Mahloudjian M, Benzing S, Kramer HJ, Schill WB, Seeger W, Grimminger F. A double-blind, randomized, placebo-controlled trial of n-3 versus n-6 fatty acid-based lipid infusion in atopic dermatitis. *J. Parenter. Enteral Nutr.* 2002 May–June; 26(3): 151–158.
112. Mayser P, Mrowietz U, Arenberger P, Bartak P, Buchvald J, Christophers E, Jablonska S, Salmhofer W, Schill WB, Kramer HJ, Schlotzer E, Mayer K, Seeger W, Grimminger F. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled, multicenter trial. *J. Am. Acad. Dermatol*. 1998 Apr; 38(4): 539–547.
113. McCarty M. High-chromium yeast for acne? *Med. Hypotheses*. 1984 Jul; 14(3): 307–310.
114. McCormack SA, Blanner PM, Zimmerman BJ, Ray R, Poppleton HM, Patel TB, Johnson LR. Polyamine deficiency alters EGF receptor distribution and signaling effectiveness in IEC-6 cells. *Am. J. Physiol*. 1998 Jan; 274.
115. Menard D, Arsenault P, Pothier P. Biologic effects of epidermal growth factor in human fetal jejunum. *Gastroenterology* 1988 Mar; 94(3): 656–663.
116. Michaelsson G, Berne B, Carlmark B, Strand A. Selenium in whole blood and plasma is decreased in patients with moderate and severe psoriasis. *Acta Derm. Venereol*. 1989; 69(1): 29–34.
117. Michaelsson G, Edqvist LE. Erythrocyte glutathione peroxidase activity in acne vulgaris and the effect of selenium and vitamin E treatment. *Acta Derm. Venereol*. 1984; 64(1): 9–14.
118. Miller AB, Gaudette LA. Cancers of skin, bone, connective tissues, brain, eye, thyroid and other specified and unspecified sites in Inuit. *Acta Oncol*. 1996; 35(5): 607–616.

119. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: Incidence. *J. Am. Acad. Dermatol.* 1994; 30: 774–778.
120. Montenegro L, Bonina F, Rigano L, Giogilli S, Sirigu S. Protective effect evaluation of free radical scavengers on UVB induced human cutaneous erythema by skin reflectance spectrophotometry. *Int. J. Cosmet. Sci.* 1995; 17(3): 91–103.
121. Muller K, Siebert M, Heidt M, Marks F, Krieg P, Furstenberger G. Modulation of epidermal tumor development caused by targeted overexpression of epidermis-type 12S-lipoxygenase. *Cancer Res.* 2002 Aug 15; 62(16): 4610–4616.
122. Muto T. Prevalence of atopic dermatitis in Japanese adults. *Br. J. Dermatol.* Jan 2003; 148(1): 117–121.
123. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J. Allergy Clin. Immunol.* 2003; 112: 252–262.
124. Novak N, Kraft S, Bieber T. Unraveling the mission of F_c epsilon RI on antigen-presenting cells. *J. Allergy Clin. Immunol.* 2003; 111: 38–44.
125. Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: Is this relevant to malignant melanoma? *Br. J. Dermatol.* 2002 Aug; 147(2): 197–213. Review.
126. Oztas M, Balk M, Ogus E, Bozkurt M, Ogus I, Ozer N. The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin. Exp. Dermatol.* 2003 Mar; 28(2): 188–192.
127. Palmantier R, George MD, Akiyama SK, Wolber FM, Olden K, Roberts JD. Cis-polyunsaturated fatty acids stimulate beta1 integrin-mediated adhesion of human breast carcinoma cells to type IV collagen by activating protein kinases C-epsilon and -mu. *Cancer Res.* 2001 Mar 15; 61(6): 2445–2452.
128. Papageorgiou PP, Chu AC. Chloroxylenol and zinc oxide containing cream (Nels cream) vs. 5% benzoyl peroxide cream in the treatment of acne vulgaris: A double-blind, randomized, controlled trial. *Clin. Exp. Dermatol.* 2000 Jan; 25(1): 16–20.
129. Parodi PW. Cows' milk fat components as potential anticarcinogenic agents. *J. Nutr.* 1997 June; 127(6): 1055–1060. Review.
130. Perkins DM, Duncan JR. The effect of gamma-linolenic acid and zinc supplementation on the growth of normal and tumour cells in vitro. *Prostaglandins Leukot. Essent. Fatty Acids* 1991 May; 43(1): 43–48.
131. Plewig G, Jansen T. Acneiform dermatoses. *Dermatology* 1998; 196(1): 102–107.
132. Preston DS, Stern RS. Nonmelanoma cancers of the skin. *N. Engl. J. Med.* 1992; 327: 1649.
133. Quinn AG, Sikkink S, Rees JL. Basal cell carcinomas and squamous cell carcinomas show distinct patterns of chromosome loss. *Cancer Res.* 1994; 54: 4756–4759.
134. Rademaker M, Wallace M, Cunliffe W, Simpson N. Isotretinoin treatment alters steroid metabolism in women with acne *Br. J. Dermatol.* 1991 Apr; 124(4): 361–364.
135. Rayman MP. The importance of selenium to human health. *Lancet* 2000 Jul 15; 356(9225): 233–241. Review.
136. Rebora AE. *Helicobacter pylori* and rosacea. *J. Eur. Acad. Dermatol. Venereol.* 2000 Sep; 14(5): 344.
137. Redman C, Scott JA, Baines AT, Basye JL, Clark LC, Calley C, Roe D, Payne CM, Nelson MA. Inhibitory effect of selenomethionine on the growth of three selected human tumor cell lines. *Cancer Lett.* 1998 Mar 13; 125(1–2): 103–110.
138. Reich R, Martin GR. Identification of arachidonic acid pathways required for the invasive and metastatic activity of malignant tumor cells. *Prostaglandins* 1996 Jan; 51(1): 1–17.
139. Reimann S, Luger T, Metze D. Topical administration of capsaicin in dermatology for treatment of itching and pain. *Hautarzt.* 2000 Mar; 51(3): 164–172.

140. Reissig D, Rassoul F, Salvetter J, Wagner O, Richter V. Effect of fatty acids on expression of endothelial leukocyte adhesion molecules. *Eur. J. Nutr.* 2003 Aug; 42(4): 224–227.
141. Rhodes LE, Shahbakhti H, Azurdia RM, Moison RM, Steenwinkel MJ, Homburg MI, Dean MP, McArdle F, Beijersbergen van Henegouwen GM, Epe B, Vink AA. Effect of eicosapentaenoic acid, an omega-3 polyunsaturated fatty acid, on UVR-related cancer risk in humans: An assessment of early genotoxic markers. *Carcinogenesis* 2003 May; 24(5): 919–925.
142. Roihu T, Kariniemi AL. Demodex mites in acne rosacea. *J. Cutan. Pathol.* 1998 Nov; 25(10): 550–552.
143. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH, Paerregaard A. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. *J. Allergy Clin. Immunol.* 2003 Feb; 111(2): 389–395.
144. Rosenfield RL, Deplewski D, Kentsis A, Ciletti N. Mechanisms of androgen induction of sebocyte differentiation *Dermatology* 1998; 196(1): 43–46.
145. Rudman S, Philpott M, Thomas G, Kealey T. The role of IGF-I in human skin and its appendages: Morphogen as well as mitogen? *J. Invest. Dermatol.* 1997 Dec; 109(6): 770–777.
146. Ryle J, Barber H. Gastric analysis in acne rosacea. *Lancet* 1920; ii: 1195–1196.
147. Sampson HA. Current reviews of allergy and immunology: Food allergy. Part 1: Immunopathogenesis and clinical disorders. *J. Allergy Clin. Immunol.* May 1999; 103(5).
148. Serwin AB, Wasowicz W, Gromadzinska J, Chodynicka B. Selenium status in psoriasis and its relationship with alcohol consumption. *Biol. Trace Elem. Res.* 2002 Nov; 89(2): 127–137.
149. Sharma V, Kaur I, Kumar B. Calcipotriol versus coal tar: A prospective randomized study in stable plaque psoriasis. *Int. J. Dermatol.* 2003 Oct; 42(10): 834–838.
150. Sharma VK, Lynn A, Kaminski M, Vasudeva R, Howden CW. A study of the prevalence of *Helicobacter pylori* infection and other markers of upper gastrointestinal tract disease in patients with rosacea. *Am. J. Gastroenterol.* 1998 Feb; 93(2): 220–222.
151. Shi H, Niki E. Stoichiometric and kinetic studies on Ginkgo biloba extract and related antioxidants. *Lipids* 1998 Apr; 33(4): 365–370.
152. Shors AR, Solomon C, McTiernan A, White E. Melanoma risk in relation to height, weight, and exercise (United States). *Cancer Causes Control.* 2001 Sep; 12(7): 599–606.
153. Skov L, Baadsgaard O. Bacterial superantigens and inflammatory skin diseases. *Clin. Exp. Dermatol.* 2000 Jan; 25(1): 57–61.
154. Smith DE, Salerno JW. Selective growth inhibition of a human malignant melanoma cell line by sesame oil in vitro. *Prostaglandins Leukot. Essent. Fatty Acids* 1992 Jun; 46(2): 145–150.
155. Snider BL, Dieteman DF. Letter: Pyridoxine therapy for premenstrual acne flare. *Arch. Dermatol.* 1974 Jul; 110(1): 130–131.
156. Snitsarenko OV. Vasoactive polypeptides in rosacea. *Vestn. Dermatol. Venerol.* 1989; (9): 42–44.
157. Soyland E, Funk J, Rajka G, Sandberg M, Thune P, Rustad L, Helland S, Middelfart K, Odu S, Falk ES, et al. Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis: A double-blind, multicentre study. *Br. J. Dermatol.* 1994 Jun; 130(6): 757–764.
158. Stahl W, Sies H. Carotenoids and protection against solar UV radiation. *Skin Pharmacol. Appl. Skin Physiol.* 2002 Sept–Oct; 15(5): 291–296. Review.

159. Stern RS, Lange R. Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J. Invest. Dermatol.* 1988 Aug; 91(2): 120–124.
160. Strauss JS, Stewart ME, Downing DT. The effect of 13-cis-retinoic acid on sebaceous glands. *Arch. Dermatol.* 1987 Nov; 123(11): 1538a–1541.
161. Stucker M, Memmel U, Hoffmann M, Hartung J, Altmeyer P. Vitamin B(12) cream containing avocado oil in the therapy of plaque psoriasis. *Dermatology* 2001; 203(2): 141–147.
162. Syed TA, Ahmad SA, Holt AH, Ahmad SA, Ahmad SH, Afzal M. Management of psoriasis with Aloe vera extract in a hydrophilic cream: A placebo-controlled, double-blind study. *Trop. Med. Int. Health* 1996 Aug; 1(4): 505–509.
163. Teelucksingh S, Mackie AD, Burt D, McIntyre MA, Brett L, Edwards CR. Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. *Lancet* 1990 May 5; 335(8697): 1060–1063.
164. Thurmon FM. The treatment of psoriasis with sarsaparilla compound. *N. Engl. J. Med.* 1942; 227: 128–133.
165. Toda M, et al. Polarized in vivo expression of IL-11 and IL-17 between acute and chronic skin lesions. *J. Allergy Clin. Immunol.* 2003; 111: 875–881.
166. Tsoureli-Nikita E, Hercogova J, Lotti T, Menchini G. Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: A study of the clinical course and evaluation of the immunoglobulin E serum levels. *Int. J. Dermatol.* 2002 Mar; 41(3): 146–150.
167. Turjanmaa K, Reunala T. Treatment of rosacea. *Acta Derm. Venereol.* 1987; 67(1): 89–91.
168. Utas S, Ozbakir O, Turasan A, Utas C. *Helicobacter pylori* eradication treatment reduces the severity of rosacea. *J. Am. Acad. Dermatol.* 1999 Mar; 40(3): 433–435.
169. Vadas P, Wai Y, Burks W, Perelman B. Detection of peanut allergens in breast milk of lactating women. *JAMA* 2001 Apr 4; 285(13): 1746–1748.
170. Vanderveen EE, Grekin RC, Swanson NA, Kragballe K. Arachidonic acid metabolites in cutaneous carcinomas: Evidence suggesting that elevated levels of prostaglandins in basal cell carcinomas are associated with an aggressive growth pattern. *Arch. Dermatol.* 1986 Apr; 122(4): 407–412.
171. Vaya J, Aviram M. Nutritional antioxidants: Mechanism of action, analyses of activities and medical application. Available online at http://www.bentham.org/cmciema1-1/vaya/vaya-ms.htm.
172. Vazquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe vera gel. *J. Ethnopharmacol.* 1996 Dec; 55(1): 69–75.
173. Vazquez FJ. Rosacea, vinegar and lemon, dysuria and *Helicobacter pylori*. *Medicina* (Buenos Aires) 1999; 59 (5 Pt 1): 469–470.
174. Veierod MB, Thelle DS, Laake P. Diet and risk of cutaneous malignant melanoma: A prospective study of 50,757 Norwegian men and women. *Int. J. Cancer* 1997 May 16; 71(4): 600–604.
175. Verma AK. Retinoids in chemoprevention of cancer. *J. Biol. Regul. Homeost. Agents* 2003 Jan–Mar; 17(1): 92–97. Review.
176. Vitaliano PP, Urbach F. The relative importance of risk factors in non-melanoma skin cancer. *Arch. Dermatol.* 1980; 116: 454–456.
177. Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, Ng SK, Munoz B, Emmett EA. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. *Cancer* 1990 Jun 15; 65(12): 2811–2817.

178. Vural P, Canbaz M, Selcuki D. Plasma antioxidant defense in actinic keratosis and basal cell carcinoma. *J. Eur. Acad. Dermatol. Venereol.* 1999 Sep; 13(2): 96–101.
179. Waldman A, Gilhar A, Duek L, Berdicevsky I. Incidence of candida in psoriasis: A study on the fungal flora of psoriatic patients. *Mycoses* 2001 May; 44(3–4): 77–81.
180. Walker C. Causation of eczema, urticaria and angioneurotic edema. *JAMA* 1918; 70: 897–900.
181. Walton S, Sheth M, Wyatt EH. Rosacea and ulcerative colitis: A possible association. *J. Clin. Gastroenterol.* 1990 Oct; 12(5): 513–515.
182. Wananukul S, Huiprasert P, Pongprasit P. Eczematous skin reactions from patch testing with aeroallergens in atopic children with and without dermatitis. *Pediatric Dermatol.* 1993; 10: 209–213.
183. Wang ZY, Huang MT, Ho CT, Chang R, Ma W, Ferraro T, Reuhl KR, Yang CS, Conney AH. Inhibitory effect of green tea on the growth of established skin papillomas in mice. *Cancer Res.* 1992 Dec 1; 52(23): 6657–6665.
184. Weimar VM, Puhl SC, Smith WH, tenBroeke JE. Zinc sulfate in acne vulgaris. *Arch. Dermatol.* 1978 Dec; 114(12): 1776–1778.
185. Werninghaus K, Meydani M, Bhawan J, Margolis R, Blumberg JB, Gilchrest BA. Evaluation of the photoprotective effect of oral vitamin E supplementation. *Arch. Dermatol.* 1994 Oct; 130(10): 1257–1261.
186. Wilkin JK. Flushing reactions: Consequences and mechanisms. *Ann. Intern. Med.* 1981 Oct; 95(4): 468–476. Review.
187. Wolf R, Ruocco V. Triggered psoriasis. *Adv. Exp. Med. Biol.* 1999; 455: 221–225. Review.
188. Wozel G, Chang A, Zultak M, Czarnetzki B, Happle R, Barth J, van de Kerkhof P. The effect of topical retinoids on the leukotriene-B4-induced migration of polymorphonuclear leukocytes into human skin. *Arch. Dermatol. Res.* 1991; 283(3): 158–161.
189. Yan L, Yee JA, Li D, McGuire MH, Thompson LU. Dietary flaxseed supplementation and experimental metastasis of melanoma cells in mice. *Cancer Lett.* 1998 Feb 27; 124(2): 181–186.
190. Yano T, Yajima S, Hagiwara K, Kumadaki I, Yano Y, Otani S, Uchida M, Ichikawa T. Vitamin E inhibits cell proliferation and the activation of extracellular signal-regulated kinase during the promotion phase of lung tumorigenesis irrespective of antioxidant effect. *Carcinogenesis* 2000 Nov; 21(11): 2129–2133.
191. Yoshizawa K, Willett WC, Morris SJ, Stampfer MJ, Spiegelman D, Rimm EB, Giovannucci E. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J. Natl. Cancer Inst.* 1998 Aug 19; 90(16): 1219–1224.
192. Young MR, Halpin J, Hussain R, et al. Inhibition of tumor production of granulocyte-macrophage colony-stimulating factor by 1 alpha, 25-dihydroxyvitamin D3 reduces tumor motility and metastasis. *Invasion Metastasis* 1993; 13: 169–177.
193. Yu G, Bjorksten B. Polyunsaturated fatty acids in school children in relation to allergy and serum IgE levels. *Pediatr. Allergy Immunol.* 1998 Aug; 9(3): 133–138.
194. Zouboulis CC, Korge B, Akamatsu H, Xia LQ, Schiller S, Gollnick H, Orfanos C. Effects of 13-cis-retinoic acid, all-trans-retinoic acid, and acitretin on the proliferation, lipid synthesis and keratin expression of cultured human sebocytes in vitro. *J. Invest. Dermatol.* 1991 May; 96(5): 792–797.
195. Zouboulis CC, Nestoris S, Adler Y, Orth M, Orfanos C, Picardo M, Camera E, Cunliffe W. A new concept for acne therapy: A pilot study with zileuton, an oral 5-lipoxygenase inhibitor. *Arch. Dermatol.* 2003 May; 139(5): 668–670.

12 Nutritional Management in the Patient with an Upper Gastrointestinal Cancer

Marcus Ferrone and James S. Scolapio

CONTENTS

12.1 INTRODUCTION

The prognosis for individuals afflicted with an upper gastrointestinal malignancy is relatively poor. With limited treatment options available to this patient population, nutrition support becomes a major component of palliative care, with the aim to correct nutritional defects and prevent further cachexia. The success of a supportive nutritional regimen either by enteral or parenteral administration is dependent on much more than just providing a calorie load to the patient. The provider must

understand not only the pathophysiology of a disease state, but also its effects on the nutritional status of the patient. Comprehension of the principles of enteral and parenteral nutrition is also of paramount importance.

This chapter reviews the current practice standards of nutritional management for patients with neoplastic illnesses of the esophagus, stomach, and pancreas. It highlights the role nutrition may play in disease, as well as the use of enteral or parenteral supplementation to correct nutritional deficiencies in this select group of patients. Although a complete review of these malignancies is beyond the scope of this chapter, the basics of pathology and treatment regimens are also discussed.

12.2 SPECIFIC NUTRITIONAL CONCEPTS IN ESOPHAGEAL CANCER

12.2.1 Brief Summary of Esophageal Cancer

Esophageal cancer is one of the least studied malignancies worldwide and carries a rather heavy mortality burden. The poor prognosis for this neoplasm is evident in a relative 5-year survival rate of less than 15% (21). Potentially, patients may be cured with surgery or multimodality therapy if diagnosed at an early stage of the disease. Unfortunately, more than 50% of patients have either unresectable tumors or radiographic evidence of metastases at the time of diagnosis (41).

The majority of esophageal cancers are either squamous cell cancers or adenocarcinomas. Although esophageal neoplasms are the sixth leading cause of cancer death globally (38), cancers arising from the esophagus are relatively uncommon in the United States (21). For example, it was anticipated that 14,250 new cases would surface in 2004, and nearly 13,300 would die from the disease. Squamous cell carcinomas comprised the vast majority of esophageal cancers diagnosed in Americans for much of the 20th century. Over the past 20 years, however, the incidence of esophageal adenocarcinoma has increased significantly in Western countries such that squamous cell and adenocarcinoma malignancies now occur with almost equal frequency (2,12).

Although the pathogenesis of esophageal cancer remains unclear, results from animal studies suggest that oxidative damage at the cellular level may initiate the carcinogenic process. Numerous factors, such as smoking or gastroesophageal reflux, which leads to inflammation, esophagitis, and increased cell turnover, might all play a role in the etiology of these highly virulent tumors (46). The risk factors for developing either form of esophageal cancer are varied but can include tobacco and alcohol use, reflux symptoms, dietary regimens, obesity, injury to the esophagus, consumption of hot beverages, and the use of certain prescription drugs such as beta-blockers or aminophylline (14). The relative importance of specific risk factors varies in different geographic regions.

The management of local-regional esophageal cancer has undergone a major evolution over the past decade, but optimal therapy for potentially resectable tumors remains unclear. In clinical practice, surgery is considered the standard treatment for early stage esophageal cancer, but its utility as monotherapy has been challenged (13,10). A combination of chemotherapy and radiation is often utilized preopera-

tively in those patients who are candidates for surgery, or this combination treatment can serve as a reasonable alternative for those individuals with unresectable tumors.

12.2.2 Dietary Issues Linked to Cancer Incidence

Several dietary practices associated with squamous cell carcinoma of the esophagus have been uncovered in Asia, a continent where esophageal cancer is particularly endemic. Pickled vegetables and preserved foods that contain nitrates, and thus give rise to N-nitroso compounds including nitrosamines, have long been implicated as constituting an increased risk of esophageal cancer (40). These carcinogenic compounds are believed to exert their mutagenic properties by inducing the host DNA to synthesize harmful alkyl adducts (50).

The chewing of betel nuts (*Areca catechu*) is a widespread custom in certain Eastern regions of the world. Many individuals indulge in the practice to experience psychoactive stimulation, but others believe it has dental protective properties. Whatever the rationale, the practice has been identified as a potential risk factor for the development of esophageal squamous cell carcinoma (37). The mechanism is believed to involve the induction of collagen synthesis secondary to the release of copper from the betel nut (49).

In other regions where this cancer is endemic, such as Iran, Russia, and South Africa, the ingestion of very hot foods and beverages has been linked to esophageal cancer. Individuals who consume large quantities of tea at temperatures greater than 65ºC may suffer thermal injury, which in turn may explain the high prevalence of diffuse esophagitis in these persons (36). The consumption of spicy foods or excessive amounts of chili is also positively associated with the risk of esophageal cancer.

One factor that may contribute to the rising incidence of esophageal adenocarcinoma in the Western world is the increasing prevalence of obesity (9). It has been postulated that obesity increases intra-abdominal pressure and promotes gastroesophageal reflux. One recent study, however, provided contradictory results; another investigation found this hypothesis to be true only in women (24,34).

Certain dietary factors may also serve as a protector against esophageal cancer. Numerous case-control and cohort studies have demonstrated that fruit and vegetable consumption have a protective effect. A high intake of cereal fiber has been noted to moderately decrease the risk of esophageal adenocarcinoma, but this is not the case in squamous cell carcinoma (47). The protective effects of cereal fibers may be due to their inability to neutralize the conversion of salivary nitrates to nitrosamines, which are mutagens. However, studies of individual foods and their cellular mechanisms of action in carcinogenesis are few. A number of observational studies, on the other hand, do exist. For example, it was determined from a study in Linxian, China, that low levels of serum selenium are associated with the development of squamous cell cancer of the esophagus (27). Two trials performed in this region suggested that selenium supplementation may be associated with a reduced risk of this cancer (3,26). In a nationwide, population-based, case-control study from Sweden with 165 cases of esophageal squamous cell carcinoma compared with 815 control subjects, those with a high intake of vitamin C, β-carotene, and α-tocopherol

showed a 40 to 50% decreased risk of squamous cell carcinoma as compared with those with low intake (46).

12.2.3 Risk Factors for Malnutrition

Malnutrition is a common finding in patients with malignancy and can adversely affect the clinical course of patients if not properly addressed. Nearly 20% of patients with esophageal carcinoma die from the resultant cachexia associated with this cancer (4). Therefore, an appraisal of nutrition status in the patient prior to surgery or radiation therapy is important.

Weight loss is reported in 57% of patients and is an independent indicator of a poor prognosis if the loss of body mass is greater than 10% (16). Up to 74% of patients with esophageal cancer have dysphagia; 17% report odynophagia at the time of diagnosis (11). Both pathologies contribute significantly to the loss of weight. Obstruction of the esophagus by a tumor can cause progressive solid food dysphagia, and this usually occurs when the esophageal lumen diameter is less than 13 mm, a situation that indicates advanced disease. Palliative endoscopic maneuvers such as esophageal dilation, laser therapy, mucosal resection, or placement of esophageal stents may be of benefit to symptomatic patients who are not candidates for tumor resection or chemoradiotherapy. Those individuals who suffer recurrent dysphagia following primary chemoradiotherapy may secure temporary relief by having an endoscopic procedure as well.

Surgical resection of localized esophageal cancer often involves partial removal of the esophagus and stomach, then connecting the residual structures to reestablish continuity of the gastrointestinal tract. Anatomical alterations of these organs usually result in a bilateral vagotomy, an outcome that has a profound effect on the function of the gastrointestinal tract. Postoperative complications can include reflux, early satiety, dysphagia, diarrhea, steatorrhea, and dumping syndrome. Complications often follow an esophagectomy and can limit the ability of an individual to obtain adequate caloric intake. Such complications can include anastomotic leak, dysmotility, early satiety, regurgitation, and vomiting. Vitamin B_{12} absorption may be decreased when a large section of the proximal stomach is removed. It is also not uncommon for esophageal strictures to develop after surgery done to inhibit the passage of foodstuff. Repeated endoscopic dilation of the remaining esophageal structure may resolve this anatomical obstruction. Esophageal stents constitute an alternative treatment option in patients who are not candidates for surgical intervention. Placement of these devices maintains the integrity of the esophageal lumen and serves as palliative care to those suffering from severe dysphagia.

Radiation therapy to the esophagus can trigger esophagitis in some patients. This complication most often resolves following cessation of treatment; however, some patients may develop fibrosis with resultant esophageal strictures. Esophagotracheal fistulas and hemorrhage are often associated with a regrowth of the malignancy and limit the possibility of enteral feeding.

12.2.4 Nutritional Management in the Esophageal Cancer Patient

A properly designed nutritional support regimen can prevent or ameliorate malnutrition and weight loss, both negative prognostic factors in this patient population. Nutritional support has been shown to suppress gluconeogenesis in patients with esophageal carcinoma, as well as increase protein synthesis and decrease catabolism (7). Individuals with mildly obstructive symptoms can be repleted with oral supplementations prior to surgery. Preoperative total parenteral nutrition (TPN) should be reserved for those patients with near total esophageal occlusion and cachexia.

When designing a nutritional support regimen, clinicians should target a caloric goal that is nearly 1.5 times the resting energy expenditure of the patient. The food or TPN should contain at least 2 g of protein per kilogram of body weight and should be provided for a minimum of 1 week preoperatively. Postoperative TPN can continue until the patient is tolerating adequate oral intake. Jejunal feeding tubes are often placed at the time of surgery in patients who undergo elective esophagogastrectomy procedures. Feedings may be resumed when normal peristalsis returns. Tube enterostomies are ideal for the patient who undergoes palliative radiation therapy because the response to radiation may only become apparent after several weeks of treatment. Complications following surgery may include an anastomotic leak that requires the patient to remain on intravenous nutrition until surgical intervention is achieved. When oral intake is possible following esophagectomy, the diet should provide for small, frequent meals rich in carbohydrates with sufficient protein and fat components.

12.3 SPECIFIC NUTRITIONAL CONCEPTS IN GASTRIC CANCER

12.3.1 Brief Summary of Gastric Cancer

The incidence of gastric cancer varies widely as a function of geographical location. In general, this malignancy shows a predilection for urban and lower socioeconomic groups and occurs with far less frequency in industrialized nations. For example, in the United States the annual incidence of gastric cancer has markedly declined over the past 50 years, from 33 to 10 cases per 100,000 men and from 30 to 5 cases per 100,000 women (33,53). Forty years ago, gastric cancer was the major human cancer afflicting Americans. The reason for the decline in the United States is not completely understood. Nevertheless, gastric cancer continues to carry a high fatality rate and remains a serious public health concern (21).

While the vast majority of malignant neoplasms of the stomach are adenocarcinomas, gastric cancers can assume a myriad of morphologic configurations and are often dependent upon the location of the lesion within the stomach. As with most other cancers, the etiology of gastric cancer remains elusive. Environmental and genetic factors and a number of underlying disorders have been associated with the development of gastric cancer. Predisposing conditions that have been associated

with an increased risk of gastric cancer include *Helicobacter pylori* (the causative agent of chronic antral gastritis), pernicious anemia (a sequel of autoimmune chronic atrophic gastritis), polyps of the stomach, hypertrophic gastropathy, immunodeficiency syndromes, and Barrett's esophagus.

The high mortality rate of gastric cancer reflects the prevalence of advanced disease at presentation. As a result, there has been renewed interest in exploring ways to improve treatment by a variety of adjuvant and neoadjuvant therapies. Strategies to combat this malignancy include radiotherapy, systemic chemotherapy, combined radiochemotherapy, and intraperitoneal chemotherapy. Although controlled trials of neoadjuvant immunotherapy have failed to demonstrate a significant survival advantage compared with surgery alone, research continues, and this modality may become important in the future (19,45). Currently surgical eradication of a gastric tumor offers the best chance for long-term survival for patients with localized disease, particularly when combined with adjuvant chemoradiotherapy (25). Some superficial gastric lesions can be treated endoscopically, but gastrectomy is the most widely used approach for the treatment of invasive gastric cancer. Total gastrectomy is usually performed for lesions in the proximal region of the stomach, while distal subtotal gastrectomy with resection of adjacent lymph nodes appears to be sufficient for lesions in the distal region of the stomach. Palliative therapy is employed in those patients with metastatic disease, but this can include surgery to relieve gastric obstruction.

12.3.2 Dietary Issues Linked to Cancer Incidence

The causes of this malignancy are attributed to dietary factors such as the consumption of heated fats or of smoked or adulterated foods. Diets rich in complex carbohydrates, in salted, pickled, or smoked foods, in dried fish, and in cooking oil have all been linked to an increased risk of gastric cancer. Such diets, although calorically sufficient or excessive, fail to provide what is necessary for optimal cellular and tissue functions because micronutrient intake, especially of vitamin A and other similar cofactors, may be deficient or borderline. The ability to ward off toxins or other chemical carcinogens is compromised in these patients and may be particularly pronounced in the stomach, the portal of entry for many carcinogens.

The nitrates and nitrites found in preserved foods have also been associated with an increased risk of gastric cancer (17). The practice of nitrite addition to preserve meat and fish has changed considerably over the years. Nitrate concentrations in food have declined, and this may be a reason why total nitrite intake has gone down. The reduced consumption of nitrites and nitrates may account for some of the decline in the prevalence of gastric cancer in the United States.

Reduced levels of ascorbic acid have been linked to the development of distal gastric cancer. Ascorbic acid is normally secreted in the stomach, but it declines in the presence of *H. pylori* gastritis (43). Because *H. pylori* is a risk factor for the development of gastric carcinomas, restoring normal ascorbic acid levels in the stomach may overcome the adverse effects of *H. pylori* and other ingested mutagens.

Consumption of a diet rich in fruits and vegetables is associated with a decreased incidence of gastric cancer. These foods may overcome the nutrient deficiency that exists in high-risk populations and minimize the effects of a potential carcinogen

responsible for gastric neoplasms. Green tea is another food that has been shown to be protective against the development of gastric cancer (23).

12.3.3 Risk Factors for Malnutrition

A primary tumor in the stomach is silent, and its host has no symptoms early in the course of the disease. The first signs of illness are secondary to metastasis and often involve anorexia and weight loss. Early satiety, bloating, pain, and vomiting are frequently signs of advanced disease. Cancer in the cardiac region of the stomach may obstruct the esophageal outlet and cause dysphagia. High nutrient uptake by the tumor and diminished intake or impaired digestion lead to subnormal levels of plasma proteins and a significant decrease in the total adenine nucleotide, creatine, and glycogen pools (44).

Postsurgical alterations in gastric anatomy can have profound effects on the storage function of the stomach and pyloric emptying mechanism. The most common nutritional problems that patients face after gastrectomy are early satiety and the inability to ingest adequate amounts of food during a meal. While malabsorption contributes to the weight loss in patients following a gastrectomy, the primary cause is poor oral intake.

Gastric cancer patients are also at risk of developing dumping syndrome following a gastrectomy procedure. Dumping syndrome occurs because of the rapid delivery of large amounts of osmotically active solids and liquids to the duodenum. Symptoms of dumping syndrome include early satiety, crampy abdominal pain, nausea, vomiting, and explosive diarrhea. Vasomotor symptoms may manifest themselves as diaphoresis, flushing, dizziness, palpitations, and an intense desire to lie down. Patients with severe dumping must often limit their food intake to avoid symptoms that in turn can lead to weight loss and, with time, to nutrient deficiencies. Individuals suffering from dumping syndrome should be encouraged to eat small, frequent meals (five or six meals per day) and maximize the protein intake in their diet. Foods chosen by the patient should be relatively low in insoluble fiber, since high fiber concentrations increase satiety and decrease transit time.

Late dumping symptoms such as sweating, fatigue, disturbed consciousness, tremor, and tachycardia can also occur in this patient population. These physiological responses result from a rapid rise and subsequent fall in blood glucose levels that appear 1 to 3 h after meals. Blunting this endocrine response can be achieved by adding a pectin derivative to the diet that prolongs gastric emptying (22).

Patients undergoing a total or near-total gastrectomy may develop fat malabsorption, which ultimately leads to a deficiency in fat-soluble vitamins. Deficits in vitamin B_{12} arise because of a lack of gastric acidity and intrinsic factor. Insufficient serum iron and calcium levels can also become evident in the postoperative setting.

12.3.4 Nutritional Management in the Gastric Cancer Patient

Indications for perioperative nutritional support for the stomach cancer patient are similar to those for esophageal cancer. TPN is indicated during the preoperative

stage for those patients suffering from complete gastric outlet obstruction. Patients who do not have an outlet obstruction should be allowed an *ad lib* diet that can be enhanced by calorically dense liquid regimens if needed.

Following a curative resection, removal of part or all of the stomach reduces its reservoir volume and significantly alters its digestive, secretory, and diluting functions. Mild to severe nutritional consequences are likely to develop in the postoperative setting. The limitations of a small gastric pouch may mean that the patient needs to consume multiple, small, balanced meals throughout the day. In many cases, inadequate gastric emptying can delay the time of discharging the patient. To avoid this, a feeding jejunostomy can be placed at the time of gastrectomy. This enteral access device requires minimal patient training, can be utilized on an outpatient basis, and provides caloric supplementation. Nocturnal jejunal feedings are also beneficial to prevent further weight loss and to maintain hydration in patients who continue to lose weight, dietary adjustments notwithstanding.

Iron, calcium, and fat-soluble vitamin deficiencies can be prevented with the aid of specific supplements or multivitamin preparations. To prevent B_{12} deficiencies requires monthly injections of cyanocobalamin. If patients become lactose intolerant, lactase-treated milk or yogurt can take the place of the standard products.

12.4 SPECIFIC NUTRITIONAL CONCEPTS IN PANCREATIC CANCER

12.4.1 Brief Summary of Pancreatic Cancer

Pancreatic cancer is one of the deadliest cancers, with a dismal 5-year survival rate of only 4% (21). In the United States, the incidence of pancreatic cancer has been relatively stable since the 1970s. Approximately 31,860 Americans will be diagnosed with pancreatic adenocarcinoma in 2004, and nearly all are expected to die from the disease. The malignancy occurs rarely before the age of 45, but its incidence rises sharply thereafter. Surgical resection is the only potentially curative treatment for pancreatic cancer. Unfortunately, because patients present late with the disease, only 15 to 20% are candidates for pancreatectomy. Furthermore, the prognosis is poor even in those in whom resection is still advisable. The 5-year survival following pancreaticoduodenectomy is only about 25 to 30% for node-negative tumors and 10% for node-positive tumors.

Pancreatic cancers include both exocrine and endocrine/islet cell tumors. The exocrine tumors are divided into two broad categories. Periampullary lesions — most commonly adenocarcinoma of the head of the pancreas and, less frequently, malignant lesions of the ampulla, duodenum, and common bile duct — lead to jaundice, weight loss, and abdominal pain. Malignancies of the body and the tail of the pancreas comprise the second category of pancreatic cancers and account for 25% of adenocarcinomas of the pancreas. Due to retroperitoneal location and distance from the common bile duct, lesions are usually large at the time of diagnosis. Common symptoms are weight loss and pain. Exocrine malignancies are rare. Most tumors secrete biologically active substances that result in specific clinical syn-

dromes. Insulinoma, gastrinoma, and other secretory tumors are examples of endocrine/islet cell cancers.

The etiology of pancreatic cancer is not known; however, there are many risk factors associated with development of the disease. Hereditary factors are important. Familial aggregation and genetic susceptibility are thought to play a role in as many as 10% of patients with pancreatic cancer (48). There appears to be no link between individuals suffering from heredity chronic pancreatitis and those developing pancreatic cancer. Some findings suggest, however, that patients with nonhereditary pancreatitis are at increased risk of developing pancreatic cancer.

Numerous epidemiologic studies have reported an association between diabetes mellitus and pancreatic cancer (42,51). Abnormal glucose metabolism, in the absence of self-reported diabetes mellitus, and diets composed of high glycemic loads have also been linked to pancreatic cancer (18). As with most cancers, cigarette smoking, diet, obesity, and physical inactivity are believed to play a role in the development of pancreatic cancer.

Management of the patient with pancreatic cancer is highly variable. It is influenced by the overall health of the patient, the presence of metastases, and the location and size of the tumor. Pancreatic cancer is usually diagnosed in a locally advanced or metastatic stage, neither of which is amenable to the only known curative therapy, complete surgical resection. Patients who have undergone surgical resection appear to benefit from adjuvant therapy using chemoradiation. Physicians should encourage patients with unresectable local-regional or metastatic pancreatic cancer to participate in investigational trials or to consider emphasis on palliative measures, rather than on aggressive attempts at treatment.

12.4.2 Dietary Issues Linked to Cancer Incidence

A diet high in fat or meat, particularly smoked or processed meats, has been linked to the occurrence of pancreatic cancer in many patients (32), but not all studies support this association (31). In experimental settings, dietary fat and protein act as promoters of pancreatic carcinogenesis. Pancreatic cancer has also been tied to obesity and physical activity. This relationship, illustrated in a cohort study, revealed a significantly increased risk of pancreatic cancer in patients with a BMI of 30 kg/m^2 or more and whose regular physical activity was minimal (30).

Consumption of fresh fruits and vegetables may provide a protective effect against pancreatic cancer (35). Diets high in fiber are also likely to decrease the risk of pancreatic cancer (28). Low serum levels of selenium and lycopene, a carotenoid present in fruits, have been found in subjects who subsequently developed pancreatic cancer (6).

12.4.3 Risk Factors for Malnutrition

There are myriad symptoms related to pancreatic cancer, but those that can have a negative impact on the nutritional status of a patient include pain, upper gastrointestinal obstruction, acute pancreatitis, anorexia, and dysgeusia. These symptoms are likely to precede actual diagnosis by at least 6 months. If patients continue on their

habitual diet, their pain may aggravate further. The Pancreatic Cancer Task Force has reported that 80% of patients with pancreatic cancer have lost weight at presentation (39), a loss that continues. At the time of death, the median loss is 25% of the pre-illness body weight (52).

Patients with pancreatic cancer often report a decrease in food intake. Gastric outlet obstruction may develop, with resultant vomiting and the inability to ingest nutrients. Pancreatic carcinomas can lead to digestive enzyme deficiencies that result in malabsorption or bile insufficiency, thereby causing reduced absorption of fats and fat-soluble vitamins. New-onset diabetes may further complicate nutritional derangements and result in continued weight loss. As food intake decreases, cachexia ensues (see Chapter 13).

12.4.4 Nutritional Management of the Pancreatic Cancer Patient

Nutritional status and quality of life can be excellent in those patients who do not have cancer recurrence following a Whipple procedure (pancreaticoduodenectomy). Postoperative complications of a Whipple procedure include malabsorption in nearly 25% of patients, as well as early satiety, rapid intestinal transit, and anorexia (29). It is necessary to try to stop diarrhea and to maintain appropriate body weight even though fat absorption cannot be restored to normal. One way to achieve this is to include pancreatic enzymes with each meal. Prescription enzyme replacement therapy may help to prevent weight loss in patients with unresectable cancer of the pancreatic head or pancreatic duct obstruction (5).

There are few clinical studies that suggest beneficial dietary interventions for patients with advanced pancreatic cancer. The administration of enteral supplements enriched with fish oils may provide weight stabilization and even weight gain and improved appetite (1). Fish oils contain ω-3 polyunsaturated fatty acids such as eicosapentanoic acid (EPA) and docosahexanoic acid. In contrast to the ω-6 fatty acids in vegetable oils, ω-3 fatty acids suppress inflammation, inhibit blood coagulation, and impede tumor growth. Polyunsaturated fatty acids such as EPA exert an inhibitory effect on human pancreatic carcinoma cell lines *in vitro* (15).

Patients suffering from an incurable or debilitating illness will often turn to complementary medical therapies as an alternative treatment modality. In one such pilot study, patients with unresectable pancreatic cancer received large doses of pancreatic enzymes and nutritional supplements. Study participants also received detoxification procedures and consumed an organic diet (20). Even though survival rates varied from 1 to 3 years, enough interest was generated to secure funding for phase III clinical trials. Another trial examined the use of a macrobiotic diet with meat and dairy product consumption reduced and intake of cereal grains and cruciferous and other dark vegetables increased. Mean survival of 23 patients on the macrobiotic diet was 17 months, whereas it was only 6 months for the controls (8).

REFERENCES

1. Barber MD, Ross JA, Preston T. (1999). The effects of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. *Br. J. Cancer* 81:80.
2. Blot WJ, Devesa SS, Fraumeni JF Jr. (1993). Continuing climb in rates of esophageal adenocarcinoma: An update. *JAMA* 270:1320.
3. Blot WJ, Li JY, Taylor PR, Guo W, Dawsey S, Wang GQ, Yang CS, Zheng SF, Gail M, Li GY. (1993). Nutrition intervention trials in Linxian, China: Supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J. Natl. Cancer Inst.* 85:1483–1492.
4. Bozzetti F, Pagnoni AM, Delvecchil M. (1980). Excessive caloric expenditure as a cause of malnutrition in patients with cancer. *Surg. Gynecol. Obstet.* 150:229.
5. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GN, van Leeuwen DJ. (1998). Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut* 42:92.
6. Burney PG, Comstock GW, Morris JS. (1989). Serologic precursors of cancer: Serum micronutrients and the subsequent risk of pancreatic cancer. *Am. J. Clin. Nutr.* 49:895–900.
7. Burt ME, Gorschboth CM, Brennan AM. (1982). A controlled, prospective, randomized trial evaluating the metabolic effects of enteral and parenteral nutrition in the cancer patient. *Cancer* 49:1092–1105.
8. Carter JP, Saxe GP, Newbold V. (1993). Hypothesis: Dietary management improves survival from nutritionally linked cancers based on analysis of representative cases. *J. Am. Coll. Nutr.* 12:209.
9. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, Dubrow R, Schoenberg JB, Mayne ST, Farrow DC, Ahsan H, West AB, Rotterdam H, Niwa S, Fraumeni JF Jr. (1998). Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J. Natl. Cancer Inst.* 90:150–155.
10. Coia, LR. (1989). Esophageal cancer: Is esophagectomy necessary? *Oncology* 3:101–110.
11. Daly JM, Fry WA, Little AG, Winchester DP, McKee RF, Stewart AK, Fremgen AM. (2000). Esophageal cancer: Results of an American College of Surgeons Patient Care Evaluation Study. *J. Am. Coll. Surg.* 190:562–572.
12. Daly JM, Karnell LH, Menck HR. (1996). National Cancer Data Base report on esophageal carcinoma. *Cancer* 78:1820–1828.
13. Earlam, R, Cunha-Melo, JR. (1980). Oesophageal squamous cell carcinoma: I. A critical review of surgery. *Br. J. Surg.* 67:381–390.
14. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, West AB, Blaser M, Blot WJ, Gail MH, Fraumeni JF Jr. (2003). Population attributable risks of esophageal and gastric cancers. *J. Natl. Cancer Inst.* 95:1404–1413.
15. Falconer JS, Ross JA, Fearon KCH. (1994). Effects of EPA and other fatty acids on growth in vitro of human pancreatic cell lines. *Br. J. Cancer* 69:826.
16. Fein R, Kelsen DP, Geller N, Bains M, McCormack P, Brennan MF. (1985). Adenocarcinoma of the esophagus and gastroesophageal junction: Prognostic factors and results of therapy. *Cancer* 56:2512–2518.
17. Forman D. Are nitrates a significant risk factor in human cancer? (1989). *Cancer Surv.* 8:443–458.

18. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. (2000). Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 283:2552–2558.
19. Gochi A, Orita K, Fuchimoto S, Tanaka N, Ogawa N. (2001). The prognostic advantage of preoperative intratumoral injection of OK-432 for gastric cancer patients. *Br. J. Cancer* 84:443–451.
20. Gonzalez NJ, Isaacs LL. (1999). Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of pancreas, with nutrition and detoxification support. *Nutr. Cancer* 33:117–124.
21. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ. (2004). Cancer statistics, 2004. *CA Cancer J. Clin*. 54:8–29.
22. Jenkins DJ, Bloom SR, Albuquerque RH, Leeds AR, Sarson DL, Metz GL, Alberti KG. (1980). Pectin and complications after gastric surgery: Normalization of postprandial glucose and endocrine responses. *Gut* 21:574–579.
23. Kono S, Hirohata T. (1996). Nutrition and stomach cancer. *Cancer Causes Control* 7:41–55.
24. Lagergren J, Bergstrom R, Nyren O. (2000). No relation between body-mass and gastroesophageal reflux symptoms in a Swedish population based study. *Gut* 47:26–29.
25. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. (2001). Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N. Engl. J. Med*. 345:725–730.
26. Mark SD, Liu SF, Li JY, Gail MH, Shen Q, Dawsey SM, Liu F, Taylor PR, Li B, Blot WJ. (1994). The effect of vitamin and mineral supplementation on esophageal cytology: Results from the Linxian Dysplasia Trial. *Int. J. Cancer* 57:162–166.
27. Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, Fraumeni JF Jr, Blot WJ, Dong ZW, Taylor PR. (2000). Prospective study of serum selenium levels and incident esophageal and gastric cancers. *J. Natl. Cancer Inst*. 92:1753–1763.
28. Martinex ME, Marshall JR, Alberts DS. (1999). Dietary fiber, carbohydrates and cancer. In *Nutritional Oncology*. Edited by Herber D, Blackburn GL, Go VLW, et al. San Diego: Academic Press; 185–192.
29. McLeod RS. (1999). Quality-of-life, nutritional status and gastrointestinal hormone profile following Whipple procedure. *Ann. Oncol*. 10(Suppl 4):281–284.
30. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. (2001). Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* 286:921–929.
31. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. (2003). Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. *Am. J. Epidemiol*. 157:1115–1125.
32. Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL. (1988). Dietary habits and past medical history as related to fatal pancreas cancer risk among adventists. *Cancer* 61:2578–2785.
33. National Cancer Institute. Annual cancer statistics review: 1973–1991. (1994). Department of Health and Human Services, Bethesda (DHHS publications no. (NIH) 94–2789).
34. Nilsson M, Lundegardh G, Carling L, Ye W, Lagergren J. (2002). Body mass and reflux oesophagitis: An oestrogen-dependent association? *Scand. J. Gastroenterol*. 37:626–630.
35. Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, Tornberg B, Wiechel KL. (1986). Diet and pancreatic cancer: A case-control study. *Am. J. Epidemiol*. 124:894–902.

36. Oettle GJ, Paterson AC, Leiman G, Segal I. (1986). Esophagitis in a population at risk for esophageal carcinoma. *Cancer* 57:2222–2229.
37. Pickwell SM, Schimelpfening S, Palinkas LA. (1994). "Betelmania": Betel quid chewing by Cambodian women in the United States and its potential health effects. *West J. Med*. 160:326–330.
38. Pisani P, Parkin DM, Bray F, Ferlay J. (1999). Estimates of the worldwide mortality from 25 cancers in 1990. *Int. J. Cancer* 83:18–29.
39. Pollard HM. (1981). The Pancreatic Cancer Task Force: Staging of cancer of pancreas. *Cancer* 47:1631.
40. Siddiqi M, Tricker AR, Preussmann R. (1988). The occurrence of preformed N-nitroso compounds in food samples from a high risk area of esophageal cancer in Kashmir, India. *Cancer Lett*. 39:37–43.
41. Siewert JR, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. (2001). Histologic tumor type is an independent prognostic parameter in esophageal cancer: Lessons from more than 1,000 consecutive resections at a single center in the Western world. *Ann. Surg*. 234:360–367.
42. Silverman DT, Schiffman M, Everhart J, Goldstein A, Lillemoe KD, Swanson GM, Schwartz AG, Brown LM, Greenberg RS, Schoenberg JB, Pottern LM, Hoover RN, Fraumeni JF Jr. (1999). Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br. J. Cancer* 80:1830–1837.
43. Sobala GM, Schorah CJ, Sanderson M, Dixon MF, Tompkins DS, Godwin P, Axon AT. (1989). Ascorbic acid in the human stomach. *Gastroenterology* 97:357–364.
44. Symreng T, Larsson J, Schildt B, Wetterfors J. (1983). Nutritional assessment reflects muscle energy metabolism in gastric carcinoma. *Ann. Surg*. 198:146–150.
45. Terashima M, Takagane A, Sasaki T. (1998). A prospective randomized trial of preoperative immunotherapy using PSK for the treatment of gastric cancer (abstract). *Proc. Am. Soc. Clin. Oncol*. 17:304a.
46. Terry P, Lagergren J, Ye W, Nyren O, Wolk A. (2000). Antioxidants and cancers of the esophagus and gastric cardia. *Int. J. Cancer* 87:750–754.
47. Terry P, Lagergren J, Ye W, Wolk A, Nyren O. (2001). Inverse association between intake of cereal fiber and risk of gastric cardia cancer. *Gastroenterology* 120:387–391.
48. Tersmette AC, Petersen GM, Offerhaus GJ, Falatko FC, Brune KA, Goggins M, Rozenblum E, Wilentz RE, Yeo CJ, Cameron JL, Kern SE, Hruban RH. (2001). Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. *Clin. Cancer Res*. 7:738.
49. Trivedy C, Baldwin D, Warnakulasuriya S, Johnson N, Peters T. (1997). Copper content in *Areca catechu* (betel nut) products and oral submucous fibrosis. *Lancet* 349:1447.
50. Wang L, Zhu D, Zhang C, Mao X, Wang G, Mitra S, Li BF, Wang X, Wu M. (1997). Mutations of O6-methylguanine-DNA methyltransferase gene in esophageal cancer tissues from Northern China. *Int. J. Cancer* 71:719–723.
51. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnsen K, Olsen JH. (1997). Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J. Natl. Cancer Inst*. 89:1360–1365.
52. Wigmore SJ, Todorov PT, Barber MD, Ross JA, Tisdale MJ, Fearon KC. (2000). Characteristics of patients with pancreatic cancer expressing a novel cancer cachectic factor. *Br. J. Surg*. 87:53–58.
53. Wingo PA, Cardinez CJ, Landis SH, Greenlee RT, Ries LA, Anderson RN, Thun MJ. (2003). Long-term trends in cancer mortality in the United States, 1930–1998. *Cancer* 97:3133–3275.

13 Nutritional Management of Cachexia of Chronic Illness

David Frankenfield and J. Stanley Smith

CONTENTS

13.1 INTRODUCTION

The inflammatory response, recognized for decades as the major metabolic feature of injury and infection, is one of the main reasons why nutrition support in such patients can be a challenge. What is only recently becoming appreciated is the extent to which the inflammatory response underlies the nutritional issues of chronic diseases (1,19). An inflammatory component may be a significant cause of changes in body composition in such disparate diseases as congestive heart failure, cancer, chronic obstructive pulmonary disease, HIV, and rheumatological disorders (11,12,17,19,28). The recognition that inflammation may drive what until recently has been thought of as purely nutritional effects of disease opens a new avenue for the management of the body wasting of disease (cachexia). This chapter will address the mechanism of the inflammatory response that leads to cachexia, distinguish emaciation due to starvation from that due to inflammation, and explore potential ways of managing the problem.

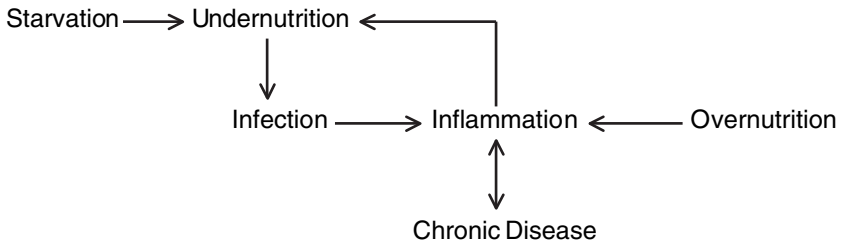

FIGURE 13.1 Nexus of overnutrition, undernutrition, infection, and disease with inflammatory response.

13.2 CLINICAL PRESENTATION OF CACHEXIA

Cachexia is a condition in which body protein and/or fat is wasted. It usually is accompanied by weight loss and anorexia. The condition has been defined in several ways. The simplest and most common description is an unintentional weight loss that exceeds 7 to 10% over a 6-month period (2). Some experts define the condition by means of markers that are specific to the protein mass of the whole body rather than body weight. This definition places the emphasis on protein as the critical body compartment. Moreover, fluid retention can mask weight loss. Cachexia can be and often is thought of as a form of malnutrition. There is much commonality and interaction between the two conditions (see Figure 13.1), yet when emaciation due to starvation or malnutrition is equated with cachexia of inflammation, some important differences are neglected.

13.3 SEMISTARVATION VS. INFLAMMATION IN THE GENESIS OF CACHEXIA

Starvation or malnutrition results from inadequate food intake, either because of a dysfunctional bowel, dysphagia, lack of appetite, or socioeconomic constraints on access to food. In the absence of disease, the body's metabolism can adapt to the lack of intake by sparing body protein and by limiting release of protein and fat from the body. Importantly, resumption of nutrient intake reverses this type of malnutrition.

Cachexia, driven by an inflammatory response, typically involves loss of appetite (anorexia) and a resulting decrease in nutrient intake. Erosion of body protein will occur, however, even if there is no interruption of nutrient supply (1,2,19). The metabolic changes in inflammation seem to be directed at quickly mobilizing muscle protein and body fat to support acute phase protein and glucose synthesis. This helps the body overcome the acute challenges to homeostasis that occur with infection or injury (19,21,24). In cachexia, the metabolic system does not spare protein as in starvation and is not turned off when nutrient intake becomes adequate.

13.4 THE INFLAMMATORY RESPONSE

The inflammatory response is a primitive, complicated, and indispensable part of the nonspecific immune system (9). Changes in body composition caused by inflammation are not imposed by the inflammatory stimulus but are in fact a part of the body's orchestrated response to the acute challenge to homeostasis that the inflammation represents. There exist, moreover, different levels of inflammation. Small-scale localized inflammatory responses occur frequently in the body with no systemic consequences (9). In fact, such responses may represent an important mechanism to increase exposure of the cellular immune system to antigen. At the next level, severity is still localized, but its effects are more obvious. This can be illustrated by the response to a foreign material, such as a wood splinter. Here the classic signs of inflammation can be seen: *rubor, tumor, calor, dolor,* and *functio laesa* (redness, swelling, pain, heat, and loss of function) (9).

A more serious challenge to homeostasis is represented by multiple injury due to trauma or surgery. Here the inflammation is more exuberant, and the systemic effects become manifest: hypermetabolism, protein catabolism, insulin resistance, fever, and acute phase protein response. At this level of inflammation, though severe, the body can still adapt and recover. However, dysregulation of inflammation at this point may cause uncontrolled sepsis leading to multiple organ failure with widespread endothelial damage and organ dysfunction. In addition, the intermediary metabolism may become deranged, and cellular immune function may collapse (9,29). It is this type of inflammation-driven illness that is the major cause of death in the ICU (9). Cachexia is a feature of patients who survive this. Once convalescence is achieved, the inflammatory metabolism normalizes and the body's normal functions can be restored with proper nutrition and exercise.

The inflammatory response, for reasons not fully understood, can become chronic. In that condition, acute phase protein synthesis is altered, the intermediary metabolism is impaired, and cachexia is present (2,11,12,17,19,28,29). This form of inflammation is believed to be maladaptive, and it is common in numerous disease states. As shown in Table 13.1 and Figure 13.1, aging and obesity also have inflammatory features that contribute to changes in body composition, function, and overall health, but these are not a topic in the current chapter. Because the inflammation never resolves, the loss of body protein and function continues to a critical level (2).

Teleologically, the inflammatory response seems to have evolved as a defense mechanism for short-term (5 to 7 d) challenges to homeostasis, such as trauma or infection. As human beings developed effective medical practices, sanitation/hygiene systems, and food production techniques, people became healthier and survived acute illnesses, living to an older age. This led to chronic illnesses becoming more common. Many of these conditions stimulate a chronic inflammatory response (2,11,12,17,19,28,29), probably a result that counteracts the initial "purpose" of the acute inflammatory response. Thus, while inflammation is important for recovery from acute illnesses, in chronic illness it may become pathological. Ironically, although the inflammatory response is part of the immune system, excessive or

TABLE 13.1
Diseases and Conditions That May Have an Important Inflammatory Component Leading to Cachexia

- Injury (surgical or traumatic)
- Infection
- Cancer
- Congestive heart failure (cardiac cachexia)
- End-stage renal disease
- End-stage liver disease
- Chronic obstructive pulmonary disease (COPD)
- Acute respiratory distress syndrome (ARDS)
- HIV/AIDS
- Inflammatory bowel diseases
- Pancreatitis
- Rheumatological diseases
- Obesity[a]
- Aging[a]

[a] These conditions are not considered in the current chapter. See Chapters 1–4.

chronic stimulation of the inflammatory response can downregulate a person's overall immune response, making the person more susceptible to infection (10).

Notwithstanding its costs to the body, inflammation confers many advantages, including the following:

1. Rapid mobilization of fuel and substrates from muscle and adipose tissue to maximize visceral functions leading to recovery (gluconeogenesis, glutamine synthesis, acute phase protein synthesis)
2. Initiation of the process of local control and elimination of the offending agent (fever response, neutrophil and macrophage recruitment)
3. Presentation of antigen to the specific immune system to induce its participation in eliminating the offending agent
4. Reduction of fluid loss to maintain hydration in the face of interrupted intake.

In other words, the inflammatory response may be thought of as providing internal nutrition, fluid resuscitation, and antibiotic therapy.

Inflammation is mediated by a host of biochemicals, including hormones, growth factors, enzymes, kinins, complements, cytokines, and eicosanoids (Figure 13.2). The initial injury stimulates local mast cells to release numerous mediators (9) that attract neutrophils and monocytes (macrophages) to the site. The cells phagocytize antigen and cell debris and release the mediators that propagate inflammation. Chief among these mediators are the cytokines and the eicosanoids. There are pro- and anti-inflammatory forms of each of these. At first, pro-inflammatory forms predominate; these are tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, prostaglandin-2

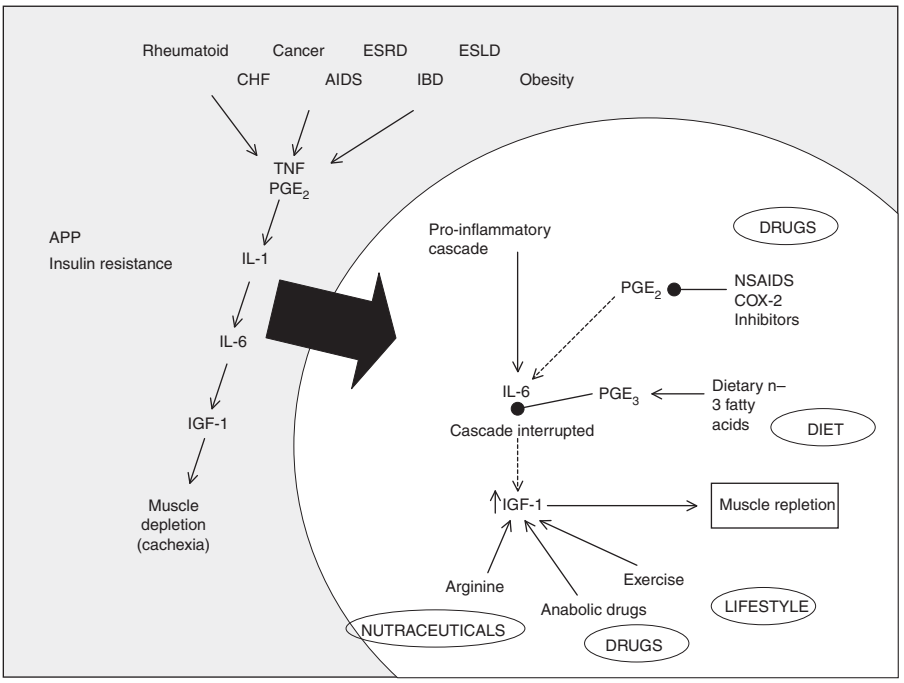

FIGURE 13.2 Simplified inflammatory cascade and potential areas to interrupt the cascade.

series (PGE_2), and leukotriene-4 (LT_4). TNF and the prostaglandins are expressed early and along with IL-1 help elicit the acute phase response (fever, acute phase protein synthesis, insulin resistance). TNF and IL-1 peak early and then disappear from plasma but have stimulated IL-6 release (9). One of the effects of IL-6 is to reduce the level of insulin-like growth factor (IGF-1), a factor that leads to muscle depletion and is central to the development of cachexia (3,14,25,30).

As the agent causing inflammation is overcome and eliminated, the anti-inflammatory cytokines (IL-4, IL-10, IL-13) and eicosanoids (PGE_3, LT_5) become predominant and bring the inflammatory response to a conclusion. This is not to say that only pro- or anti-inflammatory mediators are being expressed. Rather, there is interplay between the two types of mediators, with the anti-inflammatory molecules becoming dominant as the inflammation is resolved.

In chronic inflammation, the mediators are predominantly proinflammatory; this leads to prolonged tissue damage and systemic effects on immune function, body composition, and metabolism (i.e., cachexia). Table 13.2 lists changes in body composition and function during inflammation and methods for their detection.

13.5 CACHEXIA IN CHRONIC ILLNESS

Several theories have been advanced to explain the development of cachexia in chronic illness. These include malabsorption of nutrients, inadequate nutrient intake,

TABLE 13.2
Changes in Body Composition and Function During Inflammation and Methods for Their Detection

Parameter	Change	Detection Method
Metabolic rate	Increased resting metabolic rate Decreased physical activity Little change overall	Indirect calorimetry (portable or hand-held) (for resting metabolic rate)[a]
Body composition	Muscle atrophy Reduction in fat mass No change in extracellular water ± Weight loss depending on water status	Body weight Anthropometry Creatinine height index Bioelectrical impedance plethysmography
Serum proteins	Acute phase protein response Decreased albumin, prealbumin Increased C-reactive protein, fibrinogen	Serum albumin and C-reactive protein
Appetite	May be decreased or may be unchanged	Diet history, food records

[a] Resting metabolic rate must be interpreted in light of changes in body composition.

and reduction in physical activity leading to muscle atrophy (12). While these conditions may contribute to the development of cachexia, it is chronic inflammation that is now thought to be the major cause (12,19).

Induction of the inflammatory response requires a stimulus. Physical injury and antigen invasion are the stimuli most often described in conditions such as trauma, pancreatitis, or infection. Local areas of hypoxia may also constitute an inflammatory stimulus. Therefore, heart failure and COPD may be added to the list of conditions that cause inflammation. Conversion of self to nonself tissue (e.g., cancer) or faulty recognition of self vs. nonself tissue (e.g., inflammatory bowel disease, rheumatologic conditions) can also elicit inflammation. Table 13.1 lists a large number of chronic conditions that can have an inflammatory component.

13.6 DIAGNOSIS AND MONITORING

Cachexia of illness presents superficially like semistarvation or malnutrition. Patients suffer weight loss, hypoalbuminemia, lethargy, and so forth. Furthermore, if they have no appetite, their nutrient intake is decreased. It is easy, therefore, to confuse cachexia of illness with semistarvation or malnutrition. Also, a patient with true starvation or malnutrition may develop an infection or an acute inflammation for other reasons. This must be recognized as a separate problem from cachexia due to chronic inflammatory response. For the problem to be properly managed, it is necessary to recognize that inflammation is present. The development of cachexia in chronic illness is associated with increased mortality (18). The factors that set cachexia of illness apart from semistarvation and malnutrition include:

- There might be no interruption in nutritional intake, yet weight loss and emaciation may be occurring anyway. Body composition will show a decrease in body cell mass and possibly fat-free mass, although fat-free mass includes extracellular water, which might be expanded.
- C-reactive protein levels are likely elevated, along with depression of serum albumin, prealbumin, and transferrin.
- Oxygen consumption at rest will be elevated.
- Fever may be present.

Changes in body composition can be identified qualitatively by physical examination and anthropometrics. Temporal wasting, prominent clavicles and scapulas, and squared shoulders all tell of wasting of body protein and fat mass. The presence of edema is indicative of expanded extracellular water. A more quantitative identification of the clinical changes in fat-free mass, body cell mass, and body fat mass, as well as intracellular and extracellular water volumes, can be followed serially in the clinic using bioelectrical impedance (8,20).

Hypermetabolism can be diagnosed and monitored with indirect calorimetry. With portable calorimetry devices, this technique is becoming more practical to use in the clinical setting (26). Raw resting metabolic rate (RMR) data are not useful and so are often indexed. The traditional method of indexing the metabolic rate is as a ratio of the measured to the calculated resting metabolism of a healthy person, adjusted to body size (e.g., the Harris–Benedict equation, Mifflin–St. Jeor equation) (16,23). However, this indexing method is too imprecise and variable (13) to be used in patients who have body compositional changes and changes in body temperature that will change the relationship between metabolic rate and body size. Metabolic rate data in the patients with cachexia are most meaningful if indexed to changes in body cell mass rather than the body weight or fat-free mass (both of which are influenced by retention of fluid in the extracellular compartment).

For techniques such as bioelectrical impedance and indirect calorimetry to be useful in the diagnosis and monitoring of cachexia, standard methods of measurement must be established and followed. These are most meaningful if the patient serves as his or her own control. Otherwise, a change in values due to nonstandard conditions is likely to be incorrectly interpreted as constitutiting improvement or deterioration in the patient's metabolic state. Most clinical laboratories are equipped to measure serum albumin and C-reactive protein levels. Serum albumin may be depressed due to a variety of nutritional and nonnutritional reasons, but C-reactive protein is elevated only if inflammation is present. It is therefore essential to measure both in patients with or suspected of having cachexia.

13.7 TREATMENT

Treatment for semistarvation or malnutrition involves reestablishing adequate nutrient intake. This requires identifying and resolving physical, psychological, and financial barriers, such as dysphagia, depression, polypharmacy, social isolation, lack of access, and so forth. If weight gain and protein repletion are not attained by

nutritional means, i.e., by calculating and providing adequate amounts of energy and protein, the true requirements can be estimated with the aid of indirect calorimetry and an evaluation of the nitrogen balance. If weight gain and protein repletion are still inadequate, alteration of metabolism by inflammation is a likely cause.

In addition to providing adequate caloric and protein intake, the cachexia of chronic illness also requires interrupting the inflammatory response, thus allowing anabolic utilization of nutrients as they are consumed. The acute inflammatory response is halted when the acute problem is resolved, as when an infection is controlled or an injury has healed. Chronic illness cannot be cured but can only be managed. This means that the stimulus for inflammation cannot be stopped. Inflammation can be managed by providing medications or substances that interrupt or modify the inflammatory cascade in an anti-inflammatory direction (Figure 13.2). Several possible strategies for interrupting inflammation are under investigation;

TABLE 13.3
n-3 (α-linolenic, eicosapentanoic, dososahexanoic) and n-6 Fatty Acid (α-linoleic) Contents of Certain Foods

Food	Portion	α-Linolenic Acid (mg)	Eicosapentanoic Acid (mg)	Docosahexanoic Acid (mg)	α-Linoleic Acid (mg)
Beef sirloin	100 g	51	0	0	272
Chicken breast	100 g	30	10	20	590
Catfish (farmed)	100 g	82	49	128	1,029
Atlantic salmon (farmed)	100 g	113	690	1,457	666
Pink salmon	100 g	44	537	1,230	64
Sardines, in tomato sauce	100 g	235	532	865	123
Tuna, blue fin	100 g	0	363	1,141	68
Tuna, canned in water	100 g	2	47	223	9
Tuna, yellow fin	100 g	15	47	232	10
Soybean oil	100 g	6,800	0	0	51,000
Corn oil	100 g	700	0	0	58,000
Canola oil	100 g	9,300	0	0	20,300
Flaxseed oil	100 g	53,300	0	0	12,700
Menhaden oil[a]	100 g	1,490	13,168	8,562	2,154
Fish oil capsules[b]	100 g	0	180,000	120,000	0

[a] Menhaden oil is a marine oil used in certain tube feedings.

[b] Fish oil capsules are 1 g in size; portion of 100 g has been used in this table for comparison with foods only. Per-capsule amounts are 1800 mg eicosapentanoic acid and 1200 mg docosahexanoic acid.

Source: From USDA National Nutrient Database for standard reference.

nutritional and drug products incorporating this research have been marketed. Pharmacological options for interruption of inflammation include several of the nonsteroidal anti-inflammatory drugs and anticytokine medications. Nutritional strategies range from regular foods to functional foods to food supplements.

Among the most promising nutritional agents for promoting an anti-inflammatory milieu is the balance of n-6 to n-3 fatty acids in the body (4). Diet is the source of these fatty acids, which quickly become part of the cell membranes, influencing their characteristics and function. These fatty acids are also the raw material for eicosanoid production (27), with the type of eicosanoid a function of the membrane fatty acids. The dietary n-6 fatty acid is linoleic acid, which is incorporated into cell membranes as arachidonic acid. Arachidonic acid gives rise to proinflammatory PG_2 and LT_4. The dietary n-3 fatty acids are alpha-linolenic, eicosapentanoic (EPA), and docosahexanoic acid (DHA). The alpha-linolenic acid can be enzymatically elongated into EPA and DHA, and each of these is incorporated into cell membranes. EPA and DHA give rise to the more anti-inflammatory PG_3 and LT_5. These anti-inflammatory eicosanoids interrupt the release of IL-6, thus normalizing IGF-1 levels (31).

The typical modern Western diet is high in total fat, with the ratio of n-6 to n-3 fatty acids about 15:1. A more desirable ratio would be 2:1 to 4:1. See Table 13.3 for a list of foods rich in the various n-3 fatty acids. The nutritional treatment of the cachexia of chronic illness involves increasing caloric and protein intake by all available means. This often means ingesting dairy foods and nonmarine proteins. Such a diet will, however, keep the n-6:n-3 ratio high.

Interestingly, many pharmacological approaches to managing inflammation are aimed at blocking the enzymes that convert fatty acids to their corresponding eicosanoids (i.e., cyclooxygenase inhibitors, lipoxygenase inhibitors). Managing the inflammation process by changing dietary intake instead of inhibiting enzyme conversion may be more beneficial, because the enzymes that are being inhibited play other roles that would not be interfered with if the enzyme inhibitor is avoided.

13.8 RESEARCH FINDINGS

One of the difficulties in modulating the inflammatory response in chronic illness by nutritional means is that a given protocol applies to a specific disease, and the results cannot necessarily be generalized. For example, a study that shows an improvement in body composition and quality of life in cancer patients may not apply to patients with congestive heart failure.

Novel approaches to the management of cachexia are increasingly being applied, but this should not involve ignoring the current standard of supplemental macro- and micronutrients. Anker and Cederholm (1) have reviewed the literature on the nutritional treatment of nonmalignant cachexia. They report that in 36 randomized controlled trials, standard supplementation of nutrient intake improved function/morbidity by 60%. In 41 randomized controlled trials, standard supplementation improved anthropometric variables by 80%. However, in a large percentage of studies, standard support of caloric, protein, and micronutrient intake did not have a positive effect. The intriguing question is whether in these negative studies a more

targeted form of nutrition support would have had the desired effect. n-3 fatty acids are one of the nutrients with potential to attenuate the inflammation of cachexia. They induce anti-inflammatory prostaglandins that reduce secretion of the inflammatory IL-6 (4,27,31).

In three studies, pancreatic cancer patients consumed 3 g of EPA, a marine source of n-3 fatty acid, in a calorie/protein liquid supplement (5,6,7). As a result, patients gained weight (as fat-free mass, an indicator of anabolism), increased their grip strength, and reduced their levels of C-reactive protein and IL-6, as well as their resting metabolic rate — all markers of decreased inflammation. Responses to quality of life and functional status questionnaires indicated improved scores. In another randomized trial, daily supplementation of 18 g n-3 fatty acid improved survival time in malnourished patients with solid tumors (15).

Amino acid supplementation — specifically of arginine, glutamine, leucine, isoleucine, and valine — represents another possible mode of nutritional intervention. Because the metabolic pathways of these amino acids intersect, supplementation with all may not be required. Interestingly, two double-blind, randomized trials utilizing a commercially available amino acid supplement that contains 14 g arginine, 14 g glutamine, and 3 gβ-hydroxy-β-methylbutyrate (an analog of leucine) have shown that such supplementation can increase the fat-free mass of cachectic cancer patients (with stage IV solid tumors) and of patients with stage III AIDS (10,22).

13.9 SUMMARY

Cachexia is a common feature of many chronic illnesses. Chronic stimulation of the inflammatory response is often the cause of cachexia in a large variety of diseases. As cachexia develops, the quality of life diminishes and death may ensue. To prevent cachexia from progressing and perhaps to reverse it, it is necessary to interrupt or slow chronic inflammation, thus restoring more normal metabolism and repleting body protein. Interventions utilizing drugs or nutritional agents tend to increase body protein mass and to improve quality of life. However, mortality rates have not decreased. Therefore, simple, inexpensive nutritional interventions to manage the cachexia of illness may be more appropriate than more expensive and invasive drug therapies. A nutritional program to manage cachexia includes the following steps:

1. An early screening process to identify patients who have cachexia and to differentiate them from patients suffering from semistarvation/malnutrition.
2. Measuring C-reactive protein and albumin levels to permit further distinction of cachexia from inflammatory response and semistarvation malnutrition. Indirect calorimetry can determine if hypermetabolism is present. Bioelectrical impedance measurements provide information on the loss of fat-free mass.
3. Steps to maximize the intake of calories, protein, and micronutrients (education on oral feeding and expertise in managing tube feeding or parenteral nutrition).

4. Incorporation of anti-inflammatory nutrients (e.g., n-3 fatty acids) into the diet or tube feeding plans.
5. Review and discussion of new findings with colleagues and initiation of clinical research protocols to elucidate the role of anti-inflammation strategies in the management of the cachexia of chronic illness.

REFERENCES

1. Anker, G., and Cederholm, T. (2001) Treatment of protein-energy malnutrition in chronic non-malignant disorders. *Am. J. Clin. Nutr.* 74, 6.
2. Anker, S.D., and Coats, A.J.S. (1999) Cardiac cachexia. A syndrome with impaired survival and immune and neuroendocrine activation. *Chest* 115, 836.
3. Argiles, J.M., et al. (2000) The divergent effects of tumor necrosis factor-alpha on skeletal muscle: implications in wasting. *Eur. Cytokine Netw.* 11, 552.
4. Bagga, D., et al. (2003) Differential effects of prostaglandin derived from n-6 and n-3 polyunsaturated fatty acids on COX-2 and IL-6 secretion. *PNAS* 100, 1751.
5. Barber, M.D., et al. (2000) The metabolic response to feeding in weight-losing pancreatic cancer patients and its modulation by a fish oil-enriched nutritional supplement. *Clin. Sci.* 98, 389.
6. Barber, M.D., et al. (1999) Fish oil-enriched nutritional supplement attenuates progression of the acute phase response in weight-losing patients with advanced pancreatic cancer. *J. Nutr.* 129, 1120.
7. Barber, M.D., et al. (1999) The effect of an oral nutritional supplement enriched with fish oil on weight loss in patients with pancreatic cancer. *Br. J. Cancer* 81, 80.
8. Chertow, G.M., et al. (1995) Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J. Am. Soc. Nephrol.* 6, 75.
9. Chrousos, G.P. (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N. Eng. J. Med.* 332, 1351.
10. Clark, R.H., et al. (2000) Nutritional treatment for aquired immunodeficiency virus-associated wasting using B-hydroxy-B-methylbutyrate, glutamine, and arginine: a randomized, double-blind, placebo-controlled study. *J. Parenter Enteral Nutr.* 24, 133.
11. Debigaré, R., Coté, C.H., and Maltais, F. (2001) Peripheral muscle wasting in chronic obstructive pulmonary disease. *Am. J. Resp. Crit. Care Med.* 164, 1712.
12. Espat, N.J., Moldower, L.L., and Copeland, E.M. (1995) Cytokine-mediated alterations in host metabolism prevent nutritional repletion in cachectic cancer patients. *J. Surg. Oncol.* 58, 77.
13. Frankenfield, D.C., et al. (2003) Validation of several established equations for resting metabolic rate in obese and nonobese people. *J. Am. Diet. Assoc.* 103, 1152.
14. Frost, R.A., Lang C.H., and Gelato, M.C. (1997) Transient exposure of human myoblasts to tumor necrosis factor-alpha inhibits serum and insulin-like growth factor-I stimulated protein synthesis. *Endocrinology* 138, 4153.
15. Gogos, C.A., et al. (1998) Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy. *Cancer* 82, 395.
16. Harris J.A., and Benedict F.G. (1919) *A biometric study of basal metabolism in man*. Carnegie Institute of Washington, publication No. 279, Washington, D.C.

17. Kaysen, G., and Eisenrich, J.P. (2003) Characteristics and effects of inflammation in end-stage renal disease. *Sem. Dial.* 16, 438.
18. Kotler, D.P., et al. (1989) The magnitude of body cell-mass depletion and the timing of death from wasting in AIDS. *Am. J. Clin. Nutr.* 50, 444.
19. Kotler, D.P. (2000) Cachexia. *Ann. Inter. Med.* 133, 622.
20. Kotler, D.P., et al. (1996) Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: effects of race, sex, and disease. *Am. J. Clin. Nutr.* 64, 489S.
21. Kushner, I. (1993) Regulation of the acute phase response by cytokines. *Perspect. Biol. Med.* 36, 611.
22. May, P.E., et al. (2002) Reversal of cancer-related wasting using oral supplementation with a combination of B-hydroxy-B-methylbutyrate, arginine, and glutamine. *Am. J. Surg.* 183, 471.
23. Mifflin. M.D., et al. (1990) A new predictive equation for resting energy expenditure in healthy individuals. *Am. J. Clin. Nutr.* 51, 241.
24. Moldower, L.L., and Copeland, E.M. (1997) Pro-inflammatory cytokines, nutritional support, and cachexia syndrome. *Cancer* 79, 1828.
25. Niebauer, J., et al. (1998) Deficient insulin-like-growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine, and neurohormonal activation. *J. Am. Coll. Car.* 32, 393.
26. Nieman, D.C., Trone, G.A., and Austin, M.D. (2003) A new handheld device for measuring resting metabolic rate and oxygen consumption. *J. Am. Diet. Assoc.* 103, 588.
27. Scholz, H. (2003) Prostaglandins. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 285, R512.
28. Schulze, P.C., Gielen, S., et al. (2003) Muscular levels of proinflammatory cytokines correlate with a reduced expression of insulin like growth factor in chronic heart failure. *Basic Res. Cardiol.* 98, 367.
29. Steinborn, W., and Anker, S.D. (2003) Cardiac cachexia: Pathophysiology and clinical implications. *Basic Appl. Myol.* 13, 191.
30. Strassman, G., et al. (1993) Suramin interferes with interleukin-6 receptor binding in vitro and inhibits colon-26-mediated experimental cancer cachexia in vivo. *J. Clin. Invest.* 92, 2152.
31. Wigmore, S.J., et al. (1997) Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. *Clin. Sci.* 92, 215.

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